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Topical Review

Children With Severe Traumatic Brain Injury, Intracranial Pressure, Cerebral Perfusion Pressure, What Does it Mean? A Review of the Literature

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ABSTRACT

Severe traumatic brain injury is a leading cause of morbidity and mortality in children. In 2003 the Brain Trauma Foundation released guidelines that have since been updated (2010) and have helped standardize and improve care. One area of care that remains controversial is whether the placement of an intracranial pressure monitor is advantageous in the management of traumatic brain injury. Another aspect of care that is widely debated is whether management after traumatic brain injury should be based on intracranial pressure–directed therapy, cerebral perfusion pressure–directed therapy, or a combination of the two. The aim of this article was to provide an overview and review the current evidence regarding these questions.

Introduction

Severe traumatic brain injury (TBI) is a leading cause of mortality and disability in children. In the United States, it accounts for more than 2.8 million emergency department visits, more than 35,000 hospitalizations, and 2200 deaths per year.[1–3] The cost to the health care system after TBI is enormous. A recent study using the National Emergency Department Sample estimated the initial hospital cost associated with TBI in the United States to be nearly $30 billion.[4] Data from the Centers for Disease Control estimate the annual cost of TBI, including and beyond the initial hospitalization, to be $76.5 billion.[5] Given the associated morbidity, mortality, and resource utilization, it is not surprising that severe TBI has been an area of active and ongoing research.

The first set of *Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents* was published in 2003.[6] The introduction of these guidelines revolutionized care and gave practitioners a similar framework from which to practice evidence-based medicine with the ultimate goal of reducing further brain injury. Since that time, the guidelines have been revised and multiple studies have shown that guideline adherence is associated with reduced mortality and improved neurological outcome.[7–9] However, guideline adherence is variable and one significant barrier to adherence is, at least in part, because of guideline credibility.[10] The vast majority of evidence used to write the guidelines is observational cohort studies and not randomized controlled trials. Two important areas in the management of the child with severe TBI that remain controversial are as follows: (1) Is placement of an intracranial pressure (ICP) monitoring device useful? and (2) Is ICP-directed therapy, cerebral perfusion pressure (CPP)-directed therapy, or a combination of the two most appropriate? Therefore we aim to review the evidence for placement of an ICP monitor and for ICP- or CPP-directed management in children with severe TBI. As the adult literature on most topics is, in general, more robust than the pediatric literature, the pertinent adult literature is also reviewed.

What do ICP and CPP mean?

ICP is the pressure inside the skull. Normal ICP varies with the position of the child, age, and level of agitation. An ICP less than 5 mm Hg would be considered acceptable for an intubated and

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sedated infant, laying horizontally.[11] An upper limit of 10 mm Hg in an adult in the same position is considered normal.[11] Increased ICP is frequently seen after severe TBI. At the time of the initial event, the brain suffers a primary injury, which cannot be reversed. After the initial trauma, the brain is at risk for ongoing injury, termed secondary brain injury. Components of secondary brain injury include molecular and cellular changes that contribute to the development of cerebral edema, inflammation, and impaired autoregulation, which may ultimately lead to the development of increased ICP.[12,13] The Monro-Kellie doctrine explains that the skull is a rigid fixed system and is made of brain, cerebrospinal fluid (CSF), and blood components.[14] Initially the CSF and blood components (predominantly venous) can shift to accommodate an expanding mass (such as an intracranial hemorrhage) or developing cerebral edema, to maintain a normal ICP. However, past a certain point, the components can no longer compensate and increased ICP develops. As elevated ICP persists, this may reduce cerebral blood flow, compromise cerebral perfusion, and contribute to further neurological injury (see Fig 1). Refractory intracranial hypertension can ultimately progress to cerebral herniation.

CPP, the pressure gradient that influences cerebral blood flow and ultimately oxygen delivery, is calculated as the difference between the mean arterial pressure (MAP) and ICP. By definition, to derive the most accurate CPP, an ICP monitor is needed. Furthermore, CPP is related to and dependent on ICP. In addition, to accurately interpret the CPP, the MAP and ICP should be calibrated at the same level with the arterial line zeroed at the level of the external acoustic meatus.[15]

In the healthy brain, through the complex process of cerebral autoregulation, cerebral blood flow is maintained over a wide range of CPP (or MAP).[16] In response to increased CPP, the cerebral arterioles will vasoconstrict to maintain constant cerebral blood flow, whereas with low CPP the cerebral arterioles will vasodilate to accomplish the same goal. In the adult patient, cerebral blood flow is maintained with MAP ranging from 50 to 150 mm Hg (Fig 2).[17] In children the MAP range in which cerebral blood flow is maintained is less well defined with some suggestion that younger children may have decreased capacity for autoregulation.[18] In severe TBI, this process may be intact, impaired, or completely absent. If impaired or absent, fluctuations in blood pressure that would normally be handled well may result in hyperemia and increased ICP at the high end of the autoregulatory curve and poor cerebral perfusion and ischemia at the low end of the autoregulatory curve.

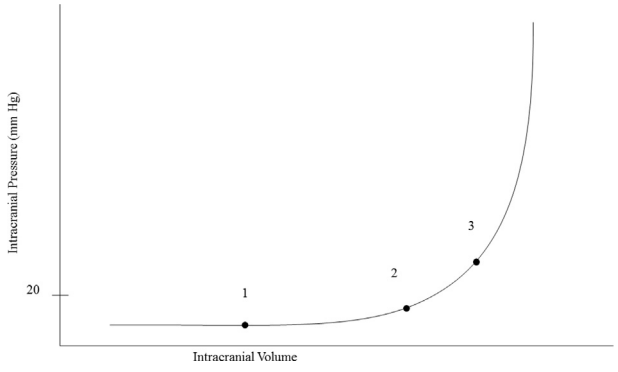

FIGURE 1. The Monro-Kellie doctrine is illustrated by the pressure-volume curve. When moving from point 1 to point 2, the intracranial volume (brain, CSF, blood, and mass or edema) increases. The ICP remains low as CSF and venous blood are displaced to compensate for the increase. When moving from point 2 to point 3, this compensatory mechanism is exhausted and any further increase in intracranial volume, from either an expanding mass or progressive edema, results in intracranial hypertension. CSF = cerebrospinal fluid; ICP = intracranial pressure.
Adapted from "Basic concepts about brain physiology and intracranial pressure monitoring," by Rodriguez-Boto, G., et al. *Neurologia*, 2015; Vol 30 (1): 16-22.

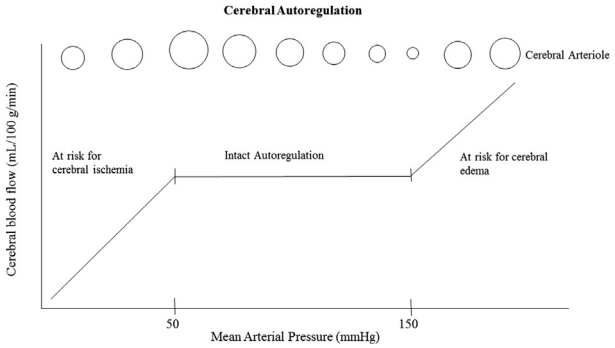

FIGURE 2. Cerebral autoregulation maintains a constant cerebral blood flow over a wide variety of mean arterial pressure or cerebral perfusion pressure. Blood flow outside the zone of autoregulation is pressure passive.
Adapted from "Raised intracranial pressure" by Dunn, LT. *J Neurol Neurosurg Psychiatry*, 2002; 73 (suppl 1): i23-i27.

Should we monitor ICP?

Severity of TBI is classified on the basis of Glasgow Coma Score (GCS). Mild TBI is defined as a GCS of 13 to 15, moderate as a GCS of 9 to 12, and severe TBI as a GCS $\leq$8.[19,20] The most recent guidelines for management of children with severe TBI released in 2012 highlight the adult recommendations for an ICP monitor, including a level II recommendation for all "salvageable" patients with severe TBI (after resuscitation GCS $\leq$8) with an abnormal head computed tomography (CT) scan, or a level III recommendation for those with a normal CT scan with two of the following features: age greater than 40 years, unilateral or bilateral motor posturing, or systolic blood pressure less than 90 mm Hg.[21] Regarding children, the guidelines state that the "use of intracranial pressure (ICP) monitoring may be considered in infants and children with severe traumatic brain injury."[21] This level III recommendation reflects the relatively low quality of evidence available on this topic. Given the level III recommendation regarding ICP monitor use, there is substantial variability in the use of ICP monitors. Many institutions routinely place ICP monitors whereas others do so much less frequently if at all.[22] Children with severe TBI who currently often undergo placement of an ICP monitor in clinical practice include children with a GCS less than 9 and an abnormal head CT, or a normal head CT with continued need for intubation, sedation, and paralysis.[21]

