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Review Article

Clinical application of target temperature management in children with acute encephalopathy—A practical review

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ABSTRACT

Acute encephalopathy is a life-threatening disease involving acute brain dysfunction, and it is one of the most important causes of mortality and severe neurological sequelae in infants and children. Approximately 30% of cases of acute encephalopathy result in some degree of neurological sequelae. Although many strategies have been proposed, effective therapies to ameliorate the outcomes of acute encephalopathy have not yet been established. Target temperature management (TTM), previously termed therapeutic hypothermia, has been shown to be effective for various brain injuries due to multiple neuroprotective mechanisms, and it may be considered to be the cornerstone of neuroprotective strategies. Consequently, TTM is currently used in the neurocritical care of adult patients with cardiac arrest with shockable rhythm and perinatal asphyxia. In addition, increasing evidence also indicates that TTM could be useful in other acute encephalopathies, including status epilepticus, acute encephalitis/encephalopathy and traumatic brain injury. In this review, we discuss the recent practical aspects of TTM as a potential intervention for various acute encephalopathies in children.

Acute encephalopathy secondary to cardiac arrest, hypoxic-ischemic encephalopathy, traumatic brain injury, status epilepticus, acute encephalitis/encephalopathy, post-anoxic encephalopathy and hepatic encephalopathy is a leading cause of death and disability in childhood. Although many strategies have been proposed, effective therapies to improve neurological outcomes have yet to be established [1,2].

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Fever (>38 °C) has been shown to exacerbate brain injury. Target temperature management (TTM), previously termed therapeutic hypothermia, has been shown to be effective for various brain injuries due to multiple neuroprotective mechanisms. These mechanisms include decreasing the metabolic rate to restore the supply and demand of oxygen, decreasing excitatory neurotransmitters (such as glutamate), limiting neuroinflammation, preventing ATP depletion, reducing free radical production and also intracellular calcium overload to avoid neuronal apoptosis. Consequently, TTM is currently used in neurocritical care of adult patients with cardiac arrest with an initial shockable rhythm and perinatal asphyxia [3–5]. Some case reports and series have also shown that TTM can be useful in other acute encephalopathies, including status epilepticus, acute encephalitis/encephalopathy, post-anoxic encephalopathy and hepatic encephalopathy. However, the protocols may differ with regards to the depth (target temperature) and duration of temperature management according to the clinical indications [6,7]. In this review, we summarize the recent practical aspects of TTM as a potential intervention for various acute encephalopathies in children.

Pediatric cardiac arrest

The etiology of pediatric cardiac arrest is different from adult cardiac arrest, and a respiratory etiology is most common in children. Fever after pediatric cardiac arrest is common and is associated with poor outcomes [8]. Therefore, TTM for pediatric cardiac arrest should be divided into two clinical scenarios: shockable rhythm (VT/VF) and non-shockable rhythm (non-VT/VT).

Shockable rhythm (VT/VF)

The 2015 American Heart Association (AHA) guidelines recommend TTM for adult cardiac arrest with an initial shockable rhythm (VT/VF) at a constant temperature between 32 °C and 36 °C for at least 24 h [3]. Based on this experience of cardiac arrest due to shockable rhythm in adults, TTM in children with shockable rhythm cardiac arrest should be the same as in adults.

Non-shockable rhythm (non-VT/VF)

Asphyxia is the most common cause of pediatric non-shockable rhythm cardiac arrest, and the etiologies of asphyxial cardiac arrest vary by age group. The 2015 AHA recommendations for TTM in pediatric cardiac arrest state, "For infants and children remaining comatose after out-of-hospital cardiac arrest (OHCA), it is reasonable either to maintain 5 days of continuous normothermia (36 °C–37.5 °C) or to maintain 2 days of initial continuous hypothermia (32 °C–34 °C) followed by 3 days of continuous normothermia. For infants and children remaining comatose after in-hospital cardiac arrest (IHCA), there is insufficient evidence to recommend cooling over normothermia [4]".

