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## Targeted Temperature Management in Pediatric Central Nervous System Disease

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### Opinion Statement

Acute central nervous system conditions due to hypoxic-ischemic encephalopathy, traumatic brain injury (TBI), status epilepticus, and central nervous system infection/inflammation, are a leading cause of death and disability in childhood. There is a critical need for effective neuroprotective therapies to improve outcome targeting distinct disease pathology. Fever, defined as patient temperature  $> 38^{\circ}\text{C}$ , has been clearly shown to exacerbate brain injury. Therapeutic hypothermia (HT) is an intervention using targeted temperature management that has multiple mechanisms of action and robust evidence of efficacy in multiple experimental models of brain injury.

Prospective clinical evidence for its neuroprotective efficacy exists in narrowly-defined populations with hypoxic-ischemic injury outside of the pediatric age range while trials comparing hypothermia to normothermia after TBI have failed to demonstrate a benefit on outcome but consistently demonstrate potential use in decreasing refractory intracranial pressure. Data in children from prospective, randomized controlled trials using different strategies of targeted temperature management for various outcomes are few but a large study examining HT versus controlled normothermia to improve neurological outcome in cardiac arrest is underway.

### Keywords

pediatric; hypothermia; neurocritical care; targeted temperature management; brain disease

### Introduction

#### Targeted Temperature Management in Pediatric Central Nervous System Conditions

Acute pediatric central nervous system (CNS) conditions, including hypoxic-ischemic encephalopathy (HIE) from cardiac arrest, traumatic brain injury (TBI), status epilepticus, and infection/inflammation are a leading cause of morbidity and mortality worldwide<sup>1-3</sup>.

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Compliance with Ethics Guidelines

Conflict of Interest

Robert Newmyer, Jenny Mendelson, and Diana Pang declare that they have no conflict of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Morbidities commonly affect multiple patient and family domains - cognition, motor function, emotional health, and quality of life - and are often life-long<sup>4-9</sup>. There is a dearth of efficacious therapies shown to improve neurological outcome, and despite the publication of treatment guidelines, care is largely supportive<sup>10-12</sup>.

Fever (> 38°C) early after CNS insult can have lasting detrimental effects on outcome<sup>13-17</sup>. HT is thought to have promising potential as a neuroprotective therapy due to its multiple mechanisms of action that involve amelioration of excitotoxicity, oxidative stress, caspase activation, mitochondrial dysfunction, membrane ion flux, and ultimately cell death<sup>18,19</sup>. HT improved histological and functional outcomes in multiple experimental models of brain ischemia and trauma. HT provided neuroprotection in a dose-dependent manner in models of hypoxia-ischemia<sup>20-22</sup>. Similar neuroprotection was found in trauma models, but when secondary insults such as hypoxia and hypotension accompanied the traumatic insult, benefits were sometimes lost<sup>23-25</sup>.

In the past decade, randomized, clinical trials (RCTs) have led to HT being implemented as standard of care in neonates with moderate-severe birth asphyxia and witnessed arrhythmia-induced adult cardiac arrest remaining comatose after resuscitation<sup>26-28</sup>. In pediatric brain disease, HT has had mixed results thus far (**Table 1**)<sup>29-31</sup>.

Critics have pointed out that previous landmark RCTs did not actively maintain normothermia in the control or normothermia arm, with many subjects in the normothermia arm having fever, possibly explaining the superior performance of hypothermia<sup>32,33</sup>. Targeted Temperature Management (TTM) is a term describing focused monitoring and tightly controlled manipulation of patient temperature, encompasses both actively controlled normothermia and induced hypothermia HT<sup>28</sup>. New data showing similar outcomes with either actively controlled normothermia or induced HT among adults surviving cardiac arrest raised fresh questions about best practices post-resuscitation. The primary advantages of controlled normothermia versus HT are largely safety-related, as both require substantial resources, monitoring, and supportive care.<sup>34</sup>

### Cardiac arrest

Fever is common after pediatric cardiac arrest and is associated with decreased survival and unfavorable neurologic outcomes<sup>15,35</sup>. Therapeutic HT has been proposed as a potential post-resuscitation neuroprotective therapy for children after notable recoveries occurred in cold-water drowning patients in the 1970s<sup>36,37</sup>. Landmark adult and neonatal studies led to the adoption of HT for these populations (32°-34°C for 12 or 24 and 72 h, respectively)<sup>26,38-42</sup>. New data suggests that TTM, a strategy of active prevention of fever (36°C) performed equivalently to HT in adults with cardiac arrest<sup>32</sup>.