ICP measurement can be performed using a variety of instruments. The historical gold standard for ICP monitoring is the use of a ventricular catheter, known as an external ventricular drain (EVD).[23] The EVD is inserted into the ventricular system (either the lateral or third ventricle) and the pressure is transduced to measure the ICP. This device has the benefit of allowing for both ICP measurement and CSF drainage as a potential therapeutic modality. However, an EVD does carry the risk of infection (meningitis or ventriculitis with an incidence ranging 0% to 22%),[24] bleeding (reported rates 18% to 41%),[25] and malposition.[23] Other monitors that allow for ICP monitoring are typically placed in the brain parenchyma itself. Current intraparenchymal monitoring devices use fiber optic technology.[11] Although, these monitors do not allow for CSF drainage they have been associated with lower rates of complications (bleeding, infection). A recent study performed using intraparenchymal ICP monitors in children noted a 3.6% rate of CSF leak, 0.5% rate of postoperative hemorrhage, and 0.3% rate of

infection.[23] One limitation of intraparenchymal monitoring is the concept of drift. An intraparenchymal monitor can only be zeroed before insertion, it cannot be recalibrated during use, and may become less accurate over time (a concept known as drift), whereas an intraventricular catheter (such as an EVD) depends on a fluid-filled drainage system and a fluid-filled transducer and can be rezeroed as often as clinically indicated.[26]

Recent literature in adult patients has questioned the utility of ICP monitoring. In 2012, Chesnut et al.[27] conducted a multicenter, controlled trial in Latin America (Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure), in which patients aged greater than 13 years were randomly assigned to pressure-monitoring or a treatment protocol based on imaging and clinical examination. They found no significant difference in survival (39% mortality in the pressure-monitoring group versus 41% in the imaging-clinical examination group). Functional recovery at six months was also not significant (favorable neurological outcome in the ICP-monitoring group of 44% versus 39% in the clinical examination group). However, this study was likely underpowered to detect morbidity or mortality differences. There was a similar length of stay in the intensive care unit yet more aggressive medical management in the imaging-clinical examination group (higher use of mannitol, hypertonic saline, and hyperventilation) compared with the monitored group. It was unclear as to whether the imaging-clinical examination group suffered complications of aggressive medical management. Generalizability of this study is limited because the trial was performed in a limited resource setting with minimal prehospital transport capabilities and variable critical care resources. These limitations are evident in the high mortality rate in this study compared with recent studies in developed countries with published in-hospital mortality rates ranging from 14% to 25%.[28–31] Another limitation to generalizability is that only intraparenchymal ICP monitors were used in this study, which do not allow for CSF removal that can be accomplished using an EVD. CSF removal in this fashion can be used as an adjunctive therapy to reduce ICP during acute management of TBI. Furthermore, no subanalysis was performed on the pediatric patients included in this study. Given these limitations, a consensus statement published following this trial noted that "for those currently monitoring ICP, the results of the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure trial should not change their practice."[32]

A recent article published in 2017 questioned the benefit of ICP monitoring on functional survival in children with TBI.[2] Bennett et al. performed a propensity-weighted effectiveness analysis using a large database approach to 3084 children with severe TBI. Thirty-two percent of children underwent ICP monitoring and no statistically significant difference was found in mortality or poor functional survival (defined as survival with placement of both a new tracheostomy and gastrostomy or discharge to hospice) between those with ICP monitors and those without. The group with ICP monitors had a longer duration of mechanical ventilation (monitoring group had a median of seven days (four to 13) compared with two days (one to four) in the nonmonitoring group), had a longer hospital length of stay (median 19 days (10 to 34) versus 6 days (3 to 14)), received more osmolar therapy (62.7% versus 25.3%), more frequent use of vasoactive medications (50.3% versus 18.3%), and more frequently underwent craniotomy or craniectomy (31.1% versus 7.3%).[2] It is unclear as to whether the more frequent use of intensive therapies in the monitoring group was related to differences in illness severity not accounted for in the propensity-matching model versus treatment solely related to the ICP monitor. Furthermore, the study used an end point of functional outcome requiring a new tracheostomy and gastrostomy, which typically implies neurological devastation. There is a wide range of other potential neurological outcomes that were not assessed in this study, which may have shown a benefit to ICP monitoring had they been assessed. The end point chosen in this study does highlight a limitation of the TBI literature in general. Much of the literature uses a primary outcome of either mortality or good neurological outcome (described by the Pediatric Extended-Version of the Glasgow Outcome Score or the Pediatric Cerebral Performance Category Score), which provides short-term outcome and lacks long-term functional information that could be obtained using formal neurobehavioral testing, which would be more pertinent to the individual patient.

Although the previous studies may make one question the utility of ICP monitoring, there are ample studies that have suggested a benefit of ICP monitoring in both adults and children after severe TBI (see Table 1). Alali et al.[33] performed a retrospective cohort study in adults with severe TBI (n = 10,628 adults; 1874 had ICP monitors), using the American College of Surgeons Trauma Quality Improvement Program (TQIP) database, and found a reduction in mortality for patients with ICP monitors (adjusted odds ratio [OR], 0.44; 95% confidence interval [CI], 0.31 to 0.63). Farahvar et al.,[30] using the TBI-Trac database (a prospectively collected database of patients with severe TBI designed as a quality improvement initiative by the New York State Department of Health and administered by the Brain Trauma Foundation) also found a mortality benefit in those treated with ICP monitors. They evaluated a population of 2134 severe TBI patients and noted that 1446 had ICP-lowering therapies. Of those that received ICP-lowering therapies, 1084 had an ICP monitor and 223 did not. At two weeks, the mortality rate for those treated with ICP monitors was 19.6% versus 33.2% for those treated without ICP monitors. Similar to the adult literature, in a retrospective cohort study using data collected by the American College of Surgeons TQIP and pediatric TQIP database of 1705 children with severe TBI, the use of an ICP monitor was associated with lower in-hospital mortality (adjusted OR, 0.5; 95% CI, 0.3 to 0.85; $P = 0.01$).[34] Importantly, the children with ICP monitors (n = 273) appeared to have more severe TBI than those without monitors (n = 1432), as the rates of "critical" head injury, defined as an Head Abbreviated Injury Scale Score of 5, were 47.25% in the ICP-monitoring group and 29.75% in the non-monitoring group. Although a high-quality randomized controlled trial providing a consensus on ICP monitoring is lacking, the reviewed data suggest that placement of an ICP monitor is not harmful and may help in management.

ICP threshold

Current Brain Trauma Foundation guidelines for the treatment of children with severe TBI provide a level III recommendation that "treatment of intracranial pressure (ICP) may be considered at a threshold of 20 mm Hg."[21] The guidelines clarify that increases in ICP ≥20 mm Hg for ≥5 minutes, warrants treatment.[21]

The threshold ICP treatment value in the pediatric TBI guidelines of greater than 20 mm Hg has largely been extrapolated from the adult literature and associations with mortality (see Table 2). A single-center retrospective analysis of 429 head-injured adult patients with ICP monitors found an increase in mortality from 17% to 47% when averaged ICP was greater than 20 mm Hg.[35] In a prospective observational study of 101 adults with severe TBI and ICP monitors, a single episode of sustained increased ICP (≥20 mm Hg for ≥15 minutes) was associated with higher mortality (48.6% of patients with a single episode versus 16.2% without sustained increased ICP, adjusted $P = 0.007$) and was an independent predictor for mortality (adjusted OR, 3.15; 95% CI, 1.11 to 8.91; $P = 0.031$).[36] In a group of 96 children with severe TBI and refractory intracranial hypertension (sustained ICP >20 mm Hg

TABLE 1.
Selected Studies Regarding Placement of an Intracranial Pressure Monitor in Patients With Severe Traumatic Brain Injury

Reference	Study Description	Results	Questions or Supports Monitor	Analysis
Study with only adults				
Alali et al.[33]	Design: Retrospective cohort study using data from the ACS TQIP N = 10,628 adults Inclusion: Age ≥16 years, admitted to a TQIP hospital, with a head AIS score ≥3, acute intracranial lesion and severe TBI with GCS ≤8 in the ED Exclusion: AIS score ≥2 in any other body region, penetrating TBI, "nonsurvivable" TBI (head AIS of 6), dead on arrival, and prior advanced directives to withhold life-sustaining interventions Purpose: To determine the association between monitoring ICP and mortality after severe TBI. To evaluate the association between ICP monitoring rate at an institutional level and TBI-related mortality Outcome: Odds of in-hospital death after TBI	Overall mortality 35.5%. Mortality of those with ICP monitor was 31.6% Using a patient-level approach, ICP monitoring was associated with significantly lower odds of death (adjusted OR, 0.44; $P < 0.0001$) Admission to a center with a higher volume of TBI patients was associated with lower mortality ($P = 0.01$) Hospitals with higher rates of ICP monitoring use were associated with lower mortality (adjusted OR of death 0.52 in quartile of hospitals with highest monitoring rate compared with the lowest quartile) Outcome: ICP monitoring was associated with lower mortality 17.6% of patients underwent ICP monitoring	Supports the use of an ICP monitor	Monitoring group was younger with less comorbidity and more severe TBI Variability in ICP monitor rates between hospitals Unexplained variability in hospital mortality
Mixed studies with both adults and children				
Chesnut et al.[27]	Design: Multicenter, parallel-group trial in Latin America with randomization to ICP-monitoring or imaging-clinical examination N = 157 in pressure-monitoring group, 167 in imaging-clinical examination group Inclusion: Age ≥13 years, GCS 3-8 (GCS-M ≤ 5) Exclusion: GCS 3 with bilateral fixed/dilated pupils, unsurvivable injury Purpose: To determine whether information derived from an ICP monitor in patients with severe TBI improves medical practice and patient outcome Outcome: Composite of survival, impaired consciousness, functional status at three and six months, neuropsychologic status at six months	Mortality: 39% ICP-monitoring group versus 41% in imaging-clinical examination No significant difference in median ICU LOS (12 days in ICP-monitoring group vs nine in the imaging-clinical examination group) Significantly more days of brain-specific treatment in the imaging-clinical examination group compared with the monitoring group (4.8 vs 3.4 days; $P = 0.002$) No significant difference in favorable GOS-E at six months (44% in the pressure-monitoring group vs 39% in the imaging-clinical examination group) Outcome: No significant difference in composite outcome score between groups (56 in pressure monitoring vs 53 in imaging-clinical examination)	Questions the utility of ICP monitoring	Limited generalizability given differences in resources available in developed versus developing countries No subanalysis of pediatric patients
Farahvar et al.[30]	Design: Retrospective study using data collected prospectively from Brain Trauma Foundation New York State database N = 1446 patients Inclusion: Severe TBI (GCS < 9), treated at participating center within 24 hours. Abnormal head CT or at least two of the three: age >40 years, hypotension, or GCS-M ≤3. Needed one ICP treatment within 48 hours of admission (mannitol, hypertonic saline, barbiturates, CSF drainage, or decompressive craniectomy) Exclusion: Died in the ED or admitted with a diagnosis of brain death. Nonparalyzed patients on day 1/2 after trauma with GCS of 3-4 and with fixed/dilated pupils were excluded from the analysis Purpose: To analyze the effect of ICP monitoring on adjusted mortality rates with severe TBI treated with ICP-lowering therapy Outcome: 14-day assessment of the patient's condition as alive or dead	Monitoring group had ICP monitor inserted within 48 hours 139 Patients were <16 years 82.9% Underwent ICP monitor placement No difference in sex, initial GCS, hypotension, or CT scan findings between those treated with ICP monitor and those treated without a monitor Age, initial GCS, hypotension, and CT findings were associated with two-week mortality Mortality rate for those with an ICP monitor was 19.6% vs 33.2% in those treated without an ICP monitor (including both children and adults) Outcome: ICP monitoring was a statistically significant predictor of two-week mortality (OR, 0.63; $P = 0.02$) after controlling for covariates	Supports the use of an ICP monitor	No information explaining why patients did not receive ICP monitors Do not know what ICP-lowering treatment patients received Evaluated outcome 14 days after admission

