Circulation

AHA FOCUSED UPDATE

2019 American Heart Association Focused Update on Pediatric Advanced Life Support

An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

ABSTRACT: This 2019 focused update to the American Heart Association pediatric advanced life support guidelines follows the 2018 and 2019 systematic reviews performed by the Pediatric Life Support Task Force of the International Liaison Committee on Resuscitation. It aligns with the continuous evidence review process of the International Liaison Committee on Resuscitation, with updates published when the International Liaison Committee on Resuscitation completes a literature review based on new published evidence. This update provides the evidence review and treatment recommendations for advanced airway management in pediatric cardiac arrest, extracorporeal cardiopulmonary resuscitation in pediatric cardiac arrest, and pediatric targeted temperature management during post–cardiac arrest care. The writing group analyzed the systematic reviews and the original research published for each of these topics. For airway management, the writing group concluded that it is reasonable to continue bag-mask ventilation (versus attempting an advanced airway such as endotracheal intubation) in patients with out-of-hospital cardiac arrest. When extracorporeal membrane oxygenation protocols and teams are readily available, extracorporeal cardiopulmonary resuscitation should be considered for patients with cardiac diagnoses and in-hospital cardiac arrest. Finally, it is reasonable to use targeted temperature management of 32°C to 34°C followed by 36°C to 37.5°C, or to use targeted temperature management of 36°C to 37.5°C, for pediatric patients who remain comatose after resuscitation from out-of-hospital cardiac arrest or in-hospital cardiac arrest.

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This 2019 focused update to the American Heart Association (AHA) pediatric advanced life support (PALS) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) is based on 3 systematic reviews[1–3] and the resulting "2019 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations" (CoSTR) from the Pediatric Life Support Task Force of the International Liaison Committee on Resuscitation (ILCOR).[4] This pediatric life support task force CoSTR addressed 3 topics: advanced airway management in pediatric cardiac arrest, extracorporeal CPR (ECPR) in pediatric cardiac arrest, and pediatric targeted temperature management (TTM) during post–cardiac arrest care. The draft pediatric CoSTRs were posted online for public comment,[5–7] and a summary document containing the final CoSTR wording has been published simultaneously with this focused update.[4]

AHA guidelines for CPR and ECC are developed in concert with ILCOR's systematic review process. In 2015, the ILCOR evidence evaluation process and the AHA development of guidelines updates transitioned to a continuous, simultaneous process, with systematic reviews performed as new published evidence warrants or when the ILCOR Pediatric Life Support Task Force prioritizes a topic. The AHA science experts review the new evidence and update the AHA's guidelines for CPR and ECC as needed, typically on an annual basis. A description of the evidence review process is available in the 2017 ILCOR summary.[8]

The ILCOR systematic review process uses the Grading of Recommendations Assessment, Development, and Evaluation methodology and its associated nomenclature to determine the strength of recommendation and certainty of effect for the CoSTR. The expert writing group for this 2019 PALS focused update analyzed and discussed the original studies and carefully considered the ILCOR Pediatric Life Support Task Force consensus recommendations[4] in light of the structure and resources of the out-of-hospital and in-hospital resuscitation systems and providers who use AHA guidelines. In addition, the writing group came to a consensus about the Classes of Recommendation and Levels of Evidence according to the nomenclature developed by the American College of Cardiology/AHA recommendations for developing clinical practice guidelines (Table)[9] by using the process detailed in the "2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care."[10]

It is important to note that this 2019 focused update to the AHA PALS guidelines re-evaluates only the recommendations for the use of advanced airway management during cardiac arrest, the use of ECPR during cardiac arrest, and the use of TTM after cardiac arrest. All other recommendations and algorithms published in "Part 12: Pediatric Advanced Life Support" in the 2015 AHA guidelines update[11] and "Part 14: Pediatric Advanced Life Support" in the "2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care"[12] remain the official recommendations of the AHA ECC Science Subcommittee and writing groups. The other recommendations contained in the 2017 and 2018 focused updates to the AHA's pediatric basic and advanced life support guidelines continue to apply to care delivered to pediatric patients in cardiac arrest.[13,14]

