Management of Pediatric Severe Traumatic Brain Injury: 2019 Consensus and Guidelines-Based Algorithm for First and Second Tier Therapies

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Objectives: To produce a treatment algorithm for the ICU management of infants, children, and adolescents with severe traumatic brain injury.

Data Sources: Studies included in the 2019 Guidelines for the Management of Pediatric Severe Traumatic Brain Injury (Glasgow Coma Scale score ≤ 8), consensus when evidence was insufficient to formulate a fully evidence-based approach, and selected protocols from included studies.

Data Synthesis: Baseline care germane to all pediatric patients with severe traumatic brain injury along with two tiers of therapy were formulated. An approach to emergent management of the crisis scenario of cerebral herniation was also included. The first tier of therapy focuses on three therapeutic targets, namely preventing and/or treating intracranial hypertension, optimizing cerebral perfusion pressure, and optimizing partial pressure of brain tissue oxygen

(when monitored). The second tier of therapy focuses on decompressive craniectomy surgery, barbiturate infusion, late application of hypothermia, induced hyperventilation, and hyperosmolar therapies. **Conclusions:** This article provides an algorithm of clinical practice for the bedside practitioner based on the available evidence, treatment protocols described in the articles included in the 2019 guidelines, and consensus that reflects a logical approach to mitigate intracranial hypertension, optimize cerebral perfusion, and improve outcomes in the setting of pediatric severe traumatic brain injury. (*Pediatr Crit Care Med* 2019; 20:269–279)

Key Words: barbiturate; decompressive craniectomy; head injury; herniation; hyperosmolar; intracranial pressure

The 2019 Third Edition of the Guidelines for the Management of Pediatric Severe Traumatic Brain Injury (TBI) presents evidence-based recommendations to inform treatment (1). The available evidence, however, remains limited, and there are many major gaps in our knowledge, thereby limiting translation of the guidelines to bedside management. Therefore, the guidelines committee (Clinical Investigators) has augmented the Third Edition with a clinical practice algorithm that offers an accompanying synthesis of both evidence- and consensus-based assistance to clinical decision-making. Of the over 90 articles contributing evidence for the 2019 Pediatric TBI Guidelines document, 68 describe a protocol that was applied by the authors to direct care (2–69). The development of an algorithm based on the current evidence, insight from the aforementioned 68 protocols, and further guided by consensus of the guidelines committee follows a logical attempt to direct greater consistency in patient care as well as standardization for future investigations. The committee believes that providing an algorithm will also be helpful given 1) the many available treatment options, 2) the low level of evidence for most of the evidence-based recommendations included in the guidelines, and 3) the fact that the results of the large Approaches and Decisions in Acute Pediatric TBI (ADAPT) comparative effectiveness study are not yet available to provide additional guidance in management (70). This algorithm may also serve as a template upon which new evidence from ADAPT can be integrated when it is available.

This algorithm builds, in several ways, on the "Critical Pathway" chapter that was originally published as part of the First Edition of the guidelines in 2003 (71). The 2012, Second Edition, update (72) of those guidelines did not feature a critical pathways section. For this edition, it was decided to update this critical pathway. However, it is presented as a companion, but separate publication in order to maintain a clear distinction between what is evidence-based and what is supplemented by our expert consensus and clinical experience. Although this document is intended to inform clinical practice and improve outcomes for patients, it is also intended to allow for and encourage innovation in care and research in areas where evidence is lacking. This report provides an algorithm outlining TBI patient care that should be used in conjunction with the recommendations and the physiologic underpinnings provided in the full Third Edition Guidelines (1).

METHODS

Design

The aim of the algorithm is to outline the approaches that are both useful to general ICU management of the pediatric patient with severe TBI as well as the TBI-specific aspects of care. The starting point assumes that the patient is comatose on neurologic examination, with a Glasgow Coma Scale (GCS) score less than or equal to 8, the airway is secured with a tracheal tube, mechanical ventilation and oxygenation goals are achieved, analgesia and sedation are adequate, a baseline cranial CT scan has been obtained (to assess the extent of brain injury and potential need for a surgical intervention), and an intracranial pressure (ICP) monitor has been placed—for the specific purpose of directing ICP and cerebral perfusion pressure (CPP) guided therapy.

Next, we considered that an algorithm capable of addressing and clarifying some of the complex nuances in care was needed. These were not described in the original, First Edition pathway (71), but now at least two issues appear to be routinely encountered in the management of pediatric patients with severe TBI. First, the variations in "tempo" and timing during which therapies are implemented in given clinical contexts. These changes often need to be individualized to the patient's needs, and it may not be as simple as following a linear approach to treatment. Second, new therapeutic choices may arise in real time from information presented by integrating or combining a range of monitoring modalities, for example combining ICP with brain tissue P_{O_2} (Pbr_{O_2}), if it is being used, or using multimodal monitoring methodologies in ICP-based decision-making. These considerations are discussed and should be implemented when appropriate when using the algorithm.

Process

In the work for the Third Edition and algorithm, the committee met on three occasions and then had two subsequent video-conferencing sessions. Transcripts of each video conference were carefully reviewed. Iterations in writing subsequently occurred and ended when there was complete consensus.

Protocols From the Third Edition Literature

In the text, when appropriate, we refer to previously published protocols in studies that met the inclusion criteria for the Third Edition of the Guidelines (1). We are aware that other treatment protocols exist for use in either pediatric or adult patients with severe TBI. Our aim is not to be inclusive of every protocol but rather to focus on those that have been used in the literature informing the latest guidelines.

The references to these protocols (2–69), are presented in chronological order, so that the reader can recognize the era from which a particular reference originated. For ease of use, historical reference dating is as follows: 1979–2002 (2–25), 2003–2011 (26–51), and 2012–2016 (52–69). These references should be taken as a guide as to how patients could have been managed, for example, saying what you do may be different than what treatments individual patients actually receive. (Exemplary descriptions of protocols, often with Figures or Tables, can be found in references [2, 3, 21, 22, 28, 29, 33, 37, 40, 47, 49, 51, 56, 59, 62, 69].)