Studies with only children				
Bennett et al.[2]	Design: Propensity-weighted comparative effectiveness study using the PHIS and NTDB databases N = 1002 with ICP monitor, 2082 without monitor Inclusion: Age <18 years with severe TBI (GCS ≤ 8 in the ED), hospital LOS >24 hours, known disposition Exclusion: Previous admission for TBI, diagnosis code for late effects of TBI, children transferred to another acute care hospital, left against medical advice Purpose: To test whether ICP monitoring is associated with improved functional survival in children with severe TBI Outcome: A composite of hospital mortality, discharge to hospice, or survival with a new gastrostomy and tracheostomy tube	Mortality was 12.4% (18.5% in ICP-monitoring group vs 9.5% in nonmonitoring group) Survival with poor functional outcome was higher in children with an ICP monitor (5.5% vs 2.1%) Children with ICP monitors had longer hospital LOS (19 vs six days; $P < 0.001$), more ventilator days (seven vs two), more days of osmolar therapy (four vs two), more days of inotropes/vasopressors (three vs two), and more days of pentobarbital (three vs one day) than those without an ICP monitor Children with monitors had higher rates of craniotomy/craniectomy (31.1% vs 7.3%) Outcome: After adjustment for patient-level differences and hospital clustering, there was no significant difference in functional survival between groups	Questions the utility of ICP monitoring	Study outcomes imply neurological devastation. Missed the opportunity to evaluate children with mild neurological impairment after severe TBI
Alali et al.[34]	Design: Retrospective cohort study using data from the ACS TQIP and from the pediatric TQIP database N = 1705 children Inclusion: Age ≤16 years, GCS ≤8. Exclusion: Patients with head AIS <3, patients unlikely to survive (head AIS = 6), those with penetrating TBI, dead on arrival to the ED, or those with significant injuries in other body regions (AIS > 2) Purpose: To examine the association between ICP monitoring and in-hospital mortality after severe TBI Outcome: Odds of in-hospital death	Overall in-hospital mortality was 14.3% 273 (16%) had ICP monitors placed. Mortality rate for those with an ICP monitor was 11% Monitored group had more severe injuries (47.25% of those in monitoring group vs 29.75% in the nonmonitoring group had a head AIS of 5) Monitored children were more likely to have subdural hematoma, traumatic subarachnoid hemorrhage, intracerebral mass lesions, cerebellar or brainstem injuries, and compressed/absent basilar cisterns. Nonmonitored patients were more likely to have fall-related injuries, be cared for at a pediatric trauma center, high-volume or university hospital, and present with hypotension Outcome: After adjusting for patient and hospital level characteristics, ICP monitoring was associated with lower in-hospital mortality (adjusted OR, 0.5; $P = 0.01$)	Supports the use of an ICP monitor	Do not know why children did not have monitors placed Unexplained variation in mortality of children with severe TBI at different institutions

Abbreviations:
ACS TQIP = American College of Surgeons Trauma Quality Improvement Program
AIS = Abbreviated injury score
CT = Computed tomography
ED = Emergency department
GCS = Glasgow Coma Scale
GCS-M = Motor component of Glasgow Coma Scale
GOS-E = Glasgow Outcome Scale-Extended
ICP = Intracranial pressure
ICU = Intensive care unit
LOS = Length of stay
NTDB = National Trauma Data Bank
PHIS = Pediatric Health Information System database
TBI = Traumatic brain injury

TABLE 2.
Selected Studies Regarding ICP Threshold for Treatment

Reference	Study Description	Results	ICP Value	Analysis
Studies with only adults				
Balestreri et al.[35]	Design: Retrospective analysis of prospectively recorded data in a unit that followed ICP/CPP protocols to maintain ICP <25 mm Hg and CPP 60-70 mm Hg N = 429 adult patients Inclusion: Severe head injury with ICP and ABP monitors for at least 12 hours Exclusion: Patients who were admitted and discharged promptly or died soon after admission were excluded Purpose: To investigate the relationships between the averaged monitored brain pressures and mortality, severe disability, and favorable outcome Outcome: six-month GOS	Mean age 34 years, median GCS was 6 28% had a good outcome, 21% were moderately disabled, 22% severely disabled, 2% in a persistent vegetative state, and 27% died Mortality increased from 17% to 47% when averaged ICP was >20 mm Hg ($P < 0.0001$) When CPP was <55 mm Hg, mortality was 81%, but for CPP >55 mm Hg, mortality was 23% ($P < 0.0001$) For CPP >95 mm Hg, mortality was 30% For CPP >95 mm Hg, rate of good/moderate outcome was 28% compared with 50% when CPP <95 ($P < 0.033$) Finding: Mortality rate was higher when mean ICP was >20 mm Hg or when CPP was <55 mm Hg. Excessive CPP >95 mm Hg had less frequent favorable outcomes	Mean ICP >20 mm Hg	Study included patients over a 10-year period, there have been multiple changes in their management protocol during that time Notes higher mortality when ICP >20 mm Hg but institutional protocol was to maintain ICP <25 mm Hg
Karamanos et al.[36]	Design: Prospective observational study of adults with severe blunt head injury, stratified by ICP and CPP N = 101 adult patients Inclusion: Blunt severe TBI (GCS ≤ 8 and/or head AIS ≥ 3), abnormal head CT Exclusion: No ICP monitor Purpose: To evaluate the association between survival and in-hospital mortality stratified by ICP (increased sustained ICP defined as single episode of ICP >20 mm Hg for ≥15 minutes) and CPP data (decreased CPP defined as a single episode of CPP <50 mm Hg) Outcome: In-hospital mortality and mortality caused by cerebral herniation	Single episode of sustained increased ICP was associated with higher mortality rates (48.6% for single episode vs 16.2% with no sustained increased ICP). Patients with increased ICP were more likely to have decreased CPP (80% with decreased CPP vs 20% without) Baseline mortality for patients with normal ICP and CPP was 16%. Mortality rate did not change when an episode of decreased CPP was added. Isolated increased ICP without evidence of decreased CPP doubled mortality (31%). When an episode of decreased CPP was added to the increased ICP, mortality rose to 45% Finding: Sustained increased ICP (>20 mm Hg) was associated with significantly higher overall mortality and mortality because of cerebral herniation (adjusted OR, 3.15; $P = 0.031$ and adjusted OR, 9.25; $P = 0.035$, respectively). Decreased CPP did not predict outcome nor have an independent impact on mortality	Sustained ICP >20 mm Hg for ≥15 minutes	Most frequent treatment for high ICP was raising head of bed, this was not standard of care for all comers All patients with increased ICP were treated whereas not all patients with low CPP were treated Those with low CPP had a higher opening ICP than those without low CPP No long-term or functional outcome information
Mixed study with both adults and children				
Honda et al.[37]	Design: Retrospective review of patients with severe TBI who underwent neuroimaging during ICP monitoring within the first seven days N = 25 patients (age 14-75, mean 44.8 years) Inclusion: Severe TBI (GCS ≤ 8), underwent perfusion CT and Xenon CT during ICP monitoring within first seven days. All patients had craniotomy and ICP insertion Exclusion: GCS-M of 6 on arrival; major organ damage/failure; hypotension (<90 mm Hg after fluid and vasopressor	Cerebral blood flow value was significantly higher at the time of ICP ≤20 mm Hg compared with when ICP >20 mm Hg (27.9 ± 12.1 vs 22.6 ± 8.7 mL/100 g/minutes; $P < 0.05$) Mean transit time was significantly lower when ICP ≤ 20 vs >20 mm Hg (6.5 ± 1.3 vs 7.8 ± 1.6 seconds; $P < 0.05$) No significant difference in cerebral blood volume based on ICP Cerebral blood flow positively correlated with CPP ($r = +0.287$, $P < 0.05$) and the mean transit time negatively correlated with	ICP >20 mm Hg	Excluded polytrauma patients if they were hemodynamically unstable at arrival, did not reassess for stability later in the course Practiced mild hypothermia (35°C-36°C). Imaging timing was not standardized, solely within the first seven days. May have been during different phases of illness (hyperemia, and so forth) Had short-term GOS outcome data but did not perform any evaluation of associations with GOS and ICP, cerebral blood flow, and so forth

