Pediatric Neurocritical Care

6

Jovany Cruz-Navarro, Darryl K. Miles,
and David L. McDonagh

Introduction

Pediatric Neurocritical Care is an emerging multidisciplinary field of clinical and experimental medicine. While there are challenges to implementing specialized units for pediatric neurologic critical care, and limited evidence on which to base clinical practice, several models now exist for pediatric neurocritical care programs in centers that are contributing to the development of treatment guidelines and protocols; including multimodal neuromonitoring [1, 2]. Recent multi-center studies investigating pediatric brain injury in stroke, status epilepticus, and hypothermia after cardiac arrest and traumatic brain injury have served to promote the feasibility of accomplishing brain-directed research in children [3–7]. Several organizations, such as the Pediatric Emergency Care Applied Research Network (PECARN) and the Pediatric Neurocritical Care Research Group (PNCRG) are working on advancing care in highly specialized training programs across the United States. Pediatric neurocritical care exists thanks to technological advances in pediatric critical care, neurology, neurosurgery, and anesthesiology. The main goal of pediatric neurocritical care is to improve outcomes in infants and children with life-threatening

J. Cruz-Navarro, MD (✉)
Department of Anesthesiology, Baylor University, Houston, TX, USA
e-mail: jnavarro@bcm.edu

D.K. Miles, MD
Department of Pediatrics, Children's Medical Center, University of Texas Southwestern, Dallas, TX, USA
e-mail: darryl.miles@utsouthwestern.edu

D.L. McDonagh
Departments of Anesthesiology & Pain Management, Neurology, and Neurosurgery, University of Texas Southwestern, Dallas, TX, USA
e-mail: david.mcdonagh@utsouthwestern.edu

A. Agrawal, G. Britz (eds.), *Pediatric Vascular Neurosurgery*,
DOI 10.1007/978-3-319-43636-4_6

neurologic injuries, and to prevent the development of secondary neurologic and non-neurologic injuries. This chapter briefly covers some of the most common neurologic conditions encountered in the pediatric intensive care unit (PICU).

Traumatic Brain Injury

Traumatic brain injury (TBI) remains a leading cause of disability and mortality in infants, children and adolescents across the United States, and constitutes a significant portion of PICU admissions [8, 9]. In the United States alone, TBI affects over half a million children ages 0–19 annually, including 630,000 emergency department visits, 60,000 hospitalizations and over 6100 deaths [10]. It is estimated that five times as many children will succumb from the devastating effects of acute brain injury (hypoxic-ischemic or traumatic) than childhood neoplasias [9]. Guidelines for the care and management of pediatric severe traumatic brain injury were first published in 2003 and updated in 2012 [11, 12].

TBI pathophysiology occurs in two known different phases of care: primary and secondary injury. Currently, there is little that can be done to reverse primary injury, which is the damage resulting at the moment of trauma. Secondary or delayed injury is most commonly caused by physiologic insults such as hypotension and hypoxia. Inflammatory, metabolic, and excitotoxic mechanisms also represent a wide spectrum of potential secondary insults, leading to cerebral edema and intracranial hypertension. Fortunately, secondary injury is a potentially preventable and treatable condition.

The Kennard principle proposes the idea that pediatric recovery after TBI would be enhanced due to a higher degree of neural plasticity in the developing brain [13]. For years, it was thought that children had a greater ability to recover from TBI. However, the Kennard principal referred to localized or focal lesions, not diffuse brain injuries; and outcome following TBI in children may not be better than in adults [14, 15]. Children suffering from TBI classified into favorable outcome groups still may exhibit long-term underappreciated cognitive and behavioral impairments [16, 17]. Moreover, in comparison with their peers, TBI leads to decreased academic achievement, lower scores on intelligence testing, reduced ability to focus, and other neurocognitive deficits [18, 19].

TBI has special connotations in the pediatric population as the impact of the injury may not be entirely evident until many years later as developmental stages are acquired. Falls, bicycle, motor pedestrian and motor vehicle collisions are the most common causes of injury in young children and adolescents. However, inflicted or abusive head trauma (AHT)- also termed non-accidental trauma (NAT)- deserves special mention as one of the leading causes of TBI in infants <2 years [20], as this is frequently associated with significantly worse outcomes than accidental mechanisms [21, 22]. Abusive TBI is typically defined by a triad of physical and radiologic findings including, hyperdense and hypodense subdural collections, retinal hemorrhages, and some degree of encephalopathy [23]. Brain injury in these patients is associated with repetitive trauma, delay in seeking medical care and

high incidence of hypoxic-ischemic injury and seizures, which all may serve to worsen neurologic outcomes [24]. Seizures have been reported to occur in as many as 77 % of AHT patients who had continuous EEG monitoring, significantly higher than rates of older children and adults with accidental mechanisms. Of particular importance is the high frequency of subclinical events. In a report by Arndt et al., subclinical seizures occurred in 16 % of children with TBI; however all of the children with only subclinical seizures were < 1 year old and subclinical status epilepticus occurred in 45 % of AHT infants [25]. In this study subclinical seizures and subclinical status epilepticus were associated with worse hospital discharge outcome scores. Thus AHT and young children may benefit from additional EEG monitoring to detect subclinical seizure activity [25]. Every year, 3 million cases of child abuse and neglect are reported to child welfare systems in the USA, and of these one-third are substantiated [26]. Despite well described injury patterns, NAT is a difficult and serious diagnosis due to the widespread implications beyond the patient [27]. Currently, serum and cerebrospinal biomarkers are under investigation to determine differences between accidental and NAT [28].

As compared to adolescents, children have a higher incidence of diffuse axonal injury (DAI), SDH, and cerebral edema [29]. In turn, adolescents show a higher incidence of DAI and contusions compared to the adult population [30]. There are also reports of a higher magnitude of cerebral edema after TBI in pediatric populations, likely due to a more heterogeneous vascular and inflammatory response [31, 32]. Also, a child's skull is more susceptible to suffer a higher degree of deformity before reaching its compliance limit [33, 34].

Animal data suggests that immature and developing cerebral tissue is at higher risk of apoptotic cell death [35]. In fact, increased levels of apoptosis-related proteins such as cytochrome c, Fas, and caspase-1 have been observed in children after TBI [36]. In addition, increased CSF levels of neuron-specific enolase which is a pro-apoptotic protein have been found after TBI [37].

Pediatric TBI Management

Cervical Spine and Airway Management

Although not as frequent as in adults, associated cervical spine (C-spine) injury can be seen after sustaining severe blunt cranial trauma. It is estimated that up to 25 % of patients suffering C-spine injury develop neurologic deficits caused by pre-hospital manipulation [38]. C-spine evaluation in children must take into consideration the anatomic development (Table 6.1). Any child at risk of having a C-spine injury must be immobilized in a neutral position until injury is ruled out. Patients less than 8 years of age are more susceptible to injury of the upper cervical spine as the maximal motion occurs at C1–C3. After 12 years of age, maximal movement occurs around C5–C6. C-spine clearance should follow the current pediatric guidelines for children with either reliable or unreliable physical examinations. In children, spinal cord injury may occur without radiographic evidence (SCIWORI) necessitating reliance on the clinical exam or magnetic resonance imaging to detect injuries that

Table 6.1 Pediatric C-spine anatomic considerations

Large head size in comparison to neck and trunk- causes increased flexion and extension in the cervical spine
Weaker cervical musculature results in greater mobility of the upper cervical spine
Horizontally inclined facet joints facilitate sliding of the upper cervical vertebrae
Increased elasticity of facet joint ligaments
Incompletely ossified vertebrae
High water content & elasticity of intervertebral disks, increases vertical loading effect

may not be evident on conventional radiographic imaging. Patients with severe TBI (i.e., TBI with coma; GCS <9), or worsening mentation should have a definitive secure airway established [39]. Initially, the airway can be opened with a jaw thrust and chin-lift maneuver while maintaining cervical immobilization (by an assistant). Endotracheal intubation is always a potentially challenging scenario in trauma patients. It is recommended to perform orotracheal intubation with in-line manual stabilization to prevent further spinal cord injury. In-line manual stabilization should be performed by an experienced provider. Nasotracheal intubation should be avoided in patients with facial trauma and/or signs of skull base fracture.