The guidelines committee has tried to be as accurate as possible in analyzing the text within the references. We realize that in some instances authors or ICUs described in the reference may have now altered their practice and no longer follow what they had previously described.

Use of Minimum Therapeutic Targets

The guidelines document includes a number of recommendations to titrate TBI care to at least some minimum target level, as in the case of ICP and CPP (1, 71, 72). The Third Edition guidelines committee considers it essential for the managing physician to recognize that in a number of important instances, the guideline recommendations (1) reflect titration of care to a minimum therapeutic target and that target might not reflect the optimal level for a given variable in an individual patient. Similarly, that target value might also be somewhat impractical to use given the desire to ensure that the value is achieved and maintained as a minimum. A CPP of 40 mm Hg, Pbr_{O_2} of 10 mm Hg, and blood hemoglobin concentration of 7 g/dL were the most notable values in this regard. Although these values represent the available evidence (1), the physician may need to maintain a value substantially above that threshold to ensure that the minimal value is never breached. Similarly, these minimum values may be insufficient and below physiologic values in some individual patients. The treating physician should integrate all of the available information and use this pathway and the guidelines within the context of each patient's unique response to various therapies to create the most optimal treatment regimen.

APPROACH TO THERAPIES

Herniation Pathway

Figure 1 summarizes various components of the first tier patient care pathways given the starting point of a secured tracheal tube, placement of an ICP monitor, and placement of an arterial and central venous catheter. CT scan and neurosurgical review have excluded the need for immediate surgery. If, however, immediate surgical intervention is required, the patient may or may not be deemed to require an ICP monitor and if so would return to the ICP pathway as shown with the dotted red line in Figure 1. Herniation can occur at any time in the ICP pathway, on presentation (i.e., in the resuscitation setting), in the course of progressive unrelenting and refractory intracranial hypertension, or in situations where it may be precipitous and/or unanticipated. The guidelines committee recognizes the need for an emergent approach to treatment that should be initiated wherever the patient resides within the treatment pathways (Herniation pathway [green], Fig. 1).

The key issue is to recognize when acute herniation of brain tissue is impending or ongoing. The clinical signs relate to traction on neural and vascular structures and/or brainstem compression. Therefore, ongoing attention to the clinical examination is essential in the unconscious patient. Transtentorial herniation will be accompanied by pupillary dilatation and bradycardia. Foramen magnum herniation leads to downbeat nystagmus, bradycardia, bradypnea, and hypertension. In the motor examination, unilateral or bilateral weakness should raise concern about subfalcine herniation. Hemiplegia should raise concern about retroalar herniation. Inappropriate motor responses to a painful stimulus will signify the level of brainstem injury. Decorticate rigidity reflects impaired brainstem activity down to the level of the red nucleus (i.e., involving corticospinal pathways at the internal capsule, cerebral hemisphere, or rostral cerebral peduncle). Decerebrate rigidity (or "extensor posturing") reflects impaired brainstem activity between the rostral midbrain and mid-pons and is seen with transtentorial herniation. Decerebrate rigidity in the arms combined with either flaccidity or weak flexor responses in the legs is seen with extensive damage to the brain stem extending down to the pons at the trigeminal level.

When the above findings are identified on examination, irrespective of whether or not there is an accompanying "spike" in ICP (in some instances ICP monitoring may not have been initiated), the clinician should consider this event as a medical emergency. However, reports on how to reverse cerebral herniation in pediatric TBI are lacking. The committee agreed that while awaiting CT scanning and neurosurgical review, the emergency medical management should include the following: manual hyperventilation with F_{IO_2} of 1.0, titrated to reversal of pupillary dilation; administration of mannitol (0.5–1 g/kg) over 10 minutes, or hypertonic saline (3%; 1–3 mL/kg, up to a maximum dose of 250 mL, or 23.4%, 0.5 mL/kg, maximum dose of 30 mL) over a similar period; and maintenance of hemodynamic stability. Note that in the setting of herniation, the efficacy of mannitol versus hypertonic saline has not been compared, and for comparison purposes, 0.5 g/kg of mannitol delivers the same osmolar dose as ~2.5 mL/kg of 3% saline. Finally, if the patient has a functioning external ventricular drain (EVD) in place, it should be emergently opened to continuous drainage if intermittent cerebrospinal fluid (CSF) drainage is being used or lowered down to a lowest level of 0 cm above the tragus if continuous drainage is being used.

Baseline Care

Initial, or "Baseline Care" (Baseline care [black], Fig. 1), should be achieved irrespective of whether intracranial hypertension has already occurred. Each of the nine components of Baseline Care will need to be considered, and the reader should refer to the Third Edition Guidelines for the evidence-based recommendations (1). With regard to the protocols, we have the following:

Maintenance of an Appropriate Level of Analgesia and Sedation (18, 19, 22–24, 27–29, 36–38, 40, 41, 47, 49–62, 64, 65, 68, 69). In general, most protocols describe using a benzodiazepine and opiate combination with the most commonly used agents being midazolam (18, 19, 23, 29, 36, 41, 51, 53–57, 59, 69) and morphine/fentanyl (18, 19, 22, 23, 29, 36, 41, 50, 51, 53–57, 59, 68, 69), respectively. The guidelines committee supports the use of a benzodiazepine-opiate combination for initial sedative/analgesic therapy.

