Appendix A

Pediatric Life Support – 2026 Evidence to Decision Tables

Table of Contents

Ventilation Parameters During Cardiac Arrest in Children (PLS 4120.02, 4080.28)

QUESTION

Should specific ventilation parameters (eg lower rate vs. ventilation with a higher rate) be used for children receiving assisted ventilation during cardiac arrest?	
POPULATION:	Children receiving assisted ventilation during cardiac arrest
INTERVENTION:	Ventilation with a specific tidal volume, respiratory rate, inspiratory time, or positive end-expiratory pressure
COMPARISON:	Ventilation with a specific tidal volume, respiratory rate, inspiratory time, or positive end-expiratory pressure
MAIN OUTCOMES:	Any clinical outcome, including but not limited to return of spontaneous circulation (ROSC), survival and survival with favorable neurologic outcome at discharge, 30 days or longer, duration of mechanical ventilation, oxygenation, blood gas parameters, progression to ARDS, barotrauma, ICU and hospital length of stay, with a preference for outcomes listed in the ILCOR COSCA(7) or P-COSCA
SETTING:	Any setting (in or out of hospital)
CONFLICT OF INTERESTS:	no conflicts of interest

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Ventilation delivery during pediatric cardiac arrest is a core component of high-quality CPR, yet optimal ventilation parameters remain uncertain. Existing evidence shows wide variability in actual ventilation practice and suggests that ventilation parameters—including rate, tidal volume, and interaction with airway strategy—may influence hemodynamics, gas exchange, ROSC, and survival. Multiple recent observational studies in adults demonstrate associations between ventilation parameters and outcomes, and the most recent pediatric in-hospital and out-of-hospital studies (Sutton 2019; Stanton 2025)[1, 2] report that higher delivered ventilation rates are associated with improved ROSC and survival outcomes, although certainty is very low. Despite this, no pediatric randomized trials exist, no comparative evidence informs tidal volume, inspiratory time, or PEEP during CPR, and practice variation remains substantial.	Effective ventilation is essential in pediatric cardiac arrest given the predominance of respiratory etiologies. Suboptimal ventilation (both hypo- and hyperventilation) has been linked in prior research to hypotension, impaired gas exchange, and reduced survival, underscoring the relevance of this question for improving CPR quality. The lack of clear evidence-based targets for key ventilation parameters creates uncertainty in clinical practice and highlights the need for evidence synthesis. Given the clinical importance, observed practice variability, and emerging but incomplete data, the Task Force agreed this is a high-priority area for evaluation.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Observational pediatric data (IHCA and OHCA) suggest that higher ventilation rates, within or slightly previous pediatric guideline ranges, are associated with higher odds of ROSC and survival with good neurological outcome (Sutton 2019; Stanton 2025). Adult observational studies and small RCTs also suggest that avoiding marked hypoventilation may improve gas exchange, hemodynamics, and survival. However, all pediatric data are observational, sample sizes are small, and estimates are imprecise, so the magnitude of benefit is very uncertain.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	Hyperventilation during CPR can decrease coronary and cerebral perfusion, lower arterial pressure, increase intrathoracic pressure, and potentially cause dynamic hyperinflation and barotrauma. These harms are well described physiologically and in adult experimental/observational work, but there are limited pediatric data directly quantifying these adverse effects. The Good Practice Statement emphasizes measuring ventilation rate and adequacy of tidal volume delivery and avoiding hypoventilation. Overall, the potential for physiologic harm is recognized but its magnitude remains uncertain.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The pediatric evidence consists of two observational studies (one IHCA, one OHCA) evaluating ventilation rate during CPR, both at serious risk of bias, with indirectness (restricted settings, advanced airway, specific monitoring) and imprecision due to small sample sizes. Adult data come from heterogeneous observational studies and small RCTs with similar concerns about risk of bias, inconsistency, and indirectness for pediatric practice. No pediatric comparative trials address tidal volume, inspiratory time, or PEEP. The TF therefore rated overall certainty as very low.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The main outcomes—ROSC, survival, and survival with favorable neurological outcome—are universally regarded as critically important by patients, families, and clinicians. These outcomes align with P-COSCA core outcomes and existing ILCOR priorities. There may be some variation in the relative importance placed on survival with significant disability versus death, but this is unlikely to materially affect decisions about ventilation parameters during CPR.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Physiologic reasoning and available pediatric data suggest that avoiding hypoventilation is beneficial. Observational pediatric studies show associations between higher delivered ventilation rates and improved ROSC and survival. Given very low certainty evidence and lack of evidence to define an upper limit for ventilation rate, the Task Force issued 2 Good Practice Statements focused on reasonable ventilation rate targets by age, ensuring measurement of ventilation rate and adequacy of tidal volume delivery, and avoiding hypoventilation.	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Delivering ventilation to achieve reasonable ventilation rate targets in children with an advanced airway relies primarily on provider technique and training, not additional consumables. Measuring ventilation rate and adequacy of tidal volume delivery (e.g., waveform capnography, ventilator measures and impedance) may require equipment that is not universally available, particularly in low-resource systems, but these tools are already in use in many pediatric resuscitation settings. Overall, resource implications are modest compared with other critical care interventions.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	In well-resourced systems, implementing the suggested ventilation rates and monitoring may be straightforward and could improve the quality of CPR. In low-resource settings where advanced airways and capnography are not consistently available, strict emphasis on monitored ventilation parameters could widen perceived gaps between guideline recommendations and what is feasible, potentially impacting equity. However, the Good Practice Statement focuses on avoiding obvious hypoventilation rather than mandating specific technology, which may mitigate inequity. The overall impact on equity is therefore uncertain.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No studies were identified that directly evaluate the cost-effectiveness of specific ventilation parameters during pediatric cardiac arrest. Delivering ventilation to achieve reasonable ventilation rate targets with an advanced airway does not require additional consumables and can generally be implemented with existing equipment and personnel. Measuring ventilation adequacy (e.g., capnography or ventilator parameters or impedance measures) may add cost in systems where such tools are not already available, but these technologies are commonly used in many resuscitation settings and serve broader purposes beyond ventilation rate guidance. Because no formal economic evaluations exist and resource implications vary widely across settings, the overall cost-effectiveness of the intervention is uncertain.	

Equity

What would be the impact on health equity?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	In well-resourced systems, implementing the suggested ventilation rates and monitoring may be straightforward and could improve the quality of CPR. In low-resource settings where advanced airways and capnography are not consistently available, strict emphasis on monitored ventilation parameters could widen perceived gaps between guideline recommendations and what is feasible, potentially impacting equity. However, the Good	

	Practice Statement focuses on avoiding obvious hypoventilation rather than mandating specific technology, which may mitigate inequity. The overall impact on equity is therefore uncertain.	

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The recommended ventilation rate targets are consistent with current pediatric resuscitation guidelines and with current practice in many systems. It is unlikely to conflict with patient or family values and is generally supported by clinicians who recognize the risks of both under- and over-ventilation during CPR. Emphasis on monitoring and avoiding extremes aligns with quality-improvement initiatives and is therefore likely acceptable to resuscitation teams and guideline developers.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Achieving reasonable ventilation rate targets in children with an advanced airway is feasible with appropriate training, team coordination, and the use of simple timing aids (e.g., metronomes or ventilator settings). Many systems already track ventilation performance using waveform capnography, ventilator readouts, or other monitoring tools, which can facilitate measurement of ventilation rate and adequacy of tidal volume delivery. However, consistent implementation may be challenging in crowded or low-resource environments, or where providers are unfamiliar with age-based ventilation targets or lack access to real-time measures. Overall, the Task Force judged the Good Practice Statements to be feasible to implement across most resuscitation settings, while acknowledging variability in resources and practice.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**

CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Good Practice Statements

For children in cardiac arrest with an advanced airway, it is reasonable to target a ventilation rate consistent with age-related physiological normal values (good practice statement).

It is reasonable to measure ventilation rate and adequacy of tidal volume delivery and avoid hypoventilation (Good Practice Statement).

There is currently no evidence to make a treatment recommendation on the upper limit for ventilation rate, tidal volume delivery, inspiratory time or positive end-expiratory pressure during cardiac arrest in children.

Justification

- This topic was prioritized by the BLS, ALS, and PLS Task Forces as a nodal review based on multiple recent observational studies9, 10 demonstrating association between ventilation parameters and outcomes as well as several small randomized trials.
- Ventilation during cardiac arrest encompasses multiple components including rate, volume, and monitoring, as well as airway devices, feedback, and integration with chest compressions.
- The previous ILCOR systematic review on pediatric ventilation rates performed in 202415 did not identify any pediatric comparative studies evaluating specific ventilation rates, and therefore no direct pediatric evidence was available to guide rate recommendations.
- The Task Force discussed that this systematic review differed from earlier work in that it was now possible to include two pediatric observational studies6, 7, providing the first comparative pediatric data evaluating ventilation rate during cardiac arrest. In the prior review, these data could only be considered indirect, and treatment recommendations were based largely on adult evidence and physiologic rationale. Despite the addition of these studies, the Task Force noted that the certainty of evidence remains very low, derived exclusively from pediatric in-hospital settings with an advanced airway and capnography in place.
- The Task Force further discussed that the ventilation rates associated with improved outcomes in Sutton 20196 were inferred from spline-based analyses rather than from prespecified, randomized comparisons. The cubic spline analysis suggested stable survival between 25 and 35 breaths/min for children older than 1 year of age and between 30 to 50 breaths/min for children younger than 1 year old, the actual ventilation rates delivered in practice were frequently even higher, and the study design did not allow determination of a causal or optimal target for ventilation rates.
- While this analysis provides helpful physiologic and observational context, it remains exploratory and should not be interpreted as defining an optimal ventilation threshold. However, when considered together with the more recent out-of-hospital evidence7, which similarly observed higher mean ventilation rates among children who achieved ROSC albeit the breaths per minute rate were much lower, the Task Force supports the overall conclusion that higher—rather than lower—ventilation rates were associated with improved outcomes in the available pediatric data, although certainty remains very low.
- Because of these limitations, the PLS Task Force agreed that the evidence remained too indirect to establish an optimal ventilation rate in children, and that no comparative pediatric data exist to inform ventilation rate in out-of-hospital arrest or in non-intubated patients. No pediatric studies have evaluated optimal tidal volume delivery or PEEP during CPR.
- The use of the adult algorithm measuring ventilation using ETCO2 waveform capnography needs validation in pediatric patients. The study by Stanton 20257 suggested it
was feasible to use, however ventilation rates observed in the study fall well below rates associated with the best outcomes.

Subgroup considerations

Age groups (infants vs. older children):
Pediatric ventilation physiology varies substantially by age. Infants have higher baseline metabolic and minute ventilation requirements, lower functional residual capacity, and are more sensitive to hypoventilation. Sutton et al. stratified ventilation thresholds by age (<1 year vs >1 year), and both age groups showed an association between higher delivered ventilation rates and improved outcomes..