Endotracheal intubation is best achieved using rapid sequence induction/intubation with application of gentle cricoid pressure. Etomidate is frequently used for this purpose as it decreases ICP without significant reductions in mean arterial pressure [40]. There is no definitive evidence showing that succinylcholine increases ICP in humans with brain injury [41, 42]. Therefore, the use of succinylcholine vs. rocuronium for rapid sequence induction should be based on other clinical factors and provider expertise. Prolonged hyperventilation during mechanical ventilation should be avoided as it may cause cerebral tissue ischemia resulting from oligemia [43]. Arterial $PaCO_2$ should be monitored and normocapnea, $PaCO_2$ 35-40 mmHg, should be targeted except in the setting of reversal of clinical herniation syndrome where lower $PaCO_2$ levels can be temporarily used. The head should be elevated, either at 30° (or equivalent reverese trendelenburg tilt) to improve cerebral venous drainage. Studies performed in adults suggest that head elevation to 30° improves CPP and reduces ICP [44]. Also, the head should be maintained in a neutral position to avoid obstruction of jugular venous outflow.

As in adults, children who are hypotensive during the first hours of hospital care have worse outcomes [45, 46]. The lower limit of systolic blood pressure should be maintained greater than the 5th percentile for age (estimated by 70 mmHg + (2 × age in years). Evidence supports that better outcomes are achieved in children who receive early fluid resuscitation [47]. Therefore, it is imperative to urgently initiate resuscitation with isotonic fluids to correct hypotension and hypovolemia.

Current guidelines for the management of pediatric TBI recommend the use of intravenous agents such as analgesics, sedatives, and neuromuscular blockers as adjuvants to prevent or minimize secondary brain injury and intracranial hypertension [12, 43]. There are few studies addressing the choice of agent, however the use of these agents should be limited to patients who are hemodynamically stable with a secure

airway. Decompressive craniectomy and barbiturate therapy are also used to reduce ICP and improve CPP. While there are currently few studies that would lend support to adopting a standard of care recommendation, these therapies may be consider using effective in "control of refractory ICP" or "treating refractory ICP" control and should be considered in children with a salvageable or recoverable injury [12]. Contrary to adult guidelines, pediatric use of propofol infusion is not FDA approved due to its associated morbidity [11]. The incidence of early post-traumatic seizures in children ranges from 5 to 43 %; risk factors include young age (<2 years), AHT, skull fracture and severe head injury [25, 48, 49]. In a randomized trial of 102 children with acute TBI, Young et al., found empiric phenytoin versus placebo did not affect the incidence of post-traumatic seizures (7 % vs. 5 %) or outcome [48]. Prophylactic anticonvulsant use varies widely among centers (10–35 %), current recommendations state that prophylactic treatment with anti-seizure medications can be considered and might decrease the onset of post-traumatic seizures in children, and improve outcomes [50, 51].

It is well known that hyperglycemia is associated with worse outcomes after TBI in adults and children. This may be secondary to worsening of lactic acidosis at a brain tissue level [52]. Sharma et al. [53] in 2009 observed that predictors of hyperglycemia were children <4 years old, GCS ≤ 8, and multiple traumatic injuries including SDH. Currently, it is not completely clear what the upper cutoff for hyperglycemia in children should be [43]. The majority of centers recommend that hyperglycemia should be corrected in acute childhood TBI. Of note, steroid administration in children following TBI has not been associated with additional benefit or improved outcomes [11]. In fact, evidence suggests increased morbidity and mortality after its use [54].

Intracranial Hypertension Management (See Also Table 6.2)

Multiple clinical trials have shown the beneficial effect of hyperosmolar therapy (mannitol or hypertonic saline) in decreasing ICP in children [55, 56]. Potential concerns with using hypertonic saline include dehydration, natriuresis, central pontine myelinolysis, and the theoretical concern for rebound intracranial hypertension in the setting of a disrupted blood brain barrier [57]. The 2012 severe pediatric TBI guidelines recommend that either bolus or infusion therapy is effective in reducing intracranial pressure in children [11]. The use of mannitol in children has not been well studied. Several potential complications have led to a decrement of its use, i.e. volume depletion, hypotension, acute renal injury particularly in hypovolemic patients, a lower reflection coefficient than sodium chloride, and the potential reverse osmotic effect leading to an increase in ICP.

Hyperventilation therapy linearly reduces CBF and ICP due to hypocapnia via cerebral vasoconstriction; sustained hyperventilation ($PaCO_2 < 30$ mmHg) has been associated with regional cerebral ischemia in up to 73 % of patients and poorer long-term outcomes [58, 59]. Current guidelines recommend against *routine* use of hyperventilation to a $PaCO_2$ less than 30 mmHg. If used, concomitant advanced neuromonitoring should be provided [11, 43].

CSF drainage works by reducing the amount of intracranial fluid and achieves immediate reductions in intracranial pressure. An external ventricular drain can be

Table 6.2 Pediatric ICP management

Evacuation of intracranial mass lesions/hematomas
Cerebrospinal fluid drainage with an external ventricular drain
Sedation ± neuromuscular blockade
Maintain adequate cerebral perfusion pressure
Hyperosmolar therapy with hypertonic saline
Mild hyperventilation $PaCO_2$ 35–40 mmHg
Hyperventilation for acute ICP spikes
Decompressive craniectomy to accommodate cerebral edema without herniation
Profound sedation- burst suppression with pentobarbital
Therapeutic hypothermia (32–34 °C) to control ICP refractory to medical management

used to both remove CSF and to monitor ICP. CSF drainage is highly effective until cerebral edema produces ventricular collapse.

Barbiturate coma is recommended in the hemodynamically stable patient when maximal medical and surgical therapy has failed to manage elevated ICP. Barbiturates decrease the cerebral metabolic rate (~50 % at the point of burst suppression), with concomitant decreases in CBF, brain bulk, and subsequently ICP [60]. Ionotropic and vasopressor support to avoid hypotension and maintain adequate mean arterial pressures are commonly required after starting barbiturate coma. Continuous EEG monitoring is used to guide therapy, both to maintain a burst suppression profile as well as to monitor for subclinical seizures (Fig. 6.1).