ADVANCED AIRWAY INTERVENTIONS IN PEDIATRIC CARDIAC ARREST

Most pediatric cardiac arrests are triggered by respiratory deterioration.[15,16] As a result, airway management and ventilation management are fundamental components of PALS. A number of options exist for airway management in pediatric cardiac arrest. Although the majority of pediatric patients can be successfully ventilated with bag-mask ventilation (BMV), this method requires interruptions in chest compressions and is associated with risk of aspiration and barotrauma. Although endotracheal intubation can partially mitigate the risk of aspiration and enables delivery of uninterrupted chest compressions, it requires specialized equipment and skilled providers. Pediatric airway anatomy differs from that of adults, so tracheal intubation may be more difficult for healthcare professionals who do not routinely intubate pediatric patients. A supraglottic airway (SGA) such as the laryngeal mask airway may be easier to place than an endotracheal tube, but it does not provide a definitive airway and does not mitigate the risk of aspiration.

Evidence Summary—Updated 2019

The 2019 ILCOR Pediatric Life Support Task Force and the AHA pediatric writing group reviewed 14 studies of advanced airway interventions in pediatric patients with cardiac arrest. This included a clinical trial,[17] 3 propensity-adjusted studies,[18–20] 8 retrospective cohort studies,[21–28] and 2 retrospective studies.[29,30] The review included evidence for the use of an advanced airway (endotracheal intubation or SGA) versus BMV only.[4] This topic was last reviewed in 2010,[12] and the previous review did not directly compare outcomes associated with these 3 modalities.

Endotracheal Intubation Compared With BMV

All 14 studies in the systematic review examined the outcomes of endotracheal intubation versus BMV during pediatric cardiac arrest. The only clinical trial in the review randomized pediatric patients with out-of-hospital cardiac arrest (OHCA) to either BMV alone or BMV followed by endotracheal intubation.[17] There was no significant difference between the groups in favorable neurological outcome or survival to hospital discharge.

Table. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated August 2015)*

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
CLASS 1 (STRONG) — **Benefit >>> Risk** **Suggested phrases for writing recommendations:** • Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • Comparative-Effectiveness Phrases†: – Treatment/strategy A is recommended/indicated in preference to treatment B – Treatment A should be chosen over treatment B	**LEVEL A** • High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
CLASS 2a (MODERATE) — **Benefit >> Risk** **Suggested phrases for writing recommendations:** • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases†: – Treatment/strategy A is probably recommended/indicated in preference to treatment B – It is reasonable to choose treatment A over treatment B	**LEVEL B-R (Randomized)** • Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs
CLASS 2b (WEAK) — **Benefit ≥ Risk** **Suggested phrases for writing recommendations:** • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	**LEVEL B-NR (Nonrandomized)** • Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
CLASS 3: No Benefit (MODERATE) (Generally, LOE A or B use only) — **Benefit = Risk** **Suggested phrases for writing recommendations:** • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other	**LEVEL C-LD (Limited Data)** • Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
Class 3: Harm (STRONG) — **Risk > Benefit** **Suggested phrases for writing recommendations:** • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	**LEVEL C-EO (Expert Opinion)** • Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Two propensity-adjusted studies were included in the review. In a database study from the Get With The Guidelines–Resuscitation registry, endotracheal intubation during in-hospital cardiac arrest (IHCA) was associated with decreased survival to hospital discharge.[18] A review from an American cardiac arrest registry, CARES (American Cardiac Arrest Registry to Enhance Survival), of pediatric patients with OHCA comparing outcomes of patients treated with BMV and those treated with endotracheal intubation found an association between BMV and more than double the rate of survival to hospital discharge (odds ratio, 2.56 [95% CI, 1.69–3.85]).[19]

SGA Placement Compared With BMV Alone

Four observational studies were identified in the 2019 ILCOR systematic review of pediatric SGA versus BMV. All were focused on patients with OHCA. Two presented propensity-adjusted cohort data,[19,20] and 2 provided simple observational data.[26,28] In the 2 propensity-adjusted reviews, from the All-Japan Utstein Registry[20] and CARES,[19] comparing outcomes of SGA versus BMV, there was no association between the use of SGA and increased favorable neurological outcome. In 2 non–propensity-matched observational studies comparing the use of SGA with BMV,[26,28] the SGA was associated with a significant increase in survival to hospital discharge and return of spontaneous circulation.