Etiology of arrest (respiratory vs. cardiac):
Children with respiratory etiologies (e.g., asphyxia, drowning, bronchiolitis) may benefit more from avoiding hypoventilation, whereas children with primary cardiac etiologies may be more susceptible to the hemodynamic consequences of hyperventilation. Neither available pediatric study provides data stratified by etiology, so the Task Force could not make etiology-specific recommendations.

Setting (IHCA vs. OHCA):
IHCA (Sutton 2019) and OHCA (Stanton 2025) studies both show directionally similar associations between higher delivered ventilation rates and better outcomes, but absolute ventilation performance and monitoring capabilities

differ across settings. OHCA care may be subject to more variability in provider experience and competence in airway management, limiting generalizability across settings.

Airway strategy (ETT vs. SGA vs. BMV):

The pediatric evidence informing the recommendation is limited to patients with *advanced airways* (almost entirely ETT or SGA). No comparative data exist for bag-mask ventilation or for comparing airway strategies. Therefore, the TF cannot assume similar ventilation dynamics or benefits in non-intubated patients.

Monitoring availability:

Both pediatric studies derived ventilation rates from post-hoc analysis of continuous physiologic waveforms, using quantitative capnography to identify ventilations in both the in-hospital study (Sutton et al.) and the out-of-hospital study (Stanton et al.). In Sutton et al., thoracic impedance–based respiratory plethysmography was used only as a supporting signal to identify periods of active chest compressions and pause time, not to count ventilations. Systems without continuous waveform capture may exhibit greater variability in delivered ventilation rates, limiting the generalizability of these associations.

Comorbidities / pre-arrest physiology:

Children with chronic lung disease (e.g., prematurity complications, neuromuscular weakness) may have different optimal ventilation parameters, but no study provided subgroup analyses by comorbidity.

Implementation considerations

Implementing reasonable ventilation rate targets for children with an advanced airway during CPR requires attention to training, team coordination, and monitoring. Achieving consistent ventilation delivery can be challenging in high-stress resuscitation environments, particularly where multiple providers rotate through airway or ventilation roles. Systems that already use waveform capnography or ventilator-based monitoring may find implementation straightforward, as these tools provide real-time feedback on ventilation rate and adequacy of tidal volume delivery. In settings without continuous monitoring, simple aids such as metronomes, timed verbal cues, or structured role assignment may help avoid hypoventilation.

Because the evidence informing this recommendation was derived entirely from children with advanced airways and real-time ventilation monitoring, implementation may be more variable where supraglottic airways or bag-mask ventilation are used. Additional emphasis on training in pediatric airway management, ventilation timing, and minimizing excessive ventilation pressures is important in these contexts.

EMS systems and hospitals should consider incorporating ventilation rate targets into pediatric resuscitation checklists, cognitive aids, and debriefing tools. Integration of ventilation monitoring into quality-improvement programs (e.g., defibrillator downloads, capnography review) may support consistent performance. As equipment availability and staffing vary across settings, flexibility is needed to adapt implementation strategies to local resources. The recommendation does not mandate new technology and can be operationalized with existing equipment, but systems lacking ventilation feedback tools may benefit from investing in low-cost solutions to support correct ventilation delivery.

Monitoring and evaluation

Monitoring ventilation quality during pediatric CPR is essential to support delivery of reasonable ventilation rate targets and to avoid hypoventilation. Systems should track ventilation rate and adequacy using available monitoring tools, such as waveform capnography, ventilator-derived respiratory rates, or impedance-based measurements. When real-time monitoring tools are unavailable, post-event review of resuscitation records, monitor/defibrillator downloads, or capnography waveforms can provide valuable information on achieved ventilation performance.

Key indicators for monitoring include:

- Delivered ventilation rate (breaths per minute), ideally captured continuously
- Variability in ventilation rate across the resuscitation
- Availability and use of ventilation monitoring tools (e.g., capnography)
- Airway strategy used and its influence on ventilation performance
- Team adherence to assigned ventilation roles during resuscitation
- Post-event debrief data, including ventilation trends in relation to hemodynamics and $EtCO_2$

Programs with established CPR quality-improvement systems may incorporate these indicators into routine case reviews, debriefings, and performance dashboards. Pediatric-specific feedback, focused team training,

and tracking of improvement over time can help reinforce correct ventilation delivery. As new evidence emerges, ongoing evaluation of clinical outcomes—especially ROSC, survival, and neurological outcome on discharge—will be important to assess the impact of ventilation practices and guide future refinements of recommendations.

Research priorities

On the basis of the identified knowledge gaps, the Task Force highlighted the following research priorities:

1. Define optimal ventilation rate targets in pediatric cardiac arrest.
    - Conduct prospective observational studies and randomized or cluster-randomized trials comparing different ventilation rate ranges in infants and children, both in-hospital and out-of-hospital.
    - Include both advanced airway and non-intubated patients (bag-mask ventilation, supraglottic airway) and report core outcomes (ROSC, survival, neurological outcome at hospital discharge).
2. Evaluate the delivery of tidal volume, inspiratory pressure, and PEEP during pediatric CPR.
    - Perform physiologic and clinical studies that compare different tidal volume delivery and PEEP strategies, including minute ventilation targets, and examine their effects on oxygenation, hemodynamics, lung injury, and longer-term outcomes.
    - Integrate continuous monitoring (e.g., capnography, airway pressure, blood gases, thoracic impedence) to understand mechanisms.
3. Characterize the physiologic consequences of hypo- and hyperventilation.
    - Undertake detailed physiologic studies (clinical and, where necessary, translational) to describe how different ventilation patterns during CPR affect $PaCO_2$, PaO_2, pH, cerebral perfusion, coronary perfusion, and blood pressure in children.
    - Link these physiologic changes to short- and long-term clinical outcomes.
    - Develop etiology-specific ventilation strategies.
4. Design studies that stratify or randomize patients according to arrest etiology (e.g., primary respiratory failure, cardiac etiology, drowning, pulmonary injury) to determine whether optimal ventilation targets differ by cause.
    - Explore whether etiology-specific protocols improve outcomes compared with a uniform ventilation strategy.

Clarify the interaction between airway strategy and optimal ventilation parameters.5. Compare ventilation performance and outcomes across airway approaches (bag-mask ventilation, supraglottic airway, endotracheal intubation) using standardized measurement of rate, volume delivery, and pressures.

- Determine whether recommended ventilation targets should differ according to airway type, and evaluate the role of feedback technologies across these strategies.
- Conduct adequately powered pediatric trials and high-quality prospective studies.

6. Prioritize large, multicenter pediatric studies—including randomized or pragmatic trials—of ventilation strategies during cardiac arrest with neurologically-intact survival as a primary outcome.
    - Embed ventilation monitoring and feedback into cardiac arrest registries and quality-improvement programs to support learning health-system approaches and enable future trials.

References

1. Stanton K, Mershad A, Kadish C, Murphy A, Lowe R, Ania I, et al. Ventilation Rates and Capnography in Pediatric Out-of-Hospital Cardiac Arrest with Advanced Airways. Prehosp Emerg Care. 2025;29(8):1072–7.
2. Sutton RM, Reeder RW, Landis WP, Meert KL, Yates AR, Morgan RW, et al. Ventilation Rates and Pediatric In-Hospital Cardiac Arrest Survival Outcomes. Crit Care Med. 2019;47(11):1627–36.

Intramuscular Epinephrine During Cardiac Arrest in Children (PLS 4090.05)

QUESTION

Should IM epinephrine vs. IV or IO or be used for cardiac arrest? (PLS 4090.05)	
POPULATION:	Children in cardiac arrest in any setting
INTERVENTION:	Intramuscular (IM) route of epinephrine administration
COMPARISON:	IV/IO administration
MAIN OUTCOMES:	Patient outcomes – ROSC (important), survival and survival with favorable neurologic outcome at any time point (critical). Process outcomes - administration of epinephrine, time to epinephrine, and accuracy of dosing
SETTING:	all settings
CONFLICT OF INTERESTS:	Janice Tijssen published previous studies on intramuscular epinephrine and is funded for a trial on IM Epinephrine.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Studying new interventions for cardiac arrest is essential because it is a common and life-threatening emergency with persistently poor survival and neurological outcomes, and only through developing, testing, and refining innovative strategies can we meaningfully improve the chances of saving lives.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	In the management of cardiac arrest, earlier epinephrine is associated with improved clinical outcomes. Meanwhile, administration of epinephrine by IV and IO routes has its challenges. IM epinephrine may be a more efficient route of administration of epinephrine. However, response to early epinephrine likely will be associated with etiology of arrest, duration of arrest, comorbidities, quality of CPR, etc. From a population perspective, the impact may be small.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	IM epinephrine safety has been demonstrated through millions of administrations in the setting of anaphylaxis. The doses used in adult OHCA are approximately 10 times greater and may pose a greater risk of necrosis. The risk of local infection is likely no greater than with an autoinjector for anaphylaxis- which is exceedingly rare. There are no safety studies of IM epinephrine in cardiac arrest. There is a potential for harm by detracting from standard of care, and by having 2 different concentrations of epinephrine for one clinical condition (1:1000 for IM epinephrine and 1:10,000 for IV/IO epinephrine).	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There are no pediatric studies of IM epinephrine in cardiac arrest.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	There is no pediatric evidence, but if there were outcomes to measure, there would be no uncertainty about the value of P-COSCA outcomes.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	There is no pediatric evidence.	

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There is no evidence, but IM epinephrine is an acceptable therapy in anaphylaxis.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no dosing studies of IM epinephrine in cardiac arrest, but pediatric epinephrine dosing is based on weight and thus cannot be prepared until a patient's weight is known. Currently, there are no commercially available prefilled syringes of 1:1000 epinephrine concentration (for greater than 0.3mg in an autoinjector). In a simulation study, the time required to prepare a syringe of 1:1000 epinephrine was equivalent to the time required to insert an IV or IO. However, the stability, sterility, and potency of pre-filled plastic epinephrine syringes have not been evaluated for durations of > 3 months. Thus, for pediatric dosing of 1:1000 epinephrine for cardiac arrest, there are feasibility concerns.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know

DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

There is insufficient pediatric evidence to recommend adding intra-arrest intramuscular (IM) epinephrine to standard resuscitation care for cardiac arrest in children.

Justification

The TF recognized that intramuscular epinephrine is an interesting area of research. In the management of cardiac arrest, earlier epinephrine is associated with improved clinical outcomes. Meanwhile, administration of epinephrine by IV and IO routes has its challenges. IM epinephrine may be a more efficient route of administration of epinephrine but it may also lead to suboptimal effects. Adult and animal studies were included in the SR for comprehensiveness but the results these should be interpreted with caution. The task force explicitly refrained from using adult-derived indirect evidence for many paediatric recommendations because of fundamental differences in arrest aetiology. Animal studies often fail to integrate standard of care post-arrest therapies and do not report neurological outcomes. In addition, time to drug administration in animals does not reflect the human clinical experience, where epinephrine administration is often delayed compared to animal studies.