(*continued on next page*)

TABLE 2. (*continued*)

Reference	Study Description	Results	ICP Value	Analysis
	resuscitation) and hypoxemia (<95% for >30 minutes) for seven days after arrival; brain herniation before Xenon CT, cardiopulmonary arrest on arrival, and polytrauma with hemodynamic instability Purpose: To clarify whether ICP >20 mm Hg is an appropriate treatment threshold Outcome: GOS at three months	the CPP ($r = -0.541$, $P < 0.05$) When ICP was ≤20 mm Hg, cerebral blood flow, cerebral blood volume, and mean transit time did not correlate with ICP When ICP was >20 mm Hg, cerebral blood flow negatively correlated ($r = -0.381$, $P < 0.05$) and mean transit time positively correlated ($r = 0.638$, $P < 0.05$) with ICP Finding: An ICP >20 mm Hg affected cerebral circulation with a negative correlation in cerebral blood flow and a positive correlation in mean transit time Supports treatment of ICP >20 mm Hg		
Studies with only children				
Jagannathan et al.[12]	Design: Retrospective review of prospectively acquired data in a pediatric trauma database N = 96 children Inclusion: Children with accidental trauma, an abnormal head CT, and refractory raised ICP (sustained >20 mm Hg) during first hour after ICP monitor placement Exclusion: Patients with no brain activity (determined by the neurosurgeon) Purpose: To discuss their experience with management of pediatric TBI and long-term outcomes in children with severe TBI and refractory ICP Outcome: Two-year GOS. If not available, the most recent clinical evaluation was used to determine the final GOS. Also used the PCRS to evaluate level of functioning	Mean age was 16.1 years. Mean presenting GCS was 5.3 34 Patients were able to achieve ICP control using medical management alone (sedation, osmolar therapy, neuromuscular blockade), 23 patients required a ventricular drain placement, and 40 patients required operative decompression Mean time until peak ICP was 69 hours after injury (range two-196 hours). Mean duration to peak ICP in the group with successful medical management was 5 (1-17) hours after the initial evaluation. Mean duration to ventricular drain placement after initial evaluation was 7 (1-32) hours Mean duration of ventriculostomy treatment was 102 hours Mean time to decompressive craniectomy for refractory intracranial hypertension was 26 hours after injury 14 Deaths related to refractory high ICP. In-hospital mortality rate was 25% Mean two-year GOS was 4 Finding: Postoperative death was most significantly correlated with the presence of refractory raised *ICP* (*>20 mm Hg*) on univariate and multivariate analyses ($P = 0.0001$). Methods used to control ICP had no correlation with death	Study: sustained ICP >20 mm Hg for first hour after ICP monitor placement Recommends: >20 mm Hg for >5 minutes likely warrants treatment	Selected a cohort of patients with intracranial hypertension up front. Could have benefited from including all children with ICP monitors placed as we know that a fair amount of children do develop refractory intracranial hypertension later than hour 1 of monitor placement All initial ICP monitor placement was an intraparenchymal monitor, therefore patients had no benefit up front of CSF removal
Esparza et al.[38]	Design: Observational cohort study N = 56 children Inclusion: GCS ≤8 at least six hours after trauma or subsequent deterioration Exclusion: GCS >8. Excluded those with transient low GCS because of seizures. Excluded those with "dominant" extracranial trauma Purpose: To analyze aspects that influence severe TBI outcomes (age, type of lesion on CT, and ICP) Outcome: In-hospital mortality. Jennett and Bond scale dichotomized as good outcome (good recovery and moderate	Mean age 7.6 years Began treatment for ICP when ≥20 mm Hg Average duration of ICP monitoring was seven days 48% of patients had ICP values >20 mm Hg When ICP was <20 mm Hg, good outcome was 93% and poor outcome was 7%. When ICP was 20-40 mm Hg, good outcome was 72% and poor outcome was 28%. When ICP was 40-60 mm Hg, poor outcome was 100%. When ICP was >60 mm Hg, poor outcome was 100% When ICP was between 20 and	ICP >40 mm Hg was associated with 100% mortality	Older study before TBI guidelines Protocol included P_{CO_2} 25-30 mm Hg and dexamethasone use for five days No child underwent decompressive craniectomy Continued medical management until 24-48 hours after cessation of intracranial hypertension Did not analyze children by injury pattern and ICP together

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TABLE 2. (*continued*)

Reference	Study Description	Results	ICP Value	Analysis
	disability) or poor outcome (severe disability, persistent vegetative state, or death)	40 mm Hg, mortality rate was 28% When ICP was >40 mm Hg, mortality was 100% Overall mortality was 32% Finding: When ICP was >40 mm Hg, mortality was 100%		
Barzilay et al.[39]	Design: Retrospective case series of children with brain injury N = 56 children (41 with head injury) Inclusion: No explicit inclusion criteria Exclusion: No explicit exclusion criteria Purpose: To evaluate association between initial GCS, initial and maximum ICP, and minimal CPP with outcome Outcome: GOS at hospital discharge	Mean age 6.2 ± 2.1 years 43% with good recovery, 30% poor recovery, and 27% died Initial GCS 3 was associated with 100% mortality. Initial GCS ≥7 had 72% good recovery, 28% poor recovery, and no mortality Max ICP noted within 48 hours of admission Max ICP in children with head trauma that survived was 16.9 ± 3.1 torr versus a maximal ICP of 53.7 ± 10.8 torr in nonsurvivors ($P < 0.01$) Minimal CPP in survivors with head injury was 65.5 ± 8.5 vs 6 ± 3.9 torr in nonsurvivors ($P < 0.01$) When initial ICP was 40 torr, all patients died. When max ICP was >40 torr, 93% died and 7% were with severe disability/persistent vegetative state Finding: An ICP >40 torr was uniformly associated with poor outcome	ICP >40 torr was uniformly associated with poor outcome	Older study before TBI guidelines All patients had ICP monitors, arterial lines. Goal P_{CO_2} was 20-25 torr and had moderate fluid restriction (2/3-3/4 maintenance). All received diuresis with furosemide. TBI patients received dexamethasone for five days Three Patients received hypothermia to 26°C-28°C No explicit inclusion/exclusion criteria
Carter et al.[40]	Design: Prospective observational study N = 35 children Inclusion: Severely brain injured children (TBI and non-TBI) with GCS ≤8 or "were thought to have suffered severe brain injury in the opinion of the treating staff" if GCS could not be determined Exclusion: Age <1 month, brain dead, or pre-existing neurological disease Purpose: To determine the predictive power of ICP and CPP with outcome in brain injured children Outcome: GOS five years after initial admission	All patients had ICP and arterial blood pressure monitoring 16 Children had good outcome at five years, six were moderately disabled, two were severely disabled, one was vegetative, and 10 were dead 25 Patients had TBI. Median patient age of child with TBI was nine years High ICP and low CPP were associated with unfavorable outcome, whereas high CPP and low ICP were associated with both favorable and unfavorable outcome No patient with an ICP >40 mm Hg had a favorable outcome. All patients with CPP <50 mm Hg had an unfavorable outcome Best threshold to predict unfavorable outcome with TBI was ICP ≥40 mm Hg and CPP ≤49 mm Hg (sensitivity/specificity for ICP was 33.3/100% and for CPP was 55.6/100%). Finding: ICP ≥40 mm Hg was associated with unfavorable neurological outcome	Peak ICP ≥40 mm Hg was associated with unfavorable neurological outcome	Goal ICP ≤20 mm Hg and CPP >30-60 mm Hg depending on age Treatment included hypothermia (33°C) Looked at solely the highest "stable" ICP and lowest stable CPP for each patient. Did not look at overall ICP burden Sample size too small to sort out the effect of age and ICP/CPP thresholds

Abbreviations:
AIS = Abbreviated Injury Score
ABP = Arterial blood pressure
CPP = Cerebral perfusion pressure
CSF = Cerebrospinal fluid
CT = Computed tomography
GCS = Glasgow Coma Score
GCS-M = Motor component of Glasgow Coma Score
GOS = Glasgow Outcome Score
ICP = Intracranial pressure
PCRS = Patient competency rating scale
TBI = Traumatic brain injury