Controlled Mechanical Ventilation. A number of ventilation-related targets have been described in protocols for initial support. For example, titrating F_{IO_2} to achieve a threshold in pulse oximetry oxygen-hemoglobin saturations (Sp_{O_2}) greater

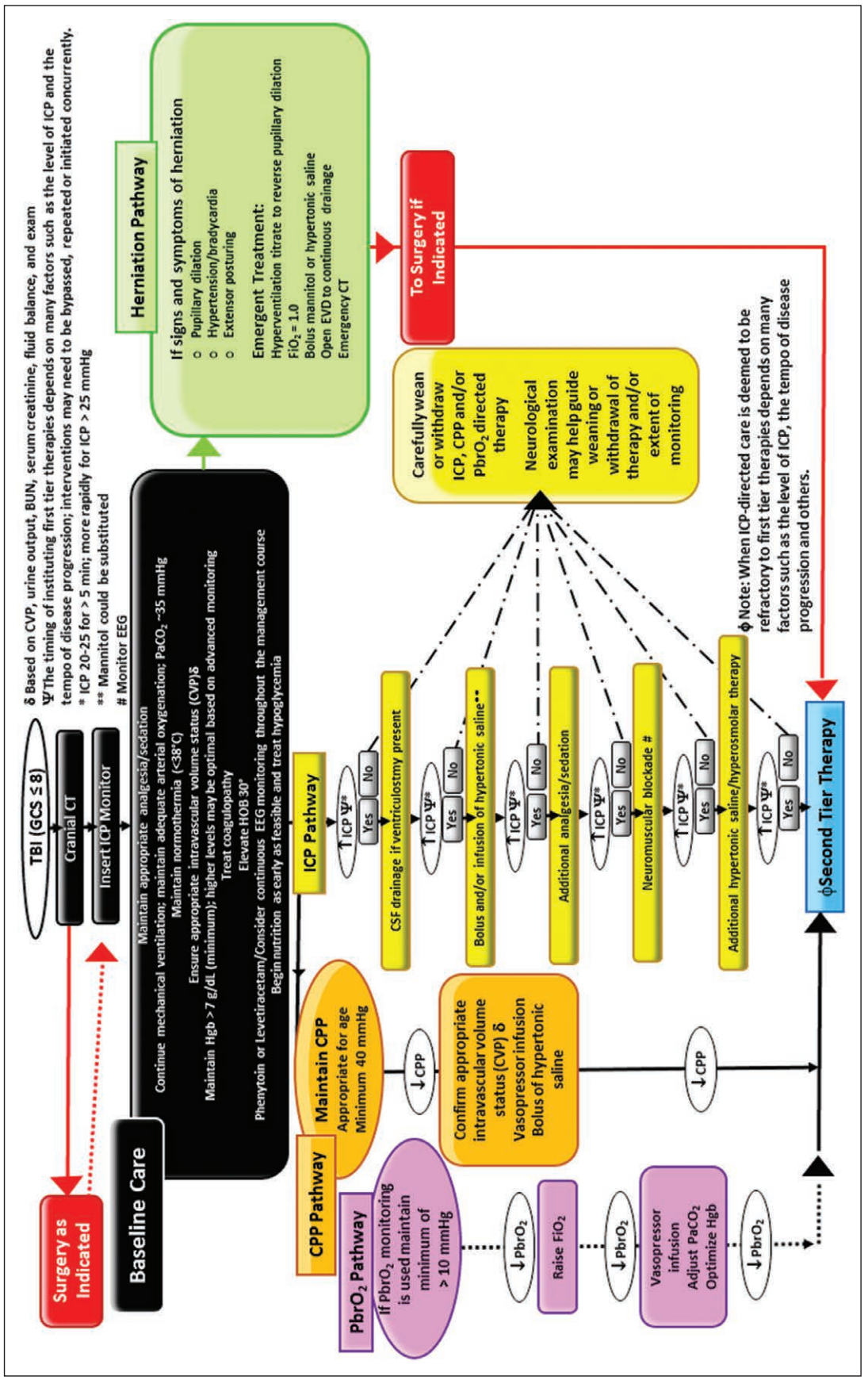

Figure 1. Evidence- and consensus-based algorithm of first tier therapies for the management of severe traumatic brain injury (TBI) in infants, children, and adolescents. The algorithm includes several components including Baseline Care (*black*), an Intracranial Pressure (ICP) Pathway (*yellow*), a Herniation Pathway (*green*), a Cerebral Perfusion Pressure (CPP) Pathway (*orange*), and a Brain Tissue Partial Pressure of Oxygen ($Pbro_2$) Pathway (*pink*). *Solid lines* identify the ICP and CPP pathways, reflecting their primary role, a *dashed line* identifies the $Pbro_2$ pathway given the fact that it represents a monitoring and management option that is less commonly used and has less literature support. A *dotted plus dashed line* identifies the weaning or withdrawal of the various interventions. As indicated in the text, the treating practitioner should integrate all of the available information and implement the Guidelines within the context of each patient's unique response to various therapies to craft the most optimal treatment regimen. In addition, although a linear approach in each pathway is provided, variations in "tempo" and timing during which therapies are implemented or weaned/withdrawn will depend on each given clinical context. For example, in some situations, a single intervention for raised ICP may suffice, whereas in others, multiple simultaneous interventions may be required. The approach will often need to be individualized to the patient's needs. If baseline care is insufficient to control intracranial pressure, then progression down the ICP and CPP pathways is indicated (*solid black line*). The *blue box* indicates the need for second tier therapy and represents the link to Figure 2. Please see text for details. BUN = blood urea nitrogen, CVP = central venous pressure, EEG = electroencephalogram, EVD = external ventricular drain, GCS = Glasgow Coma Scale, Fio_2 = fraction of inspired oxygen, Hgb = hemoglobin, HOB = head of bed.

than 92% up to greater than 99% (16, 19, 27, 36, 69). Alternatively, titrating FIO_2 to achieve PaO_2 to achieve a threshold of at least 75 (6) or 80 (22) or 90 (2, 3, 19, 29) or 100 mm Hg (4, 5, 23, 47, 51, 64). The guidelines committee advises a target PaO_2 of 90–100 mm Hg. Some protocols describe the application of positive end-expiratory pressure (PEEP) to keep exposure to FIO_2 less than 0.50 (2). Recent articles do not describe the level of PEEP that could be needed to maintain oxygenation targets, but in the older protocols, we find the following: 3–5 cm H_2O (22, 23), up to 6 cm H_2O (4), up to 8 cm H_2O (29), and up to 10 cm H_2O (33). Finally, minute ventilation should be adjusted to achieve an initial target in $PaCO_2$. There is a history of protocols targeting various ranges of $PaCO_2$ generally from 25 to 40 mm Hg (2–13, 16–19, 22, 23, 26–29, 31, 32, 36, 37, 39, 40, 47–65, 68, 69), but some older protocols targeting even less than 25 mm Hg (2, 7, 9, 12, 13, 16, 21). The guidelines committee supports targeting $PaCO_2$ between 35 and 40 mm Hg, which is consistent with an initial target in a number of protocols (18, 22, 28, 29, 31–33, 36, 37, 40, 47–51, 53, 54, 57, 59, 62, 65, 68, 69).