Subgroup considerations

No subgroup data available

Implementation considerations

There are no dosing studies of IM epinephrine in cardiac arrest, but pediatric epinephrine dosing is based on weight and thus cannot be prepared until a patient's weight is known. Currently, there are no commercially available prefilled syringes of 1:1000 epinephrine concentration (for greater than 0.3mg in an autoinjector). In a simulation study, the time required to prepare a syringe of 1:1000 epinephrine was equivalent to the time required to insert an IV or IO. However, the stability, sterility, and potency of pre-filled plastic epinephrine syringes has not been evaluated for durations of > 3 months. Thus, for pediatric dosing of 1:1000 epinephrine for cardiac arrest, there are feasibility concerns.

Monitoring and evaluation

Research priorities

There are no pediatric studies evaluating intramuscular epinephrine in cardiac arrest. The TF suggests that there is sufficient biological plausibility and equipoise for this therapy to warrant human pediatric trials. Future studies should evaluate IM epinephrine compared to no epinephrine (e.g., in low resourced settings), in addition to IM epinephrine compared to IV/IO epinephrine, in children with cardiac arrest.

There are no dosing studies of IM epinephrine in cardiac arrest. Future studies should evaluate the pharmacokinetic profile of IM epinephrine in cardiac arrest to inform dosing.

There are no safety studies of IM epinephrine in cardiac arrest. There is a potential for harm by detracting from standard of care, and by having 2 different concentrations of epinephrine for one clinical condition (1mg/ml [1:1000] for IM epinephrine vs 0.1mg/ml [1:10,000] for IV/IO epinephrine).

References:

1. Alshaikh R, Sheikh A, Fleming C, Garcia-Bournissen F, Tijssen JA. Intramuscular epinephrine in cardiac arrest: a systematic review. *Resusc Plus*. 2025;26:101133. doi: 10.1016/j.resplu.2025.101133
2. Palatinus HN, Johnson MA, Wang HE, Hoareau GL, Youngquist ST. Early intramuscular adrenaline administration is associated with improved survival from out-of-hospital cardiac arrest. *Resuscitation*. 2024;201:110266. doi: 10.1016/j.resuscitation.2024.110266
3. Pugh AE, Stoecklein HH, Tonna JE, Hoareau GL, Johnson MA, Youngquist ST. Intramuscular adrenaline for out-of-hospital cardiac arrest is associated with faster drug delivery: a feasibility study. *Resusc Plus*. 2021;7:100142. doi: 10.1016/j.resplu.2021.100142
4. Lim D, Lee SH, Kim DH, Kang C, Jeong JH, Lee SB. The effect of high-dose intramuscular epinephrine on the recovery of spontaneous circulation in an asphyxia-induced cardiac arrest rat model. *BMC Cardiovasc Disord*. 2021;21:113. doi: 10.1186/s12872-021-01917-7
5. Mauch J, Ringer S, Spielmann N, Weiss M. Impact of catecholamines in cardiac arrest due to acute asphyxia--a study in piglets. *Paediatr Anaesth*. 2014;24:933–939. doi: 10.1111/pan.12457
6. Mauch J, Ringer SK, Spielmann N, Weiss M. Intravenous versus intramuscular epinephrine administration during cardiopulmonary resuscitation - a pilot study in piglets. *Paediatr Anaesth*. 2013;23:906–912. doi: 10.1111/pan.12149
7. Redding JS, Asuncion JS, Pearson JW. Effective routes of drug administration during cardiac arrest. *Anesth Analg*. 1967;46:253–258.
8. O'Reilly M, Tijssen JA, Lee TF, Ramsie M, Cheung PY, Schmolzer GM. Intramuscular versus intravenous epinephrine administration in a pediatric porcine model of cardiopulmonary resuscitation. *Resusc Plus*. 2024;20:100769. doi: 10.1016/j.resplu.2024.100769

Vasopressor Use During Cardiac Arrest in Children (PLS 4080.21)

QUESTION

Should Vasopressor vs No vasopressor be used for children during cardiac arrest?	
POPULATION:	Infants and children (excluding newborns) in cardiac arrest who received chest compressions in any setting
INTERVENTION:	Any use of vasopressors (epinephrine, vasopressin, or combination of vasopressors)
COMPARISON:	No vasopressor use
MAIN OUTCOMES:	Critical clinical outcomes, including short-term survival and neurological outcomes (e.g., hospital discharge, 28 days, 30 days, and 1 month), and long-term survival and neurological outcomes (e.g., 3 months, 6 months, and 1 year) as per Pediatric Core Outcome Set for Cardiac Arrest
SETTING:	Any setting (in-hospital or out-of-hospital)
PERSPECTIVE:	
BACKGROUND:	Despite being a cornerstone of advanced life support protocols in children, the efficacy of vasopressors in improving survival and neurological outcomes is unclear.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Administration of epinephrine in paediatric cardiac arrest has been traditionally taught as a fundamental part of advanced life support despite a lack of evidence that it improves patient-centered outcomes such as long-term neurological outcomes.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	The search strategy identified 954 unique records, of which 21 were selected for full-text review. Of these, 5 satisfied all inclusion and exclusion criteria. Two papers were pre-hospital retrospective, propensity-score matched cohort studies (Amoako 2023[1], Matsuyama 2020[2]). The two studies provided low certainty of evidence for the critical outcomes (downgraded for serious risk of bias and serious indirectness) and very low certainty of evidence for the important outcomes (downgraded for serious risk of bias, very serious inconsistency, and serious	A randomized trial of epinephrine in out-of-hospital cardiac arrest in adults highlighted the lack of overall improvement in neurologically intact survival in the epinephrine group.

	indirectness). The remaining three observational studies (Banerjee 2020, Rodríguez-Núñez 2006, Dieckmann 1995)[3-5] did not adjust for epinephrine administration in their analyses and therefore excluded from the meta-analysis. No RCTs were identified. While survival to hospital discharge is highly desirable, further studies are needed to evaluate long term neurological outcomes of pre-hospital administration of epinephrine for paediatric out-of-hospital cardiac arrest. These patient-centered clinical outcomes should be studied.	

Certainty assessment							№ of patients		Effect	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vasopressor use (epinephrine)	no vasopressor (no epinephrine)	Adjusted Risk Ratio (95% CI)	Risk difference (95% CI)
Favorable neurological outcome at 1-month										
1	non-randomised studies Matsuyama, 2020[20]	serious[a]	not serious	serious[c,d]	not serious	none	11/304 (3.6%)	8/304 (2.6%)	**1.56** (0.61 to 3.96)	**15 more per 1,000** (from 11 fewer to 92 more)
Favorable neurological outcome at hospital discharge										
1	non-randomised studies Amoako, 2023[21]	serious[b]	not serious	serious[c]	not serious	none	32/713 (4.5%)	27/713 (3.8%)	**1.23** (0.67 to 2.25)	**9 more per 1,000** (from 13 fewer to 50 more)
1 month survival										
1	non-randomised studies Matsuyama, 2020[20]	serious[b]	not serious	serious[c,d]	not serious	none	31/304 (10.2%)	24/304 (7.9%)	**1.13** (0.67 to 1.93)	**10 more per 1,000** (from 27 fewer to 78 more)
Survival to Hospital Discharge										
1	non-randomised studies Amoako, 2023[21]	serious[b]	not serious	serious[c]	not serious	none	45/713 (6.3%)	36/713 (5.0%)	**1.38** (0.87 to 2.19)	**19 more per 1,000** (from 7 fewer to 64 more)
Pre-hospital ROSC										
2	non-randomised studies Matsuyama, 2020[20]; Amoako, 2023[21]	serious[b]	very serious[b]	serious[c]	not serious	none	157/1017 (15.4%)	97/1017 (9.5%)	**1.64** (1.26 to 2.13)	**63 more per 1,000** (from 28 more to 145 more)

CI: confidence interval; **RR:** risk ratio

a. Due to missing data

b. Difference in study population (age)

c. Not a direct comparison

d. The population is limited to children greater than 8 years old

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	While there are no direct undesirable anticipated effects that were reported in the included studies, the resources that may be needed for additional equipment, training and maintenance of skillsets of EMS personnel to enable the administration of adrenaline/epinephrine in paediatric out-of-hospital cardiac arrests may be substantial. These advanced interventions should be evaluated against other priorities of healthcare systems in committing significant resources to implement pre-hospital administration of adrenaline/epinephrine in paediatric cardiac arrest, especially in resource-limited settings. The 2 studies included for meta-analysis were from advanced EMS systems that could provide pre-hospital advanced paediatric life support.	There are some potential drawbacks in epinephrine administration in an out-of-hospital setting. A recent cohort study highlighted that among pediatric out-of-hospital cardiac arrest treated by emergency medical service in the United States, there was at least one severe adverse safety event (eg, failure to give an indicated medication,

		10-fold medication overdose) occurred in 610/1019 (60%) patients, and 310/1019 (30%) patients had 2 or more adverse events. The only factor associated with severe adverse safety events was young age. A randomized trial of epinephrine in out-of-hospital cardiac arrest in adults demonstrated that administration of epinephrine increased 30-day survival rates, although a larger proportion of patients in the epinephrine group were more significantly neurologically impaired.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Based on the 2 propensity-score matched studies included for meta-analysis, the use of epinephrine in the out-of-hospital setting did demonstrate an improved ROSC rate (Amoako 2023, Matsuyama 2020) and survival to hospital discharge in only 1 study (Amoako 2023). However, there were significant limitations in the studies. While both retrospective studies were propensity score matched and statistical adjustments were made to account for potential confounders in both studies, the cohorts that received epinephrine pre-hospital versus those who did not within the same EMS systems could still be inherently different.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or	There is no uncertainty or variability in using mortality (survival to hospital discharge) as a valued clinical outcome. However, patient-centered clinical outcomes such as long-term neurological function were not evaluated.	For existing systems that have EMS can provide advanced paediatric life support for paediatric out-of-hospital cardiac arrest, longitudinal evaluation of the outcomes of administration of adrenaline/epinephrine

variability ● No important uncertainty or variability		to improve patient-centred clinical outcomes such as long-term neurological outcomes are needed.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The evidence is supportive of the administration of epinephrine in paediatric out-of-hospital cardiac arrest to significantly improve ROSC rates and probably short-term mortality outcomes. In any healthcare system that has advanced EMS life support teams that are trained and have the necessary resources to administer epinephrine for paediatric cardiac arrest patients in the out-of-hospital setting, these would likely result in similar clinical outcomes. Future specific research will need to focus on the prospective evaluation of mature EMS systems that are already able to provide advanced life support to paediatric cardiac arrest patients in the pre-hospital setting to evaluate patient-centric clinical outcomes, especially long-term neurological outcomes, with the use of the administration of adrenaline/epinephrine.	Our task force reaffirms that in mature EMS systems that can provide advanced paediatric life support, the administration of epinephrine in paediatric out-of-hospital cardiac arrests is still recommended. The cost-effectiveness of healthcare systems committing significant resources to train and maintain skillsets in developing EMS systems or in resource-limited settings, so that EMS personnel may be able to obtain vascular access for the administration of epinephrine in the pre-hospital setting, is still unknown.

