How I Cool Children in Neurocritical Care

Ericka L. Fink · Patrick M. Kochanek ·
Robert S. B. Clark · Michael J. Bell

Abstract Brain injury is the leading cause of death in our pediatric ICU [Au et al. Crit Care Med 36:A128, 2008]. Clinical care for brain injury remains largely supportive. Therapeutic hypothermia has been shown to be effective in improving neurological outcome after adult ventricular-arrhythmia-induced cardiac arrest and neonatal asphyxia, and is under investigation as a neuroprotectant after cardiac arrest and traumatic brain injury in children in our ICU and other centers. To induce hypothermia in children comatose after cardiac arrest we target 32–34°C using cooling blankets and intravenous iced saline as primary methods for induction, for 24–72 h duration with vigilant re-warming. The objective of this article is to share our hypothermia protocol for cooling children with acute brain injury.

Keywords Neurocritical care · Hypothermia · Child · Cardiac arrest · Traumatic brain injury

Contemporary Therapeutic Hypothermia in the PICU

Mild (32–34°C) hypothermia is being investigated as a neuroprotectant in critically ill children with acute brain

E. L. Fink · P. M. Kochanek · R. S. B. Clark · M. J. Bell
Department of Critical Care Medicine, Children's Hospital
of Pittsburgh of UPMC, Pittsburgh, PA 15224, USA

E. L. Fink (✉) · P. M. Kochanek · R. S. B. Clark · M. J. Bell
The Safar Center for Resuscitation Research, Department
of Critical Care Medicine, 3434 Fifth Avenue,
Pittsburgh, PA 15260, USA
e-mail: finkel@ccm.upmc.edu

injury and used therapeutically in our multidisciplinary pediatric intensive care unit (PICU). Brain injury is the leading cause of death in our pediatric ICU [1]. Selected children post-cardiac arrest, traumatic brain injury (TBI), stroke and central nervous system infection undergo temperature management for neuroprotection, intracranial pressure management, or to manage fever (>38°C) [2–5].

Two randomized controlled trials (RCTs) involving hypothermia and brain injury originating at the Children's Hospital of Pittsburgh are enrolling subjects in our PICU. Cool Kids is a multicenter trial comparing hypothermia versus normothermia for children after TBI, and the primary outcome is mortality [NCT00222742]. The second is a single center pilot study comparing serum and imaging biomarkers of brain injury in children surviving cardiac arrest after randomization to 24 or 72 h of hypothermia [NCT00797680].

Despite considerable involvement in the development of hypothermia as a therapy and years of experience applying it in clinical care, we have found that the application of hypothermia requires an unremitting commitment from a knowledgeable medical team to prevent adverse events and maximize beneficial effects. We will discuss our experience using hypothermia in the two conditions where it is most frequently used in our PICU—cardiac arrest and TBI, emphasizing proactive strategies to maximize benefits and prevent the potential hazards of its application.

Cardiac Arrest

Stimulated by the landmark RCTs in 2002 demonstrating improved neurological outcome using mild hypothermia in adults with ventricular-arrhythmia-induced cardiac arrest, we began cooling children who were comatose (Glasgow

coma scale (GCS) score ≤ 8) after resuscitation [6, 7]. Our population is clearly different—the etiology of cardiac arrest in 90% of children is asphyxia versus ~60% ventricular-arrhythmia in adults [8, 9]. Adults included in the RCTs were witnessed arrests, and experience a different pathobiology—one that does not feature profound hypoxemia and hypotension before the arrest. The asphyxial pattern portends a more severe neuropathology versus ventricular-arrhythmia as shown in laboratory studies [10]. In addition, in the PICU, cardiac arrest occurs in the context of a developing brain. Children have poor hospital survival rates of 8–24% (out-of-hospital vs. in-hospital cardiac arrest, respectively) and no brain-directed therapies are generally applied after cardiac arrest and resuscitation [11–14].