Maintaining Normothermic Core Temperature and Preventing and Treating Fever. Protocols have described initial targets for maintaining temperature at values greater than 35°C and less than 38°C (4, 5, 9, 19, 27, 28, 36, 39, 44, 46, 52, 54–57, 59, 62, 65, 69) or avoidance of "hyperthermia" or maintenance of "normothermia" (18, 24, 29, 38, 51, 64). The guidelines committee supports the choice to target normothermia, with an upper limit of less than 38°C.

Ensuring an Appropriate Intravascular Volume Status. This target is achieved using central venous pressure (CVP) monitoring, assessment of urine output, blood urea nitrogen, serum creatinine, clinical examination, and also includes making decisions about fluid management (i.e., fluid volume, fluid balance, and type of fluid), baseline target for plasma concentration of sodium ($[Na^+]$), baseline glucose level, and when to start nutrition. A target of "euvolemia" or "normovolemia" is described in a few protocols (21, 22, 24, 29, 36, 47, 61, 62). Protocols that are more recent have described a target threshold in CVP between 4 and 10 mm Hg (47, 59, 69) or between 8 and 12 mm Hg (33). The initial fluid volume is variously described with the older protocols using fluid restriction less than 75% of maintenance values (4, 9, 16, 19, 38). The committee considers that targeting normovolemia requires at least 75% maintenance fluids (22, 25, 46, 62, 69) and that a neutral fluid balance should be achieved with a urine flow rate of greater than 1 mL/kg/hr (22). In regard to the decision about initial fluid prescription, the committee supports the use of normal saline (NS); the choices are whether to add 5% dextrose (5 g/dL) in the first 48 hours of ICU care (16, 22, 69) and when to start nutrition (22, 23, 29, 59, 69) and by what route (22, 23, 59). With regard to glucose target, protocols have described targeting normoglycemia or a concentration up to 180 mg/dL (22, 29, 69). Insulin should be used if the glucose level is greater than 198 mg/dL on two consecutive measurements (29, 62). Vigilant glucose monitoring should be in place to avoid the risk of hypoglycemia. In regard to baseline $[Na^+]$ target, many protocols use ranges with a lower limit greater than 135 mEq/L and an upper limit less than 150 mEq/L (19, 21, 22, 29, 38, 53, 59, 62, 69). The committee considers that an initial target should be $[Na^+]$ greater than 140 mEq/L. Serum sodium levels greater than 150 mEq/L might of course be necessary as directed in the chapter on hyperosmolar therapy in the full guidelines document (1). The committee also supports the initial use of 5% dextrose in NS IV infusion in younger patients to avoid hypoglycemia and the initial use of NS IV infusion in older patients. Nutritional support should be started as early as possibly, generally by 72 hours.

Maintaining Minimum Blood [Hemoglobin]. Only a few protocols describe an early [hemoglobin] target with thresholds of 7 g/dL (hematocrit 21%) (69), 9.0 g/dL (54), 10.0 g/dL (hematocrit 30%) (19, 42), 11.0 g/dL (29), or 12 g/dL (33). In order to be consistent with the [hemoglobin] threshold used in general ICU care (73), the committee supports a minimum target greater than 7.0 g/dL in the pediatric patient with severe TBI.

Treatment of Coagulopathy. Optimal treatment of coagulopathy is complex after severe TBI, and few protocols have described their criteria or practice (25, 28, 37, 40, 56, 58, 61). Treatment of abnormal coagulation variables is recommended prior to insertion of ICP or $PbrO_2$ monitors. In a study of 157 adults with TBI and ICP monitor insertion (74), at an international normalized ratio (INR) value less than or equal to 1.6, bleeding complications were infrequent, and use of fresh frozen plasma to normalize INR below this threshold delayed monitor insertion and was not recommended. In the setting of decompressive craniectomy in children, intraoperative blood loss was substantially greater when INR was 1.36 ± 0.13 versus 1.17 ± 0.11 (61). In that report, coagulopathy was defined as platelet count less than 100,000 per mm^3, INR greater than 1.2, and activated partial thromboplastin time of greater than 36 seconds. Caution is advised given that recent work suggests that overresuscitation with plasma to normalize INR after TBI in children may worsen coagulopathy, producing fibrinolysis shutdown, and that treatment of coagulopathy should address active bleeding and/or be titrated to thromboelastography (75).

Neutral Head Positioning With Head-of-Bed Elevation. Neutral head position is well described in older protocols and is a given in modern practice (18, 28, 48, 50, 56, 57, 59, 62, 65, 69). The angle of head-of-bed elevation has been variously described using any angle from 0° up to 45° head-up positioning (2, 11, 12, 16, 18, 19, 21, 22, 24, 26–28, 31, 32, 36, 38, 47–52, 54–59, 61, 62, 64, 65, 67–69). The committee supports the use of neutral head positioning with an initial head-of-bed elevated to 30°, as the most consistent practice described in recent protocols (52, 54–59, 61, 62, 64, 65, 67–69).

Antiepileptic Drug Therapy and Use of Continuous Electroencephalography. The committee did not arrive at a consensus on the indications for antiepileptic drugs (AEDs) or the type of medication and dosing that should be used if deciding to prescribe an AED. This decision reflects the content of the Third Edition Guidelines on AEDs (1). Protocols have described using AEDs (18, 22, 51, 53, 56, 57, 59, 62, 65, 67), and, pragmatically, if a decision has been made to prescribe an AED, then levetiracetam is considered easier

to administer in comparison with (fos) phenytoin, although either is acceptable within the guidelines. Regarding the use of continuous electroencephalography (cEEG), as indicated in Figure 1, evidence supports considering its use throughout the management course, particularly when neuromuscular blockade is used. However, there are insufficient data to confirm that treatment of seizures improves outcome in pediatric TBI.