Decompressive craniectomy should be considered in pediatric patients who are experiencing signs of cerebral herniation or in those with intracranial hypertension refractory to medical treatment. The ideal timing for performance is still a debate (early vs. late/rescue). Decompressive craniectomy can clearly be life-saving with good neurologic outcome in select cases. However, the application and timing of this surgery is debated as the evidence base is limited, particularly in children. Decompressive craniectomy has been reported in small pediatric case series and retrospective studies to be effective in lowering ICP in children with refractory ICP elevation with reports of good outcomes [61, 62]. Recommendations are limited by the small sample size, single center and retrospective design and lack of adequate case controls for comparison. Taylor et al., randomized 27 children with severe TBI and refractory ICP to early bitemporal decompressive craniectomy (mean 19.2 h form injury) versus maximal medical therapy. The mean ICP was lower in the craniectomy group 48 h after randomization and outcome appeared to be improved (normal or mild disability 54 % in craniectomy group versus 14 % in the medical group) [63]. The Decompressive Craniectomy in Diffuse Traumatic Brain Injury (DECRA) trial did not show benefit to bifrontal craniectomy in comparison to medical therapy in adults (Median age ~24 years) [64]. ICP was reduced, along with length of stay in the intensive care unit, but neurologic outcomes at 6 months were worse. The rescueICP (Randomised Evaluation of Surgery with Craniectomy for

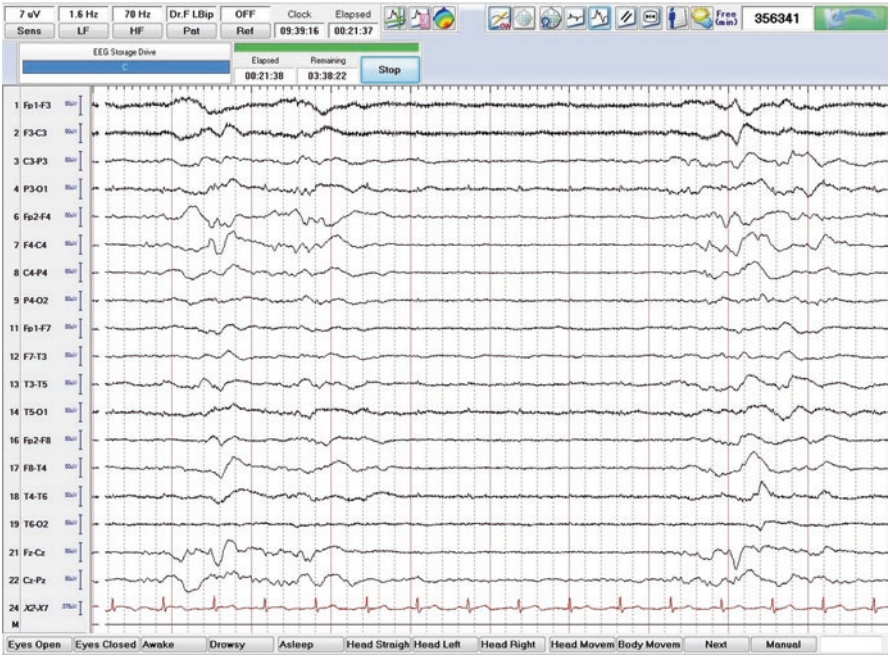

Fig. 6.1 Typical burst-suppression pattern observed during EEG recording while in pentobarbital coma

Uncontrollable Elevation of Intra-Cranial Pressure) trial has finished enrollment but results have not yet been published [65]. Randomized trials are needed in children to determine the safety, efficacy, timing, and optimal patient population for decompressive craniectomy in pediatric TBI patients.

Therapeutic hypothermia can be used to lower ICP (decreases cerebral metabolic rate ~6 % per degree Celsius) and it remains a therapeutic option for controlling refractory ICP [66], however 2 prospective randomized clinical trials have failed to demonstrate a benefit of early prophylactic hypothermia on neurologic outcome [3, 4]. In these studies, children with severe TBI were randomized to hypothermia 32–34 °C within 6–8 h of injury for either 24 or 48–72 h, versus normothermia 36.5–37.5 °C, with slow rewarming. The authors found no difference in the proportion of children with unfavorable outcomes at 3 or 6 months. *Hyperthermia* is thought to be injurious in the setting of acute brain injury of any etiology. Therefore, 'targeted temperature management' is becoming standard of care in the patient with acute neurologic injury [67]. A prospective multi-center international trial is ongoing, Approaches and Decisions for Acute Pediatric TBI (ADAPT) trial that will use a comparative effectiveness strategy to test intracranial hypertension therapies, brain tissue oxygenation monitoring, hyperventilation, and nutrition on neurologic outcome in severe pediatric TBI. With a proposed enrollment of 1000 children, this will be the largest prospective dataset in pediatric TBI obtained to date.

Hypoxic Ischemic Brain Injury

Neonatal asphyxia remains a common cause of hypoxic brain insults in the pediatric population. Unlike TBI, high level evidence exists for the efficacy of therapeutic hypothermia in this setting. Standard of care in neonatal resuscitation is the induction of moderate hypothermia for the treatment of moderate-severe hypoxic ischemic encephalopathy [68]. American Heart Association Guidelines [68] recommend a target temperature of 33.5–34.5 °C (initiated within 6 h of birth) for 72 h followed by a controlled rewarming period, avoiding overshoot hyperthermia. Neonates seem particularly sensitive/vulnerable to hyperoxia, so FiO_2 should be minimized with pulse oximetry guidance.

Unlike adults, the primary mechanism for cardiac arrest in children is secondary to respiratory failure, thus establishment of an airway, oxygenation and ventilation with bag mask ventilation (BMV) or endotracheal intubation should be rapidly instituted. Standard therapy for post-anoxic cerebral resuscitation should be targeted at optimizing systemic hemodynamic and physiologic variables and avoiding secondary insults. Poor prognostic factors include myoclonic status, non-reactive or burst suppression pattern on EEG, absent pupillary reflex at 72 h and abnormal somatosensory evoked potentials.

The role of induced moderate hypothermia in neuroprotection of children beyond the neonatal period is less clear. Pediatric Advanced Life Support (PALS) guidelines suggested that the immediate induction of therapeutic hypothermia (Temperature 32-34 °C) may be beneficial but that further study is needed [69]. In a multicenter study of Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) trial, 295 comatose children were randomized within 6–8 h of return of spontaneous circulation after cardiac arrest to either a target temperature of 33.0 for 48 hours vs. 36.8. I am not sure if it is important but in this study normothermia was also controlled for 5 days after the injury or 36.8 °C [5]. In this study, which first published the out-of-hospital cohort, there was no difference in 1-year neurologic function or survival in the hypothermia group vs. the controlled normothermia group. Analysis of the in-hospital arrest cohort and subgroup analysis may provide additional insight data. Hyperthermia should be avoided after cardiac arrest as it increases cellular energy metabolism and release of excitotoxicity chemicals and accelerates apoptotic pathways. In neonates after HIE, the odds of death or disability are increased 3.6–4 fold for each 1 °C increase above 38 °C [70]. Additionally, hypotension and hyperventilation should be avoided in these patients to avoid cerebral hypoperfusion and oligemia.

Stroke

Although more common in the elderly, arterial and venous strokes also occur in neonates, infants, and young adolescents, and result in significant mortality and long-term disability [71]. Overall, the occurrence is at least as frequent as the number of pediatric tumors [72]. Reported incidence is variable, ranging from 0.9 to 13

Table 6.3 Causes of acute ischemic stroke in children [76, 78, 79]

Source	Most common cause	Other potential causes
Cardiac	Congenital heart disease	PFO, MVP, endocarditis
Hematologic	Sickle cell disease	Anemia, antiphospholipid, Protein C and S deficiency, AT III deficiency
Vasculopathy	Focal cerebral arteriopathy of childhood [78]	Moyamoya, traumatic dissection, vasculitis, post-varicella arteriopathy
Metabolic		CADASIL (cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
		Fabry disease
		Menkes disease
		Homocystinuria
		Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
Illicit drug abuse	Cocaine and methamphetamine	Heroin, marijuana, opiates

cases per 100,000 children [73, 74]. Neonates represent the group at the highest risk, with an incidence for ischemic and hemorrhagic stroke of 1 per 3500, and 1 per 16,000 live births respectively [73, 75]. Whereas in adults ischemic stroke is more common, hemorrhagic stroke is more equally distributed in children due to the higher prevalence of vascular malformations.

