

# Pediatric Severe Traumatic Brain Injury : Updated Management

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Traumatic brain injury (TBI) is the leading cause of death and disability in children. Survivors of severe TBI are more susceptible to functional deficits, resulting in disability, poor quality of life, cognitive decline, and mental health problems. Despite this, little is known about the pathophysiology of TBI in children and how to manage it most effectively. Internationally, efforts are being made to expand knowledge of pathophysiology and develop practical clinical treatment recommendations to improve outcomes. Here we discuss recently updated evidence and management of severe pediatric TBI.

**Key Words :** Traumatic brain injury · Pediatrics · Critical care · Intracranial pressure · Practice guideline.

## INTRODUCTION

Traumatic brain injury (TBI) is the leading cause of death or severe disability in children older than 1 year. From 1997 to 2007, the United States Centers for Disease Control and Prevention reported that 73276 children died from TBI<sup>10</sup>. Another study analyzing the discharge data from more than 3000 hospitals in 30 states found that more than 29000 cases of hospitalized children with TBI and 4907 with severe TBI had a combined mortality rate of 24.2%<sup>17</sup>. Internationally, the impact of TBI on childhood mortality and disability is similar<sup>12</sup>. Moreover, the long-term effect of severe TBI on children's health is enormous. Approximately 61% of children with moderate-to-severe TBI experience disability. Estimates conclude that at least 145000 children aged 0–19 years are currently living with long-term symptoms of TBI<sup>29</sup>.

The morbidity associated with TBI is significantly higher in children than in adults. Because children exhibit more neuroplasticity than adults, they are expected to recover better, but the opposite seems true for severe TBI. This is due to the physical characteristics of children, who have weak neck muscles and relatively large heads, which increase the risk of brain damage during trauma. In addition, children's brains have higher water content due to incomplete myelination, which renders the brain more vulnerable to traumatic forces<sup>4,16</sup>. In addition, since high energy expenditure is required for neural network formation and synaptic branching development, it is susceptible to ischemic damage due to increased intracranial pressure (ICP) and decreased cerebral blood flow (CBF)<sup>31</sup>.

Therefore, understanding the mechanisms of severe pediatric TBI is necessary to improve the quality of management. This article reviews the literature on the appropriate manage-

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ment of severe pediatric TBI.

## PATHOPHYSIOLOGY

Several methods have been used to define severe TBI, most of which rely on the Glasgow coma scale (GCS). Specifically, TBI is considered severe with a GCS score of  $\leq 8$ <sup>23)</sup>. The primary damage in TBI is mechanical contusion after direct impact. The consequent inflammatory responses and apoptotic cascade activation result in secondary brain damage. This contributes to the propagation of the injury and the development of cerebral edema. Cerebral edema is a frequent complication of pediatric TBI and can arise from a combination of cytotoxic and osmolar swelling, and vasogenic edema. Cerebral edema peaks 24–72 hours after TBI and exacerbates neuronal damage by limiting CBF. It is essential to anticipate the worsening of cerebral edema in patients with severe TBI, which, if not prevented, can ultimately lead to refractory increased ICP, brain herniation, and death<sup>15,21)</sup>.

## DIAGNOSIS AND NEUROIMAGING

Rapid imaging is important for identifying the extent of the primary damage and triaging those patients who might require early surgical intervention. Due to its fast results and availability, computed tomography (CT) is the primary modality used for this purpose. However, routine, repeated head CT after initial imaging without clinical changes is not recommended<sup>22)</sup>. Magnetic resonance imaging (MRI) is more sensitive than CT in evaluating intracranial pathologies such as diffuse axonal injury. However, there is no evidence to support the efficacy of routine MRI in immediate management. After the patient is stabilized, MRI can be performed to further delineate the extent of intracranial injuries and aid in prognostication.