The successful application of hypothermia in neonates with birth asphyxia was encouraging but produced new questions [15]. There were now RCTs showing that 12, 24, and 72 h of mild hypothermia were effective after cardiac arrest in adults or asphyxia in term newborns, but none addressed the question, (1) is mild hypothermia effective after asphyxial cardiac arrest in children, (2) what is the best duration of hypothermia to prevent delayed cell death in the developing brain without increasing adverse events associated with hypothermia, (3) given that researchers were able to classify newborns by severity of encephalopathy and in one case demonstrate that the moderately encephalopathic group preferentially benefitted from hypothermia versus the more severely injured group, can the same be done for children, and (4) how best to accomplish re-warming?

We examined our practices from 2000 to 2006 and found that we tended to cool children with an insult severity and other factors that have generally been associated with poor outcome—namely, out-of-hospital, unwitnessed arrests requiring multiple doses of epinephrine to achieve ROSC [3]. During this period, there were no guidelines for who and how to cool, resulting in a large variation of target temperatures, duration of cooling, and re-warming [3]. We developed guidelines and electronic order sets for our PICU based on literature review and clinical experience to improve quality of care and patient outcome [16, 17].
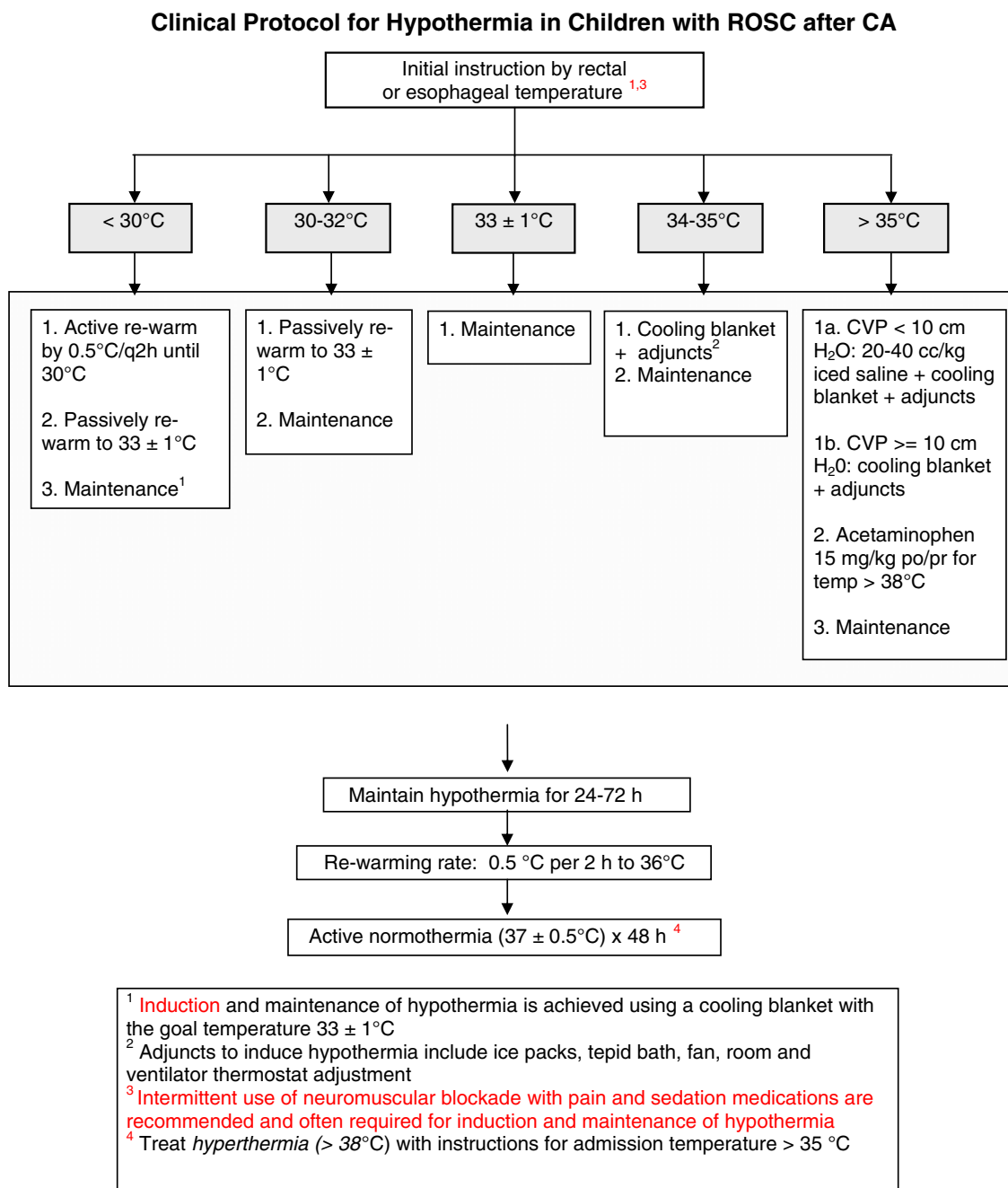
Patient Eligibility