Common causes of acute ischemic stroke in children include embolic sources from congenital cardiac defects, sickle cell disease, and head and neck infections (Table 6.3). Venous strokes can be due to dehydration, infection, and hyperosmolar states. Etiology varies again in young adults, with vasculopathy, cardiac defects, smoking, pregnancy, drug use, hypercoagulable states, and premature atherosclerosis among the most common [76]. Hemorrhagic strokes are most commonly due to arteriovenous malformations, cavernomas, tumors, and coagulopathy [77].

Clinical Presentation

Diagnosis of stroke in children is frequently delayed, with an average time to establish a diagnosis of >24 h [80–82]. The delay in diagnosis may be related to the community misperception that children are not at risk for strokes and that pediatric patients are likely to manifest more subtle non-focal signs such as seizures or altered mental status [83]. Also, a low clinical suspicion for acute ischemic stroke by healthcare providers plays an important role in the diagnostic delay as stroke symptoms are often attributed to other more common diagnoses [84]. Even with more classic signs such as hemiparesis and aphasia, presentation to a tertiary pediatric facility is delayed; advanced stroke centers and evidence based protocols are lacking for children. Whereas in neonates seizures often are the presenting symptom, the most common clinical presentation of stroke in older children is hemiparesis, with the middle cerebral artery territory being most frequently affected [85].

Evaluation and Management

Neuroimaging is a cornerstone of stroke diagnosis in children. CT is no longer recognized as the gold standard initial test in children. Current United Kingdom guidelines recommend performing MRI as soon as possible after admission, as MRI is more sensitive than CT in detecting ischemic stroke [86]. Also, MRI will help differentiating clinical conditions mimicking stroke (migraine, seizure, encephalitis, other intracranial lesion) which may be seen in a significant proportion of patients.

As stroke etiology in children can encompass a broad spectrum of conditions, beyond a general laboratory and toxicology screens, patients should be evaluated for hypercoagulable states (i.e. Protein C and S deficiency, homocysteine, Lupus, Factor V Leiden), intracardiac lesions, vasculitis, and mitochondrial disorders.

Pediatric stroke management closely follows the guidelines adapted for adults (https://www.rcplondon.ac.uk/sites/default/files/documents/stroke-in-childhood-guideline.pdf) [87]. However, anticoagulation and thrombolysis therapy may differ. Currently, alteplase (rt-PA) is not FDA approved for use in children less than 18 years of age with ischemic stroke, and endovascular thrombolysis/mechanical thrombectomy are not routinely used in children <14 years of age [88]. For adolescents >15 years, thrombolytic use should be considered on an individual basis. Now in 2015, with 5 prospective randomized trials [89] demonstrating the superiority of stent-like retrievers over intravenous rt-PA in improving the outcome of adults with acute large vessel stroke, the application of mechanical thrombectomy to pediatric acute ischemic stroke is likely to expand.

Currently, there are no trials showing the efficacy of anticoagulation or antithrombotic therapy in children with acute arterial ischemic stroke. The American Heart Association considers reasonable the use of LMWH or unfractionated heparin until full work-up is completed [88]. The Royal College of Physicians recommends the use of aspirin as initial therapy (https://www.rcplondon.ac.uk/sites/default/files/documents/stroke-in-childhood-guideline.pdf) (Table 6.4).

Intensive care unit management of pediatric stroke patients largely follows adult treatment goals. Intubation is instituted for airway protection due to depressed level of conciousness or for maintenance of oxygenation and ventilation. Euvolemia and adequate mean arterial systemic pressure should be maintained. Anticonvulsant medications may be considered in individual cases, and patients should have their temperature controlled to prevent fever. Depending on the stroke etiology pediatric neurosurgery, neurology and neuro-interventional radiology consults may be required. Management of intracranial hypertension may require ICP monitoring, sedatives, hyperosmolar therapy and barbiturate therapy. Decompressive craniectomy is reserved for children presenting with large stroke(s) involving the middle cerebral artery territory causing malignant (i.e., life threatening) cerebral edema with intracranial hypertension, midline shift, and decline in neurologic exam [90].

Table 6.4 Recommendations vary for management of specific causes of ischemic stroke

Cause	Royal college of physicians[a]	AHA [88]	American academy of chest physicians [87]
Unknown etiology	Aspirin 3–5 mg/kg	UFH or LMWH (1 mg/kg every 12 h) up to 1 week until cause determined	UFH or LMWH or aspirin until cardioembolic and dissection sources are excluded
Cardiac source *(Embolic, arterial dissection, hypercoagulable state)*	Individualized based on provider expertise	Goal directed therapy towards specific cardiac pathology	LMWH for >6 weeks *Cervical arterial dissection:* UFH or LMWH as a bridge to oral anticoagulation
Sickle cell disease	Exchange transfusion to HbS <30 % of total Hgb	Hydration, correction of hypoxemia and hypotension Exchange transfusion to HbS <30 %	Intravenous hydration and exchange transfusion to HbS <30 %

Recommendations [87, 88] based on source of stroke
NS normal saline, *PFO* patent foramen ovale, *MVP* mitral valve prolapse
[a]https://www.rcplondon.ac.uk/sites/default/files/documents/stroke-in-childhood-guideline.pdf

Status Epilepticus (SE)

SE is one of the most common pediatric neurologic emergencies. Traditionally, SE is defined as a seizure that lasts more than 30 min, or occurs frequently enough that the patient does not recover consciousness in between episodes [91]. However, some experts suggest that SE definition should include those patients with seizures lasting more than 5–10 min [92], as the risk for a worse outcome and the potential for seizures to be refractory to anti-seizure medications increases with longer ictal duration [93].

The highest incidence of SE is observed during the first year of life due to febrile seizures [94]. Risk factors identified with recurrent SE are symptomatic established epilepsy [91], young age at onset, and genetic syndromes (i.e. Angelman syndrome, Dravet syndrome) [95]. SE may also be the manifestation of metabolic abnormalities, CNS infections, tumors, illicit drug abuse, hypoxic-ischemic injuries, child abuse, heat stroke, TBI and fever, among others [94].

Of great importance is to diminish secondary complications associated with SE, including hypoxia, acidosis, myoglobinuria, hyperkalemia, intracranial hypertension, and hemodynamic instability [96]. SE can be fatal in some cases, accounting for mortality close to 10 % [95, 97–99]. Long-term outcomes depend on the underlying cause, the duration of event, and the child's age [98].

Management

In patients with epilepsy, it is crucial to know the response to previous antiepileptic drugs to guide the treatment approach, and to obtain a focused history from parents or caregivers. Common causes for SE in children are intercurrent infection, recent changes in medications, missed medications, or inadequate antiepileptic medication dosing. The approach should include an assessment of respiratory and circulatory status, intravenous access, and neurologic examination to determine type and possible precipitants. Laboratory workup should include screening for infection, level of current AEDs, sodium, and glucose levels. Neuroimaging studies (CT and/or MRI) are used to exclude other pathologies (such as hematoma, tumor, or stroke) and should be used in patients who have new onset SE, focal neurologic deficits or have not responded to initial therapy by regaining consciousness. Continuous video EEG may also be appropriate for SE management for patients with persistent encephalopathy, especially if the child's neurologic status is impaired beyond baseline making clinical correlation difficult or for assessment for non-convulsive SE.