## ICP MONITORING

In 2019, the third edition of the Guidelines for the Management of Pediatric Severe TBI was updated (Table 1)<sup>22-24,26)</sup>. ICP monitoring is recommended to improve the clinical outcomes of all patients with severe pediatric TBI. Although the evidence for the efficacy of this method is only correlative and

**Table 1.** Summary of the updated 2019 Brain Trauma Foundation recommendations

Topic	Recommendation	Updated content
ICP monitoring	To improve overall outcomes (level III)	Use of ICP monitoring is suggested.
ICP threshold	To improve overall outcomes (level III)	Treatment of ICP for values <20 mmHg is suggested.
CPP threshold	To improve overall outcomes (level III)	1. Treatment to maintain CPP at a minimum of 40 mmHg is suggested. 2. Treatment should be administered for CPP values between 40 and 50 mmHg. Age-specific thresholds may exist.
Hyperosmolar therapy	For ICP control (level II)	Hypertonic saline (3%) is recommended at doses of 2–5 mL/kg over 10–20 minutes.
	For ICP control (level III)	Hypertonic saline (23.4%) is suggested for refractory ICP at doses of 0.5 mL/kg.
Sedation and analgesia	For ICP control (level III)	Avoid bolus of midazolam and/or fentanyl to control ICP due to the risk of cerebral hypoperfusion.
Temperature control	To improve overall outcomes (level II)	Prophylactic moderate hypothermia (32–33°C) is not recommended over normothermia.
	To improve overall outcomes (level III)	Moderate hypothermia (32–33°C) is suggested for the control of refractory ICP.
Decompressive craniectomy	For ICP control (level III)	Suggested to treat neurologic deterioration, herniation, or intracranial hypertension refractory to medical management.

ICP : intracranial pressure, CPP : cerebral perfusion pressure.

achieves class III for long-term outcomes related to ICP monitoring, a few studies support the association of successful ICP-guided management with improved survival and neurologic outcomes<sup>3,6</sup>.

An association between sustained increased ICP (generally >20 mmHg) and poor neurologic outcome or death has been demonstrated in pediatric patients in previous studies. Therefore, the therapeutic target threshold for ICP is suggested to be less than 20 mmHg<sup>2,13</sup>. However, individual reports do support lower ICP thresholds (15 mmHg)<sup>9</sup>, while other pediatric studies suggest higher values (40 mmHg)<sup>11</sup>. Thus, although an ICP threshold of 20 mmHg is generally used as reference, the optimal threshold for ICP-guided therapy should be individualized according to age, severity of the damage, and clinical findings.

## CEREBRAL PERFUSION PRESSURE (CPP)

CPP, defined as the difference between mean arterial pressure (MAP) and mean ICP, is the pressure gradient that drives blood flow to the brain. A continuously low CPP is associated with poor outcomes in patients with severe TBI. In children, the healthy CPP range may vary depending on the age. A recent study reported age specific CPP thresholds associated with poor outcomes<sup>20</sup>. However, the Guidelines for the Management of Pediatric Severe TBI only recommend keeping the minimum CPP >40 mmHg<sup>24</sup>.

Recent research of adult patients has attempted to determine the optimal individual CPP value by calculating the autoregulatory status index based on real-time ICP and MAP. This method has been proposed as an optional strategy in the fourth edition of the Guidelines for the Management of Severe TBI<sup>8</sup>. For pediatric patients, small-scale studies have been undertaken<sup>25,30</sup>. Optimal individualized CPP-directed therapy is expected to play an important role in improving the outcomes of pediatric TBI.

## BASELINE CARE

Baseline care comprises several therapies that should be administered to achieve better outcomes and ICP control at the stage of initial management. It consists of the following nine

components: proper sedation, euvolemic status achievement, fever treatment, coagulopathy correction, minimum hemoglobin (7.0 g/dL) maintenance, neutral head positioning with 30° head-of-bed elevation, and antiepileptic drug therapy<sup>24</sup>. As the occurrence of electrographic seizures after severe TBI is higher in children than in adults, occurring in up to 70% of cases, seizure prophylaxis for these patients is recommended. The prophylactic use of antiepileptic drugs prevents early post-traumatic seizures<sup>26</sup>.