TABLE 3.
Selected Studies Regarding Duration of ICP Elevation

Reference	Study Description	Results	ICP Timing	Analysis
Study with only adults				
Stein et al.[42]	Design: Prospective observational study N = 191 adults with severe TBI Inclusion: Age >17 years, TBI verified by CT, ICP monitor (GCS ≤0.6 and positive CT were criteria for monitor) Exclusion: No explicit exclusion criteria Purpose: To collate objective ICP data in the first seven days after severe TBI with patient outcome Outcome: In-hospital mortality, TBI-related mortality (brain death), hospital/ICU LOS. GOS-E at >3 months from initial injury (dichotomized to good 5-8, and poor outcome 1-4)	In-hospital mortality was 22.5%. Brain death in 3.7%. At hospital discharge, 77% of patients were still alive. For those with functional outcome data available at three months (123 survivors), 77.2% had good functional outcome Median ICP maximum was 66.2 mm Hg (IQR 24.6-40.1). Median mean ICP was 14.6 mm Hg (IQR 9.8-18.2). Median percent time with ICP >20 mm Hg was 10.4% (IQR 2.1-31.3) and median time with ICP >30 mm Hg was 0.8% (IQR 0-5.3) Median ICP and percent time with ICP >20 mm Hg was significantly higher in the 84-180 hours of time period than the zero-84 hours of period Those with poor functional outcome had more intracranial hypertension in hours 84-180 Multivariate analysis revealed that after 84 hours of monitoring, every 5% increase in pressure times time dose of ICP >20 mm Hg, was independently associated with 21% higher odds of having a poor functional outcome (adjusted OR, 1.21; $P = 0.03$) Findings: 43% of the cohort had their peak ICP after five days	43% of cohort still had peak ICP after five days	Criteria for insertion of ICP monitor were not GCS ≤8, but instead was GCS ≤6 Lost 17% of patients to follow-up Only 70 patients had ICP data for more than six hours (>50%) of each study window Looked at any episode of ICP ≥20 mm Hg, no matter the duration
Mixed study with adult and children				
Stocchetti et al.[43]	Design: Prospective observational study N = 201 patients Inclusion: Age >14 years, with ICP monitor in place for more than 12 hours, and with TBI Exclusion: No explicit exclusion criteria Purpose: To describe the incidence/severity of raised ICP after TBI and to record the associated time course Outcome: GOS at six months from the initial injury	Mean age 39 years, median GCS-M was 4 At six months: 18% died, 6% were in a vegetative state, 21% had severe disability, 18% had moderate disability, and 37% had a good recovery Average of 106 hours of ICP; 74 patients were still monitored five days after injury 155 Patients had an ICP >20 mm Hg for at least five minutes. Highest mean ICP was 20 mm Hg (range 6-53 mm Hg, S.D. 7.7); 82 patients had a highest mean ICP >20 mm Hg; 165 patients had CPP <60 mm Hg for at least five minutes When analyzed over time, mean ICP increased until days 12-13; however, the number of patients monitored decreased on a daily basis 1/3 of cases had their highest mean ICP during first 2 days, 1/3 over day 3/4. By day 5, 80% of cases had highest mean ICP. After injury by day 10, 99% had their highest mean ICP Findings: Approximately half of the cohort had their highest mean ICP by day 3. However, more than 25% had their peak ICP after day 5	Half of the cohort had highest mean ICP by day 3, 25% after day 5	Initial head of bed position was 15-20° For standard management for high ICP, goal $Paco_2$ was 30-35 mm Hg, for reinforced management goal 25-29 mm Hg, for extreme management, goal <25 mm Hg Looked at mean ICP values every 12 hours Their policy for discontinuing ICP monitoring requires 24 hours of no increased ICP

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TABLE 3. (*continued*)

Reference	Study Description	Results	ICP Timing	Analysis
Study with only children				
Jagannathan et al.[12]	Design: Retrospective review of prospectively acquired data in a pediatric trauma database N = 96 children Inclusion: Children with accidental trauma, an abnormal head CT, and refractory raised ICP (sustained >20 mm Hg) during the first hour after ICP monitor placement Exclusion: Patients with no brain activity (determined by the neurosurgeon) Purpose: To discuss their experience with management of pediatric TBI and long-term outcomes in children with severe TBI and refractory ICP Outcome: Two-year GOS. If not available, the most recent clinical evaluation was used to determine the final GOS. Used PCRS to evaluate level of functioning	Mean age was 16.1 years. Mean presenting GCS was 5.3 34 Patients were able to achieve ICP control using medical management alone (sedation, osmolar therapy, neuromuscular blockade), 23 patients required a ventricular drain placement, and 40 patients required operative decompression Mean time until peak ICP was 69 hours after injury (range two-196 hours). Mean duration to peak ICP in the group with successful medical management was 5 (1-17) hours after the initial evaluation. Mean duration to ventricular drain placement after initial evaluation was 7 (1-32) hours Mean duration of ventriculostomy treatment was 102 hours Mean time to decompressive craniectomy for refractory intracranial hypertension was 26 hours after injury 14 Deaths related to refractory increased ICP. In-hospital mortality rate was 25% Mean two-year GOS was 4 Finding: Postoperative death was most significantly correlated with the presence of refractory increased ICP (>20 mm Hg) on univariate and multivariate analyses ($P = 0.0001$). Methods used to control ICP had no correlation with death	Mean time to peak ICP was 69 (2-196) hours after injury	Selected a cohort of patients with intracranial hypertension up front. Could have benefited from including all children with ICP monitors placed as we know that a fair amount of children do develop refractory intracranial hypertension later than hour 1 of monitor placement All initial ICP monitor placement was an intraparenchymal monitor, therefore patients had no benefit up front of CSF removal

Abbreviations:
CSF = Cerebrospinal fluid
CT = Computed tomography
GCS = Glasgow Coma Score
GCS-M = Motor component of Glasgow Coma Score
GOS = Glasgow Outcome Score
GOS-E = Glasgow Outcome Score-extended
ICP = Intracranial pressure
ICU = Intensive care unit
IQR = Interquartile range
LOS = Length of stay
PCRS = Patient competency rating scale
TBI = Traumatic brain injury

during the first hour of monitor placement), 85% were able to achieve ICP control with medical therapy, ventriculostomy, and/or surgery. Fifteen percent were unable to achieve ICP control (defined as a persistent ICP greater than 20) and died. Jagannathan et al.[12] ultimately concluded that postoperative death was most significantly correlated to refractory intracranial hypertension.

Although there has been much literature that has shown an association with increased ICP and mortality, it has been unclear as to what the threshold for the initiation of ICP-lowering agents should be (15 versus 20 versus 25 mm Hg). However, a small, recent, retrospective study by Honda et al. evaluated neuroimaging performed on 25 adults with severe TBI. Using Xenon CT and perfusion CT scans, they found that cerebral blood flow was negatively correlated and the mean transit time was positively correlated, with ICP values greater than 20 mm Hg. This suggests that at an ICP greater than 20 mm Hg, cerebral circulation is affected and provides an impetus to begin treatment for intracranial hypertension at an ICP greater than 20 mm Hg in adult patients.[37] Similar studies have not been performed in children, but it is known that there is a higher risk of mortality when the ICP approaches 40 mm Hg.[38–40] Treatment options for intracranial hypertension include CSF drainage (which can be particularly impactful if hydrocephalus is present), osmolar agents (mannitol and hypertonic saline), controlled hyperventilation, sedation, neuromuscular blockade, barbiturates, and neurosurgical intervention. If there is a focalized expanding hematoma, surgical evacuation may be performed. A recent systematic review of the currently available pediatric literature suggests that decompressive