In children, 2 retrospective observational studies showed no difference in hospital mortality between patients who received or did not receive therapeutic HT<sup>43,44</sup>. It is notable that HT was not protocolized in terms of patient eligibility, time to target temperature, target temperature choice, duration of therapy, or rewarming schedule in either study. Children who were cooled were noted to be sicker than those who were not cooled prior to induction in terms of having had longer duration of pulselessness and more unwitnessed out-of-

hospital events. Children in whom HT was applied required more frequent electrolyte replacement and received more insulin infusions than non-HT patients. Additionally, children with temperatures below the low range of traditional target temperature range (< 32° C) had higher mortality, postulated to be due to poikilothermia secondary to severe HIE. A recent Cochrane systematic review concluded that there was “no evidence from RCTs to support or refute the use of therapeutic HT” after pediatric cardiac arrest<sup>45</sup>. In children with cardiac arrest, the 2010 International Liaison Committee on Resuscitation (ILCOR) Pediatric Task Force statement recommended that “Therapeutic HT (32°C to 34°C) may be considered for infants and children who remain comatose following resuscitation from cardiac arrest”<sup>12</sup>.

To date, no prospective, RCT of HT after pediatric cardiac arrest has been published, although results from the Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA), a large international trial that separately examines HT versus controlled normothermia after out-of-hospital and in-hospital pediatric cardiac arrest is highly anticipated<sup>33</sup>. Prospective detailed instructions on implementing TTM and HT in pediatric CA are lacking, but some publications offer guidance<sup>46,47</sup>.

### Status epilepticus

Fever is associated with increased risk of seizures in susceptible children<sup>48,49</sup>. HT has been shown to decrease seizure frequency and duration in experimental models of status epilepticus<sup>50,51</sup>. In an early case series (5 adults and 1 child), HT (31-36.5°C) when used as an adjunct to antiepileptic medications, successfully terminated status epilepticus<sup>51</sup>.

The mechanism underlying the antiepileptic effect of HT remains unclear but hypotheses include alteration of postsynaptic voltage-gated channels, disturbance of membrane polarity via ion pumps, and reduction of presynaptic excitatory transmitter release<sup>52-55,56,57</sup>. Interestingly, the anti-epileptic effects of commonly used medications such as benzodiazepines can be potentiated by adjunctive HT via decreased blood brain barrier permeability leading to increased intracerebral drug concentrations<sup>58</sup>.

In a contemporary case series of 4 adults with status epilepticus, endovascular HT (31-35°C) was used in addition to midazolam and/or pentobarbital infusions<sup>59</sup>. Seizures were successfully aborted during treatment but returned in 2 patients post-rewarming. One patient death due to sepsis was thought to have been influenced by the combined immunosuppressive effect of HT and pentobarbital. No prospective comparative data exist regarding the use of controlled normothermia or HT in pediatric status epilepticus, but cases are informative. An infant treated with controlled normothermia (36°C) for 4 days resulted in marked reduction of seizure frequency and decrease of intravenous, antiepileptic dosing<sup>60</sup>. An older series of 3 children were treated with HT (30-31°C) and concurrent barbiturate therapy for 2-5 days with resultant termination of seizures<sup>61</sup>. Guillems et al included 5 children with refractory status epilepticus due to varying diagnoses in which HT was applied. Temperatures were maintained 32-35°C for 24-120 hours with varying rewarming approaches to successfully terminate seizures<sup>62</sup>. Three patient deaths were attributed to underlying disease. Three surviving patients had mild cognitive, functional, and/or behavioral deficits noted. Serious adverse events included sepsis (n=1), lactic

acidosis (n=2), and hypokalemia (n=3). In a recent case report, HT to 33-34°C in a 4 month old child with malignant migrating partial seizures of infancy and SCN1A had success in terminating status epilepticus during HT but seizures recurred post-rewarming<sup>63</sup>.

Guidelines for the treatment of status epilepticus in adults were published by the Neurocritical Care Society (NCS) in 2012 and 2 pediatric centers have published their treatment protocols without specifying a definitive role for HT<sup>64-66</sup>. The NCS guidelines remark HT to be an emerging therapy “with limited data on the safety and effectiveness of these treatments for refractory status epilepticus” and therefore “recommend to reserve these therapies to patients who do not respond to refractory status epilepticus antiepileptic drug treatment.” A recent review by the Pediatric Status Epilepticus Research Group notes HT to be an emerging therapy for refractory status epilepticus but makes no treatment recommendation<sup>67</sup>.