## ANALGESIA AND SEDATION

Elevated ICP may be caused by pain or anxiety. Therefore, the use of analgesics and sedatives has become an important routine treatment for ICP control. However, due to a lack of evidence and specific guidelines, the choice of the type of medication and its dosage is entirely at the discretion of clinicians<sup>24</sup>. The use of bolus midazolam or fentanyl should be avoided, as it exacerbates the increase in ICP. In addition, prolonged continuous infusion of propofol for increased ICP regulation and sedation is not recommended, as per the guidelines of the Food and Drug Administration<sup>24</sup>.

## HYPEROSMOLAR THERAPY

Intravenous osmotic therapy is widely used to control ICP, with mannitol being routinely employed for increased ICP in children with severe TBI. Usually, 20% mannitol is administered at a dose ranging between 0.5 and 1.0 g/kg, and administration is repeated according to the ICP value. However, mannitol increases the risk of hypovolemia and hypotension, which must be avoided in severe TBI<sup>24</sup>.

Therefore, hypertonic saline (HTS) is the most popular treatment option for increased ICP. HTS has been rapidly replacing mannitol in North America, as it is associated with the more favorable cerebral hemodynamics and fastest resolution of increased ICP in children with severe TBI and was the only medication that improved CPP<sup>28</sup>. In a pediatric double-blinded study, 3% saline resulted in a more significant reduction in ICP than 0.9% saline. The suggested dosage for continuous infusion of 3% saline ranges between 0.1 and 1.0 mL/kg per hour and is administered on a sliding scale<sup>14</sup>. The

minimum dose required to maintain ICP <20 mmHg should be used.

Intravenous bolus administration of 23.4% HTS can be used to treat refractory increased ICP, which is defined as an ICP >20 mmHg lasting longer than 5 minutes that is unresponsive to a stepwise therapeutic protocol including sedation, analgesia, head elevation, mild hyperventilation, mild hypothermia (35–36°C), neuromuscular blocker, and inotropic support to achieve age-appropriate CPP. The suggested dose is 0.5 mL/kg, with a maximum of 30 mL<sup>22)</sup>.

To minimize complications, it is recommended that, during hyperosmolar therapy, serum sodium levels exceeding 160 mEq/L be avoided.

## COMA THERAPY

High-dose barbiturate therapy is recommended for hemodynamically stable patients with refractory increased ICP. Pentobarbital has been found to be effective in lowering ICP in children with severe TBI. During phenobarbital infusion, continuous electroencephalogram (EEG) monitoring to confirm burst-suppression EEG patterns is beneficial for phenobarbital dose titration. Because hypotension is frequent, careful monitoring is necessary. In addition, ventilator-associated pneumonia is common; therefore, preemptive surveillance is required. During coma therapy, if ICP remains stable below 20 mmHg for 24 hours, phenobarbital can be gradually discontinued over 24–96 hours<sup>22)</sup>.

## TARGETED TEMPERATURE MANAGEMENT

Maintaining normothermia is essential for pediatric patients with severe TBI, as fever exacerbates secondary brain injury<sup>27)</sup>. Therefore, therapeutic hypothermia reduces cerebral edema, prevents the progression of secondary brain injury, and reduces ICP. Its effectiveness has been proven in animal studies of TBI<sup>32)</sup>. However, clinical studies have shown that, compared to normothermia (36.5–37°C), early moderate hypothermia (32–33°C) did not lead to improved outcomes<sup>1,5,19)</sup>. Therefore, prophylactic moderate hypothermia is not recommended. Despite these results, the Guidelines for the Management of Pediatric Severe TBI recommend moderate hypother-

mia in cases of refractory increased ICP based on studies that showed significant effects of lowered ICP in patients who were subjected to therapeutic hypothermia<sup>7)</sup>.