FIRST TIER THERAPIES

Figure 1 also illustrates three tier 1 pathways that cover management of 1) raised ICP (ICP pathway [yellow]), 2) inadequate CPP (CPP pathway [orange]), and 3) inadequate $Pbro_2$ ($Pbro_2$ pathway [pink]).

ICP Pathway

The protocols in the Third Edition literature have referred to various initial ICP target values, from less than 15 mm Hg (13, 14, 18, 19, 24, 28) to less than 20 mm Hg (2, 3, 6, 7, 9, 11, 12, 21, 22, 27, 29–37, 40, 42, 45, 48–62, 64, 65, 68, 69), and up to less than 25 mm Hg (4, 10, 43, 52) (yellow, Fig. 1). Some protocols also suggest that the ICP target can be guided by $Pbro_2$ level (33, 36, 42, 45, 49, 50, 53, 54, 67, 69). Alternatively, if using jugular bulb jugular vein saturation (Sjo_2) monitoring (18, 24, 25, 60), then the range in ICP between 20 and 25 mm Hg should be guided by confirming Sjo_2 values between 55% and 75% (25). The majority of protocols, however, describe using an initial ICP less than 20 mm Hg. Last, some protocols describe that when using an EVD, the drainage level is set as low as 3–5 cm H_2O, or up to 27.2 cm H_2O above the tragus (2.2–3.7 and 20 mm Hg, respectively), and used for venting or diverting CSF (3, 6, 12, 17, 18, 21, 22, 26, 28, 31–33, 36, 40, 42, 43, 48–50, 54–60, 62, 63, 65, 67–69).

With regard to the threshold in ICP at which an intervention beyond baseline care (Fig. 1, yellow) is used, many protocols describe both a level of ICP and duration at that level (2–4, 8, 11, 14, 15, 18, 22, 23, 27, 29–31, 50, 52, 58, 62, 64, 68, 69). A threshold of greater than 20 mm Hg is commonly used (see paragraph above), with need for intervention after 5 minutes (2, 30, 50, 64, 68, 69) or 10 (3, 11) or 15 (58) or 20 (31) or 30 minutes (22, 27, 52). Taken together—the protocols describing initial ICP target and threshold for intervention—the guidelines committee supports the use of less than 20 mm Hg as an initial ICP target in all age groups and also supports the need for an intervention when ICP is raised greater than 20 mm Hg for at least 5 minutes.

As will be discussed later, the level of ICP and the "tempo" of progression can importantly influence the approach to management, in particular the rapidity of linear, or sequential, progression through first tier interventions (Fig. 1, ICP pathway [yellow]). For example, an ICP elevation between 20 and 25 mm Hg warrants a stepwise progression in the options. In this instance, the initial therapeutic intervention should be CSF drainage when using an EVD. If CSF drainage is ineffective for controlling ICP, or is not being used, a bolus and/or infusion of hypertonic saline should be administered, unless there are contraindications to use of hypertonic saline, such as platelet count less than 100×10^9/L or abnormal clotting with INR greater than 1.4 or rise in creatinine more than twice baseline value (14, 21, 22, 25, 38, 39, 48–51, 53–59, 61–66, 68, 69). A bolus dose of mannitol may be considered as an alternative to hypertonic saline in this setting (2–14, 16–19, 22–24, 26–29, 31, 32, 36–40, 47–57, 59–65, 68, 69), although the evidence for such practice is lacking since no studies were identified for use on this topic in the Third Edition Guidelines (1). Additional boluses of hyperosmolar therapy and/or increases in the rate of infusion of hypertonic saline follow for additional spikes and/or progressive increases in ICP. As hyperosmolar therapy is escalated, the patient's volume status and osmolarity should be carefully monitored (see Baseline Care, black, Fig. 1). With hypertonic saline, the upper limit of approximately 360 mOsm/L has been suggested (21, 56, 57, 59, 65, 68), whereas lower thresholds up to 320 mOsm/L have been suggested for mannitol (2, 4, 9, 11–13, 17, 22, 28, 50, 54, 55, 59, 62). If hyperosmolar therapy proves ineffective, additional analgesia and/or sedation should be considered, along with potential initiation of neuromuscular blockade (2, 4, 5, 7, 10, 11, 15, 16, 18, 21, 22, 27, 28, 32, 36–38, 40, 43, 48, 50–61, 64, 65, 68, 69), as outlined in the algorithm.

At all times, all key physiologic variables germane to the management of raised ICP including arterial blood gases, serum electrolytes, osmolarity, blood urea nitrogen, serum creatinine, and [hemoglobin] should be serially monitored, and mean arterial blood pressure (MAP), temperature, and end-tidal CO_2 continuously monitored in order to proactively detect abnormalities that may influence therapeutic decisions, such as the presence of hypercarbia or progressive renal dysfunction, among others. When ICP-directed care is deemed to be refractory to first tier therapies, second tier therapies are indicated (**Fig. 2**).

CPP Pathway

Often, when ICP is increased, CPP can still be maintained (orange, Fig. 1). As outlined in the Third Edition Guidelines, there is literature supporting maintenance of a minimum value of 40 mm Hg along with support for consideration of implementing age-specific thresholds between 40 and 50 mm Hg, with infants at the lower end and adolescents at the upper end of this range (1). It should be recognized that these represent minimum acceptable values and that higher values may often be maintained in order to prevent patients from being at risk of falling below these thresholds and the risk of cerebral hypoperfusion/ischemia. CPP-directed interventions include ensuring appropriate intravascular volume status with an adequate CVP, generally between 4 and 10 mm Hg (see section on "Baseline Care" and CPP Pathway, Fig. 1). Some protocols in the literature also suggest targeting MAP or systolic blood pressure (sBP), including aiming for normal blood pressure (BP) for age (i.e., 50th percentile MAP) (29, 38, 47, 51, 69), MAP greater than 65 mm Hg (24) or greater than 90 mm Hg (47) or between 100 and 110 mm Hg (33), sBP greater than "70 + (2 × age in years)" mm Hg (29) or greater than 95 mm Hg (60), but maintained below 140 mm Hg (2).