Although the optimum duration at the target temperature (33 °C) in pediatric asphyxial cardiac arrest remains to be elucidated [9–12], experience of neonates with perinatal asphyxia suggests that comatose survivors who are resuscitated from asphyxial arrest may benefit from cooling at 33 °C for 72 h. In our recent study, 72 h of therapeutic hypothermia was associated with a better 1-month survival rate and 6-month neurological outcomes than normothermia in our pediatric patients with asphyxial out-of-hospital cardiac arrest. Further studies are required to address the duration of TTM in pediatric cardiac arrest [13].

Hypoxic-ischemic encephalopathy in newborns

Fulfilling the TTM criteria of the AHA guidelines

Therapeutic hypothermia is effective in term infants with hypoxic-ischemic encephalopathy. The 2015 AHA guidelines recommend that infants born at $\geq$ 36 weeks of gestation with evolving moderate to severe hypoxic-ischemic encephalopathy should be given TTM (32 °C–34 °C) within 6 h following birth, with continuation for 72 h and slow rewarming over at least 4 h [5].

Not fulfilling the TTM criteria of the AHA guidelines

However, it is unknown whether other neonatal patient groups may benefit from therapeutic hypothermia. Smit et al. conducted an observational study with prospective data of infants who did not fulfill the standard cooling criteria over a 6-year period in a regional cooling center [14]. They included infants cooled for >6 postnatal hours, late preterm infants, and infants with postnatal collapse, major cranial hemorrhage, congenital cardiac disease and surgical conditions, and found no significant differences in complication rates and long-term outcomes between the groups. They concluded that TTM can be considered for infants with neonatal encephalopathy who both do and do not fulfill the standard TTM criteria of the AHA guidelines.

Traumatic brain injury

Traumatic brain injury (TBI) is the other leading cause of morbidity and mortality in children. Fever after TBI exacerbates brain injury and worsens the outcome, and experimental models of TBI suggest that TTM is neuroprotective. TTM (32 °C–34.5 °C) has been trialed in pediatric patients both as a treatment for refractory intracranial hypertension and to improve neurological outcomes in the setting of severe (Glasgow Coma Scale score $\leq$ 8) TBI [15–19]. TTM for pediatric TBI has been demonstrated to improve refractory intracranial hypertension, but with no difference in neurologic outcomes and a trend toward higher mortality (Table 1).

Pediatric guidelines for severe TBI make distinct recommendations for the use of TTM to treat refractory hypertension and to improve neurological outcomes [1]. The guidelines provide level II evidence for recommending TTM (32 °C–33 °C) to treat refractory intracranial hypertension for a duration of up to 48 h, followed by rewarming relatively slowly to prevent rebound intracranial hypertension (0.5–1 °C) over 12–24 h. Therefore, TTM (32 °C–34 °C for

Table 1 Clinical trials of targeted temperature management on severe pediatric traumatic brain injury.

References	Case no.	Age (y)	Goal temp (°C)	Duration of TTM (h)	Outcome
Biswas et al. (PCS) (2002) [15]	21	1–11	32–34	48	TH decreased ICP No difference of outcome (3 m PCPC 1: HT 50% versus NT 63.7%)
Adelson et al. (phase II RCT) (2005) [16]	75	6.8 ± 3.4	32–33	48	TH decreased ICP, rebound ICP in some patients
Hutchison et al. (multinational RCT) (2008) [17]	225	9.8 ± 4.9	32.5	24	TH decreased ICP, rebound ICP in some patients No difference of outcome (6 m PCPC≦3: HT 69% versus NT 78%)
Adelson et al. (phase III RCT) (2013) [18]	77	3.4–14.6	32–33	48–72	No difference in outcomes (3 m GOS 1–2: HT 56.4% versus NT 57.9%)
Beca et al. (phase II RCT) (2015) [19]	92	6.9–14.2	32–33	72	No difference in outcomes (12 m PCPC≦3: HT 83% versus NT 88%)

Abbreviations: Temp: temperature; TTM: targeted temperature management; TH: therapeutic hypothermia; ICP: intracranial pressure; m: months; RCT: randomized controlled trial; PCPC: Pediatric Cerebral Performance Category; GOC: Glasgow outcome scale; [#]: reference.