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	There is a paucity of studies looking at resources required to train, maintain skillsets, and provide the necessary equipment and drugs needed for EMS systems to administer epinephrine in paediatric out-of-hospital cardiac arrests. There are no studies looking at the health economic impact and benefits of EMS to be able to deliver vasopressors in paediatric out-of-hospital cardiac arrests in resource-rich healthcare systems, but also in resource-limited countries. However, the resources needed are likely to be substantial in developing EMS systems while probably not significant in mature EMS systems that currently provide advanced paediatric life support.	The advocacy to administer adrenaline/epinephrine in pediatric out-of-hospital cardiac arrests should consider additional trainin g and resources in different healthcare settings to provide these advanced life support measures.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	It is of note that these 2 propensity-score matched studies were from healthcare settings with advanced EMS systems. There were no studies identified that evaluated the resources required to train, maintain skillsets, and provide the necessary equipment and drugs needed for EMS systems to administer epinephrine in paediatric out-of-hospital cardiac arrests.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	There were no studies identified that evaluated the cost-effectiveness of EMS systems having EMS personnel sufficiently trained and resources allocated to enable the provision of advanced paediatric life support to administer epinephrine in the out-of-hospital setting versus not having one is unknown.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	There were no studies identified that looked directly at the health-economic impact and benefits of EMS to be able to deliver vasopressors in paediatric out-of-hospital cardiac arrests in all settings, including in resource-limited countries. Further studies should look not only at resource-rich healthcare institutions but also in healthcare institutions from resource-limited countries. When powered with more analyzable data, these should be stratified by resource availability e.g. Gross National Income or Sociodemographic Index status of the country.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes	The administration of epinephrine improved ROSC rates in advanced EMS systems that can or already provide advanced paediatric life support in paediatric out-of-hospital cardiac arrest.	

● Yes ○ Varies ○ Don't know	In developing EMS systems or healthcare settings with significant resource limitations, the feasibility of administrating epinephrine in paediatric out-of-hospital cardiac arrests is unknown due to a lack of studies on its cost-effectiveness.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In advanced EMS systems that can provide advanced paediatric life support for paediatric out-of-hospital cardiac arrests, the evidence suggests that administration of epinephrine improved outcomes of ROSC and survival to hospital discharge; favoring the intervention. In developing EMS systems or countries with significant resource limitations, the feasibility of administrating epinephrine in paediatric out-of-hospital cardiac arrests is unknown due to a lack of studies.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies

EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest the use of epinephrine in pediatric out-of-hospital cardiac arrest (weak recommendation, very low-certainty evidence).
We suggest the use of epinephrine in pediatric in-hospital cardiac arrest (Good Practice Statement).

Justification

While there is limited evidence in paediatric out-of-hospital cardiac arrest, administration of epinephrine did improve ROSC and survival to hospital discharge. While there was no data available for the IHCA setting, the Task Force considered that the OHCA data should be used as indirect evidence.
There is a paucity of studies looking at patient-centered clinical outcomes, such as long-term neurological outcomes. Administering epinephrine in paediatric out-of-hospital cardiac arrest would be justifiable in existing EMS systems that provide advanced paediatric life support.

There is a paucity of studies looking at resources required to train, maintain skillsets, and provide the necessary equipment for EMS systems to administer epinephrine in paediatric out-of-hospital cardiac arrests. Future studies should be undertaken to evaluate the ability of EMS systems to provide advanced care in paediatric out-of-hospital cardiac arrest, to better inform equity issues of such systems in both resource-rich healthcare but also in resource-limited countries.

Subgroup considerations

· Age-subgroups: infants, children and adolescents in out-of-hospital cardiac arrest
· Early versus Late epinephrine in shockable rhythms
· Non-shockable rhythms – asystole versus PEA (versus bradycardia)
· Resource high versus resource low settings (eg Low & middle income countries).
· Single-tiered versus Tiered EMS response (BLS/ALS) systems

Implementation considerations

· Resourcing
· Feasibility
· Cost-effectiveness
· Equity and Acceptability

Monitoring and evaluation

Evidence updates will be reviewed annually for the PICOST

Research priorities

· Future studies should include patient-centered outcomes such as long-term neurological outcomes.
· Further studies should address whether specific sub-populations might potentially benefit (or not) from the administration of epinephrine in the pre-hospital settings.
· Cost-effectiveness and feasibility of the provision of advanced paediatric life support in the pre-hospital settings to facilitate the administration of adrenaline/epinephrine, in paediatric out-of-hospital cardiac arrest while ensuring high-quality basic life support, should be explored in all healthcare settings, including in LMICs. The task force considers the biological plausibility and equipoise sufficient to justify pediatric trials comparing initial dosing of IM epinephrine to IV, IO, alternate routes (eg, intranasal), or no epinephrine (eg, in low-resource settings where intravascular access is unavailable)

REFERENCES

1. Amoako J, Komukai S, Izawa J, Callaway CW, Okubo M. Evaluation of Use of Epinephrine and Time to First Dose and Outcomes in Pediatric Patients With Out-of-Hospital Cardiac Arrest. JAMA Netw Open. 2023;6(3):e235187.
2. Matsuyama T, Komukai S, Izawa J, Gibo K, Okubo M, Kiyohara K, et al. Pre-Hospital Administration of Epinephrine in Pediatric Patients With Out-of-Hospital Cardiac Arrest. Journal of the American College of Cardiology. 2020;75(2):194–204.
3. Banerjee P, Ganti L, Stead TG, Vera AE, Vittone R, Pepe PE. Every one-minute delay in EMS on-scene resuscitation after out-of-hospital pediatric cardiac arrest lowers ROSC by 5. Resusc Plus. 2021;5:100062.
4. Dieckmann RA, Vardis R. High-dose epinephrine in pediatric out-of-hospital cardiopulmonary arrest. Pediatrics. 1995;95(6):901–13.
5. Rodriguez-Nunez A, Lopez-Herce J, Garcia C, Carrillo A, Dominguez P, Calvo C, et al. Effectiveness and long-term outcome of cardiopulmonary resuscitation in paediatric intensive care units in Spain. Resuscitation. 2006;71(3):301–9.

Temperature Control After Cardiac Arrest in Children: ATM at 32-34°C vs. ATM at 36-37.5°C (PLS 4210.03, part 1)

QUESTION

Should Active temperature management (ATM) 32-34°C vs. ATM 36-37.5°C be used for children post cardiac arrest?	
POPULATION:	Children post cardiac arrest
INTERVENTION:	Active temperature management (ATM) 32-34°C
COMPARISON:	ATM 36-37.5°C
MAIN OUTCOMES:	Favorable neurological outcome; Favorable neurological outcome (Bayesian); Health related quality of life; Survival; Survival (Bayesian)
SETTING:	paediatric critical care environment
PERSPECTIVE:	The perspectives include those of children and their families, clinicians, and healthcare systems. Families generally prioritize survival with good neurological outcome, but there is variability in values regarding acceptable outcomes, as highlighted by the P-COSCA initiative. Clinicians seek evidence-based strategies to improve outcomes after pediatric cardiac arrest, while healthcare systems must consider resource allocation, feasibility, and equity in access to advanced therapies.
BACKGROUND:	Cardiac arrest in children is a rare but devastating event, with a significant proportion of survivors experiencing severe neurological injury. Active temperature management (ATM) has been proposed as a neuroprotective strategy, based on evidence from preclinical models and neonatal hypoxic-ischemic injury. However, clinical trials in children have not demonstrated clear superiority of hypothermia over normothermia for survival or neurological outcomes. Both approaches require intensive care resources, and there is ongoing debate regarding optimal temperature targets, implementation strategies, and the impact on long-term outcomes.
CONFLICT OF INTERESTS:	The following intellectual conflicts of interest have been declared. B Scholefield, A Guerguerian and A Topjian were co-investigators on the THAPCA-IH trial. A Topjian, H Krishnan, and A-M Guerguerian are co-investigators/site PIs in the P-ICECAP study. B Scholefield, A Topjian, H Krishan and A-M Guerguerian will be excluded from study selection, data abstraction and risk of bias assessment. No members of the writing group have any financial conflicts of interest.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A significant number of pediatric cardiac arrest survivors are left with severe neurologic injury. Active targeted temperature management (ATM) (as part of post-cardiac arrest care), has been shown in pre-clinical models of pediatric cardiac	

	arrest and as part of care after neonatal hypoxic ischemic injury, to improve rates of survival and neurologic outcome by modifying post-cardiac arrest syndrome. Clinical interventions that improve pediatric outcomes from cardiac arrest would be viewed as important and desirable by society.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Improvement in the important outcome of favorable neurological outcome is a highly desired effect from the neuro-protective intervention. The systematic review identified two approaches to analysis of the THAPCA out of hospital cardiac arrest trial data. The original primary analysis using frequentist statistical analysis and a secondary Bayesian analytical approach. The Pediatric Life Support Task Force considered both types of analysis in addition to non-randomized controlled evidence in children. **Good neurobehavioral survival**: For the critical outcome of long-term good neurobehavioral survival (1 year), from 2 RCTs (Moler 2015 , Moler 2017), (1 out-of-hospital (OH) and 1 in-hospital cardiac arrest (IHCA) study) with 517 children who achieved return of circulation but remained comatose with a Glasgow Coma Scale Motor Score <5, showed no statistical benefit or harm of ATM 32-34°C compared to ATM 36-37.5°C (RR=1.05, 95% CI 0.80-1.39).	The SR examined both estimates of effect for the pooled analysis (OHCA and IHCA) and OHCA or IHCA alone. The TF also reviewed the new analysis since the previous systematic review, which included the Bayesian re-analysis of the THAPCA-OH study (Harhay 2023), and a study reporting on the Health-Related Quality of Life at a median of 3 years outcome in a mixed cohort of IHCA and OHCA patients (Magee 2022). For the critical outcome of long-term good neurobehavioral survival (1 year) using Bayesian analysis in the OHCA population only, the evidence of low certainty (downgraded for imprecision) from 1 Bayesian reanalysis of the THAPCA-OH RCT (Harhay 2022) showed a posterior median absolute benefit of 6.8% (95% Credible Interval: -1.9% to 15.4%) with a probability of any benefit of 94%. For the critical outcome of long-term survival (1 year) using Bayesian analysis in the OHCA population only, the evidence of low certainty (downgraded for imprecision) from 1 Bayesian reanalysis of the THAPCA-OH RCT (Harhay 2022) showed a posterior median absolute benefit of 6.8% (95% Credible Interval: -1.9% to 15.4%) with a probability of any benefit of 94%.