The PICU physician is responsible for choosing to initiate hypothermia. All ages and all etiologies—i.e., drowning, trauma, ingestion, cardiomyopathy—are eligible. Children who are awake or following commands are ineligible. Children who localize to stimulation with altered mental status are a source of debate as are infants arresting outside the perinatal period whose neurological status is

notoriously difficult to categorize and the Glasgow coma scale too insensitive to be definitive. An observation period (1–2 h) can be used to aid in better defining the child's neurological status, but delays could reduce the efficacy of hypothermia [18, 19]. There is no hard rule regarding duration of pulselessness since this variable is often inaccurate or possibly of limited value in the pediatric arena; for example, a child that had experienced 30 min of hypoxemia but only 1 min of no flow may still present with coma and brain injury after resuscitation. Children with a do not resuscitate status after ROSC are ineligible, as are children in whom the PICU physician initiate brain death evaluation since this requires patients to be ≥35°C in the state of Pennsylvania.

Temperature Management: Target Temperature, Induction Methods, and Duration of Hypothermia

We use both an esophageal and rectal thermometer if possible—one for monitor display and the other driving the cooling blanket at the foot of the bed, which is not immediately visually accessible in the busy, crowded bed space. Axillary temperatures are notoriously inaccurate and bladder temperatures are less readily available in our unit.

The target temperature of 32–34°C appeared to be relatively safe and efficacious [4, 6, 7, 11, 12]. Experimental data concluded that the attainment of target temperature should occur as quickly as possible to be effective, but no definitive time limit on delay to cooling initiation has been identified [18–21]. Up to 40% of children post-cardiac arrest present at or below target temperature after ROSC and ICU admission [3]. Thus, our preferred method of attaining target temperature is stratified based on the patient's presenting temperature (Fig. 1). For example, if the child is 36°C and the central venous pressure is <10 mmHg or the physical examination is consistent with absence of fluid overload, we will rapidly cool the patient with 20–40 cc/kg iced normal saline i.v. over 10–20 min and application of a cooling blanket below and sometimes on top of the patient (currently a Blanketrol II device). Adjuncts such as ice packs, fan with lukewarm bath, and reducing the temperature of the room and/or ventilator humidification system serve as adjuncts. We rigorously avoid i.v. push of the iced saline because of the increased risk of profound bradycardia. Thus far we have found iced saline infusion in children with acute brain injury to be effective and relatively safe [22]. As many patients present with lung disease, we rarely use gastric lavage for concern for aspiration. Note that infants and children do not always have cuffed tracheal tubes. Alternatively, if the patient presents at 28°C, we will actively re-warm using the Blanketrol II by 0.5°C every 2 h until 30°C, then passively re-warm to 33 ± 1°C. Neuromuscular blockade and

Clinical Protocol for Hypothermia in Children with ROSC after CA

Initial instruction by rectal
or esophageal temperature [1,3]

| < 30°C | 30-32°C | 33 ± 1°C | 34-35°C | > 35°C |

< 30°C	30-32°C	33 ± 1°C	34-35°C	> 35°C
1. Active re-warm by 0.5°C/q2h until 30°C 2. Passively re-warm to 33 ± 1°C 3. Maintenance[1]	1. Passively re-warm to 33 ± 1°C 2. Maintenance	1. Maintenance	1. Cooling blanket + adjuncts[2] 2. Maintenance	1a. CVP < 10 cm H₂O: 20-40 cc/kg iced saline + cooling blanket + adjuncts 1b. CVP >= 10 cm H₂0: cooling blanket + adjuncts 2. Acetaminophen 15 mg/kg po/pr for temp > 38°C 3. Maintenance