TABLE 4.
Studies Involving the Use of Cerebral Perfusion Pressure–Guided Therapy

Reference	Study Description	Results	CPP Threshold	Analysis
Studies with only adults				
Balestreri et al.[35]	Design: Retrospective analysis of prospective data in a unit that followed ICP/CPP protocols to maintain ICP <25 mm Hg and CPP 60-70 mm Hg N = 429 adult patients Inclusion: Severe head injury with ICP and ABP monitors for at least 12 hours Exclusion: Patients who were admitted and discharged promptly or died soon after admission were excluded Purpose: To investigate the relationships between the averaged monitored brain pressures and mortality, severe disability, and favorable outcome Outcome: Six-month GOS	Mean age 34 years, median GCS was 6 28% had a good outcome, 21% were moderately disabled, 22% severely disabled, 2% in a persistent vegetative state, and 27% died Mortality increased from 17% to 47% when averaged ICP was >20 mm Hg ($P < 0.0001$) When CPP was <55 mm Hg, mortality was 81%, but for CPP >55 mm Hg, mortality was 23% ($P < 0.0001$) For CPP >95 mm Hg, mortality was 30% For CPP>95 mm Hg, rate of good/moderate outcome was 28% compared with 50% when CPP was <95 ($P < 0.033$) Finding: Mortality rate was higher when mean ICP was >20 mm Hg or when CPP was <55 mm Hg. Excessive CPP >95 mm Hg had less frequent favorable outcomes	CPP >55 mm Hg but potentially <95 mm Hg	Study included patients over a 10-year period, there have been multiple changes in their management protocol during that time Notes higher mortality when ICP >20 mm Hg but institutional protocol was to maintain ICP <25 mm Hg
Mixed studies with both adults and children				
Allen et al.[51]	Design: Prospective observational cohort study using the Brain Trauma Foundation's TBI-trac database N = 2074 patients Inclusion: Admitted <24 hours from injury with GCS <9, GCS-M <6 for at six hours after injury Exclusion: Patients who died in the ED or were admitted with brain death. Excluded nonpharmacologically paralyzed patients on day 1 or 2 after trauma with GCS 3 or 4, with fixed and dilated pupils Purpose: To examine the relationship between minimum CPP thresholds and mortality rates in age-grouped pediatric TBI patients Outcome: Survival or mortality at 14 days after injury	Age breakdown: 55 patients from zero to five years, 65 from six to 11 years, 197 from 12 to 17 years, and 1757 in the ≥18-year-old group 382 Patients (18%) died within two weeks Survival was higher in groups with CPP-H events (CPP higher than threshold) versus those with CPP-L events (CPP lower than the threshold) across different ages (zero-11 years: 91.4% vs 30%, $P < 0.0001$, 12-17 years 87.7% vs 80.8%, $P = 0.32$, and in patients >18 years: 84% vs 62.3%, $P < 0.0001$) Percentage of patients with increased ICP was highest in patients with CPP-L events and lowest in patients with CPP-H events Suggests that CPP targets should be age specific Finding: Defined a CPP threshold stratified by age, recommended CPP goals of >50 or 60 mm Hg in adults, >50 mm Hg in six-17-year olds, and >40 mm Hg for those aged zero-five years	CPP goals of >50 or 60 mm Hg in adults, >50 mm Hg in six-17-year olds, and >40 mm Hg for those aged zero-five years	Also tracked ICP data and defined increased ICP as >25 mm Hg for those ≥1 year and >20 mm Hg for those <1 year Smaller sample size for children No standardized treatment protocol within institutions Evaluated only 14-day survival
Donnelly et al.[52]	Design: Single-center retrospective analysis of prospectively collected data N = 729 patients Inclusion: Severe TBI with ICP monitor, age >12 years Exclusion: Patients with <12 hours of ICP-monitoring data, GOS or PRx data available Purpose: To continuously and automatically determine the CPP range with intact PRx. Compared performance of the dynamic individual CPP autoregulation thresholds with the CPP optimal target and recommended fixed	Mean age 42 (±17) years Mean ICP was 15.1 (±6.2) mm Hg and was higher in those who died (18.4 ± 8.2 mm Hg; $P < 0.001$) Mean CPP was 78.2 ± 8.2 mm Hg and was lower in those who died (76.8 ± 9.5 mm Hg; $P = 0.008$) Mean CPP optimal was 78.6 ± 7.9 mm Hg PRx values indicating intact cerebral autoregulation were ≤0.3 Percentage of time spent with CPP less than the lower limit of reactivity was associated with both unfavorable outcome (OR, 1.04; $P < 0.001$) and mortality (OR,	Individualized per patient	Patients were cared for over a 20-year window, treatment algorithms/protocols have likely been modified during that time No discussion about treatment in general (CO_2 goals, and so forth)

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TABLE 4. (*continued*)

Reference	Study Description	Results	CPP Threshold	Analysis
	CPP thresholds by evaluating the relationship with outcome Outcome: GOS at six months	1.06; $P < 0.001$), after adjustment for age, initial GCS, and mean ICP Findings: It was possible to determine an optimal CPP for each individual patient and time spent with a CPP less than CPP optimal was associated with unfavorable neurological outcome and mortality		
Studies with only children				
Downard et al.[53]	Design: Retrospective review N = 118 children Inclusion: Age <15 years with brain injury on CT Exclusion: No ICP monitor placed within 24 hours of injury or if a neurological procedure was performed at an outside institution Purpose: To evaluate the association between CPP and outcome Outcome: GOS based on last recorded patient interaction	Mean age 7.4 ± 4.6 years Overall mortality was 28%; 40% of children had a good outcome and 21% had some disability but were independent No patient with mean CPP <40 mm Hg survived No significant difference in mortality or GOS when mean CPP was divided into deciles from 40 to >70 mm Hg Mean CPP <40 mm Hg (adjusted OR ∞) or mean ICP >20 mm Hg (adjusted OR 10.9) significantly increased the risk of death When CPP <40 mm Hg group was excluded, no difference in GOS regardless of mean CPP Finding: Mean CPP <40 mm Hg was uniformly associated with mortality	CPP <40 mm Hg was uniformly associated with mortality	Evaluated only the first 48 hours of CPP data No standardized treatment protocol Defined hypotension as MAP <70 mm Hg for all ages
Mehta et al.[45]	Design: Single-center, retrospective review N = 22 children Inclusion: Age <2 years with severe TBI and ICP monitor Exclusion: No explicit exclusion criteria Purpose: To determine ICP and CPP thresholds associated with favorable and unfavorable neurological outcome after severe TBI in young children Outcome: GOS at six months from injury, dichotomized into favorable (1-2) versus unfavorable (3-5)	Mean age 6.1 ± 1.4 months. Median GCS was 7 (3-11) Half of all patients had an unfavorable outcome. Mortality rate was 13.6% Daily mean ICP and CPP were not different between groups over the first seven days. No difference in number of hourly readings of ICP >20 mm Hg between groups In favorable outcome group, 0.05% of time was spent with ICP >20 mm Hg vs 16.3% in the unfavorable outcome group (although data in unfavorable group was dominated by two patients) Children with favorable outcome had significantly fewer hourly readings of CPP 45 mm Hg than children with unfavorable outcome (zero vs two hours; $P = 0.046$). No difference in number of hourly readings of CPP <40 or 50 mm Hg between outcomes Finding: Children with unfavorable outcome had more hourly readings of CPP <45 mm Hg compared with those with favorable outcome. Suggested threshold of 45 mm Hg	CPP <45 mm Hg was more frequently seen in children with an unfavorable outcome	Treatment algorithm aimed for ICP <20 mm Hg and CPP >50 mm Hg Small sample size Low incidence of ICP >20 mm Hg Data collection was hourly and may have missed subtle changes that did not persist for an hour
Young et al.[44]	Design: Analysis of prospectively collected data N = 12 children Inclusion: TBI patients (GCS < 8), with abnormal head imaging, with an ICP monitor, failed to demonstrate early clinical improvement (had a poor neurological examination with sedative medications on hold) Exclusion: Those unlikely to	Mean age was 6.25 years. Survival at ICU discharge and six months was 66% Average duration of data collection was 3.5 days Used a PRx >0.2 to indicate impaired autoregulation Mean ICP was significantly lower in children who survived than those who did not (13.1 ± 3.2 vs 21.6 ± 42.9 mm Hg; $P = 0.003$).	Survivors spent more time with CPP within 10 mm Hg of optimal CPP	No patient underwent surgical decompressive hemicraniectomy Of note, treatment was not modified based on individual PRx or CPP optimal data, solely observational recording. Treatment was based on ICP and CPP data Small sample size Only able to calculate CPPopt <60% of the time

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TABLE 4. (*continued*)

Reference	Study Description	Results	CPP Threshold	Analysis
	survive for over 24 hours were excluded, as were those with nonaccidental trauma Purpose: To describe multimodal monitoring for children with severe TBI. Particularly evaluating CPP optimal targets based on PRx Outcome: Primary outcome was survival. Assessed at the time of discharge from the ICU and at six months from initial injury	Survivor group had less time with raised ICP (>20 mm Hg) compared with nonsurvivors (9.7 + 9.8% vs 60.5 ± 67.4%; $P = 0.003$) Survivors had a median PRx of 0.02 ± 0.19 vs 0.39 ± 0.62 in deceased patients ($P = 0.02$) In survivors, time spent with CPP < CPP opt by more than 10 mm Hg was low (4.7 ± 5.7% of total time vs 15.12 ± 30.74% in nonsurvivors, $P = 0.04$) Survivors spent 90.7 ± 12.6% of time within 10 mm Hg of CPP optimal compared with 70.6 ± 21.8% in nonsurvivors ($P = 0.02$) Findings: Survivors spent more time with CPP within 10 mm Hg of CPP optimal compared with nonsurvivors		

Abbreviations:
ABP = Arterial blood pressure
CPP = Cerebral perfusion pressure
CT = Computed tomography
ED = Emergency department
GCS = Glasgow Coma Score
GCS-M = Motor component of Glasgow Coma Score
GOS = Glasgow Outcome Score
ICP = Intracranial pressure
MAP = Mean arterial pressure
OR = Odds ratio
PRx = Pressure reactivity index
TBI = Traumatic brain injury

craniectomy may have a beneficial role in controlling ICP and improving long-term outcome in children.[41] The individual specifics of each treatment for both children and adults, including mechanism of action, and a stepwise treatment algorithm are outside the scope of this review.

How long to treat ICP?

Current Brain Trauma Foundation guidelines do not address a suggested duration of ICP monitoring. Cerebral edema, a known contributor to intracranial hypertension, is thought to develop shortly after the primary injury and is known to progress over the initial two to three days[42] as "up to 40% of patients with TBI show substantial worsening during the first 48 hours in the ICU."[13] Therefore after severe TBI patients typically undergo aggressive medical management for intracranial hypertension in the early portion of their clinical course. However, the expected duration of intracranial hypertension is patient dependent and heterogeneous, thus making a definitive recommendation for treatment duration difficult.