With regard to the "what and how" of targeting in the CPP pathway, the committee supports the following approach.

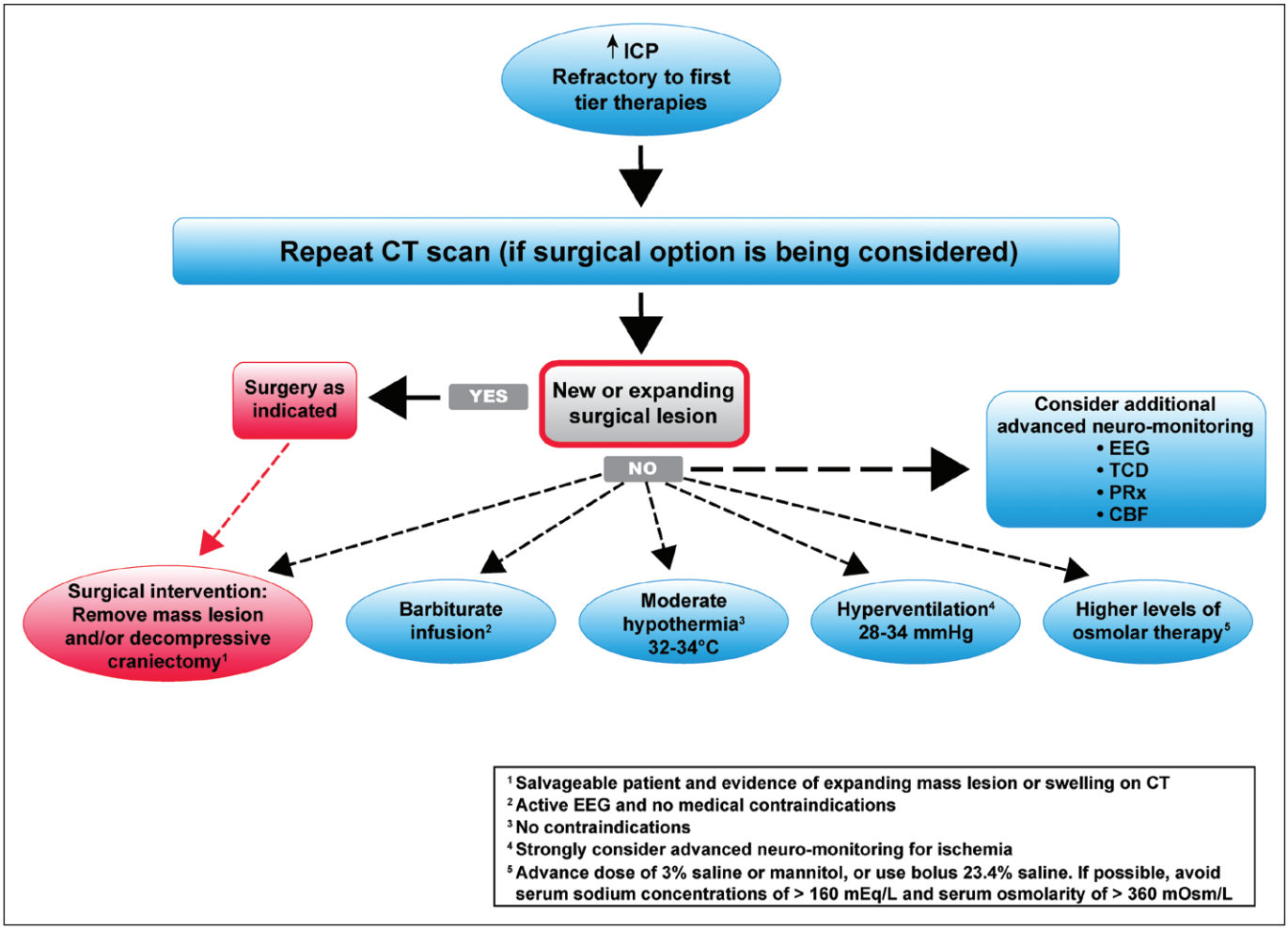

Figure 2. Evidence- and consensus-based algorithm of second tier therapies for the management of severe traumatic brain injury in infants, children, and adolescents. The algorithm is linked to the first tier therapy algorithm (Fig. 1) and represents the treatment options for refractory intracranial hypertension when tier 1 approaches are inadequate. These therapies may be applied singly, serially, or in combinations. In addition, as shown, the management of refractory intracranial hypertension in the second tier phase may be aided by the use of advanced monitoring. Please see text for details. CBF = cerebral blood flow, EEG = electroencephalogram, ICP = intracranial pressure, PRx = pressure reactivity index, TCD = transcranial Doppler untrasonography.

The CVP target is achieved by a fluid volume bolus (54, 59). The BP target is achieved by ensuring normovolemia (9, 24, 29, 51, 59) before using vasopressors such as dopamine or norepinephrine (4, 9, 14, 22, 28, 33, 38, 51–53). Last, since ICP and CPP are of course coupled, any interventions targeting raised ICP (Fig. 1, ICP [yellow] and CPP [orange] pathways) often, but do not always, improve CPP. For example, treatment of raised ICP with a bolus of hypertonic saline is associated with improvements in both ICP and CPP, whereas administration of fentanyl or barbiturates, on average, produce a reduction in ICP without improving CPP—potentially due to cardiac suppression (2, 9, 11, 68). Implicit in the CPP pathway is the practice of tolerating mild intracranial hypertension in the presence of adequate CPP (sometimes referred to as "permissive intracranial hypertension") as an alternative to immediate initiation of second tier therapies. There is insufficient evidence available to strongly prioritize between these alternative approaches. However, it is important to recognize that an approach that focuses exclusively on CPP is unacceptable since herniation can occur precipitously in the setting of markedly elevated ICP even when CPP has been maintained.