### Traumatic brain injury

Fever after TBI exacerbates brain injury and worsens outcome<sup>68,69,70</sup>. Studies in rat models of TBI suggested that HT is neuroprotective<sup>71,72</sup>. Neuroprotective mechanisms of action of HT noted in experimental models include decreased brain metabolism, attenuation of proinflammatory cytokines, decrease in free radical production, decrease in toxic metabolites and excitatory substances, prevention of apoptosis, and preservation of high-energy phosphates and mitochondrial dysfunction<sup>27,73,74,75</sup>. Therapeutic HT has been trialed in patients both as a treatment for refractory intracranial hypertension and to improve neurological outcome in the setting of severe (GCS score  $\leq$  8) TBI.

Four RCTs have been performed in children with severe TBI to evaluate HT (32-34.5 °C) versus controlled normothermia for effect on outcome<sup>30,31,76,77</sup>. In a small RCT (n=21), HT was effective in decreasing ICP as an adjunct to standard treatment<sup>76</sup>. Adelson et al's phase II RCT (n=75) reported that 48 hours of HT could be performed safely and reduced ICP compared with children in the normothermia group. Rebound intracranial hypertension was occasionally noted after rewarming<sup>31</sup>. A multinational RCT in 17 centers randomized 225 children to HT or normothermia for 24 hours and rewarmed at 0.5 C per hour<sup>30</sup>. HT conveyed no functional outcome or mortality benefit at 6 months post-TBI. Instead, there was a trend toward increased mortality in the HT vs. normothermia group (p=0.06). HT was also effective in decreasing ICP in this study, but rebound hypotension (and decreased cerebral perfusion pressure) requiring vasoactive support in the rewarming period occurred more frequently in the HT group than in the normothermia group. Most recently, the Cool Kids Trial, a phase III multinational 15 center RCT, randomized 77 children to HT or normothermia for 48-72 hours followed by rewarming at a relatively slow rate of 0.5-1°C over 12-24 hours<sup>77</sup>. The study was terminated for futility on interim analysis without a difference in outcome or adverse events between treatment groups.

Chapter 9 in the pediatric guidelines for severe TBI make distinct recommendations for the use of HT to treat of refractory hypertension and to improve neurological outcome. First, the guidelines provide level II evidence for recommending moderate HT (32-33°C) to treat refractory intracranial hypertension for a duration of up to 48 hours, followed by rewarming relatively slowly to prevent rebound intracranial hypertension (0.5-1 °C) over 12-24 hours<sup>10</sup>.

Next, the guidelines make a level II recommendation for *avoidance* of moderate HT (32–33°C) initiated early after severe TBI for neuroprotection followed by a rewarming of 0.5°C per hr. A level III recommendation was made for the early administration of HT for 48 hours duration with slow rewarming (no faster than 0.5 C every 3-4 hours) as a neuroprotective strategy.

### CNS infection/inflammation

Neither controlled normothermia nor HT is a standard treatment for pediatric CNS infection/inflammation, which encompasses infectious encephalitis, post-infectious encephalitis, and bacterial meningitis. However, case reports and series indicate HT has been used to treat various viral and post-viral CNS pathologies.

Rationale for using TTM in CNS infection and inflammatory disease is to mitigate cytokine-mediated inflammation that may be exacerbated by fever and sepsis. In a case-control study by Ichiyama et al., inflammatory markers, including interleukin (IL)-6, IL-10, soluble tumor necrosis factor receptor 1 (sTNFR1) were increased in the serum and cerebrospinal fluid (CSF) of 13 children with viral syndromes complicated by fever, acute encephalopathy, RSE, and poor outcome<sup>78</sup>.

Kawano, et al performed a retrospective observational study of 43 children with acute viral encephalitis complicated by acute necrotizing encephalopathy, hemorrhagic shock and encephalopathy syndrome, or acute encephalopathy with refractory seizures. Children underwent HT (33.5-35°C) or normothermia<sup>79</sup>. Duration of hypothermia was between 48-72 hours and management of fevers in the normothermia group was not described. Children who underwent HT within 12 hours of presentation had better Pediatric Cerebral Performance Category (PCPC) scores compared to those who were kept normothermic. PCPC scores were worse in children with HT initiated at greater than 12 hours following presentation.