	For the critical outcome of intermediate-term good neurobehavioral survival (6 months), from 1 adjusted observational cohort study (Doherty 2009) with 79 children who achieved ROSC after OH or IHCA, showed no statistical benefit or harm of ATM <35°C compared to ATM 36-37.5°C or no ATM (aOR=0.50, 95% CI 0.11-2.22) **Survival:** For the critical outcome of long-term survival (1 year), from 2 RCTs (Moler 2015, Moler 2017), (1 OH and 1 IHCA study) with 614 children who achieved return of circulation but remained comatose with a Glasgow Coma Scale Motor Score <5, showed no statistical benefit or harm of ATM 32-34°C compared to ATM 36-37.5°C (RR=1.14, 95% CI 0.94-1.37) For the critical outcome of intermediate-term survival (6 months), from 1 adjusted observational cohort study (Doherty 2009) with 79 children who achieved ROSC after OH or IHCA showed no statistical benefit or harm of ATM <35°C compared to ATM 36-37.5°C or no ATM (aOR=0.50, 95% CI 0.11-2.22) For the critical outcome of short-term survival (30 days or hospital discharge), from 3 non-randomized observational cohort studies (Doherty 2009 , Fink 2010, Magee 2022) with 388 children who achieved ROSC showed no statistical benefit or harm of ATM 32-36°C compared to ATM 36-37.5°C or no ATM. Due to significant clinical	

	heterogeneity, these studies could not be pooled. **Health-Related Quality of Life:** For the important outcome of health-related quality of life (HRQoL), from 1 adjusted observational cohort study (Magee 2022) with 128 children after OH or IHCA showed improved HRQoL physical summary scores in the ATM 33°C group compared to the ATM 36°C group (MD=11.2 HRQoL score higher, 95% CI 3.1 higher to 19.3 higher).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		ATM of 32-34°C may result in increased duration of stay in ICU owing to later assessment of neurological prognosis. This could result in increased costs for uncertain benefit

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of effect was very low when assessed with GRADE. Summary of data is presented below. *See Appendix 1*	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly	The main outcome for children after cardiac arrest is survival with good neurological function, which is generally	

important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	considered highly important by families and clinicians. However, the P-COSCA (Pediatric Core Outcome Set for Cardiac Arrest) identified that stakeholders also value outcomes such as: Quality of life, Functional status, and Long-term neurodevelopment. There is considerable variability in values: Some families prioritize any survival, even with severe disability. Others consider survival without meaningful neurological recovery unacceptable. Cultural, social, and individual factors influence these preferences, creating uncertainty about how much weight different families place on neurological outcomes versus survival alone.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know	The point estimate for the two randomized controlled trial primary analysis did not identify a benefit of the intervention over the comparison for the clinically important outcomes. The Bayesian re-analysis of the THAPCA-OH study (Harhay 2023), and a study reporting on the Health-Related Quality of Life at a median of 3 years outcome in a mixed cohort of IHCA and OHCA patients (Magee 2022) were in favor of the intervention (temperature target 33C).	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	The cost of active temperature management was not assessed in the identified literature.	Delivery of active temperature management within the included studies required a high resource environment (e.g. ICU), invasive temperature monitoring and the use of servo-controlled external cooling devices. These would require significant resources to acquire, use and maintain.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	True cost of the intervention is unknown. No literature assessing cost was identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No studies examined the cost-effectiveness of the intervention compared to the comparison.	Both ATM 32-34°C and ATM 36-37.5°C require ICU-level care, continuous temperature monitoring, and trained staff. It is unknown if ATM 32-34°C increases nursing workload which would raise costs compared to ATM 36-37.5°C.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact	The impact on health equity was not identified in the literature.	Implementation of active temperature management after pediatric cardiac arrest may increase health inequities. Temperature Management protocols require specialized

○ Probably increased ○ Increased ○ Varies ● Don't know		equipment, trained personnel, and intensive monitoring, which are more available in high-resource settings. Hospitals in low-resource or rural areas may lack these capabilities, limiting access for certain populations. This could widen disparities in survival and neurological outcomes for children.

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No studies directly examined the acceptability of the intervention.	Active temperature management use after cardiac arrest in children has been described in numerous studies. However, recent studies also include a proportion of children after cardiac arrest not receiving active temperature management.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	ATM is in use in many institutions. This approach requires considerable investment in personnel, training and other resources. Feasible in larger centers with sufficient resources.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know

RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

We recommend using active temperature management* (ATM) for comatose infants and children following OHCA or IHCA (strong recommendation, low certainty evidence).
We recommend using ATM to prevent central temperatures >37.5°C (strong recommendation, low certainty evidence).
We suggest that ATM protocols follow one of the published THAPCA trial interventions: (a) ATM 32–34°C for 48 hours, followed by gradual rewarming and maintenance at 36–37.5°C until a total of 120 hours, or (b) ATM 36–37.5°C for 120 hours total, as current evidence does not show superiority of either temperature target and there is insufficient evidence to recommend alternative durations (weak recommendation, low certainty evidence).
*Active temperature management (ATM) is defined as intentionally controlling a patient's body temperature to a specific temperature target range using a standardized management protocol. This includes all cooling and warming methods, temperature maintenance duration, pharmacotherapy, and monitoring strategies to achieve and sustain the desired target temperature.

Justification

The recommendation for either active temperature management at 32–34°C (ATM hypothermia) or 36–37.5°C (ATM normothermia) in comatose infants and children after cardiac arrest is conditional and based on low certainty of evidence. The available randomized controlled trials (RCTs) and observational studies do not demonstrate a clear benefit or harm of hypothermia compared to normothermia for the critical outcomes of survival and favorable neurological outcome at one year. The primary frequentist analysis of RCTs showed no statistically significant difference, while a Bayesian re-analysis suggested a possible benefit for hypothermia, but with wide credible intervals and moderate certainty, limiting confidence in the result.

The PLS TF agreed that following IHCA, there is insufficient evidence to support or refute the use of induced hypothermia (ATM 32-34°C) compared with active temperature management at normothermia (ATM 36-37.5°C) (or an alternative temperature).
However, following OHCA, there is some evidence supporting the use of induced hypothermia (ATM 32-34°C for 48 hours) compared with active temperature management at normothermia (ATM 36-37.5°C) in comatose patients. However, the body of evidence remains insufficient to provide a separate treatment recommendation.
Health-related quality of life data is limited, with one non-randomized study suggesting improved physical summary scores in the hypothermia group, but the certainty of evidence is very low due to methodological limitations and confounding. Both interventions require ICU-level care, invasive temperature monitoring, and specialized equipment, resulting in significant resource requirements. The true cost and cost-effectiveness of hypothermia versus normothermia are unknown, as no studies directly addressed these outcomes.
Equity concerns are notable, as implementation of active temperature management protocols may increase disparities in access and outcomes between high-resource and low-resource settings. There is also important variability in how families and clinicians value outcomes, as highlighted by the P-COSCA statement, with some prioritizing survival regardless of neurological status and others emphasizing meaningful neurological recovery.
Given the lack of clear superiority of either approach, the balance of effects varies depending on the analytic method and outcome considered. The intervention is probably acceptable and feasible in well-resourced centers but may be challenging to implement universally. Therefore, a conditional recommendation for either hypothermia or normothermia is appropriate, allowing for individualized decision-making based on patient context, available resources, and family values

Subgroup considerations

Out-of-Hospital Cardiac Arrest (OHCA): Evidence from the THAPCA-OH trial and its Bayesian re-analysis suggests a possible benefit of induced hypothermia (32–34°C) compared to normothermia (36–37.5°C) for favorable neurological outcome and survival, although the certainty of evidence remains low and the credible intervals are wide. As such, while some support exists for hypothermia in OHCA, the data are insufficient to make a strong recommendation for one approach over the other.
In-Hospital Cardiac Arrest (IHCA): The THAPCA-IH randomized controlled trial found no significant difference between hypothermia and normothermia for the main outcomes of survival and favorable neurological outcome at one year. This suggests that, for IHCA, either temperature management strategy may be appropriate, or there is no evidence to support the superiority of hypothermia over normothermia.
Given these findings, recommendations should acknowledge that the evidence base and potential benefits may differ between OHCA and IHCA populations. Individualized decision-making is warranted, considering the setting of cardiac arrest, patient characteristics, and available resources.
Patient stratification: no studies were identified using a risk stratification approach to select patients to receive ATM 32–34°C or ATM 36–37.5°C . Future research into whether risk-stratification tools could determine whether children with moderate risk of hypoxic-ischemic encephalopathy (HIE), who may not be at the extremes of severity, could experience improved outcomes with either ATM therapy would be helpful.

Implementation considerations

Implementation of either ATM 32–34°C or ATM 36–37.5°C for children post cardiac arrest requires ICU-level care, invasive temperature monitoring, and trained staff, making it feasible primarily in well-resourced centers. Standardized protocols, ongoing staff education, and monitoring for complications are essential for safe and effective delivery. In resource-limited settings, strict normothermia may be a more practical alternative, and equity in access should be considered. Engaging families in shared decision-making and clearly communicating risks, benefits, and uncertainties are crucial, while institutions should monitor outcomes and participate in quality improvement to optimize care. TTM has been successfully implemented in many tertiary pediatric centers internationally

Monitoring and evaluation

Institutions implementing active temperature management (ATM) for children after cardiac arrest should routinely monitor key clinical outcomes, including survival rates, neurological function at discharge and follow-up, and health-related quality of life. Adverse events such as arrhythmias, infections, electrolyte disturbances, and complications related to temperature management should be tracked. Compliance with standardized temperature management protocols and timeliness of initiation should be evaluated. Data collection should support ongoing quality improvement. Participation in multicenter registries or collaborative research can enhance benchmarking and contribute to the evidence base.

Research priorities

- Conduct further high-quality randomized controlled trials comparing hypothermia (32–34°C) and normothermia (36–37.5°C) in children after cardiac arrest, focusing on long-term neurological outcomes and survival.
- Ascertain rate of cooling/rewarming and duration
- Evaluate health-related quality of life and functional outcomes using standardized measures, such as those recommended by the P-COSCA initiative.
- Assess cost-effectiveness and resource utilization for both temperature management strategies in diverse healthcare settings, including low-resource environments.
- Investigate implementation barriers and facilitators, especially in centers with limited access to specialized equipment or trained personnel.
- Perform subgroup analyses to distinguish effects in patients supported on ECLS or following ECPR.
- Encourage participation in multicenter registries and collaborative research to enhance data quality and generalizability.
- Future studies should focus on developing and validating risk stratification tools to guide individualized treatment decisions and optimize outcomes for these patients

References

1. Moler, F. W., Silverstein, F. S., Holubkov, R., Slomine, B. S., Christensen, J. R., Nadkarni, V. M., Meert, K. L., Browning, B., Pemberton, V. L., Page, K., Gildea, M. R., Scholefield, B. R., Shankaran, S., Hutchison, J. S., Berger, J. T., Ofori-Amanfo, G., Newth, C. J., Topjian, A., Bennett, K. S., Koch, J. D., Pham, N., Chanani, N. K., Pineda, J. A., Harrison, R., Dalton, H. J., Alten, J., Schleien, C. L., Goodman, D. M., Zimmerman, J. J., Bhalala, U. S., Schwarz, A. J., Porter, M. B., Shah, S., Fink, E. L., McQuillen, P., Wu, T., Skellett, S., Thomas, N. J., Nowak, J. E., Baines, P. B., Pappachan, J., Mathur, M., Lloyd, E., van der Jagt, E. W., Dobyns, E. L., Meyer, M. T., Sanders, R. C.,Jr., Clark, A. E., Dean, J. M., Investigators, Thapca Trial. Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children.N Engl J Med; Jan 26 2017.
2. Moler, Frank W., Silverstein, Faye S., Holubkov, Richard, Slomine, Beth S., Christensen, James R., Nadkarni, Vinay M., Meert, Kathleen L., Clark, Amy E., Browning, Brittan, Pemberton, Victoria L., Page, Kent, Shankaran, Seetha, Hutchison, Jamie S., Newth, Christopher J. L., Bennett, Kimberly S., Berger, John T., Topjian, Alexis, Pineda, Jose A., Koch, Joshua D., Schleien, Charles L., Dalton, Heidi J., Ofori-Amanfo, George, Goodman, Denise M., Fink, Ericka L., McQuillen, Patrick, Zimmerman, Jerry J., Thomas, Neal J., van der Jagt, Elise W., Porter, Melissa B., Meyer, Michael T., Harrison, Rick, Pham, Nga, Schwarz, Adam J., Nowak, Jeffrey E., Alten, Jeffrey, Wheeler, Derek S., Bhalala, Utpal S., Lidsky, Karen, Lloyd, Eric, Mathur, Mudit, Shah, Samir, Wu, Theodore, Theodorou, Andreas A., Sanders, Ronald C.,Jr., Dean, J. Michael. Therapeutic hypothermia after out-of-hospital cardiac arrest in children.The New England journal of medicine; 2015.