Pharmacologic management is based on the guidelines published by the Neurocritical Care Society in 2012 [100]. Benzodiazepines (lorazepam, midazolam, or diazepam) are first-line treatment as they can quickly achieve seizure control. If seizures persist for 10 min after at least 2 doses of BDZ, fosphenytoin should be loaded at a dose of 20 mg/kg IV. If seizures persist, a third-line drug is initiated (phenobarbital, valproic acid, levetiracetam, lacosamide) and placement of a secure airway should be considered. For refractory SE (RSE) cases not responsive to standard therapies treatment options are multiple. Intravenous anesthetics are administered with continuous EEG guidance. Intravenous infusions of midazolam at high doses may be used to achieve seizure control; or pentobarbital infusion to produce burst-suppression pattern. Severe hypotension and or respiratory depression may occur with initiation of IV infusions requiring mechanical ventilation or vasopressor support, thus airway and continuous hemodynamic monitoring should be available when starting these therapies. After 24-48 h of seizure control, the infusion is slowly titrated to off (over many hours) and the patient is monitored for seizure recurrence. Ketamine infusions have been reported in small case series to be effective in RSE in children who failed to respond to barbiturate therapy [101]. Propofol is infrequently used in pediatrics, due to the risk of propofol infusion syndrome [102].

Multimodal Cerebral Monitoring

A fundamental goal of neurocritical care is to prevent the development of secondary neurologic injury after the initial (and typically irreversible) cerebral insult. In the brain-injured child multiple physiologic parameters need to be simultaneously managed and optimized in order to achieve the best posible outcome. In addition to standard physiologic monitors (pulse oximeter, EKG, blood pressure), patients with neurologic conditions frequently require specific cerebral monitoring to avoid and promptly recognize the occurrence of secondary injuries. Such monitors include ICP measurement devices (Fig. 6.2), measures of global and regional cerebral

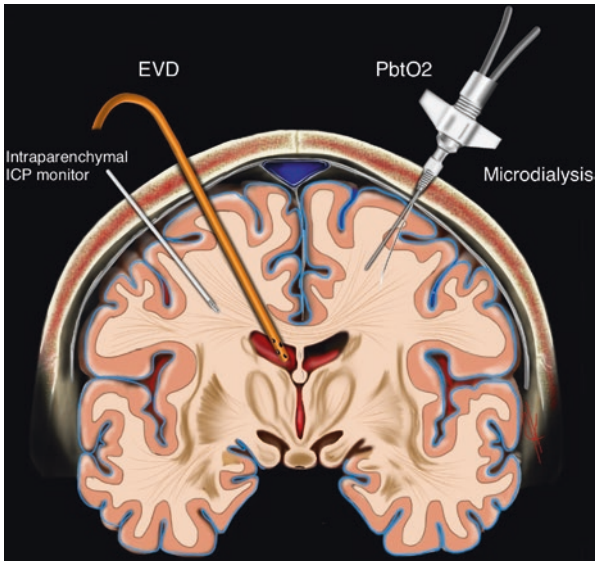

Fig. 6.2 Diagram demonstrating multimodal monitoring

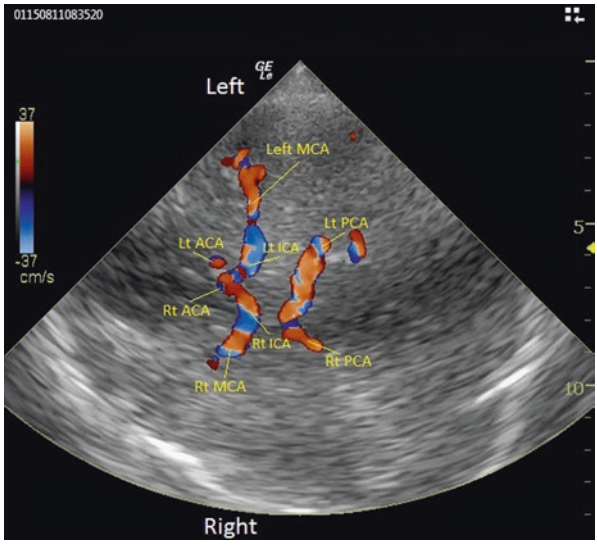

Fig. 6.3 Circle of Willis defined by color-coded transcranial Doppler ultrasound

oxygenation [near infrared spectroscopy (NIRS), jugular venous oxygen saturation ($SjvO_2$), or partial brain tissue oxygen tension ($PbtO_2$)], measures of cerebral metabolism (cerebral microdialysis), continuous EEG monitoring (discussed above), transcranial Doppler ultrasound (Fig. 6.3), and cerebral blood flow (CBF) measurements [103]. Multimodal neuromonitoring involves understanding not only displayed numbers, but also data acquisition, informatics challenges, device interoperability-related issues, and longitudinal data analysis, among others. Observational

studies suggest that multimodal neuromonitoring provides accurate and unique information when used to individualize management of severe head injured patients. Clinical outcome data are sparse.

Partial Brain Tissue Oxygen Tension ($PbtO_2$)

$PbtO_2$ can be measured by inserting an oxygen electrode into the brain parenchyma. Cerebral blood tissue oxygen tension is continuously measured and threshold values for treatment are generally to maintain $PbtO_2 > 15–20$ mmHg [11, 104]. Most of the current pediatric data is focused on TBI, however, there are some other potential applications for this technology including pediatric stroke, and management of cerebral edema during diabetic ketoacidosis [105, 106]. Low levels have been associated with poor outcomes after TBI [107].

Jugular Venous Oximetry ($SjvO_2$)

Through retrograde cannulation of the internal jugular vein, $SjvO_2$ can be measured at the level of the jugular bulb. Normal values in adults are considered to be between 55 and 75 mmHg [108]. There is limited evidence for the utility of its use in pediatric or adult population.

Cerebral Microdialysis

Cerebral microdialysis allows the determination of the metabolic state of the brain. An intraparenchymal probe is inserted into the brain tissue to determine levels of extracellular pyruvate, lactate, glucose, glutamate, and glycerol [109]. In adults, elevation of lactate, and/or a lactate:pyruvate ratio >40, are suggestive of anaerobic metabolism which could exacerbate secondary cerebral injury [110]. Currently, there is limited evidence for its application in children. A small pilot study by Richards et al., in 2003, showed that decreased glutamine:glutamate ratio could be an outcome predictor after brain injury [111]. Overall, its current use can be considered experimental [112].

Thermal Diffusion Cerebral Blood Flow and Cerebral Oximetry

Point-of-care continuous cerebral blood flow monitoring at a regional (such as lobar) or *global* level is a holy grail in neurocritical care but beyond currently available technology. Quantitative CBF can be obtained with CT perfusion, MR perfusion, or positron emission tomography (PET), but not in a frequent or continuous manner that would allow titration of hemodynamic and intracranial pressure therapies. *Focal* cerebral blood flow can be monitored continuously with thermal diffusion technology using a parenchymal probe inserted through a cranial bolt. However, whether such data allows optimization of outcome, or simply exposes the patient to added risk, requires further study. Trancutaneous near-infrared cerebral oximetry can be used to monitor cerebral oxygen saturation in a continuous manner in the intensive care unit. While new monitors are being developed, data to support widespread use in neurocritical care is very limited [103].