SGA Placement Compared With Endotracheal Intubation

Four observational studies (2 were propensity adjusted) also compared endotracheal intubation with SGA in pe-

diatric patients with OHCA. When compared, neither SGA nor endotracheal intubation was associated with a significant increase or decrease in favorable neurological outcome or survival to hospital discharge.[19,20,26,28] Similarly, when SGA and endotracheal intubation were compared, neither was associated with significant improvement in survival to hospital admission. However, 1 cohort study found improved survival associated with endotracheal intubation compared with SGA.[28]

Additional Considerations

The pediatric ILCOR CoSTR authors attempted to conduct a subgroup analysis to compare outcomes of pediatric IHCA and OHCA, as well as traumatic versus medical causes of arrest. Outcomes from IHCA and OHCA were similar. However, very few studies focused on IHCA; these included 1 propensity-matched cohort study[18] and 2 other cohort studies.[23,27] Outcomes of traumatic and nontraumatic arrest could not be compared because published studies included only a small number of patients identified as having traumatic arrest.

Recommendation—Updated 2019

1. **BMV is reasonable compared with advanced airway interventions (endotracheal intubation or SGA) in the management of children during cardiac arrest in the out-of-hospital setting (*Class 2a; Level of Evidence C-LD*).**

We cannot make a recommendation for or against the use of an advanced airway for IHCA management. In addition, no recommendation can be made about which advanced airway intervention is superior in either OHCA or IHCA.

Discussion

The use of advanced airways in pediatric cardiac arrest was last reviewed by ILCOR in 2010, with the following recommendation: "In the prehospital setting it is reasonable to ventilate and oxygenate infants and children with a bag-mask device, especially if transport time is short (Class IIa, LOE [Level of Evidence] B)."[12] This 2019 focused update reaffirms the 2010 recommendation with no significant changes. In addition, we highlight the evidence associated with the use of specific types of airway intervention, endotracheal intubation and SGAs, comparing their effects with those of BMV. The evidence for this recommendation was largely from observational studies, so reported findings must be interpreted as associated with, rather than caused by, the intervention. However, the writing group agreed that a Class 2a recommendation was appropriate. When used by providers with proper experience and training, BMV was not associated with inferior outcomes compared with endotracheal intubation or SGA; thus, BMV is a reasonable alternative to these advanced airways, which may require more specific training or equipment. During OHCA, transport time, provider skill level and experience, and equipment availability should be considered in the selection of the most appropriate airway intervention. If BMV is ineffective despite appropriate optimization, more advanced airway interventions should be considered.

The writing group determined that there was insufficient evidence to make any recommendation about advanced airway management for IHCA and could not determine whether either endotracheal intubation or SGA was superior in either setting.

ECPR FOR IHCA

The use of extracorporeal membrane oxygenation (ECMO) as a form of mechanical circulatory rescue for failed conventional CPR (ie, ECPR) has gained popularity since its first use as a form of postcardiotomy rescue in children after surgery for congenital heart disease.[31,32] *ECPR* is defined as the rapid deployment of venoarterial ECMO during active CPR or for patients with intermittent return of spontaneous circulation. ECPR is a resource-intense, complex multidisciplinary therapy that traditionally has been limited to large academic medical centers with providers who have expertise in the management of children with cardiac disease. Judicious use of ECPR for specialized patient populations and within dedicated and highly practiced environments has proved successful, especially for IHCA with reversible causes.[33] ECPR use rates have increased, with single-center reports in both adults and children suggesting that application of this therapy across broader patient populations may improve survival after both OHCA and IHCA.[34–36]