3. Harhay, Michael O., Blette, Bryan S., Granholm, Anders, Moler, Frank W., Zampieri, Fernando G., Goligher, Ewan C., Gardner, Monique M., Topjian, Alexis A., Yehya, Nadir. A Bayesian Interpretation of a Pediatric Cardiac Arrest Trial (THAPCA-OH).NEJM evidence; 2023.
4. Doherty, Dermot R., Parshuram, Christopher S., Gaboury, Isabelle, Hoskote, Aparna, Lacroix, Jacques, Tucci, Marisa, Joffe, Ari, Choong, Karen, Farrell, Rosemarie, Bohn, Desmond J., Hutchison, James S.. Hypothermia therapy after pediatric cardiac arrest.Circulation; 2009.
5. Magee, Aidan, Deschamps, Rachel, Delzoppo, Carmel, Pan, Kevin C., Butt, Warwick, Dagan, Misha, Forrest, Anri, Namachivayam, Siva P.. Temperature Management and Health-Related Quality of Life in Children 3 Years After Cardiac Arrest.Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies; 2022.
6. Fink, Ericka L., Kochanek, Patrick M., Clark, Robert S. B., Bell, Michael J.. How I cool children in neurocritical care.Neurocritical care; 2010.

APPENDICES

Appendix 1

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ATM 36-37C	Risk with ATM 32-34C				
Favorable neurological outcome 1-year RCT	Study population		**RR 1.05** (0.80 to 1.39)	517 (2 RCTs)[1,2]	⨁◯◯◯ Very low[a,b]	
	256 per 1,000	**269 per 1,000** (356 to 205)				
Favorable neurological outcome (Bayesian) (follow-up: median 12 months)	Posterior median absolute benefit: 6.8% (95% CrI: –1.9% to 15.4%) Probability of any benefit: 94%		-	(1 RCT)[3]	⨁⨁◯◯ Low[c,d]	
Non-Randomized, Favorable Neurological Outcome, Medium-term Outcome follow-up: 6 months	Study population		**OR 0.50** (0.11 to 2.22)	79 (1 non-randomised study)[4]	⨁◯◯◯ Very low[c,e,f,g,h]	
	580 per 1,000	**408 per 1,000** (754 to 132)				
Health related quality of life, non-randomized, - adjusted. Mean difference in HRQoL	The mean health related quality of life, non-randomized, - adjusted. Mean difference in HRQoL was **0** HRQoL score	MD **11.2 HRQoL score higher** (3.1 higher to 19.3 higher)	-	128 (1 non-randomized study)[5]	⨁◯◯◯ Very low[i,j]	
RCT, Survival, 1 year outcome	Study population		**RR 1.14** (0.94 to 1.37)	614 (2 RCTs)[1,2]	⨁◯◯◯ Very low[a,b]	
	380 per 1,000	**434 per 1,000** (521 to 358)				
Survival, RCT. (Bayesian) (follow-up: median 12 months)	Posterior median absolute benefit: 6.8% (95% CrI: –1.9% to 15.4%) Probability of any benefit: 94%		-	(1 RCT)[3]	⨁⨁◯◯ Low[c,d]	
Non-randomized, Survival, Short-term outcome	Study population		**OR 0.93** (0.40 to 2.12)	479 (3 non-randomized studies)[4,5,6]	⨁◯◯◯ Very low[b,e,f,k,l,m,n,o]	
	577 per 1,000	**559 per 1,000** (743 to 353)				
Non-Randomized, Survival, Medium-term Outcome (follow-up: 6 months) follow-up: 6 months	Study population		**OR 0.50** (0.11 to 2.22)	79 (1 non-randomized study)[4]	⨁◯◯◯ Very low[c,e,f,g,p]	
	620 per 1,000	**449 per 1,000** (784 to 152)				

a. One study population was OHCA and the other IHCA.
b. Reported risk ratio and confidence interval inconclusive.
c. Single study
d. Based on conventional sample size calculations for a clinically meaningful effect, the study is underpowered.
e. Doherty 2009- Severe confounding by indication: hypothermia group had significantly worse baseline characteristics (more infants, longer arrest duration, higher ECMO use, higher organ dysfunction scores)
f. Doherty 2009- Significant practice variation: 2 of 5 centers never used hypothermia
g. 94% in-hospital cardiac arrests, only 6% out-of-hospital 68-72% cardiac etiology (vs. typical OHCA with predominantly respiratory/asphyxial causes) 56-66% occurred within 14 days after surgery (mostly cardiac surgery) Predominantly post-surgical population not representative of general pediatric cardiac arrest patients
h. Adjusted OR for unfavorable outcome (PCPC 4-6): 2.00 (95% CI 0.45-9.01)
i. No randomization. Treatment at discretion of clinician. Propensity score matching attempted, but significant loss of patients in attempt to match.
j. Wide confidence intervals. Exclusion of several patients through propensity score matching (including most severe patient population)
k. Fink-2010 hypothermia patients had more unwitnessed arrests, more epinephrine doses, longer CPR duration
l. Fink 2010- No protocolized treatment allocation
m. Magee-2022- hypothermia group was younger, had longer CPR duration, higher lactate, lower pH, much higher ECMO use (72% vs. 22%)
n. Doherty 2009 adjusted OR: 2.50 (95% CI 0.55-11.49), P=0.238 (favoring normothermia, not significant) Fink 2010 adjusted OR for hypothermia mortality: 0.47, P=0.2 (favoring hypothermia, not significant) Magee 2022 adjusted OR: 1.30 (95% CI 0.57-2.98) (favoring normothermia, not significant)
o. Outcome timing varies across studies: Doherty: 30-day mortality Fink: Hospital discharge Magee: PICU mortality
p. adjusted mortality OR 1.99, 95% CI 0.45 to 8.85, P=0.502

Temperature Control After Cardiac Arrest in Children: any Active Temperature Management (ATM) vs no ATM (PLS 4210.03, part 2)

QUESTION

Should Comparison of Active Temperature Management (any temperature) vs. No Active Temperature Management be used for children after cardiac arrest?	
POPULATION:	Children after cardiac arrest
INTERVENTION:	Active Temperature Management (any temperature)
COMPARISON:	No Active Temperature Management
MAIN OUTCOMES:	Favorable neurological outcome, survival
SETTING:	paediatric critical care environment
PERSPECTIVE:	The perspectives include those of children and their families, clinicians, and healthcare systems. Families generally prioritize survival with good neurological outcome, but there is variability in values regarding acceptable outcomes, as highlighted by the P-COSCA initiative. Clinicians seek evidence-based strategies to improve outcomes after pediatric cardiac arrest, while healthcare systems must consider resource allocation, feasibility, and equity in access to advanced therapies.
BACKGROUND:	Cardiac arrest in children is a rare but devastating event, with a significant proportion of survivors experiencing severe neurological injury. Active temperature management (ATM) has been proposed as a neuroprotective strategy, based on evidence from preclinical models and neonatal hypoxic-ischemic injury. However, clinical trials in children have not demonstrated clear superiority of hypothermia over normothermia for survival or neurological outcomes. The use of ATM protocols also allows the avoidance of fever. Absence of an ATM protocol may therefore increase risk of secondary brain injury following cardiac arrest in children. ATM requires intensive care resources, and there is ongoing debate regarding optimal temperature targets, implementation strategies, and the impact on long-term outcomes.
CONFLICT OF INTERESTS:	The following intellectual conflicts of interest have been declared. B Scholefield, A Guerguerian and A Topjian were co-investigators on the THAPCA-IH trial. A Topjian, H Krishnan, and A-M Guerguerian are co-investigators/site PIs in the P-ICECAP study. B Scholefield, A Topjian, H Krishan and A-M Guerguerian will be excluded from study selection, data abstraction and risk of bias assessment. No members of the writing group have any financial conflicts of interest.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A significant number of pediatric cardiac arrest survivors are left with severe neurologic injury. Active targeted temperature management (ATM) (as part of post-cardiac arrest care), has been shown in pre-clinical models of pediatric cardiac arrest and as part of care after neonatal hypoxic ischemic injury, to	