$Pbro_2$ Pathway

Since $Pbro_2$ monitoring is being more widely used and reported (33, 36, 42, 45, 49, 50, 53, 54, 67, 69), the guidelines committee has added a new pathway in tier 1 (pink, Fig. 1). This pathway is only useful when $Pbro_2$ monitoring is being used. A minimum target level of 10 mm Hg is supported by currently available evidence (1), although these studies have generally failed to outline whether the monitor was inserted into the uninjured or injured brain (obviously influencing the interpretation of the findings). Interventions that can specifically increase $Pbro_2$ include raising FIO_2, raising MAP with vasopressors, increasing $PaCO_2$ to increase cerebral blood flow (CBF), and optimizing blood [hemoglobin] (33, 36, 42, 45, 49, 54, 69). Often, given the coupling between ICP, CPP, and $Pbro_2$, interventions directed at ICP and CPP will result in an improvement in $Pbro_2$ values. There are also situations where ICP and CPP are adequate, but $Pbro_2$ is low. For example,

consider the instance when the patient has been maintained with a number of ICP therapies and the monitoring variables show ICP consistently less than 20 mm Hg for 24 hours and CPP between 40 and 50 mm Hg, while receiving a moderate level of hyperosmolar therapy, sedation, neuromuscular blockade, and $PaCO_2$ targeting of 35 mm Hg. Now, what if the $PbrO_2$ monitoring shows a downward trend reaching 9 mm Hg? In this instance, the clinician might consider carefully reducing minute ventilation, which will increase $PaCO_2$ and, in consequence, increase CBF. This manipulation might also raise $PbrO_2$ at the same time as avoiding rise in ICP to an unacceptable level (33, 42, 54, 69).

Variations in Pathway "Tempo" and Therapeutic Choices in First Tier Decision-Making

The guidelines committee considered it important to provide linear sequences to the algorithm for first tier management of ICP, CPP, and $PbrO_2$ (if monitored) in pediatric patients with severe TBI (Fig. 1). However, it also recognized that issues related to both the rate of progression of intracranial disease (i.e., "tempo") as well as nonlinear approaches (i.e., concurrent rather sequential) are warranted in some cases. For example, rapid progression of disease severity can lead to progression through the entire first tier of therapy in a matter of hours or less. Similarly, complex scenarios can be encountered that cross treatment pathways. Interventions such as treatment to improve CPP with vasopressor support in a patient who has impaired BP autoregulation of CBF can increase cerebral blood volume (CBV) and worsen ICP. In contrast, when BP autoregulation of CBF is preserved, raising MAP can reduce CBV and consequently reduce ICP. These complex responses to therapeutic interactions cross pathways (as shown in Fig. 1) and must be recognized and understood when optimizing the titration of care in complex TBI patients.

SECOND TIER THERAPIES

For intracranial hypertension, or inadequate CPP or $PbrO_2$, refractory to first tier interventions (Fig. 1), second tier therapies (blue) should be considered when the physician believes that the patient may benefit from additional interventions targeting these three variables (Fig. 2). In this circumstance, the Third Edition guidelines committee agreed that a repeat CT scan should be performed, if it can be done safely, in order to identify any lesions that could be corrected surgically. In that setting, the presence or absence of a new or expanding surgical lesion could be important to clinical decision-making. Additional advanced neuromonitoring could also be helpful in guiding second tier therapies. Consensus was achieved that the second tier therapies that should be considered include neurosurgery and/or four medical options. With regard to neurosurgery, decompressive craniectomy includes several options for choice of surgical approach, for example unilateral hemicraniectomy or bilateral frontotemporal craniectomy, with or without duraplasty and with or without evacuation of subdural or intraparenchymal hematoma (1). The timing and indications for decompressive craniectomy for intracranial hypertension vary in the protocols described in the literature. For example, removal of a mass lesion could be indicated for an expanding lesion with refractory ICP (Fig. 2, dashed red line), or surgical decompression may be indicated in the setting of diffuse swelling when ICP is refractory (16, 22, 29, 31, 34, 35, 37, 43) or when hypertonic saline treatment has failed (38, 47, 59, 62) or when barbiturates have failed (24, 26–28, 32, 36, 38, 40, 48, 49, 51, 52, 54, 56, 58, 60, 61, 63, 69) (Fig. 2, dashed black line).

The other second tier therapies, discussed in the sections below, include barbiturate infusion, late moderate hypothermia, induced hyperventilation, and higher levels of hyperosmolar therapy (Fig. 2). Patients should be evaluated for contraindications to each of the second tier medical therapies; the indications for selecting and applying them (individually, serially, or sometimes more than one at the same time) in an individual patient are left to the discretion of the managing physician. Finally, literature defining the best approach to the use of second tier therapies after decompressive craniectomy is also lacking, and thus these same recommendations apply in that setting.

Barbiturate Infusion

A number of protocols describe the dosing and timing strategy for using barbiturate anesthesia (2–14, 16, 17, 19, 21–28, 31, 32, 35, 36, 38–40, 47–54, 56–64, 68, 69). The most frequently described medication is pentobarbital (9, 11, 12, 16, 21, 23, 54, 57, 59, 62, 68, 69). Its use is considered when osmotherapy and hyperventilation have failed to maintain ICP less than 25 mm Hg (9–12, 14, 27, 36, 38, 40, 51, 52, 58–62), which can mean more frequent than 4 hourly dosing of osmotic diuretics or hypertonic saline or induced hypocapnia. If barbiturate infusion fails to control ICP, as defined by persistent ICP greater than 25 mm Hg, decompressive craniectomy, or one of the other second tier therapies, should be considered, recognizing once again that the order of use of second tier therapies is at the discretion of the clinician and often varies from center to center. In patients with ICP maintained less than 20 mm Hg for 24 hours while receiving a stable pentobarbital infusion dose, the infusion can be decreased and then withdrawn over 24–96 hours. During barbiturate infusion therapy, close attention should be given to volume state and CVP, as well as MAP and CPP (see above, CPP Pathway). Vasopressors are often needed to maintain an adequate CPP (2).