Evidence Summary—Updated 2019

The ILCOR Pediatric Life Support Task Force and the AHA pediatric writing group reviewed 3 studies on the use of ECPR in pediatric cardiac arrest. The first study was a retrospective review (2000–2008) of the Get With The Guidelines–Resuscitation registry of pediatric patients with IHCA after cardiac surgery.[37] On adjusted multivariate analysis, the use of ECPR was associated with higher rates of survival to hospital discharge than conventional CPR. A second review of the same database used a propensity analysis to examine the association of ECPR with favorable neurological outcome in patients with IHCA of any origin.[38] During an 11-year period (January 2000–December 2011), 3756 patients were enrolled, with 591 receiving ECPR. Compared with conventional CPR, the use of ECPR was associated with higher favorable neurological outcome at hospital discharge (odds ratio, 1.78 [95% CI, 1.31–2.41]).

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A third study was a single-center retrospective review of patients with congenital heart disease who experienced cardiac arrest during cardiac catheterization.[39] During a total of 7289 cardiac catheterization procedures, 70 infants and children had cardiac arrest; of these, 18 (26%) received ECPR. The use of ECPR was associated with worse survival to hospital discharge compared with conventional CPR, although there was no adjustment for potential confounding variables.

The pediatric ILCOR systematic review and CoSTR[4,6] found no published studies reporting the outcomes after the application of ECPR for pediatric OHCA.

Recommendation—Updated 2019

1. **ECPR may be considered for pediatric patients with cardiac diagnoses who have IHCA in settings with existing ECMO protocols, expertise, and equipment (*Class 2b; Level of Evidence C-LD*).**

There is insufficient evidence to recommend for or against the use of ECPR for pediatric patients experiencing OHCA or for pediatric patients with noncardiac disease experiencing IHCA refractory to conventional CPR.

Discussion

The 2015 AHA PALS guidelines suggested that ECPR "be considered for pediatric patients with cardiac diagnoses who have IHCA in settings with existing ECMO protocols, expertise, and equipment (Class IIb, LOE [Level of Evidence] C-LD)."[11] There were no prospective comparative analyses comparing survival and neurological outcomes between conventional CPR and ECPR. This is not surprising given the potential ethical and logistical challenges in recruiting children for a prospective randomized trial during a cardiac arrest. However, data from large multicenter registry and retrospective propensity score analyses in child and adult populations suggest that ECPR may provide a significant survival benefit when used for refractory cardiac arrest.[38,40,41] Presumably, without ECPR, many of these patients would have died as a result of failed resuscitation attempts.

Current survival to hospital discharge rates for critically ill children experiencing IHCA resuscitated with conventional CPR range from 29% to 44%.[42,43] In contrast, recent ECPR studies of pediatric IHCA have reported survival to hospital discharge rates for mixed cardiac and noncardiac intensive care unit populations as high as 48%.[32,44,45] Additional analyses reported that ECPR in the cardiac intensive care unit was associated with higher survival to hospital discharge rates in patients with surgical cardiac disease compared with patients in the general intensive care unit setting (73% versus 42%, respectively).[46–48] Our understanding of neurological function after resuscitation with ECPR consists of single-center follow-up analyses[49,50] and the results of a randomized prospective trial of therapeutic hypothermia after IHCA.[51]

There is insufficient information about neurological complications and outcomes (ie, hemorrhagic/ischemic stroke, seizure) associated with the use of ECPR in infants and children. In a multicenter randomized trial of therapeutic hypothermia after IHCA, only 30.5% of patients who received ECPR for IHCA had good neurobehavioral outcomes at 12 months of age.[51] In patients who received ECPR, therapeutic hypothermia, compared with normothermia, tended to be associated with lower survival with good neurobehavioral outcome at 1 year.[51]

Single-center analyses lack consistency in reported measures of neurological function/status yet demonstrate favorable neurological outcomes for the majority of survivors at follow-up (median range, 25–52 months).[49,50] Post–cardiac arrest care for patients undergoing ECPR should include ongoing surveillance for neurological injury through the end of the ECMO course.