## DECOMPRESSIVE CRANIECTOMY (DC)

DC is recommended in pediatric severe TBI for treating neurological deterioration, herniation, or refractory increased ICP, achieving level III of recommendations. The timing of DC in pediatric patients with severe TBI is a matter of debate. Primary DC is usually undertaken as soon as possible, while secondary DC is performed according to the patient's ICP. The optimal timing, most appropriate surgical technique, and specific benefits of DC for children are not well-studied.

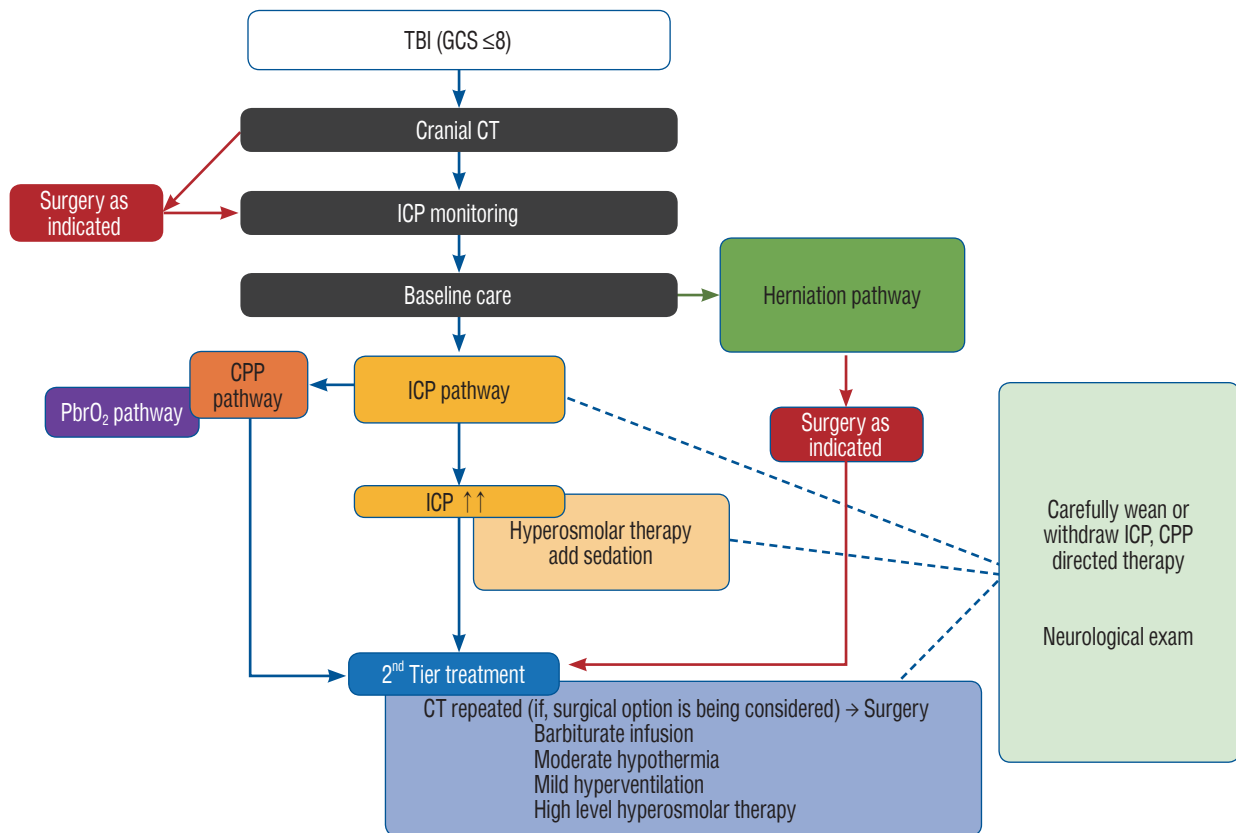
Despite its effective results in lowering ICP, DC is associated with significant early and late complications, including expansion of contusion volume, hemorrhagic infarction, seizures, infection, hygroma, and hydrocephalus<sup>18,33)</sup>. Thus, the decision to perform DC should be carefully assessed by a multidisciplinary team (neurosurgeons and neuro-intensivists), and parents should be appropriately informed of the surgical risks and clinical prognosis<sup>23)</sup>.