Maintain hypothermia for 24-72 h

Re-warming rate: 0.5 °C per 2 h to 36°C

Active normothermia (37 ± 0.5°C) x 48 h [4]

[1] Induction and maintenance of hypothermia is achieved using a cooling blanket with the goal temperature 33 ± 1°C
[2] Adjuncts to induce hypothermia include ice packs, tepid bath, fan, room and ventilator thermostat adjustment
[3] Intermittent use of neuromuscular blockade with pain and sedation medications are recommended and often required for induction and maintenance of hypothermia
[4] Treat *hyperthermia (> 38*°C) with instructions for admission temperature > 35 °C

Fig. 1 Clinical protocol for therapeutic hypothermia in children surviving cardiac arrest. *ROSC* return of spontaneous circulation, *CA* cardiac arrest, *CVP* central venous pressure

sedation are provided for children during induction and maintenance to attain target temperature as fast as possible, to prevent shivering, discomfort, and agitation. The cooling blanket manufacturer and your institution's skin care team can provide recommendations for the type of a skin barrier required for the particular product. Unnecessary barriers can effectively prevent temperature manipulation. Unfortunately devices specifically targeted for cooling children

have not been developed [23]. Duration of hypothermia remains a clinical decision, but 24–72 h is advised based on previous RCTs.

In certain cases, the target temperature is modified to 35°C if the child has evidence or increased risk of coagulopathy, bleeding, or continued arrhythmia but may benefit from therapy. There is experimental evidence supporting 35°C as an equivalently efficacious target temperature as

32–34°C although certainly much more investigation needs to be done on this matter [24]. If hypothermia was not applied for neuroprotection, aggressive treatment and even active prevention of fever (>38°C) is indicated after cardiac arrest, which may include cooling blanket use (set to 37°C) with neuromuscular blockade and sedation in addition to acetaminophen, ice packs, and iced saline [25–27]. Indeed targeted temperature management with strict prevention of hyperthermia rather than reaction to fevers is likely to be optimal [28, 29].

Re-warming

We recognize that prospectively evaluated data on re-warming methods and rate after hypothermia are lacking. Using available data from the adult and neonatal RCTs, we recommend that re-warming should not occur faster than 0.5°C every 2 h, to guard against cerebral hyperperfusion and vasogenic edema [30, 31]. We found that transition above 34–35°C is often associated with peripheral vasodilation and sometimes hypotension requiring fluid resuscitation. Printing a schedule of target temperatures during rewarming has been well received by our nurses and has resulted in less protocol deviation. Electrolyte replacement is usually not necessary during rewarming, and some groups have reported hyperkalemia during this period [32].

Continuous temperature monitoring is maintained for 48 h after re-warming to maintain normothermia, and fever is actively prevented or treated aggressively using measures similar to those for induction of hypothermia with the addition of acetaminophen. Although there are data showing fever early after brain injury is associated with poor outcome, there are no data to suggest when fever is no longer a hazard [26, 33].

Pharmacologic Adjuncts: Sedation, Pain Control, and Neuromuscular Blockade

Remifentanil or fentanyl is used for pain control and intermittent lorazepam is recommended for sedation. Our goal is to provide comfort but to also allow for frequent neurological assessment. Neuromuscular blockade with vecuronium or cisatracurium are often continued during maintenance hypothermia if there is difficulty sustaining target temperature, and drug "holidays" are employed daily. Cisatracurium is preferred when there is evidence of hepatic or renal injury. Some patients have significant lung injury and may require neuromuscular blockade for adequate oxygenation and ventilation. We are mindful that many of the drugs we give to our patients can have their kinetics and function dramatically affected by body temperature [34].