POST–CARDIAC ARREST TTM

TTM refers to continuous maintenance of patient temperature within a narrowly prescribed range. In initial studies of temperature management after cardiac arrest in adults[52] and after hypoxic-ischemic insult in neonates,[53] therapeutic hypothermia (32°C–34°C) was compared with standard (uncontrolled) temperature management that did not include fever prevention. In these early studies, fever in the control group may have contributed to worse outcomes and to the comparatively higher survival reported in the group treated with hypothermia. More recent studies compared what was described as therapeutic hypothermia (32°C–34°C) with controlled normothermia (36°C–37.5°C), with fever actively prevented.[16,54] These treatment modalities are now referred to as TTM 32°C to 34°C and TTM 36°C to 37.5°C, respectively.

Therapeutic hypothermia treats reperfusion syndrome after cardiac arrest by decreasing metabolic demand, reducing free radical production, and decreasing apoptosis.[55] It is not clear whether TTM to different temperature ranges has the same impact.

Evidence Summary—Updated 2019

The 2019 ILCOR pediatric CoSTR summarized the evidence supporting the use of TTM (32°C–34°C) after IHCA or OHCA in infants, children, and adolescents <18 years of age.[4,7] This pediatric review was triggered by the publication of the results of the THAPCA-IH trial (Therapeutic Hypothermia After Pediatric Cardiac Ar-

rest In-Hospital), a randomized controlled trial of TTM 32°C to 34°C versus TTM 36°C to 37.5°C for IHCA.[54] Unlike previous ILCOR reviews and several earlier AHA PALS guidelines, the ILCOR pediatric CoSTR[4] and this 2019 PALS focused update are based only on evidence from pediatric studies; this update did not consider evidence extrapolated from adult studies. The writing group agreed that pediatric patients receiving TTM after cardiac arrest differ substantially from adult patients because infants and children have different causes of cardiac arrest, initial arrest rhythms, and techniques and equipment used for TTM, as well as differences in post–cardiac arrest care, compared with adults.

The THAPCA-IH trial was a large, multi-institutional, prospective, randomized controlled study of infants and children 2 days to 18 years of age. Methods and outcomes analyzed were identical to the 2015 THAPCA-OH trial (Therapeutic Hypothermia After Pediatric Cardiac Arrest Out-of-Hospital).[16] Both THAPCA studies evaluated the association between temperature targets and outcomes in children who received chest compressions for at least 2 minutes, were comatose (motor Glasgow Coma Scale score <5), and were dependent on mechanical ventilation after return of spontaneous circulation; both studies used the same protocol.[16,54] The only difference between the studies was the location of the arrest of the enrolled patients. The primary outcome evaluated for both trials was favorable neurobehavioral outcome at 1 year, with secondary outcomes of survival at 1 year and change in neurobehavioral outcome. In both studies, temperature targets were actively maintained for 120 hours with the use of anteriorly and posteriorly placed automated cooling blankets. Temperature was continuously and centrally monitored. Patients in the TTM 32°C to 34°C group were cooled to a core temperature of 33°C (range, 32°C–34°C) with neuromuscular blockade and sedation for the first 48 hours. They were then rewarmed over a minimum of 16 hours and actively maintained at 36.8°C (range, 36°C–37.5°C) for the remainder of the study. Patients in the TTM 36°C to 37.5°C cohort received identical care except for a targeted temperature of 36.8°C (range, 36°C–37.5°C) for the entire 5-day intervention period.[16,54]

The THAPCA-IH trial was halted for futility after enrollment of 59% of targeted patients because the primary outcome (favorable neurobehavioral outcome at 1 year) did not differ significantly between the TTM 32°C to 34°C (36%, 48 of 133) and TTM 36°C to 37.5°C (39%, 48 of 124; relative risk, 0.92% [95% CI, 0.67–1.27]; *P*=0.63) groups. Secondary outcomes, including a change in neurobehavioral outcome score by at least 1 SD from prearrest baseline at 1 year (30% versus 29%; *P*=0.70), survival at 28 days (63% versus 59%; *P*=0.40), and survival at 1 year (49% versus 46%; *P*=0.56), did not differ between TTM groups. There were no significant differences between the temperature groups in the frequency of adverse events, including infection, need for transfusion, and serious arrhythmias within the first 7 days.[54]