	improve rates of survival and neurologic outcome by modifying post-cardiac arrest syndrome. Clinical interventions that improve pediatric outcomes from cardiac arrest would be viewed as important and desirable by society.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Three non-randomized observational studies were identified to address this question. (1)(2)(3) Two studies used data from the same registry (2)(3) and were not combined in pooled analysis where they reported the same outcome. All patients included in the three studies had OHCA. **Favorable Neurological Outcome:** For the critical outcome of short-term good neurobehavioral survival (at hospital discharge), from 2 adjusted observational cohort studies (1)(3) with 877 children who achieved ROSC showed statistical benefit of ATM (any temperature) compared to no active temperature management (OR=1.21, 95% CI 1.05-1.40; ARR=3.0%, or 30 more patients/1000, 95% CI 7 more to 56 more patients/1000). **Survival:** For the critical outcome of short-term survival (30 days or hospital discharge), from 2 adjusted observational cohort studies (1)(2) with 830 children who achieved ROSC showed no statistical benefit or harm of ATM (any temperature) compared to no active temperature management (OR=1.06, 95% CI 0.67-1.68; ARR=1.4%, or 14 more patients/1000, 95% CI 92 fewer to 129 more patients/1000).	Three non-randomized observational studies reported different ATM protocols. In Chang 2016 (1), the intervention group received mild therapeutic hypothermia (MTH) with a target temperature of 32–34°C, and the median achieved temperature was 33.0°C (IQR 32.6–33.6). The duration of hypothermia was at least 12 hours but was not strictly protocolized, and the total duration was not reported. The control group did not receive hypothermia, with a median temperature of 35.4°C (IQR 34.7–36.2), and no active temperature management was provided; duration details were not reported. Matsui 2022 (2) investigated targeted temperature management (TTM) with a target range of 33–36°C, but both the duration of intervention and the actual temperatures achieved were not reported. The control group received no active TTM, and temperature or duration details were also not reported. In Namba 2025 (3), the intervention consisted of TTM with a target temperature of 32–36°C, typically maintained for 24 hours, although the total duration was not specified. The control group did not receive active TTM, and temperature and duration details were not reported. Across all studies, the control groups received no active temperature management, with limited reporting on actual temperature and duration parameters.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Unknown. A concern of providing no ATM in patients after cardiac arrest, is the development of fever. This has been reported to be associated with worse neurobehavioral outcome followin g cardiac arrest and brain injury in children.	Across these three pediatric OHCA studies, adverse events were not systematically collected or reported (including rates of fever or temperature about 38C without ATM). Only Chang 2016 flags (in discussion) the general risk of unintended overcooling with certain cooling methods, but this was not quantified in their cohort. Consequently, the magnitude of undesirable effects for TTM vs control is uncertain based on these data.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Overall certainty of evidence was very low across both important clinical outcomes. *See Appendix 1*	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertaint y or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The main outcome for children after cardiac arrest is survival with good neurological function, which is generally considered highly important by families and clinicians. However, the P-COSCA (Pediatric Core Outcome Set for Cardiac Arrest) identified that stakeholders also value outcomes such as: Quality of life, Functional status, and Long-term neurodevelopment. There is considerable variability in values: Some families prioritize any survival, even with severe disability. Others consider survival without meaningful neurological recovery unacceptable. Cultural, social, and individual factors influence these preferences, creating uncertainty about how much weight different families place on neurological outcomes versus survival alone.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost of active temperature management was not assessed in the identified literature. However, in comparison to no active temperature management the task force assumed that moderate to large cost is required to deliver the intervention.	Delivery of active temperature management within the included studies required a high resource environment (e.g. ICU), invasive temperature monitoring and the use of servo-controlled external cooling devices. These would require significant resource to acquire, use and maintain. I t is possible that may lengthen ICU stay before neurological prognostication.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	True cost of the intervention is unknown. No literature assessing cost was identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No studies examined the cost-effectiveness of the intervention compared to the comparison.	ATM at any temperature requires ICU-level care, continuous temperature monitoring, and trained staff.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	The impact on health equity was not identified in the literature.	Implementation of active temperature management after pediatric cardiac arrest may increase health inequities. Temperature Management protocols require specialized equipment, trained personnel, and intensive monitoring, which are more available in high-resource settings. Hospitals in low-resource or rural areas may lack these capabilities, limiting access for certain populations. This could widen disparities in survival and neurological outcomes for children.

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No studies directly examined the acceptability of the intervention.	Active temperature management use after cardiac arrest in children has been described in numerous studies. However, the included studies also identify a proportion of children after cardiac arrest not receiving active temperature management.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	ATM is in use in many institutions. This approach requires considerable investment in personnel, training and other resources. Feasible in larger centers with sufficient resources.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We recommend using active temperature management* (ATM) for comatose infants and children following OHCA or IHCA (strong recommendation, low certainty evidence).
We recommend using ATM to prevent central temperatures >37.5°C (strong recommendation, low certainty evidence).

Related recommendation(s)

1. Should Active temperature management (ATM) 32-34°C vs. ATM 36-37.5°C be used for children post cardiac arrest?

We suggest that ATM protocols follow one of the published THAPCA trial interventions: (a) ATM 32–34°C for 48 hours, followed by gradual rewarming and maintenance at 36–37.5°C until a total of 120 hours, or (b) ATM 36–37.5°C for 120 hours total, as current evidence does not show superiority of either temperature target and there is insufficient evidence to recommend alternative durations (weak recommendation, low certainty evidence).

*Active temperature management (ATM) is defined as intentionally controlling a patient's body temperature to a specific temperature target range using a standardized management protocol. This includes all cooling and warming methods, temperature maintenance duration, pharmacotherapy, and monitoring strategies to achieve and sustain the desired target temperature.

Justification

The recommendation to use active temperature management (ATM) for children after cardiac arrest is based on very low certainty evidence from three non-randomized observational studies, all in out-of-hospital cardiac arrest (OHCA) populations. These studies suggest a moderate benefit for favorable neurological outcome (OR 1.21, 95% CI 1.05–1.40), but no significant effect on short-term survival (OR 1.06, 95% CI 0.67–1.68). The magnitude of undesirable effects, including fever, arrhythmias, bleeding, and accidental overcooling, is unknown, as adverse events were not systematically reported. The risk of fever in the absence of ATM is a concern, given its association with worse neurological outcomes, but rates were not reported. Implementation of ATM requires moderate to large resources, including ICU-level care, invasive monitoring, and specialized equipment, which may limit feasibility and equity in resource-limited settings. There is variability in values and preferences among families and clinicians, but survival with good neurological outcome is generally prioritized. Overall, the balance of effects probably favors the intervention, but the recommendation remains weak due to low certainty of evidence and resource considerations.
This recommendation is made in tandem with the other EtD table: Should Active temperature management (ATM) 32-34°C vs. ATM 36-37.5°C be used for children post cardiac arrest?

Subgroup considerations

No subgroup analysis was performed. All patients in the studies evaluated or ATM (any temperature) versus no ATM included children following OHCA only.

Implementation considerations

Active temperature management protocols require standardized procedures, trained ICU staff, and access to continuous temperature monitoring and cooling devices. Institutions should ensure clear documentation of temperature targets, duration, and management of complications. Resource limitations may affect feasibility, especially in smaller or less-resourced centers. Equity should be considered, as access to ATM may be limited in rural or low-resource settings. Ongoing staff education and protocol review are recommended to optimize delivery and safety

Monitoring and evaluation

Institutions should monitor key outcomes including survival, neurological status at discharge, and adverse events such as fever, arrhythmias, bleeding, and accidental overcooling. Compliance with ATM protocols, timeliness of initiation, and duration of therapy should be tracked. Data collection should support continuous quality improvement, and regular review of outcomes should inform protocol adjustments. Where possible, participation in multicenter registries or collaborative research is encouraged to enhance benchmarking and contribute to the evidence base.

Research priorities

- Systematically assess adverse events, including fever rates, arrhythmias, bleeding, and accidental overcooling, in both intervention and control groups.
- Evaluate cost-effectiveness and resource utilization for ATM in diverse healthcare settings.
- Explore family and clinician perspectives on acceptable outcomes and treatment choices.
- Develop and validate risk stratification tools to identify subgroups who may benefit most from ATM.
- Encourage participation in multicenter registries and collaborative research to improve data quality and generalizability

REFERENCES SUMMARY

1. Chang, Ikwan, Kwak, Young Ho, Shin, Sang Do, Ro, Young Sun, Lee, Eui Jung, Ahn, Ki Ok, Kim, Do Kyun. Therapeutic hypothermia and outcomes in paediatric out-of-hospital cardiac arrest: A nationwide observational study.Resuscitation; 2016.
2. Matsui, Satoshi, Hirayama, Atsushi, Kitamura, Tetsuhisa, Sobue, Tomotaka, Hayashi, Takuro, Takei, Hirokazu, Tanizawa, Naoko, Ohnishi, Yasuhiro, Kuratani, Saori, Sameshima, Tomohiro, Yoshino, Go, Kurosawa, Hiroshi, Tanaka, Ryojiro. Target Temperature Management and Survival with Favorable Neurological Outcome After Out-of-Hospital Cardiac Arrest in Children: A Nationwide Multicenter Prospective Study in Japan.Therapeutic hypothermia and temperature management; 2022.
3. Namba, Takeshi, Nishikimi, Mitsuaki, Emoto, Ryo, Kikutani, Kazuya, Ohshimo, Shinichiro, Matsui, Shigeyuki, Shime, Nobuaki. Effect Size of Targeted Temperature Management in Pediatric Patients with Post-Cardiac Arrest Syndrome According to the Severity.Life (Basel, Switzerland); 2024.

APPENDICES

Appendix 1

Outcomes	Anticipated absolute effects[·] (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with No Active Temperature Management	Risk with Comparison of Active Temperature Management (any temperature)				
Favorable neurological outcome, non-randomized, adjusted, short term outcome.	Study population		**OR 1.21** (1.05 to 1.40)	877 (2 non-randomized studies)[1,2]	⨁◯◯◯ Very low[a,b,c,d,e,f]	
	182 per 1,000	**212 per 1,000** (238 to 189)				
Survival, non-randomized, adjusted, short-term outcome	Study population		**OR 1.06** (0.67 to 1.68)	830 (2 non-randomized studies)[1,3]	⨁◯◯◯ Very low[a,b,g,h,i]	
	406 per 1,000	**420 per 1,000** (534 to 314)				

a. Chang 2016- Hypothermia group had higher proportion of shockable rhythms (23.5% vs. 7.6%, P<0.01)
b. Chang 2016- 13 patients with unknown neurological status excluded
c. Namba 2024- Significant baseline differences between TTM and no-TTM groups: Different primary causes of arrest (P=0.01) Different initial rhythms (26.4% VF/VT in TTM vs. 5.6% in no-TTM, P<0.001) TTM group had shorter time to ROSC (34 vs. 40 minutes, P=0.008) Higher ECMO use in TTM group (17.6% vs. 5.1%, P<0.001)
d. Namba 2024- TTM decision based on clinician judgment, potentially influenced by perceived prognosis
e. Used propensity score only for first to fourth quintiles
f. Chang 2016: Adjusted OR 1.22 (95% CI 0.59-2.51) Namba 2024:adjusted OR (first to fourth quintiles only): 1.21 (95% CI 1.04-1.40), P=0.014

g. Mastsui 2022- Confounding by indication: Significant baseline differences between TTM and non-TTM groups Different first documented rhythms (shockable rhythm higher in TTM group: 51.1% vs. 10.0%) TTM group more likely to have cardiac cause (46.8% vs. 25.8%) Higher ECLS use in TTM group (25.5% vs. 6.7%)
h. Chang 2016: Adjusted OR 1.05 (95% CI 0.59-1.88), P not significant
i. Matsui 2022: IPTW OR 1.07 (95% CI 0.50-2.31), not significant

Temperature Control After Cardiac Arrest in Children: temperature duration (PLS 4120.03, part 1)

QUESTION

Should Active temperature management (ATM) for one duration (e.g. 24 hrs.) vs. ATM for another duration (e.g. 72 hrs.) be used for children after cardiac arrest?	
POPULATION:	Children after cardiac arrest
INTERVENTION:	Active temperature management (ATM) for one duration (e.g. 24 hrs.)
COMPARISON:	ATM for another duration (e.g. 72 hrs.)
MAIN OUTCOMES:	Favorable neurological outcome, survival
SETTING:	paediatric critical care environment
PERSPECTIVE:	The perspectives include those of children and their families, clinicians, and healthcare systems. Families generally prioritize survival with good neurological outcome, but there is variability in values regarding acceptable outcomes, as highlighted by the P-COSCA initiative. Clinicians seek evidence-based strategies to improve outcomes after pediatric cardiac arrest, while healthcare systems must consider resource allocation, feasibility, and equity in access to advanced therapies.
BACKGROUND:	Cardiac arrest in children is a rare but devastating event, with a significant proportion of survivors experiencing severe neurological injury. Active temperature management (ATM) has been proposed as a neuroprotective strategy, based on evidence from preclinical models and neonatal hypoxic-ischemic injury. However, clinical trials in children have not demonstrated clear superiority of hypothermia over normothermia for survival or neurological outcomes. Both approaches require intensive care resources, and there is ongoing debate regarding optimal temperature targets, implementation strategies, and the impact on long-term outcomes.
CONFLICT OF INTERESTS:	The following intellectual conflicts of interest have been declared. B Scholefield, A Guerguerian and A Topjian were co-investigators on the THAPCA-IH trial. A Topjian, H Krishnan, and A-M Guerguerian are co-investigators/site PIs in the P-ICECAP study. B Scholefield, A Topjian, H Krishan and A-M Guerguerian will be excluded from study selection, data abstraction and risk of bias assessment. No members of the writing group have any financial conflicts of interest