## NUTRITION

Recently, proper nutritional therapy has been found to be essential for critically ill patients, including those with severe TBI. Proper nutrition is expected to prevent the progression of secondary brain injury and improve prognosis. However, only a few studies have been conducted on patients with TBI. If patients are hemodynamically stable, enteral feeding should be started within 72 hours after injury<sup>24)</sup>.

## CONSENSUS-BASED ALGORITHM IMPLEMENTING THE UPDATED GUIDELINE

An evidenced- and consensus-based algorithm for the management of severe TBI in pediatric patients was suggested in the Guidelines for the Management of Pediatric Severe TBI (Fig. 1)<sup>22,26)</sup>. The algorithm includes the following components: an ICP-driven management pathway, a herniation-triggering



**Fig. 1.** The evidence- and consensus-based algorithm of the management for the severe TBI in pediatric patients. The algorithm includes several components, such as baseline care (black), an ICP pathway (yellow), a herniation pathway (green), a CPP pathway (orange), and a PbrO<sub>2</sub> pathway (purple). Solid lines identify the ICP and CPP pathways, reflecting their primary role. If baseline care is insufficient to control ICP, first-tier interventions progressing down the ICP pathway. The blue box indicates the need for second-tier therapy. TBI : traumatic brain injury, GCS : Glasgow coma scale, CT : computed tomography, ICP : intracranial pressure, PbrO<sub>2</sub> : brain tissue partial pressure of oxygen, CPP : cerebral perfusion pressure.

pathway, a CPP pathway, and a brain tissue partial pressure of oxygen pathway. Treatment methods such as surgery, hyperosmotic treatment, barbiturate coma treatment, and target temperature management were applied, and their application order also followed the guidelines<sup>26)</sup>.

Treatment practitioners can create optimal treatment therapies by integrating all available information and implementing guidelines within the patient's unique response to various treatments. In addition, this algorithm allows for changes in the timing and tempo of the treatment being implemented or withdrawn according to a given clinical context, leaving room for personalization according to the patient's needs.

## LIMITATIONS

The updated ICP- and CPP-driven treatments show the

possibility of goal-directed, tailored therapy that could lead to improved clinical outcomes. However, the updated guidelines are still limited, as they are based on the results of small studies, none of which achieve level I evidence. Future studies should be conducted to obtain higher-level evidence.

The implementation of the current guidelines might also present as an obstacle. In fact, ICP monitoring does not or cannot be performed in many countries or regions, as exemplified by the results of global prospective cohort studies, that showed that only 33–62% of patients underwent ICP monitoring<sup>26)</sup>. For the full implementation of ICP monitoring in clinical practice, solid evidence must be presented that suggests that ICP-based monitoring and treatment are essential to improve prognosis. In addition, it is necessary to compile treatment guidelines that do not include ICP monitoring.

## CONCLUSION

The Guidelines for the Management of Pediatric Severe TBI have been updated to include better treatment options even if the evidence remains insufficient. Future research is needed to confirm the effectiveness of the current recommendations. High variability in treatment algorithms, particularly for monitoring and targeting, still exists. The treatment algorithm should be adjusted according to individual needs and circumstances.

## AUTHORS' DECLARATION

### Conflicts of interest

No potential conflict of interest relevant to this article was reported.

### Informed consent

This type of study does not require informed consent.

### Author contributions

Conceptualization : EJH; Visualization : EJH; Writing - original draft : EJH; Writing - review & editing : EJH

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