48–72 h) to treat refractory intracranial hypertension in children with TBI should be effective, although the rewarming phase is critical and should be conducted at a very slow rate (0.5–1 °C over 12–24 h).

Refractory status epilepticus

Refractory status epilepticus is associated with high morbidity and mortality. In animal models, hypothermia has been shown to abort seizures [20]. The antiepileptic effect of hypothermia remains unclear, however hypotheses include reduction of presynaptic excitatory transmitter release, alterations of postsynaptic voltage-gated channels, and disturbance of membrane polarity via ion pumps [21]. Although no prospective comparative data exist regarding the use of controlled normothermia or therapeutic hypothermia in pediatric refractory status epilepticus, many case reports have demonstrated the effectiveness of therapeutic hypothermia in treating refractory status epilepticus in children [22–27]. Interesting, Shein et al. reported a 4-month-old child developed SE that was refractory to multiple antiepileptic drug treatment, including continuous midazolam infusion. Finally, electrographic seizures stopped after a 43-h period of therapeutic hypothermia with a target rectal temperature of 33°C–34 °C. However, seizures recurred 10 h after rewarming. The ketogenic diet was started and seizures were controlled within 48 h of institution of the ketogenic diet [25]. Because both of therapeutic hypothermia and a ketogenic diet have multiple neuroprotective mechanism, it is reasonable that concurrent therapeutic hypothermia and a ketogenic diet may be considered for treating refractory status epilepticus in children [28]. Because of various etiologies and no standard protocol in these case reports, it is difficult to summarize the best temperature and duration of TTM in pediatric refractory status epilepticus. Table 2 summarizes the published literature for targeted temperature management in pediatric refractory status epilepticus.

The Neurocritical Care Society (NCS) guidelines for the treatment of status epilepticus in adults report that therapeutic hypothermia is an emerging therapy with limited data on the safety and effectiveness for refractory status epilepticus. Therefore, they recommend only using this therapy for patients with refractory status epilepticus who do not respond to conventional antiepileptic drug treatment [29,30]. A recent review by the Pediatric Status Epilepticus Research Group also reported that therapeutic hypothermia is an emerging therapy for refractory status epilepticus, but made no treatment recommendations [29,31].

Acute encephalitis/encephalopathy

Acute encephalopathy/encephalopathy encompasses infectious encephalitis, post-infectious encephalitis, and bacterial meningitis, and is also one of the most important causes of mortality and severe neurological sequelae in infants and children. The rationale for using therapeutic hypothermia in acute encephalitis/encephalopathy is to mitigate cytokine-mediated inflammation that may be exacerbated by fever and sepsis [32]. However, only two retrospective studies and a few case reports have reported the use of TTM to treat acute encephalitis/encephalopathy due to various viral and post-viral pathologies [29,32–36] (Table 3). Kawano et al. reported 27 children with acute encephalopathy/encephalitis receiving hypothermia (33–35 °C) compared with 16 children receiving normothermia. They found early hypothermia (≦12 h) could improve neurologic outcomes (Pediatric Cerebral Performance Category Scale ≦ grade 3 (early hypothermia (≦12 h) 14/17 (82.4%) versus late hypothermia (>12 h) 2/10 (20%) versus normothermia 9/16 (56.3%)) [35]. Nishiyama et al. retrospectively evaluated 57 children with acute encephalopathy and

Table 2 Summary of published literature for targeted temperature management for pediatric refractory status epilepticus.