The THAPCA-OH trial analyzed data from 260 patients. There was no significant difference in the primary outcome between patients treated with TTM 32°C to 34°C and those treated with TTM 36°C to 37.5°C (20% versus 12%; relative risk, 1.59 [95% CI, 0.89–2.85]). There were also no differences in secondary outcomes, including change in neurobehavioral scores from baseline, survival at 28 days, or survival at 1 year.[16]

Recommendations—Updated 2019

1. **Continuous measurement of core temperature during TTM is recommended (*Class 1; Level of Evidence B-NR*).**
2. **For infants and children between 24 hours and 18 years of age who remain comatose after OHCA or IHCA, it is reasonable to use either TTM 32°C to 34°C followed by TTM 36°C to 37.5°C or to use TTM 36°C to 37.5°C (*Class 2a; Level of Evidence B-NR*).**

There is insufficient evidence to support a recommendation about treatment duration. The THAPCA (Therapeutic Hypothermia After Pediatric Cardiac Arrest) trials used 2 days of TTM 32°C to 34°C followed by 3 days of TTM 36°C to 37.5°C or used 5 days of TTM 36°C to 37.5°C.

Discussion

Since publication of the 2015 PALS guidelines, an additional randomized controlled trial of TTM of comatose children after IHCA has been published.[54] This in-hospital study, from the same investigational team and with the same treatment protocol as the out-of-hospital study,[16] compared post–cardiac arrest TTM 32°C to 34°C with TTM 36°C to 37.5°C. Together, these trials form the basis of the current guidelines. Although several pediatric observational studies were also included in the ILCOR evidence review,[7] the observational studies had differing inclusion and exclusion criteria and varying protocols for temperature management, duration of TTM, and definitions of harm.[56–59] In addition, although there are several randomized controlled trials of TTM within the adult population, the ILCOR Pediatric Life Support Task Force and this writing group placed a higher value on pediatric data because the adult studies include patients with arrest causes, disease states, and outcomes that differ from those of children and thus would provide only indirect evidence.

Although there were no significant differences in outcomes between the 2 TTM groups in the THAPCA trials (ie, therapeutic hypothermia versus therapeutic normothermia), hypothermia has been shown to be advantageous in animal models and neonatal hypoxic injury and

in mediating the adverse effects of the post–cardiac arrest syndrome. Given the severity of neurological injury that many children demonstrate after resuscitation from cardiac arrest, cardiac arrest poses a substantial public health burden, representing large numbers of years lost, which makes potential interventions to improve neurological injury and survival a critical priority.

Although interpretation of many studies of pediatric patients resuscitated from IHCA or OHCA is challenged by low-quality evidence in heterogeneous populations, most observational studies have yielded similar findings.[56–59] These studies used different control groups, arrest locations, age groups, causes of arrest, duration of TTM, and type of follow-up. Despite 1 small observational study of TTM in OHCA survivors demonstrating statistical improvement in neurological recovery[59] and an observational study of IHCA demonstrating worse neurological outcomes and survival after TTM,[56] the majority of studies have demonstrated no differences in intensive care unit duration of stay, neurological outcomes, and mortality with the use of therapeutic hypothermia versus controlled normothermia.

Both THAPCA trials[16,54] and 2 observational studies[60,61] used active normothermia to maintain temperature below the febrile range. The other 7 observational studies[56–59,62–64] analyzed in the systematic review[3] did not control temperature in the control group; thus, there was a risk of fever that could have contributed to worse outcomes in the control group. This lack of temperature regulation in the control groups is a key limitation and a potential source of bias in these studies. Fever is common after a hypoxic-ischemic event such as cardiac arrest and has been shown from registry data to be associated with worse outcomes after cardiac arrest.[65] The negative results of recent TTM trials may be explained by the active maintenance of normothermia in control patients rather than a true noneffect of hypothermia. The early trials of hypothermia in both neonates and adults did not prevent fever, whereas later trials did.[53,66,67] A more recent TTM trial in neonates receiving ECMO used normothermic temperatures in the control group and did not demonstrate differences in outcomes or adverse effects.[68] Whether using TTM 32°C to 34°C followed by TTM 36°C to 37.5°C or using TTM 36°C to 37.5°C for infants and children who remain comatose after return of spontaneous circulation, the avoidance of fever is paramount.