Late Application of Moderate Hypothermia

Early moderate hypothermia has been tested in clinical trials (28, 39, 56, 62) and is not recommended (1). However, the guidelines committee considers that late application of moderate hypothermia during the second tier stage of management as an option, and, to date, there are some protocols in the literature describing its use to control refractory intracranial hypertension (2, 4–6, 9, 31, 48, 54, 58, 61, 63). The more recent reports used a target temperature of 32–33°C (54) or 34–35°C (58).

Induced Hyperventilation and Hyperosmolar Therapies

Hyperventilation, with what would now be considered significant hypocapnia (between 15 and 30 mm Hg), is well described in the older protocols to treat late (> 24 hr) and refractory intracranial hypertension (2–5, 11, 18). Protocols combining gradations in level of hypocapnia along with respective targeted levels in [Na^+] and osmolarity and depth of sedation/anesthesia are also described (14, 21, 25, 58). For example, the so-called "Hypertonic Saline Sliding Scale" protocol, at its most intense level, has a hyperventilation target of a $PaCO_2$ between 28 and 34 mm Hg while also targeting serum [Na^+] between 155 and 160 mEq/L and osmolarity between 320 and 340 mOsm/L, along with use of a pentobarbital infusion at a rate of 2–4 mg/kg/hr (21, 58).

Integration of Advanced Monitoring

The first and second tier algorithms in Figures 1 and 2 suggest that several advanced monitoring approaches could be used to optimize the titration of therapies in these complex patients. The techniques available include $PbrO_2$ monitoring, cEEG, transcranial Doppler ultrasound assessments of CBF velocity, and BP autoregulation of CBF assessments based on the ICP-to-BP cross-correlation coefficient (i.e., pressure reactivity index, [PRx]). A discussion of each of these approaches is found in the Third Edition Guidelines (1). Specific recommendations for choice of the advanced monitoring devices and/or the details of their use for the modification or titration of therapy are beyond the scope of this algorithm. Experience with these approaches is often limited to a small number of centers and/or to clinical investigation. However, a few examples of how advanced monitoring can modify care may be helpful. $PbrO_2$ monitoring can aid in determining whether or not hyperventilation therapy in a second tier application is producing concerning reductions of tissue oxygenation. Similarly, cEEG monitoring can identify whether or not unrecognized subclinical status epileptics is contributing to the development of intracranial hypertension. Serial CBF assessments might reveal marked flow reductions to potentially ischemic levels when hyperventilation is escalated. Finally, PRx may be used to identify a potentially "optimal" CPP level as an endpoint for targeting therapies, although this method provides only a global value while the status of autoregulation and optimal CPP level may be regionally dependent.

Weaning of Therapies

At any time along the treatment pathways described in Figures 1 and 2, when ICP, CPP, and $PbrO_2$ (if monitored) are normalized and remain stable for 12–24 hours, consideration should be given to carefully withdrawing interventions targeting these variables. In general, the interventions are withdrawn in the reverse order of their application. Also, the duration of stability that needs to be seen to prompt consideration of further withdrawal of a given therapy often is influenced by the time since injury (e.g., consideration may need to be given to the possibility that brain swelling is still developing) and is often longer when weaning second rather than first tier therapies. The prior severity of the derangement can also influence the "tempo" of withdrawal of therapies. For example, a patient who experienced refractory intracranial hypertension now on second tier therapies including barbiturate infusion, therapeutic hypothermia, or hypertonic saline sliding scale may need to demonstrate 24 hours of stability before attempting weaning. In some cases, the neurologic examination may help guide withdrawal of therapies or monitoring devices, particularly when the treatment intensity level is low.

Management of Severe Pediatric TBI Without ICP Monitoring

We recognize that some centers do not routinely monitor ICP to guide management in infants and children with severe TBI (76, 77) and that children without ICP monitoring are thus managed with other therapeutic approaches. To our knowledge, evidence in the literature supporting selection of therapies for severe pediatric TBI without ICP monitoring, including published protocols, is lacking. Even the published evidence provided for aspects of baseline care, in the current and all prior editions of the guidelines documents for severe pediatric TBI, is provided in a setting where ICP and CPP were being actively monitored and managed. A detailed protocol for the management of severe TBI without ICP monitoring in adults (and adolescents 13 yr old and older) has been published and included the use of serial imaging (CT at 48 hr and 5–7 d after injury) and clinical examination (pupillary response and GCS score) to guide therapy (76). To our knowledge, a published report of its use is not available in severe pediatric TBI. Even the aforementioned recent report by Bennett et al (77) did not provide a treatment protocol and only indicated that mechanical ventilation was used in 81.3% of patients, osmolar therapy in 25.3%, vasopressors in 18.3%, pentobarbital in 5.8%, and craniectomy in 7.3%. In addition, any such protocol or approach would almost certainly be based on prior clinical experience and literature on the result of effects of such therapies on ICP in infants and children with severe TBI (78).

SUMMARY

We provide an algorithm of care for the bedside clinician based on both evidence and consensus that reflects a logical approach to mitigate intracranial hypertension, optimize cerebral perfusion and oxygenation, prevent or reverse cerebral herniation, and improve outcomes in the setting of pediatric severe TBI. Background or maintenance care germane to all pediatric patients with severe TBI along with two tiers of therapy were formulated. Issues of "tempo" of progression through the algorithm and the fact that the therapeutic targets often represent minimal target values should be recognized. A multidisciplinary team approach to implementing this treatment algorithm throughout the ICU course is optimal. Finally, this algorithm represents an approach to acute care that sets the stage for important medical, surgical, and rehabilitation approaches in the subacute and delayed postinjury periods with the goal of optimizing long-term outcomes in infants, children, and adolescents with severe TBI.

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