Physiological and Neurological Monitoring

We aim to achieve adequate oxygenation (PaO_2 target 100–200 mmHg), ventilation ($PaCO_2$ target 40 mmHg), age-appropriate blood pressure [35, 36] and perfusion, which usually require placement of arterial and central venous catheters, and titration of mechanical ventilation. These interventions are often placed or performed simultaneously and generally require a team approach. We use an alpha-stat approach to blood gas management. Hypotension can be secondary to an underlying problem (e.g., sepsis), post-arrest myocardial dysfunction, or volume depletion from hypothermia or re-warming. Hypertension can be secondary to seizures, inadequate sedation, or a physiological response to cerebral edema.

The prevalence of seizures in this group (>40%) is high and often non-convulsive. In neonates with birth asphyxia, seizures are independently associated with poor outcome [37, 38]. Many children do not have seizures until rewarming occurs [39]. We recommend continuous EEG if it is available or an initial EEG obtained as soon as technically feasible. It remains unclear whether prophylactic anti-epileptic drugs are indicated for all children surviving cardiac arrest, however, we treat with anticonvulsants in this setting if seizures are clinically suspected [40]. Most children (especially out-of-hospital cardiac arrests) will have a brain CT on admission to evaluate for intracranial pathology as an etiology for the arrest or for early prognostication (e.g., massive cerebral edema, loss of gray-white interface). In our center, brain magnetic resonance brain imaging (MRI) is often performed in surviving "stable" patients at ~1 week to assist with prognostication. In addition, in an ongoing RCT comparing 24 vs. 72 h of cooling in our center, we are evaluating brain MR spectroscopy and serum biomarkers as key surrogate endpoints [41–43].

Adverse Events: Surveillance

Although the adult and neonatal RCTs did not show increased frequency of adverse events in the hypothermia versus normothermia groups, our experience showed that cooled children required more electrolyte replacement versus normothermic children, and over-cooling (<32°C) was associated with poor outcome [3]. Close attention must be paid to all potential adverse effects of hypothermia including infection (prudent removal of vascular and urinary catheters and daily surveillance cultures), fluid and electrolyte depletion (frequent laboratory surveillance), coagulopathy (monitoring for evidence of bleeding and prothrombin, partial thromboelastin time, and platelet counts), overcooling (continuous temperature monitoring),

and avoidance of rapid re-warming [44, 45] (Appendix—Supplementary material).

Other Supportive Care Considerations

All patients receive early consultation for physical therapy (within 3 days), measures for the prevention of deep venous thromboses, and most receive referrals for rehabilitation because over half of survivors will have long-term neurological injury. Children may require treatment and devices for increased tone and contractures as well as functional testing prior to initiation of oral feeding.

Initially, we infuse D5 or D10 normal saline with or without potassium for maintenance fluid to maintain serum sodium concentration. There is no consensus for glucose control but insulin is frequently used to maintain blood glucose < 180–200 mg/dl and bedside testing every hour to prevent hypoglycemia. In our retrospective study, insulin was used more frequently in cooled vs. non-cooled children even though both groups had the same initial blood glucose [3]. No specific guidelines are available regarding nutrition, particularly in the setting of hypothermia, but attention to glucose delivery, caloric needs, and early initiation of gut feeding is recommended.

Special Situation: Transport

Many of our out-of-hospital cardiac arrest patients are transferred from outlying facilities. As the transport physicians for CHP we advise outside facilities how to prevent secondary brain injury including frequent temperature monitoring, not actively warming patients and maintaining normothermia. Our transport team will often apply ice packs around the patient's head for air or ground travel since our catchment area reaches hundreds of miles in diameter. Safety remains the largest concern for cooling at outside facilities with little to no experience, and feasibility of cooling safely on transport is an important unexplored issue since these children already require vigorous attention by the transport team to basic and advanced life support. Over-cooling frequently occurred in transported neonates undergoing hypothermia therapy in a recent publication [46].

Education and Implementation

To help facilitate adherence to the guidelines and promote safer implementation of hypothermia, we arranged interactive sessions with nursing and incorporated their feedback. We developed an electronic order set for children with cardiac arrest that integrates basic elements for admission to the PICU (i.e., i.v. fluids choices, options for inotropes, and elevate head of bed to 30°) along with orders specific to therapeutic hypothermia (Appendix—Supplementary material). Pre-set laboratory orders for electrolytes (every 6 h for N days) and nursing-specific communications are also included. Adherence to these guidelines is being monitored and adjustments made as we learn from our experiences and new evidence in the literature becomes available.