References	Case no.	Age	Indication	Goal temp (°C)	Duration of TTM (h)	Seizure recurrence after rewarming
Vastola et al. (CR) (1969) [22]	1	16 y	Encephalitis	37	24	No recurrent (100%)
Orlowski et al. (CR) (1984) [23]	3	6-18 y	Encephalitis, Reye's syndrome and unknown neurodegenerative disease	30–31	48–120	No recurrent (2, 66.7%) Recurrent focal seizures (1, 33.3%)
Elting et al. (CR) (2010) [24]	1	5 m	Hemimegalencephaly	35.3	3	No recurrent (100%)
Shein et al. (CR) (2012) [25]	1	4 m	SCN1A mutation, Dravet syndrome	33–34	43 h, then again for 24 h	Recurrent seizures, requiring ketogenic diet (0%)
Lin et al. (CR) (2012) [26]	2	4 -10 y	Fever infection-related epilepsy syndrome	33	72–120	No recurrent (100%)
Guilliams et al. (CR) (2013) [27]	5	5 m-15 y	Varied etiology (Hydrocephalus, POLG-1 mutation, Anti-NMDAR encephalitis)	32–35	24–120	No recurrent (100%)

Abbreviations: m: months; temp: temperature; TTM: targeted temperature management; [#]: reference.

Table 3 Summary of published literature of targeted temperature management for acute encephalitis/encephalopathy.

References	Case no.	Age (y)	Goal temp (°C)	Duration of TTM (h)	Outcome
Yokota et al. (CR) (2010) [32]	1	5	34	72	Stabilizing immune activation and brain edema
Vargas et al. (CR) (2012) [33]	1	4	34	48	Lacked cognitive deficits, Intention tremor
Ichikawa et al. (CR) (2013) [34]	1	3	34	144	Mild intention tremor
Kawano et al. (RCS) (2011) [35]	43	2–5	33.5–35	48–72	Early HT (≦12 h): 14/17 (82.4%) versus Late HT (>12 h): 2/10 (20%) versus NT: 9/16 (56.3%)
Nishiyama et al. (RCS) (2015) [36]	57	6.9–14.2	34.5–36	72	PCPC 1: TTM: 23/23 (100%) versus NT: 24/34 (70.6%)

Abbreviations: Temp: temperature; TTM: targeted temperature management; CR: case report; RCS; retrospective cohort study; h: hours; HT: hypothermia therapy; NT: normothermia; TTM: targeted temperature management; [#]: reference.

AST levels below 90 IU/l, including 23 children received TTM (34.5–36 °C) and they concluded that TTM associated with better neurologic outcome Pediatric Cerebral Performance Category Scale with grade 1 in acute encephalopathy without AST elevation (TTM 23/23 (100%) versus normothermia 24/34 (70.6%)) [36]. The results of these studies showed that TTM was effectiveness in improving the neurological outcomes of acute encephalitis/encephalopathy; however there are currently no reports of the use of TTM for pediatric bacterial meningitis.

Although there are comprehensive guidelines for the diagnosis and treatment of pediatric encephalitis and meningitis [29,37–39], TTM is only briefly mentioned as an adjunctive therapy for bacterial meningitis [37]. Apart from this, high-quality studies with a large number of cases investigating the effectiveness and safety of the clinical methods used in TTM for acute encephalitis/encephalopathy are lacking.

Post-anoxic encephalopathy (near drowning, carbon monoxide intoxication)

There is currently no consensus on the optimal therapy for post-anoxic encephalopathy without cardiac arrest secondary to near drowning or carbon monoxide (CO) poisoning

and CO-associated delayed neurological sequelae. Only a few case reports and small retrospective studies have reported on the use of TTM for post-anoxic encephalopathy secondary to near drowning or acute CO poisoning and CO-associated delayed neurological sequelae. Conn et al. reported remarkable recovery results with the use of hypothermia in near-drowning patients [40]. However, two small retrospective studies suggested that the application of deep and sustained hypothermia in near drowning patients with no vital signs on admission only increased the survival rate but did not improve neurological outcomes [41,42]. With regards to CO poisoning, Feldman et al. reported that a combination of hyperbaric oxygen and TTM produced successful results. In addition, the authors suggested that the use of bundle therapy with TTM-based methods may be considered [43]. Moreover, adult cardiac arrest and neonatal asphyxia studies have also shown that TTM can improve neurologically intact survival, suggesting that its efficacy in asphyxial injury should be reconsidered [44,45]. Based on experience with neonatal asphyxia, we suggest TTM (32 °C–34 °C) continuation for 72 h, and slow rewarming with 0.5–1 °C over 12–24 h. Further investigations are warranted regarding the effects of TTM on post-anoxic encephalopathy.