Two case reports describe the use of HT in encephalitis. A previously healthy 4 year old female with Influenza A complicated by acute necrotizing encephalopathy presented with tonic posturing and seizure without cerebral edema<sup>80</sup>. HT (34°C) was initiated on the 6th day of illness and was maintained for a predetermined duration of 2 days. She also received methylprednisolone and intravenous immunoglobulin (IVIG), although the timing of these medications in relation to HT were not described. At a 7 month follow-up visit, the patient lacked cognitive deficits but had a persistent intention tremor. Another case report described a 3 year old Japanese boy with acute demyelinating encephalomyelitis (ADEM) due to mumps<sup>81</sup>. Despite completing high-dose corticosteroid therapy, he developed decerebrate posturing and severe cerebral edema and uncal herniation on CT on the 4th day of illness. HT (34°C) was initiated and maintained for 6 days, with concurrent with IVIG and repeat corticosteroid therapy provided. Indications for rewarming were not reported. At 52 days, the patient also had a mild intention tremor. All patients in these reports received appropriate antiviral (e.g. oseltamivir and/or acyclovir) and antibiotic medications and some received anti-epileptic drug treatment. Complications of HT were similar to that of studies in other studies, including hypotension, hypokalemia, hyperglycemia, and coagulopathy.

There are no reports of HT used in pediatric patients with bacterial meningitis. However, a recent RCT compared HT (32-34°C) for 48 h versus passive normothermia in 98 adults with bacterial meningitis. The study was stopped early as patients in the HT group had higher mortality than patients in the normothermia group (51% vs 31%,  $p=0.04$ )<sup>82</sup>.

Although there are comprehensive guidelines for the diagnosis and treatment of pediatric encephalitis and meningitis, TTM, including fever control and HT, is only briefly mentioned in Chaudhuri, et al for consideration as an adjunctive therapy in bacterial meningitis<sup>83-85</sup>. Recommendations for anti-inflammatory management do include corticosteroids, IVIG, and plasmapheresis.

## Conclusions

Fever occurring in the early period of pediatric brain disease is associated with worse outcome. Close temperature monitoring in the acute treatment period and implementation of TTM to prevent fever in critically ill children may therefore be vital components of neurocritical care support but are untested in prospective RCTs. Despite efficacy in various experimental models of brain disease, therapeutic HT has thus far demonstrated limited utility in pediatrics, but important RCTs utilizing TTM in pediatric cardiac arrest are pending.

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**Table 1**

## Recommendation for clinical use of HT and Level of Evidence

	<b>Recommendation for clinical use of HT</b>	<b>Level of Evidence</b> *
Cardiac arrest	<ol style="list-style-type: none"> <li>1. Therapeutic HT (32°C to 34°C) may be considered for children who remain comatose after resuscitation from cardiac arrest.</li> <li>2. It is reasonable for adolescents resuscitated from sudden, witnessed, out-of-hospital VF cardiac arrest.</li> <li>3. Monitor temperature continuously, if possible, and treat fever (38°C) aggressively with antipyretics and cooling devices because fever adversely influences recovery from ischemic brain injury.</li> </ol>	Class IIb, LOE C Class IIa, LOE C Class IIa, LOE C
Status epilepticus	<ol style="list-style-type: none"> <li>1. Case reports and animal data suggest HT may assist with refractory seizure termination. No current recommendation for clinical use.</li> </ol>	Class IIb, LOE C
Traumatic brain injury	<ol style="list-style-type: none"> <li>1. RCT data suggests a role for efficacy of HT decreasing intracranial pressure.</li> <li>2. RCT data suggest not helpful, but a possible harmful role, of HT.</li> </ol>	Class III, LOE A
CNS inflammation	<ol style="list-style-type: none"> <li>1. European Federation of Neurologic Societies (EFNS) guidelines on the management of community-acquired bacterial meningitis in older children and adults briefly mention normothermia or moderate hypothermia as an adjunctive therapy<sup>77</sup></li> </ol>	Class III, LOE

Class II: Conflicting evidence or divergence of opinion exists.

Class IIa: Weight of evidence or opinion favors utility or efficacy.

Class IIb: Weight of evidence or opinion is less well established.

Class III: Evidence or general agreement that the procedure or treatment is either not useful or effective or in some cases may be harmful.

LOE A: Data derived from multiple randomized clinical trials

LOE B: Data derived from a single randomized clinical trial

LOE C: Consensus expert opinion

\* Class I: Evidence or general agreement that a procedure or treatment is useful and effective.