Transcranial Doppler Ultrasound

Doppler ultrasound (typically 2 MHz) insonated through the temporal bone 'windows', foramen magnum, and orbits can be used to assess cerebral blood flow velocity and direction. Coupled with B-mode sonography, transcranial Duplex can be performed (Fig. 6.3) in order to obtain some information regarding vascular anatomy [103]. TCD is routinely used for vascular screening in sickle cell disease but has not seen widespread adoption in pediatric neurocritical care; however, it is extremely low risk and can be used to assess pediatric cerebrovascular disease including vasospasm, TBI/post-traumatic vasospasm, and for the assessment of cerebral blood flow (ie, global oligemia vs. hyperemia) [113, 114].

Conclusion

In summary, pediatric neurocritical care is an emerging field in which providers must be able to integrate multiple neurologic specialties in the care of the brain-injured child. Neurologic injury and disorders are common in the PICU, representing approximately 20% of all admissions, and are associated with a longer length of stay and higher mortality than general ICU patients [1, 115]. Pathways into pediatric neurocritical care are less established than adult neurocritical care programs and need to be matured. Finally, an ever expanding evidence base, both for neurocritical care pharmacotherapeutics and advanced cerebral monitoring technologies, is shaping the field and will warrant the need for increased numbers of subspecialized pediatric neurointensivists.

References

1. Wainwright MS, Grimason M, Goldstein J, et al. Building a pediatric neurocritical care program: a multidisciplinary approach to clinical practice and education from the intensive care unit to the outpatient clinic. Semin Pediatr Neurol. 2014;21:248–54.
2. Tasker RC. Pediatric neurocritical care: is it time to come of age? Curr Opin Pediatr. 2009;21:724–30.
3. Adelson PD, Wisniewski SR, Beca J, et al. Comparison of hypothermia and normothermia after severe traumatic brain injury in children (Cool Kids): a phase 3, randomised controlled trial. Lancet Neurol. 2013;12:546–53.
4. Hutchison JS, Ward RE, Lacroix J, et al. Hypothermia therapy after traumatic brain injury in children. N Engl J Med. 2008;358:2447–56.
5. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. N Engl J Med. 2015;372:1898–908.
6. Chamberlain JM, Okada P, Holsti M, et al. Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. JAMA. 2014;311:1652–60.
7. Amlie-Lefond C, Bernard TJ, Sebire G, et al. Predictors of cerebral arteriopathy in children with arterial ischemic stroke: results of the International Pediatric Stroke Study. Circulation. 2009;119:1417–23.
8. Au AK, Carcillo JA, Clark RS, Bell MJ. Brain injuries and neurological system failure are the most common proximate causes of death in children admitted to a pediatric intensive care unit. Pediatr Crit Care Med J Soc Crit Care Med World Feder Pediatr Inten Crit Care Soc. 2011;12:566–71.

9. Kilbaugh TJ, Huh JW, Berg RA. Neurological injuries are common contributors to pediatric intensive care unit deaths: a wake-up call. Pediatr Crit Care Med J Soc Crit Care Med World Feder Pediatr Inten Crit Care Soc. 2011;12:601–2.
10. Faul M XL, Wald MM, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths, 2002–2006. In: Control NCfIPa, editor. 2010. p. 15.
11. Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents – second edition. Pediatr Crit Care Med J Soc Crit Care Med World Feder Pediatr Inten Crit Care Soc. 2012;13 Suppl 1:S1–82.
12. Adelson PD, Bratton SL, Carney NA, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Pediatr Crit Care Med J Soc Crit Care Med World Feder Pediatr Inten Crit Care Soc. 2003;4:S2–75.
13. Luerssen TG, Klauber MR, Marshall LF. Outcome from head injury related to patient's age. A longitudinal prospective study of adult and pediatric head injury. J Neurosurg. 1988;68:409–16.
14. Ewing-Cobbs L, Prasad MR, Kramer L, et al. Late intellectual and academic outcomes following traumatic brain injury sustained during early childhood. J Neurosurg. 2006;105:287–96.
15. Laurent-Vannier A, Brugel DG, De Agostini M. Rehabilitation of brain-injured children. Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg. 2000;16:760–4.
16. Bonnier C, Marique P, Van Hout A, Potelle D. Neurodevelopmental outcome after severe traumatic brain injury in very young children: role for subcortical lesions. J Child Neurol. 2007;22:519–29.
17. Koelfen W, Freund M, Dinter D, Schmidt B, Koenig S, Schultze C. Long-term follow up of children with head injuries-classified as “good recovery” using the Glasgow Outcome Scale: neurological, neuropsychological and magnetic resonance imaging results. Eur J Pediatr. 1997;156:230–5.
18. Ewing-Cobbs L, Prasad MR, Swank P, et al. Social communication in young children with traumatic brain injury: relations with corpus callosum morphometry. Int J Dev Neurosci. 2012;30:247–54.
19. Gerrard-Morris A, Taylor HG, Yeates KO, et al. Cognitive development after traumatic brain injury in young children. J Int Neuropsychol Soc. 2010;16:157–68.
20. Keenan HT, Runyan DK, Marshall SW, Nocera MA, Merten DF, Sinal SH. A population-based study of inflicted traumatic brain injury in young children. JAMA. 2003;290:621–6.
21. Barlow KM, Thomson E, Johnson D, Minns RA. Late neurologic and cognitive sequelae of inflicted traumatic brain injury in infancy. Pediatrics. 2005;116:e174–85.
22. Keenan HT, Hooper SR, Wetherington CE, Nocera M, Runyan DK. Neurodevelopmental consequences of early traumatic brain injury in 3-year-old children. Pediatrics. 2007;119:e616–23.
23. Adamo MA, Drazin D, Smith C, Waldman JB. Comparison of accidental and nonaccidental traumatic brain injuries in infants and toddlers: demographics, neurosurgical interventions, and outcomes. J Neurosurg Pediatr. 2009;4:414–9.
24. Ichord RN, Naim M, Pollock AN, Nance ML, Margulies SS, Christian CW. Hypoxic-ischemic injury complicates inflicted and accidental traumatic brain injury in young children: the role of diffusion-weighted imaging. J Neurotrauma. 2007;24:106–18.
25. Arndt DH, Lerner JT, Matsumoto JH, et al. Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort. Epilepsia. 2013;54:1780–8.
26. Glick JC, Staley K. Inflicted traumatic brain injury: advances in evaluation and collaborative diagnosis. Pediatr Neurosurg. 2007;43:436–41.
27. Barnes PD. Imaging of nonaccidental injury and the mimics: issues and controversies in the era of evidence-based medicine. Radiol Clin North Am. 2011;49:205–29.