In a study of 201 adults with severe TBI who underwent ICP monitoring, approximately one third experienced their highest mean ICP for the first two days of monitoring and another one third for more than days three to four. Eighty percent experienced their highest mean ICP after injury by day 5 and 99% by day 10.[43] In another prospective study of 191 adults with severe TBI and an ICP monitor, more than 50% of patients had their highest ICP after 84 hours of monitoring and 43% had their highest ICP after five days.[42] In a study of 96 children with severe TBI and increased ICP on presentation, peak ICP occurred at a mean of 69 hours after injury (range two-196 hours).[12] These studies suggest that intracranial hypertension is not only common during early hospitalization, but can persist for upward of one week. Recent studies (see Table 3) cite duration of ICP monitoring in children and adults with severe TBI ranging from 3.5 to seven days or longer.[27,44–48] Therefore providers must determine on an individual basis duration of monitoring and medical management of intracranial hypertension for their patients. Given the variability of monitoring duration in the literature, one potential strategy could include monitoring ICP until the patient has at least 24 hours without intracranial hypertension, a strategy that has been adopted in a number of institutions.[49,50]

CPP-Guided therapy

The current Brain Trauma Foundation guidelines provide level III evidence, that a "minimum cerebral perfusion pressure (CPP) of 40 mm Hg may be considered in children with TBI" and further specify that there may be "age-specific thresholds (range 40-50 mm Hg) with infants at the lower and adolescents at the upper end of this range."[21]

Similar to the ICP literature, an association between insufficient CPP and mortality has been noted (see Table 4). In a retrospective analysis of 429 adults with severe TBI and invasive arterial and ICP monitoring who underwent goal-directed ICP- and CPP-directed therapy, mortality increased when CPP was less than 55 mm Hg.[35] Interestingly, in this study they also noted that there may be an upper acceptable limit of CPP as they found that the rate of favorable outcome decreased when CPP was greater than 95 mm Hg. In a retrospective study of 118 children with severe TBI and ICP monitors, without a standardized treatment protocol, no patient with a mean CPP less than 40 mm Hg survived.[53] A smaller study of 22 children with severe TBI aged less than two years who underwent ICP monitoring found that children with unfavorable

TABLE 5.
Studies Highlighting Both ICP and CPP

Reference	Study Description	Results	Analysis
Study with only adults			
Balestreri et al.[35]	Design: Retrospective analysis of prospectively recorded data in a unit that followed ICP/CPP protocols to maintain ICP <25 mm Hg and CPP 60-70 mm Hg N = 429 adult patients Inclusion: Severe head injury with ICP and ABP monitors for at least 12 hours Exclusion: Patients who were admitted and discharged promptly or died soon after admission were excluded Purpose: To investigate the relationships between the averaged monitored brain pressures and mortality, severe disability, and favorable outcome Outcome: Six-month GOS	Mean age 34 years, median GCS was 6 28% had a good outcome, 21% were moderately disabled, 22% severely disabled, 2% in a persistent vegetative state, and 27% died Mortality increased from 17% to 47% when averaged ICP was >20 mm Hg ($P < 0.0001$) When CPP was <55 mm Hg, mortality was 81%, but for CPP >55 mm Hg, mortality was 23% ($P < 0.0001$) For CPP >95 mm Hg, mortality was 30% For CPP >95 mm Hg, rate of good/moderate outcome was 28% compared with 50% when CPP was <95 ($P < 0.033$) Finding: Mortality rate was higher when mean ICP was >20 mm Hg or when CPP was <55 mm Hg. Excessive CPP >95 mm Hg had less frequent favorable outcomes	Study included patients over a 10-year period, there have been multiple changes in their management protocol during that time Notes higher mortality when ICP >20 mm Hg but institutional protocol was to maintain ICP <25 mm Hg
Mixed studies with both adults and children			
Feng et al.[60]	Design: Retrospective review of adults with severe TBI who deteriorated after hospitalization N = 245 patients Inclusion: Patients with severe TBI. It was noted who after hospitalization experienced a spontaneous decrease in GCS by two points or more from prior examination, a loss of pupillary reactivity, pupillary asymmetry >1 mm, or other deterioration sufficient to warrant immediate surgical intervention Exclusion: No explicit exclusion criteria Purpose: To investigate the influence of ICP and CPP on neurological deterioration and outcome Outcome: GOS at six months from the initial injury	Age range 14-63 years Of 245 patients, 103 had neurological deterioration Mortality rate for those without deterioration was 16.2%, 54.2% had a favorable outcome. With deterioration, mortality was 66.7% and 18.3% had a favorable outcome Patients with initial ICP ≤30 mm Hg had relative risk for deterioration of 0.274, when ICP was >30 mm Hg, relative risk was 3.459, and when ICP was >40 mm Hg, relative risk was 5.167 If initial CPP was <60 mm Hg, relative risk for neurological deterioration was 2.243, if CPP was ≥70 or 80 mm Hg, the relative risk was 0.761 and 1.092, respectively If ICP was ≥30 mm Hg before or during deterioration, mortality was 73% vs 32% in those with ICP <30, regardless of CPP ($P < 0.01$) When ICP was ≤30 mm Hg and CPP was ≥60 mm Hg, mortality was 28% (46% favorable outcome). When ICP was >30 mm Hg and CPP was <60 mm Hg, mortality rate was 84% (9% favorable outcome) When ICP was >30 and CPP was ≥60 mm Hg, or ICP was ≤30 mm Hg and CPP was <60 mm Hg, mortality was 49% and 43%, respectively Finding: Most powerful predictor of neurological deterioration was ICP >30 mm Hg. CPP also had a prognostic power when <60 mm Hg	No specific exclusion criteria Evaluated intracranial hypertension as ICP >30 mm Hg No specific discussion about treatment, no mention of CO_2 goals within their program No discussion about surgical intervention (ventriculostomy vs decompression) Have no real idea about timing of their data, besides initial ICP/CPP data
Stein et al.[61]	Design: Prospective observational study N = 60 patients Inclusion: Age >14 years, admission within six hours of injury, GCS <9, TBI confirmed on imaging, and placement of an ICP monitor Exclusion: Injury to any other body region with AIS >3, nonsurvivable brain injury, or ICP monitor placed >24 hours after injury Purpose: To evaluate whether a relationship exists between brief episodes of intracranial hypertension and cerebral hypoperfusion and outcome after severe TBI Outcome: In-hospital mortality and hospital/ICU length of stay. GOS-E calculated at six months from initial injury (GOS-E 1-4 vs GOS-E 5-8)	Mean age 33.9 ± 14.1 years. Had 8678 hours of data Mortality rate was 13.3%; 61.7% had a favorable neurological outcome (GOS-E 5-8) There were significantly more episodes of low CPP (CPP < 50) in the group with GOSE 1-4 versus 5-8 (9.8 ± 8.5 vs 4.7 ± 6.8, respectively, $P = 0.02$) Significantly more mean brief episodes per day of ICP >30 (0.52 ± 0.45 vs 0.29 ± 0.27; $P = 0.02$), CPP <50 (0.65 ± 0.39 vs 0.28 ± 0.38; $P < 0.001$), and CPP <60 (1.09 ± 0.66 vs 0.7 ± 0.66; $P = 0.002$) in patients with GOSE 1-4 compared with those with GOS-E 5-8 Number of brief episodes of CPP <50, CPP <60 demonstrated high predictive power for unfavorable functional outcome Finding: There were more episodes of raised ICP and lower CPP in patients with unfavorable outcomes, dichotomized by GOS-E	Excluded polytrauma Small sample size, study underpowered Do not know whether patients had prolonged episodes of intracranial hypertension or cerebral hypoperfusion