Traumatic Brain Injury

The use of mild hypothermia in the management of children with severe TBI is an approved second tier therapy for refractory intracranial hypertension [47]. However, the results of the recent Canadian multicenter RCT suggest that this therapy did not confer beneficial effects on long-term outcome when applied as a neuroprotective therapy and that hypotension during rewarming merits special attention [48]. In this study, subjects in the hypothermia arm reached target temperature by 8 h after injury therefore maintenance of hypothermia was shorter than intended (total hypothermia time nearer 16 h rather than 24 h). Moreover, significant hypotension and need for vasoactive support was observed in the hypothermia group during rewarming, suggesting that clinical protocols need to address these safety concerns in future trials or clinical use. As a result, this trial has cast significant doubt on the utility of hypothermia for TBI in children.

In comparison to cardiac arrest or other conditions, unique opportunities and challenges exist in cooling children with TBI. In general, the traumatically injured child presents to the hospital either hypo- or euvolemic, depending upon many factors (distance from the scene to the point-of-care, associated injuries somatic organs or extremities, blood loss, resuscitative efforts of prehospital personnel and others). As such, administration of iced-saline as a means toward achieving rapid cooling is an attractive therapy, accomplishing two goals with a single maneuver. In contrast, cardiac arrest victims may have cardiac dysfunction and administration of iced-saline in a rapid manner may be deleterious to cardiac performance. Moreover, TBI often occurs outdoors (especially with sporting injuries, motor vehicle, or pedestrian accidents) and the child victim may arrive at the hospital already hypothermic depending on the ambient temperature. Care needs to be taken during resuscitation within the Emergency Department to avoid rapid changes of temperature and avoidance of hyperthermia from rapid warming. Finally, brain oxygen monitors are now increasingly being used as a goal-directed target after TBI, which provide an assessment of brain temperature along with the partial pressure of oxygen within the brain interstitium. It is possible that future studies may target brain temperature as a more directed goal to produce brain protection after TBI.

Several aspects of TBI make cooling more challenging. Additional injuries to the traumatically injured child may decrease the efficiency of surface cooling methods, with injured extremities or other body parts splinted with plaster or other barriers that minimize surface contact with cooling blankets. Movement of the child onto cooling blankets is more challenging if multiple systemic injuries are coincident with the brain injury. Finally, the severely injured child may need surgery for life-threatening thoracic or abdominal injury and coordinating temperature control while the child is under general anesthesia in an operating room more problematic.

While differences in cooling techniques are relatively minor between the two conditions, rewarming after TBI is uniquely ICP-driven in the majority of centers utilizing the therapy. One of the most consistent findings of all hypothermia trials is the finding that hypothermic children and adults have decreased intracranial pressure during cooling [2, 49, 50]. Due to this effect, rewarming protocols have been designed to avoid and respond to rebound intracranial hypertension. As such, rewarming protocols are often halted if ICP increases above a critical threshold (usually ICP > 20 mmHg). In general, ICP is not measured after cardiac arrest and there are no currently published studies that base rewarming on ICP or other findings.

Conclusion

In summary, we present a practical discussion on our procedures for using therapeutic hypothermia for neuroprotection in children with cardiac arrest and TBI. Although practices will vary by institution, mechanisms should be in place to prevent, recognize, and treat known complications of hypothermia therapy.