28. Berger RP, Adelson PD, Richichi R, Kochanek PM. Serum biomarkers after traumatic and hypoxemic brain injuries: insight into the biochemical response of the pediatric brain to inflicted brain injury. Dev Neurosci. 2006;28:327–35.
29. Emeriaud G, Pettersen G, Ozanne B. Pediatric traumatic brain injury: an update. Curr Opin Anaesthesiol. 2011;24:307–13.
30. Giza CC, Mink RB, Madikians A. Pediatric traumatic brain injury: not just little adults. Curr Opin Crit Care. 2007;13:143–52.
31. Aldrich EF, Eisenberg HM, Saydjari C, et al. Diffuse brain swelling in severely head-injured children. A report from the NIH Traumatic Coma Data Bank. J Neurosurg. 1992;76:450–4.
32. Kochanek PM. Pediatric traumatic brain injury: quo vadis? Dev Neurosci. 2006;28:244–55.
33. Coats B, Margulies SS. Material properties of human infant skull and suture at high rates. J Neurotrauma. 2006;23:1222–32.
34. Ibrahim NG, Margulies SS. Biomechanics of the toddler head during low-height falls: an anthropomorphic dummy analysis. J Neurosurg Pediatr. 2010;6:57–68.
35. Bittigau P, Sifringer M, Felderhoff-Mueser U, Ikonomidou C. Apoptotic neurodegeneration in the context of traumatic injury to the developing brain. Exp Toxicol Pathol. 2004;56:83–9.
36. Satchell MA, Lai Y, Kochanek PM, et al. Cytochrome c, a biomarker of apoptosis, is increased in cerebrospinal fluid from infants with inflicted brain injury from child abuse. J Cereb Blood Flow Metab. 2005;25:919–27.
37. Berger RP, Pierce MC, Wisniewski SR, et al. Neuron-specific enolase and S100B in cerebrospinal fluid after severe traumatic brain injury in infants and children. Pediatrics. 2002;109:E31.
38. Chung S, Mikrogianakis A, Wales PW, et al. Trauma association of Canada Pediatric Subcommittee National Pediatric Cervical Spine Evaluation Pathway: consensus guidelines. J Trauma. 2011;70:873–84.
39. Adelson PD, Bratton SL, Carney NA, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 3. Prehospital airway management. Pediatr Crit Care Med J Soc Crit Care Med World Feder Pediatr Inten Crit Care Soc. 2003;4:S9–11.
40. Bramwell KJ, Haizlip J, Pribble C, VanDerHeyden TC, Witte M. The effect of etomidate on intracranial pressure and systemic blood pressure in pediatric patients with severe traumatic brain injury. Pediatr Emerg Care. 2006;22:90–3.
41. Clancy M, Halford S, Walls R, Murphy M. In patients with head injuries who undergo rapid sequence intubation using succinylcholine, does pretreatment with a competitive neuromuscular blocking agent improve outcome? A literature review. Emerg Med J. 2001;18:373–5.
42. Kovarik WD, Mayberg TS, Lam AM, Mathisen TL, Winn HR. Succinylcholine does not change intracranial pressure, cerebral blood flow velocity, or the electroencephalogram in patients with neurologic injury. Anesth Analg. 1994;78:469–73.
43. Hardcastle N, Benzon HA, Vavilala MS. Update on the 2012 guidelines for the management of pediatric traumatic brain injury – information for the anesthesiologist. Paediatr Anaesth. 2014;24:703–10.
44. Feldman Z, Kanter MJ, Robertson CS, et al. Effect of head elevation on intracranial pressure, cerebral perfusion pressure, and cerebral blood flow in head-injured patients. J Neurosurg. 1992;76:207–11.
45. Pigula FA, Wald SL, Shackford SR, Vane DW. The effect of hypotension and hypoxia on children with severe head injuries. J Pediatr Surg. 1993;28:310–4; discussion 315–6.
46. Samant UB, Mack CD, Koepsell T, Rivara FP, Vavilala MS. Time of hypotension and discharge outcome in children with severe traumatic brain injury. J Neurotrauma. 2008;25:495–502.
47. Zebrack M, Dandoy C, Hansen K, Scaife E, Mann NC, Bratton SL. Early resuscitation of children with moderate-to-severe traumatic brain injury. Pediatrics. 2009;124:56–64.
48. Young KD, Okada PJ, Sokolove PE, et al. A randomized, double-blinded, placebo-controlled trial of phenytoin for the prevention of early posttraumatic seizures in children with moderate to severe blunt head injury. Ann Emerg Med. 2004;43:435–46.

49. Liesemer K, Bratton SL, Zebrack CM, Brockmeyer D, Statler KD. Early post-traumatic seizures in moderate to severe pediatric traumatic brain injury: rates, risk factors, and clinical features. J Neurotrauma. 2011;28:755–62.
50. Schierhout G, Roberts I. Withdrawn: antiepileptic drugs for preventing seizures following acute traumatic brain injury. Cochrane Database Syst Rev. 2012;(6):CD000173.
51. Tilford JM, Simpson PM, Yeh TS, et al. Variation in therapy and outcome for pediatric head trauma patients. Crit Care Med. 2001;29:1056–61.
52. Zygun DA, Steiner LA, Johnston AJ, et al. Hyperglycemia and brain tissue pH after traumatic brain injury. Neurosurgery. 2004;55:877–81; discussion 882.
53. Sharma D, Jelacic J, Chennuri R, Chaiwat O, Chandler W, Vavilala MS. Incidence and risk factors for perioperative hyperglycemia in children with traumatic brain injury. Anesth Analg. 2009;108:81–9.
54. Alderson P, Roberts I. Corticosteroids for acute traumatic brain injury. Cochrane Database Syst Rev. 2005;(1):CD000196.
55. Huang SJ, Chang L, Han YY, Lee YC, Tu YK. Efficacy and safety of hypertonic saline solutions in the treatment of severe head injury. Surg Neurol. 2006;65:539–46; discussion 546.
56. Peterson B, Khanna S, Fisher B, Marshall L. Prolonged hypernatremia controls elevated intracranial pressure in head-injured pediatric patients. Crit Care Med. 2000;28:1136–43.
57. Qureshi AI, Suarez JI. Use of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension. Crit Care Med. 2000;28:3301–13.
58. Adelson PD, Clyde B, Kochanek PM, Wisniewski SR, Marion DW, Yonas H. Cerebrovascular response in infants and young children following severe traumatic brain injury: a preliminary report. Pediatr Neurosurg. 1997;26:200–7.
59. Skippen P, Seear M, Poskitt K, et al. Effect of hyperventilation on regional cerebral blood flow in head-injured children. Crit Care Med. 1997;25:1402–9.
60. Nordstrom CH, Messeter K, Sundbarg G, Schalen W, Werner M, Ryding E. Cerebral blood flow, vasoreactivity, and oxygen consumption during barbiturate therapy in severe traumatic brain lesions. J Neurosurg. 1988;68:424–31.
61. Figaji AA, Fieggen AG, Peter JC. Early decompressive craniotomy in children with severe traumatic brain injury. Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg. 2003;19:666–73.
62. Skoglund TS, Eriksson-Ritzen C, Jensen C, Rydenhag B. Aspects on decompressive craniectomy in patients with traumatic head injuries. J Neurotrauma. 2006;23:1502–9.
63. Taylor A, Butt W, Rosenfeld J, et al. A randomized trial of very early decompressive craniectomy in children with traumatic brain injury and sustained intracranial hypertension. Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg. 2001;17:154–62.
64. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med. 2011;364:1493–502.
65. Patel K, Kolias AG, Hutchinson PJ. What's new in the surgical management of traumatic brain injury? J Neurol. 2015;262:235–8.
66. Orliaguet GA, Meyer PG, Baugnon T. Management of critically ill children with traumatic brain injury. Paediatr Anaesth. 2008;18:455–61.
67. McGinniss J, Marshall P, Honiden S. Novel Uses of Targeted Temperature Management. Clin Chest Med. 2015;36:385–400.
68. Kattwinkel J, Perlman JM, Aziz K, et al. Part 15: neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122:S909–19.
69. Kleinman ME, Chameides L, Schexnayder SM, et al. Part 14: pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122:S876–908.
70. Laptook A, Tyson J, Shankaran S, et al. Elevated temperature after hypoxic-ischemic encephalopathy: risk factor for adverse outcomes. Pediatrics. 2008;122:491–9.
71. deVeber GA, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. J Child Neurol. 2000;15:316–24.