Although these treatment recommendations apply to both OHCA and IHCA, it is important to recognize that outcomes of OHCA and IHCA differ in several key determinants. Response intervals are inherently longer for OHCA, as are the times to initiation of CPR, airway management, pharmacological therapies, and defibrillation. The presence of comorbidities, initial rhythms, and arrest causes all differ between children with OHCA and those with IHCA. However, because the conclusions of the 2 THAPCA trials[16,54] were the same, we have made a merged recommendation for both OHCA and IHCA.

The ILCOR pediatric ECPR systematic review included multiple subgroup analyses evaluating the critical outcomes of favorable neurobehavioral function and survival at multiple time points.[3] These subgroup analyses included location of arrest (OHCA versus IHCA), presumed cause of arrest (cardiac, asphyxial, drowning), and use of ECMO. Although no subgroup analysis was found to favor one treatment over another, the analyses were limited because only 1 randomized trial exists for each location, and the small sample sizes and lack of conformity within the observational trials prevented the pooling of data. Subgroup analyses of adverse events, including infection, serious bleeding, and recurrent cardiac arrest, were feasible from only the 2 randomized controlled trials. These studies found no statistical difference in positive outcomes or complications between TTM 32°C to 34°C and TTM 36°C to 37.5°C groups in either THAPCA trial.[16,54] Significant limitations persist even in the randomized trials, which affects the certainty of any recommendation about TTM during post–cardiac arrest care. Patient recruitment, especially in the randomized trials, occurred over many years, during which recommendations for CPR changed, including the recent changes to put greater emphasis on CPR quality. The exclusion criteria were extensive and may have excluded some patients who might have benefitted from TTM. Finally, and significantly, across the sites, there was no consistent use of a post–cardiac arrest care bundle such as identifying and supporting optimal blood pressure, metabolic or oxygen/ventilation targets, and methods of supportive care.

In the randomized trials,[16,54] the duration of TTM was 120 hours (5 days). In the observational trials, the duration of hypothermia varied from 24 to 72 hours.[56,58–64] Similarly, the duration of the rewarming period varied. Because no randomized trial tested the duration of TTM, the writing group felt that there was insufficient evidence to make a specific recommendation on this important aspect of the therapy.

Given the uncertainty of the effect of TTM, limitations of the data analysis, and lack of demonstrable harm, we agree that it is reasonable for clinicians to use TTM to 32°C to 34°C followed by TTM 36°C to 37.5°C or to use TTM 36°C to 37.5°C. Clinicians should consistently implement the strategy that can most safely be performed for a specific patient in a specific clinical environment. Regardless of strategy, providers should strive to prevent fever >37.5°C.

ARTICLE INFORMATION

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Robert Michael Sutton	The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine	NHLBI (PI on CPR Quality Improvement trial)*	None	None	Roberts and Durkee†; Lowis and Gellen*; Donahue, Durham, and Noonan*	None	None	None

(*Continued*)

Writing Group Disclosures Continued

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Alexis A. Topjian	The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine	NIH (subaward)*	None	None	Plaintiff*	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Douglas Diekema	University of Washington	None	None	None	None	None	None	None
Elizabeth A. Greene	University of New Mexico	None	None	None	None	None	None	None
Justin M. Jeffers	Johns Hopkins University	None	None	None	None	None	None	None
Mary E. McBride	Lurie Children's Heart Center	None	None	None	None	None	None	None
Mark Meredith	University of Tennessee	None	None	None	None	None	None	None
Halden F. Scott	Children's Hospital Colorado	AHRQ (PI on a K08 from AHRQ studying prediction and diagnosis of pediatric septic shock. I do not directly receive personal funds from the grant.)*	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Significant.

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