References

1. Au AK, Carcillo JA, Clark RS, Bell MJ. Brain injury contributes to greater than 90% of deaths in previously healthy children in the PICU. Crit Care Med. 2008;36:A128.
2. Adelson PD, Ragheb J, Kanev P, et al. Phase II clinical trial of moderate hypothermia after severe traumatic brain injury in children. Neurosurgery. 2005;56:740–54. discussion-54.
3. Fink EL, Clark RSB, Kochanek PM, Watson RS. Mild therapeutic hypothermia in a cohort of patients surviving cardiac arrest. Pediatr Crit Care Med. 2010;11(1):66–74.
4. American Heart Association. American Heart Association (AHA) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) of pediatric and neonatal patients: pediatric advanced life support. Pediatrics. 2006;117: e1005–28.
5. 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 14. The role of temperature control following severe pediatric traumatic brain injury. Pediatr Crit Care Med. 2003;4:S53–5.
6. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002;346:557–63.
7. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549–56.
8. Meert KL, Donaldson A, Nadkarni V, et al. Multicenter cohort study of in-hospital pediatric cardiac arrest. Pediatr Crit Care Med. 2009;10:544–53.
9. Moler FW, Meert K, Donaldson AE, et al. In-hospital versus out-of-hospital pediatric cardiac arrest: a multicenter cohort study. Crit Care Med. 2009;37:2259–67.
10. Vaagenes P, Safar P, Moossy J, et al. Asphyxiation versus ventricular fibrillation cardiac arrest in dogs. Differences in cerebral resuscitation effects—a preliminary study. Resuscitation. 1997; 35:41–52.
11. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet. 2005;365:663–70.
12. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med. 2005;353:1574–84.
13. Nadkarni VM, Larkin GL, Peberdy MA, et al. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. JAMA. 2006;295:50–7.
14. Young KD, Seidel JS. Pediatric cardiopulmonary resuscitation: a collective review. Ann Emerg Med. 1999;33:195–205.
15. Hoehn T, Hansmann G, Buhrer C, et al. Therapeutic hypothermia in neonates. Review of current clinical data, ILCOR recommendations and suggestions for implementation in neonatal intensive care units. Resuscitation. 2008;78:7–12.
16. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation. 2007;73:29–39.
17. Clifton GL, Choi SC, Miller ER, et al. Intercenter variance in clinical trials of head trauma—experience of the National Acute Brain Injury Study: hypothermia. J Neurosurg. 2001;95:751–5.
18. Nozari A, Safar P, Stezoski SW, et al. Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation. Circulation. 2006;113:2690–6.
19. Kuboyama K, Safar P, Radovsky A, Tisherman SA, Stezoski SW, Alexander H. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit Care Med. 1993;21: 1348–58.
20. Colbourne F, Corbett D. Delayed postischemic hypothermia: a six-month survival study using behavioral and histological assessments of neuroprotection. J Neurosci. 1995;15:7250.
21. Hickey RW, Ferimer H, Alexander HL, et al. Delayed, spontaneous hypothermia reduces neuronal damage after asphyxial cardiac arrest in rats. Crit Care Med. 2000;28:3511–6.
22. Fink EL, Kochanek PM, Clark RSB, Bell MJ. Induction of hypothermia and fever control using intravenous iced saline in pediatric neurocritical care. Crit Care Med. 2009;37:A162.
23. Mayer SA, Kowalski RG, Presciutti M, et al. Clinical trial of a novel surface cooling system for fever control in neurocritical care patients. Crit Care Med. 2004;32:2508–15.
24. Logue ES, McMichael MJ, Callaway CW. Comparison of the effects of hypothermia at 33 degrees C or 35 degrees C after cardiac arrest in rats. Acad Emerg Med. 2007;14:293–300.
25. Greer DM, Funk SE, Reaven NL, Ouzounelli M, Uman GC. Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. Stroke. 2008;39:3029–35.

26. Laptook A, Tyson J, Shankaran S, et al. Elevated temperature after hypoxic-ischemic encephalopathy: risk factor for adverse outcomes. Pediatrics. 2008;122:491–9.

27. Natale JE, Joseph JG, Helfaer MA, Shaffner DH. Early hyperthermia after traumatic brain injury in children: risk factors, influence on length of stay, and effect on short-term neurologic status. Crit Care Med. 2000;28:2608–15.

28. Dietrich WD, Busto R, Valdes I, Loor Y. Effects of normothermic versus mild hyperthermic forebrain ischemia in rats. Stroke. 1990;21:1318–25.