72. Jordan LC, Hillis AE. Challenges in the diagnosis and treatment of pediatric stroke. Nat Rev Neurol. 2011;7:199–208.
73. Agrawal N, Johnston SC, Wu YW, Sidney S, Fullerton HJ. Imaging data reveal a higher pediatric stroke incidence than prior US estimates. Stroke. 2009;40:3415–21.
74. Earley CJ, Kittner SJ, Feeser BR, et al. Stroke in children and sickle-cell disease: Baltimore-Washington Cooperative Young Stroke Study. Neurology. 1998;51:169–76.
75. Armstrong-Wells J, Johnston SC, Wu YW, Sidney S, Fullerton HJ. Prevalence and predictors of perinatal hemorrhagic stroke: results from the kaiser pediatric stroke study. Pediatrics. 2009;123:823–8.
76. Poisson SN, Schardt TQ, Dingman A, Bernard TJ. Etiology and treatment of arterial ischemic stroke in children and young adults. Curr Treat Options Neurol. 2014;16:315.
77. Jordan LC, Hillis AE. Hemorrhagic stroke in children. Pediatr Neurol. 2007;36:73–80.
78. Tolani AT, Yeom KW, Elbers J. Focal cerebral arteriopathy: the face with many names. Pediatr Neurol. 2015;53:247–52.
79. Cardenas JF, Rho JM, Kirton A. Pediatric stroke. Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg. 2011;27:1375–90.
80. Gabis LV, Yangala R, Lenn NJ. Time lag to diagnosis of stroke in children. Pediatrics. 2002;110:924–8.
81. McGlennan C, Ganesan V. Delays in investigation and management of acute arterial ischaemic stroke in children. Dev Med Child Neurol. 2008;50:537–40.
82. Srinivasan J, Miller SP, Phan TG, Mackay MT. Delayed recognition of initial stroke in children: need for increased awareness. Pediatrics. 2009;124:e227–34.
83. Zimmer JA, Garg BP, Williams LS, Golomb MR. Age-related variation in presenting signs of childhood arterial ischemic stroke. Pediatr Neurol. 2007;37:171–5.
84. Rafay MF, Pontigon AM, Chiang J, et al. Delay to diagnosis in acute pediatric arterial ischemic stroke. Stroke. 2009;40:58–64.
85. Amlie-Lefond C, Sebire G, Fullerton HJ. Recent developments in childhood arterial ischaemic stroke. Lancet Neurol. 2008;7:425–35.
86. Kucinski T, Vaterlein O, Glauche V, et al. Correlation of apparent diffusion coefficient and computed tomography density in acute ischemic stroke. Stroke. 2002;33:1786–91.
87. Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141: e737S–801.
88. Roach ES, Golomb MR, Adams R, et al. Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. Stroke. 2008;39:2644–91.
89. Furlan AJ. Endovascular therapy for stroke – it's about time. N Engl J Med. 2015;372:2347–9.
90. Smith SE, Kirkham FJ, Deveber G, et al. Outcome following decompressive craniectomy for malignant middle cerebral artery infarction in children. Dev Med Child Neurol. 2011;53: 29–33.
91. Berg AT, Shinnar S, Levy SR, Testa FM. Status epilepticus in children with newly diagnosed epilepsy. Ann Neurol. 1999;45:618–23.
92. Lowenstein DH, Alldredge BK. Status epilepticus. N Engl J Med. 1998;338:970–6.
93. Eriksson K, Metsaranta P, Huhtala H, Auvinen A, Kuusela AL, Koivikko M. Treatment delay and the risk of prolonged status epilepticus. Neurology. 2005;65:1316–8.
94. Singh RK, Stephens S, Berl MM, et al. Prospective study of new-onset seizures presenting as status epilepticus in childhood. Neurology. 2010;74:636–42.
95. Chin RF, Neville BG, Peckham C, et al. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet. 2006;368:222–9.
96. Hanhan UA, Fiallos MR, Orlowski JP. Status epilepticus. Pediatr Clin North Am. 2001;48: 683–94.

97. Kravljanac R, Jovic N, Djuric M, Jankovic B, Pekmezovic T. Outcome of status epilepticus in children treated in the intensive care unit: a study of 302 cases. Epilepsia. 2011;52:358–63.
98. Raspall-Chaure M, Chin RF, Neville BG, Bedford H, Scott RC. The epidemiology of convulsive status epilepticus in children: a critical review. Epilepsia. 2007;48:1652–63.
99. Raspall-Chaure M, Chin RF, Neville BG, Scott RC. Outcome of paediatric convulsive status epilepticus: a systematic review. Lancet Neurol. 2006;5:769–79.
100. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17:3–23.
101. Rosati A, L'Erario M, Ilvento L, et al. Efficacy and safety of ketamine in refractory status epilepticus in children. Neurology. 2012;79:2355–8.
102. Wolf A, Weir P, Segar P, Stone J, Shield J. Impaired fatty acid oxidation in propofol infusion syndrome. Lancet. 2001;357:606–7.
103. Grinspan ZM, Pon S, Greenfield JP, Malhotra S, Kosofsky BE. Multimodal monitoring in the pediatric intensive care unit: new modalities and informatics challenges. Semin Pediatr Neurol. 2014;21:291–8.
104. Beynon C, Kiening KL, Orakcioglu B, Unterberg AW, Sakowitz OW. Brain tissue oxygen monitoring and hyperoxic treatment in patients with traumatic brain injury. J Neurotrauma. 2012;29:2109–23.
105. Allen BB, Hoffman CE, Traube CS, Weinstein SL, Greenfield JP. Continuous brain tissue oxygenation monitoring in the management of pediatric stroke. Neurocrit Care. 2011;15:529–36.
106. O'Brien NF, Mella C. Brain tissue oxygenation-guided management of diabetic ketoacidosis induced cerebral edema*. Pediatr Crit Care Med J Soc Crit Care Med World Feder Pediatr Inten Crit Care Soc. 2012;13:e383–8.
107. Figaji AA, Zwane E, Thompson C, et al. Brain tissue oxygen tension monitoring in pediatric severe traumatic brain injury. Part 1: relationship with outcome. Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg. 2009;25:1325–33.
108. Robertson CS, Gopinath SP, Goodman JC, Contant CF, Valadka AB, Narayan RK. SjvO2 monitoring in head-injured patients. J Neurotrauma. 1995;12:891–6.
109. Goodman JC, Robertson CS. Microdialysis: is it ready for prime time? Curr Opin Crit Care. 2009;15:110–7.
110. Sahuquillo J, Merino MA, Sanchez-Guerrero A, et al. Lactate and the lactate-to-pyruvate molar ratio cannot be used as independent biomarkers for monitoring brain energetic metabolism: a microdialysis study in patients with traumatic brain injuries. PLoS One. 2014;9:e102540.
111. Richards DA, Tolias CM, Sgouros S, Bowery NG. Extracellular glutamine to glutamate ratio may predict outcome in the injured brain: a clinical microdialysis study in children. Pharmacol Res. 2003;48:101–9.
112. Hutchinson PJ, Jalloh I, Helmy A, et al. Consensus statement from the 2014 International Microdialysis Forum. Intensive Care Med. 2015.
113. O'Brien NF, Maa T, Reuter-Rice K. Noninvasive screening for intracranial hypertension in children with acute, severe traumatic brain injury. J Neurosurg Pediatr. 2015;16:420–25.
114. O'Brien NF, Reuter-Rice KE, Khanna S, Peterson BM, Quinto KB. Vasospasm in children with traumatic brain injury. Intensive Care Med. 2010;36:680–7.
115. Bell MJ, Carpenter J, Au AK, et al. Development of a pediatric neurocritical care service. Neurocrit Care. 2009;10:4–10.