Hepatic encephalopathy

Hepatic encephalopathy is often complicated by increased intracranial pressure (ICP), and hypothermia can reduce ICP by modulating multiple pathophysiologic mechanisms that are believed to be important in its pathogenesis. The potential of using TTM to lower ICP in patients with hepatic encephalopathy has been explored in adults. The results of three adult case series showed that TTM (32 °C–33 °C) was an effective and safe bridge to liver transplants in patients with acute hepatic failure with increased ICP resistant to standard medical therapy [46–48]. However, no pediatric case series have been reported (Table 4). Further studies are needed to confirm the effect of TTM on pediatric hepatic encephalopathy.

Summary

Acute encephalopathy in children and newborns involves various pathological conditions such as cardiac arrest, asphyxia, infection, post-anoxic and metabolic issues caused by brain dysfunction. Fever in the early period of acute

Table 4 Summary of published literature of targeted temperature management for hepatic encephalopathy.

References	Case no.	Age (y)	Goal temp (°C)	Duration of TTM (h)	IICP before and after hypothermia
Jalan et al. (PCS) (1999) [46]	7	16–46	32–33	8–14	45 (25–49) mm Hg reduced to 16 (13–17) mm Hg
Jalan et al. (PCS) (2003) [47]	5	20–38	32–33	–	No significant increase in ICP during the OLT
Jalan et al. (PCS) (2004) [48]	14	24 ± 3.1	32–33	10–118	36.5 ± 2.7 mm Hg reduced to 16.8 ± 1.5 mm Hg

Abbreviations: Temp: temperature; TTM: targeted temperature management; ICP: intracranial pressure; OLT: orthotopic liver transplantation; PCS: prospective cohort study; [#]: reference.

Table 5 The protocol of targeted temperature management in selected clinical scenarios at our hospital.

Clinical Scenario	Protocol (Targeted temperature and duration)
Cardiac arrest	
Shockable rhythm CA (VT or VF)	32–34 °C or 36 °C at least 24 h
Non-shockable rhythm CA (non-VT or VF)	32–34 °C for 2 days following 3 day normothermia or 5 days of normothermia (36 °C–37.5 °C)
Neonatal hypoxic-ischemic encephalopathy (HIE)	
Neonatal HIE (fulfilling the AHA guideline criteria)[a]	Moderate or severe HIE, should be treated within 6 h of delivery to 32–34 °C for 72 h, at slow rewarming rate
Neonatal HIE-other (not fulfilling the AHA guideline criteria)	32–34 °C for 72 h, at slow rewarming rate
Others	
Traumatic brain injury with severe IICP	32–34 °C for 48 h, at slow rewarming rate (0.5–1 °C over 12–24 h)
Status epilepticus	**Stage of SE based protocol:** SE: 34–36 °C for 12–24 h, RSE: 33–35 °C for 1–2 day, SRSE: 32–34 °C for 3–5 days, at slow rewarming rate
Acute encephalitis/encephalopathy	**GCS based protocol:** GCS: 9–11: 34–36 °C for 48–72 h GCS: ≦8: 32–34 °C for 48–120 h
Hypoxic encephalopathy (Near drowning, CO intoxication)	32–34 °C for 72 h, at slow rewarming rate
Hepatic encephalopathy	32–33 °C bridge to liver transplant

[a] The AHA guidelines criteria: Infants born at ≥ 36 weeks of gestation, evolving moderate to severe hypoxic-ischemic encephalopathy, within 6 h following birth.

encephalopathy in children and newborns are associated with worse outcomes. Close temperature monitoring and the use of TTM to prevent fever in the acute stage may therefore be a vital component of neurocritical care support. In children and newborns with acute encephalopathy, it is preferable to develop protocol-based treatment according to the clinical scenario and the severity of complications (Table 5). A prospective, protocol-based trial using different strategies of TTM for various clinical scenarios is needed.

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Conflicts of Interest

The authors declare no conflicts of interest.

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