29. Kim Y, Busto R, Dietrich WD, Kraydieh S, Ginsberg MD. Delayed postischemic hyperthermia in awake rats worsens the histopathological outcome of transient focal cerebral ischemia. Stroke. 1996;27:2274–80. discussion 81.

30. Lavinio A, Timofeev I, Nortje J, et al. Cerebrovascular reactivity during hypothermia and rewarming. Br J Anaesth. 2007;99:237–44.

31. Steiner T, Friede T, Aschoff A, Schellinger PD, Schwab S, Hacke W. Effect and feasibility of controlled rewarming after moderate hypothermia in stroke patients with malignant infarction of the middle cerebral artery. Stroke. 2001;32:2833–5.

32. Rittenberger JC, Guyette FX, Tisherman SA, DeVita MA, Alvarez RJ, Callaway CW. Outcomes of a hospital-wide plan to improve care of comatose survivors of cardiac arrest. Resuscitation. 2008;79:198–204.

33. Suffoletto B, Peberdy MA, van der Hoek T, Callaway C. Body temperature changes are associated with outcomes following in-hospital cardiac arrest and return of spontaneous circulation. Resuscitation. 2009;80(12):1365–70.

34. Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: A focus on hypothermia-mediated alterations on the cytochrome P450 enzyme system. Crit Care Med. 2007;35:2196–204.

35. Report of the Second Task Force on Blood Pressure Control in Children—1987. Task Force on Blood Pressure Control in Children. National Heart, Lung, and Blood Institute, Bethesda, Maryland. Pediatrics. 1987;79:1–25.

36. Park M. Pediatric cardiology for practitioners. 3rd ed. St. Louis: Mosby; 1996.

37. Nishisaki A, Sullivan J 3rd, Steger B, et al. Retrospective analysis of the prognostic value of electroencephalography patterns obtained in pediatric in-hospital cardiac arrest survivors during three years. Pediatr Crit Care Med. 2007;8:10–7.

38. Glass HC, Glidden D, Jeremy RJ, Barkovich AJ, Ferriero DM, Miller SP. Clinical neonatal seizures are independently associated with outcome in infants at risk for hypoxic-ischemic brain injury. J Pediatr. 2009;155:318–23.

39. Abend NS, Topjian A, Ichord R, et al. Electroencephalographic monitoring during hypothermia after pediatric cardiac arrest. Neurology. 2009;72:1931–40.

40. Evans DJ, Levene MI, Tsakmakis M. Anticonvulsants for preventing mortality and morbidity in full term newborns with perinatal asphyxia. Cochrane Database Syst Rev. 2007;18: CD001240.

41. 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.

42. Ashwal S, Holshouser BA, Tomasi LG, et al. 1H-magnetic resonance spectroscopy-determined cerebral lactate and poor neurological outcomes in children with central nervous system disease. Ann Neurol. 1997;41:470–81.

43. Topjian AA, Lin R, Morris MC, et al. Neuron-specific enolase and S-100B are associated with neurologic outcome after pediatric cardiac arrest. Pediatr Crit Care Med. 2009;10:479–90.

44. Polderman KH. Application of therapeutic hypothermia in the ICU: opportunities and pitfalls of a promising treatment modality. Part 1: Indications and evidence. Intensive Care Med. 2004;30: 556–75.

45. Polderman KH. Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality—part 2: practical aspects and side effects. Intensive Care Med. 2004;30:757–69.

46. Fairchild K, Sokora D, Scott J, Zanelli S. Therapeutic hypothermia on neonatal transport: 4-year experience in a single NICU. J Perinatol. 2009 [Epub ahead of print].

47. 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 17. Critical pathway for the treatment of established intracranial hypertension in pediatric traumatic brain injury. Pediatr Crit Care Med. 2003;4: S65–7.

48. Hutchison JS, Ward RE, Lacroix J, et al. Hypothermia therapy after traumatic brain injury in children. N Engl J Med. 2008;358: 2447–56.

49. Marion D, Obrist W, Carlier P, Penrod L, Darby J. The use of moderate therapeutic hypothermia for patients with severe head injuries: a preliminary report. J Neurosurg. 1993;79:354–62.

50. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med. 2001;344: 556–63.