Studies with only children			
Downard et al.[53]	Design: Retrospective review N = 118 children Inclusion: Age <15 years with brain injury on CT Exclusion: No ICP monitor placed within 24 hours of injury or if a neurological procedure was performed at an outside institution Purpose: To evaluate the association between CPP and outcome Outcome: GOS calculated based on last recorded patient interaction	Mean age 7.4 ± 4.6 years Overall mortality was 28%; 40% of children had a good outcome and 21% had some disability but were independent No patient with mean CPP <40 mm Hg survived No significant difference in mortality or GOS when mean CPP was divided into deciles from 40 to >70 mm Hg Mean CPP <40 mm Hg (adjusted OR ∞) or mean ICP >20 mm Hg (adjusted OR 10.9) significantly increased the risk of death When CPP <40 mm Hg group was excluded, no difference in GOS regardless of mean CPP Finding: Mean CPP <40 mm Hg and mean ICP >20 mm Hg significantly increased risk of death	Evaluated only the first 48 hours of CPP data No standardized treatment protocol Defined hypotension as MAP <70 mm Hg for all ages
Carter et al.[40]	Design: Prospective observational study N = 35 children Inclusion: Severely brain injured children (TBI and non-TBI) with GCS ≤8 or "were thought to have suffered severe brain injury in the opinion of the treating staff" if GCS could not be determined Exclusion: Age <1 month, brain dead, or pre-existing neurological disease Purpose: To determine the predictive power of ICP and CPP with outcome in brain injured children Outcome: GOS five years after initial admission	All patients had ICP and arterial blood pressure monitoring 16 Children had good outcome at five years, six were moderately disabled, two were severely disabled, one was vegetative, and 10 were dead 25 Patients had TBI. Median patient age of child with TBI was nine years High ICP and low CPP were associated with unfavorable outcome, whereas high CPP and low ICP were associated with both favorable and unfavorable outcomes No patient with an ICP >40 mm Hg had a favorable outcome. All patients with CPP <50 mm Hg had an unfavorable outcome The best threshold to predict unfavorable outcome with TBI was ICP ≥40 mm Hg and CPP ≤49 mm Hg (sensitivity/specificity for ICP was 33.3/100% and for CPP was 55.6/100%) Finding: CPP ≤49 mm Hg was associated with unfavorable neurological outcome	Goal ICP ≤20 mm Hg and CPP >30-60 mm Hg depending on age Treatment included hypothermia (33°C) Looked at solely the highest "stable" ICP and lowest stable CPP for each patient. Did not evaluate overall ICP burden Sample size too small to sort out age and ICP/CPP thresholds
Prabhakaran et al.[54]	Design: Randomized, prospective pilot study N = 17 children (12 CPP arm, 5 ICP arm) Inclusion: Age six months-16 years, admission GCS ≤8, ventriculostomy placement, and accidental trauma Exclusion: Those with clinical brain death evident on admission were excluded. Those for whom death was imminent were excluded (brain injury with refractory hypoxemia or hypotension despite resuscitation), as were patients felt to be the victim of nonaccidental trauma Purpose: To compare ICP- versus CPP-targeted therapy in children with severe TBI Outcome: Death and functional outcome using the GOS at 3, 6, and 12 months after injury	Median GCS in ICP group was seven vs six in the CPP group. CPP group also had more frequently nonreactive pupils 55% vs 25% in the ICP group The CPP group had more use of vasoactive medications. The use of volume resuscitation and mannitol was similar between groups Median ICP was similar between groups (17.5 mm Hg in ICP group vs 18 in the CPP group, $P = 0.47$) Median CPP was 68.5 mm Hg in the ICP group versus 74.5 in the CPP group ($P = 0.07$) In the ICP group, all patients survived, two had mild impairment and two had hemiparesis with moderate impairment. One patient was lost to follow-up In the CPP group, two patients died, one was lost to follow-up, four were unimpaired, and five had mild impairment Finding: No significant differences in outcome between ICP- and CPP-targeted therapy	Different P_{CO_2} goals between groups (ICP 20-30 vs 35-45 mm Hg in the CPP group) Different head of bed positions between groups (ICP at 30° vs supine in CPP) Aimed for high CPP, ICP group goal CPP was ≥50 mm Hg versus in the CPP group goal was ≥60 mm Hg for those aged <2 years and ≥70 for those aged >2 years Small sample size, inadequately powered

Abbreviations:
ABP = Arterial blood pressure
AIS = Abbreviated Injury Score
CPP = Cerebral perfusion pressure
CT = Computed tomography
GCS = Glasgow Coma Score
GOS = Glasgow Outcome Score
GOS-E = Glasgow Outcome Score-extended
ICP = Intracranial pressure
MAP = Mean arterial pressure
OR = Odds ratio
P_{CO_2} = Partial pressure of carbon dioxide
TBI = Traumatic brain injury

outcomes had more hourly readings of CPP less than 45 mm Hg compared with those with favorable outcomes, with no notable difference in hours spent with ICP greater than 20 between the groups.[45]

To further support the association between inadequate CPP and mortality, Allen et al.[51] recently performed an observational cohort study using data from the TBI-trac database. In a cohort of 2074 patients, including 317 children aged less than 18 years, they found lower survival with prolonged exposure to a CPP less than an age-specific threshold. Furthermore, they proposed the following age-specific CPP thresholds: greater than 40 mm Hg for children zero to five years, greater than 50 mm Hg for children six to 17 years, and greater than 50 or 60 mm Hg for adults. In general, there are two ways to manipulate the CPP, either by lowering the ICP or increasing the MAP. Methods to reduce ICP include CSF drainage, osmolar therapy, controlled hyperventilation, normothermia, sedation, barbiturates, neuromuscular blockade, and neurosurgical intervention (evacuation of mass lesions and/or decompressive craniectomy). Methods to augment the CPP via increasing the MAP include fluid resuscitation and/or the use of vasoactive agents. The details of each individual therapy and stepwise approach to management for both children and adults are outside the scope of this article.

ICP versus CPP

Only one trial exists that compared CPP-targeted therapy with ICP-targeted therapy in children with severe TBI.[54] This small feasibility trial compared an ICP-targeted therapy group (target ICP less than 20 mm Hg, maintained CPP $\geq$50 mm Hg, maintained head of bed 30°, $Paco_2$ 20 to 30 mm Hg, and used norepinephrine only for hemodynamic instability) versus CPP-targeted therapy group (no target ICP, maintained supine, maintained CPP $\geq$60 mm Hg for children aged less than two years, maintained CPP $\geq$70 mm Hg for children aged two or more years, $Paco_2$ 35 to 45 mm Hg, and used norepinephrine to maintain CPP after fluid resuscitation) in a cohort of 15 children (11 CPP, 4 ICP). Although the CPP group aimed for a higher than expected CPP based on age-specific thresholds, head of bed and $Paco_2$ goals were different between groups, and there was no statistically significant difference in outcome based on ICP- or CPP-targeted therapy. Furthermore, this study was small, underpowered, and CO_2 goals were a significant confounder as hypocapnia has been associated with cerebral ischemia and mortality in children with TBI.[55,56] No head-to-head large randomized trials using ICP- versus CPP-guided therapies exist in either adult or pediatric patients with severe TBI.

Integrated ICP/CPP

There is a controversy between health care providers regarding whether acute management of the TBI patient should be approached after an ICP- or CPP-guided therapy. There is mixed literature with some studies favoring the use of ICP-guided therapy and others favoring the use of CPP-directed therapy. Rationale for these opinions largely stems from concerns about the side effects or limitations of each approach. Given that CPP-directed therapy is primarily related to fluid resuscitation and/or vasoactive support, some studies have shown that adult patients may have more cardiorespiratory complications.[57] However, much of this literature targeted a supratherapeutic CPP, which could have exposed the patient to more fluid and/or vasoactive medications than those who targeted a more conservative CPP goal. In contrast, an ICP-only–guided therapy, particularly when autoregulation is impaired or absent, may not maintain an adequate blood pressure to perfuse the brain and result in secondary cerebral ischemia.

Current Brain Trauma Foundation guidelines do not address the utility of individualized goals for CPP and solely mention potential age-based CPP thresholds. With the advent of recent integrated technologies and advanced monitoring, there is ongoing research into finding individualized, patient-specific goals that do not rely solely on ICP or CPP but instead integrate the two. For example, Donnelly et al.[52] recently published a study in which retrospective data from 729 adults with severe TBI were reviewed. By using the arterial blood pressure and the ICP monitor, they were able to evaluate the cerebrovascular pressure reactivity index (PRx) and ultimately determine the optimal CPP for each patient. PRx is defined as a correlation coefficient between MAP and ICP, with values ranging from -1 to $+1$. When this value is positive, it implies that MAP and ICP are positively correlated and autoregulation is not intact whereas when PRx is negative, this suggests that autoregulation is intact.[58] By plotting PRx against CPP, they were able to create a U-shaped CPP-PRx curve to define the optimal CPP, the value in which PRx is the most negative. The most negative PRx suggests that autoregulation is at its best capacity in an individual patient and maintenance in this range may protect the brain from cerebral ischemia or cerebral edema. Donnelly et al.[52] found that a CPP less than the optimal CPP at a given ICP was associated with both unfavorable outcome (OR, 1.04; 95% CI; 1.02 to 1.06; $P < 0.001$) and mortality (OR, 1.06; 95% CI, 1.04 to 1.08; $P < 0.001$). In a prospective observational study of 12 children with severe TBI, survivors spent more time with a CPP close (within 10 mm Hg) to optimal CPP compared with nonsurvivors (90.7 $\pm$ 12.6% compared with 70.6 $\pm$ 21.8%; $P = 0.02$).[44] Targeting an individualized CPP as opposed to a generic or age-dependent threshold CPP may improve neurological outcomes. Although this strategy is relatively new, in a recent survey of 66 neurotrauma centers in Europe that treat adults with TBI, 25 centers (38%) reported targeting “individualized” CPP goals.[59] However, an interventional study targeting optimal CPP goals in children is lacking.

In addition to studies evaluating continuous PRx monitoring to determine optimal CPP, other studies have evaluated the utility of guiding treatment on both the ICP and CPP monitored in the traditional way at the bedside (see Table 5). In a study of 245 adults with severe TBI, Feng et al.[60] found that reduction in intracranial hypertension and maintenance of a goal CPP were both important to avoid neurological deterioration. This finding is similar to the observation of Balestreri et al.[35] on a mortality association with both increased ICP and low CPP. Stein et al.[61] found that even brief episodes (five minutes) of either inadequate CPP or intracranial hypertension were associated with unfavorable functional neurological outcome. In the study of Downward et al.[53] on children with severe TBI, not only did they find an association with mortality for CPP less than 40 mm Hg, but they also found a mortality association with ICP greater than 20 mm Hg. ICP and CPP were both accurate predictors of unfavorable outcome in the study of Carter et al.[40] on children with brain injury.

Conclusions

Few randomized controlled trials of appropriate management of children suffering with TBI have been undertaken. Therefore the Brain Trauma Foundation guidelines are based on limited available literature. What is available, however, suggests that it may be reasonable to place ICP monitors and to aggressively treat intracranial hypertension and maintain an age-appropriate CPP. Furthermore, multimodal monitoring and targeting of various physiologic parameters including ICP, CPP, and PRx in combination rather than in isolation may improve the understanding of individual responses to TBI and better guide management.

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