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A significant number of pediatric cardiac arrest survivors are left with severe neurologic injury. Active targeted temperature management (ATM) (as part of post-cardiac arrest care), has been shown in pre-clinical models of pediatric cardiac arrest and as part of care after neonatal hypoxic	

	ischemic injury, to improve rates of survival and neurologic outcome by modifying post-cardiac arrest syndrome. Clinical interventions that improve pediatric outcomes from cardiac arrest would be viewed as important and desirable by society.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	One pilot RCT was identified to address this question. **Favorable Neurological Outcome:** For the critical outcome of short-term good neurobehavioral survival (at hospital discharge), from 1 RCT (Fink 2017) with 34 children showed no statistical benefit or harm of 24 hours ATM 33°C compared to 72 hours ATM 33°C (RR=0.86, 95% CI 0.36-2.02; ARR= -5.8%, or 58 fewer patients/1000, 95% CI 264 fewer to 420 more patients/1000). **Survival:** For the critical outcome of short-term survival (at hospital discharge), from 1 RCT (Fink 2017) with 34 children showed no statistical benefit or harm of 24 hours ATM 33°C compared to 72 hours ATM 33°C (RR=0.69, 95% CI 0.41-1.16; ARR= -23.7%, or 237 fewer patients/1000, 95% CI 451 fewer to 122 more patients/1000).	One pilot RCT was identified to address this question. An ongoing multi-center RCT, The Pediatric Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients (P-ICECAP) trial (https://www.clinicaltrials.gov/study/NCT05376267) was also identified, but no results have been reported. The taskforce noted the two THAPCA trials (1, 2) used protocolized time-based therapy in both intervention and comparison arms (ATM 32-34C: 48 hours at target temperature, gradual rewarming and maintenance at 36-37.5C until 120 hours total duration of ATM, verses ATM 36-37.5C for 120 hours total duration). A systematic review with a network meta-analysis was also identified (3); however, the task force did not feel the comparison groups of normothermia equated to zero hours of therapy. Therefore, the task force did not use the studies comparing ATM 32-34C for a set duration with a comparison group of ATM 36-37.5C or no temperature control.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		A prolonged period of ATM therapy may increase risk of adverse effects or side effects of the therapy.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	*See Appendix 1*	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The main outcome for children after cardiac arrest is survival with good neurological function, which is generally considered highly important by families and clinicians. However, the P-COSCA (Pediatric Core Outcome Set for Cardiac Arrest) identified that stakeholders also value outcomes such as: Quality of life, Functional status, and Long-term neurodevelopment. There is considerable variability in values: Some families prioritize any survival, even with severe disability. Others consider survival without meaningful neurological recovery unacceptable. Cultural, social, and individual factors influence these preferences, creating uncertainty about how much weight different families place on neurological outcomes versus survival alone.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The point estimate for the one randomized controlled trial primary analysis did not identify a benefit of the intervention over the comparison for the clinically important outcomes.	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	The cost of active temperature management was not assessed in the identified literature.	Delivery of active temperature management within the included study required a high resource environment (e.g. ICU), invasive temperature monitoring and the use of servo-controlled external cooling devices. These would require significant resources to acquire, use and maintain. Increased duration of ATM therapy may be associated with increased cost related to ICU length of stay.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	True cost of the intervention is unknown. No literature assessing cost was identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No studies examined the cost-effectiveness of the intervention compared to the comparison.	Both ATM 32-34°C for 24 hours and ATM 32-34°C for 72 hours require ICU-level care, continuous temperature monitoring, and trained staff. It is unknown if ATM 32-34°C for 72 hours increases nursing workload which would raise costs compared to 24 hours.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	The impact on health equity was not identified in the literature.	Implementation of active temperature management after pediatric cardiac arrest may increase health inequities. Temperature Management protocols require specialized equipment, trained personnel, and intensive monitoring, which are more available in high-resource settings. Hospitals in low-resource or rural areas may lack these capabilities, limiting access for certain populations. This could widen disparities in survival and neurological

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	No studies directly examined the acceptability of the intervention.	Active temperature management use after cardiac arrest in children has been described in numerous studies. However, recent studies also include a proportion of children after cardiac arrest not receiving active temperature management.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	ATM is in use in many institutions. This approach requires considerable investment in personnel, training and other resources. Feasible in larger centers with sufficient resources.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

We suggest that ATM protocols follow one of the published THAPCA trial interventions: (a) ATM 32–34°C for 48 hours, followed by gradual rewarming and maintenance at 36–37.5°C until a total of 120 hours, or (b) ATM 36–

37.5°C for 120 hours total, as current evidence does not show superiority of either temperature target and there is insufficient evidence to recommend alternative durations (weak recommendation, low certainty evidence).

Related recommendation(s)

1. Should Active temperature management (ATM) 32-34°C vs. ATM 36-37.5°C be used for children post cardiac arrest?

We recommend using active temperature management* (ATM) for comatose infants and children following OHCA or IHCA (strong recommendation, low certainty evidence).

We recommend using ATM to prevent central temperatures >37.5°C (strong recommendation, low certainty evidence).

*Active temperature management (ATM) is defined as intentionally controlling a patient's body temperature to a specific temperature target range using a standardized management protocol.

Justification

The recommendation regarding the optimal duration of active temperature management (ATM) for children after cardiac arrest is based on very limited evidence. Only one small pilot randomized controlled trial directly compared 24 hours versus 72 hours of hypothermia and found no statistically significant difference in short-term survival or favorable neurological outcome between the two durations. (4) The certainty of evidence is very low due to the small sample size, methodological limitations, and wide confidence intervals. No studies have assessed longer-term outcomes, cost-effectiveness, or acceptability of different durations. Both approaches require significant ICU resources, and longer durations may increase costs and risk of adverse effects, but these have not been systematically studied. Given the lack of clear benefit or harm and the absence of robust comparative data, there is insufficient evidence to recommend a duration of ATM different from the protocols used in the THAPCA-OH and THAPCA-IH trials. (1, 2) Further research is needed to determine if specific durations confer greater benefit or risk.

Subgroup considerations

No subgroups were considered.

Implementation considerations

Implementation of active temperature management for varying durations requires standardized protocols, trained ICU staff, and access to invasive temperature monitoring and servo-controlled cooling devices. Centers should ensure clear documentation of the chosen duration, monitor for complications, and provide ongoing education for clinical teams. Resource limitations may affect the feasibility of longer durations, and institutions should consider local capacity when selecting protocols.

Monitoring and evaluation

Institutions should routinely monitor clinical outcomes such as survival, neurological status at discharge, and adverse events (e.g., infections, electrolyte disturbances, arrhythmias) associated with different ATM durations. Compliance with protocol, timeliness of initiation, and duration of therapy should be tracked. Data collection should support continuous quality improvement and inform future protocol adjustments.

Research priorities

- Conduct adequately powered randomized controlled trials comparing different durations of ATM in children after cardiac arrest, focusing on both short- and long-term neurological outcomes and survival.
- Assess the impact of ATM duration on adverse events, ICU length of stay, and resource utilization.
- Evaluate cost-effectiveness and feasibility of various ATM durations in diverse healthcare settings.
- Explore family and clinician perspectives on acceptable durations and outcomes.

- Develop and validate risk stratification tools to identify subgroups who may benefit from specific ATM durations.
- Evaluate effect of duration of ATM in specific subgroups (OHCA, IHCA and those requiring ECLS/ECPR).

REFERENCES

1. Moler, F. W., Silverstein, F. S., Holubkov, R., Slomine, B. S., Christensen, J. R., Nadkarni, V. M., Meert, K. L., Browning, B., Pemberton, V. L., Page, K., Gildea, M. R., Scholefield, B. R., Shankaran, S., Hutchison, J. S., Berger, J. T., Ofori-Amanfo, G., Newth, C. J., Topjian, A., Bennett, K. S., Koch, J. D., Pham, N., Chanani, N. K., Pineda, J. A., Harrison, R., Dalton, H. J., Alten, J., Schleien, C. L., Goodman, D. M., Zimmerman, J. J., Bhalala, U. S., Schwarz, A. J., Porter, M. B., Shah, S., Fink, E. L., McQuillen, P., Wu, T., Skellett, S., Thomas, N. J., Nowak, J. E., Baines, P. B., Pappachan, J., Mathur, M., Lloyd, E., van der Jagt, E. W., Dobyns, E. L., Meyer, M. T., Sanders, R. C.,Jr., Clark, A. E., Dean, J. M., Investigators, Thapca Trial. Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children.N Engl J Med; Jan 26 2017.

2. Moler, Frank W., Silverstein, Faye S., Holubkov, Richard, Slomine, Beth S., Christensen, James R., Nadkarni, Vinay M., Meert, Kathleen L., Clark, Amy E., Browning, Brittan, Pemberton, Victoria L., Page, Kent, Shankaran, Seetha, Hutchison, Jamie S., Newth, Christopher J. L., Bennett, Kimberly S., Berger, John T., Topjian, Alexis, Pineda, Jose A., Koch, Joshua D., Schleien, Charles L., Dalton, Heidi J., Ofori-Amanfo, George, Goodman, Denise M., Fink, Ericka L., McQuillen, Patrick, Zimmerman, Jerry J., Thomas, Neal J., van der Jagt, Elise W., Porter, Melissa B., Meyer, Michael T., Harrison, Rick, Pham, Nga, Schwarz, Adam J., Nowak, Jeffrey E., Alten, Jeffrey, Wheeler, Derek S., Bhalala, Utpal S., Lidsky, Karen, Lloyd, Eric, Mathur, Mudit, Shah, Samir, Wu, Theodore, Theodorou, Andreas A., Sanders, Ronald C.,Jr., Dean, J. Michael. Therapeutic hypothermia after out-of-hospital cardiac arrest in children.The New England journal of medicine; 2015.

3. Amagasa, Shunsuke, Yasuda, Hideto, Oishi, Takatoshi, Kodama, Sota, Kashiura, Masahiro, Moriya, Takashi. Target Temperature Management Following Pediatric Cardiac Arrest: A Systematic .Cureus; 2022.

4. Fink, Ericka L., Clark, Robert S. B., Berger, Rachel P., Fabio, Anthony, Angus, Derek C., Watson, R. Scott, Gianakas, John J., Panigrahy, Ashok, Callaway, Clifton W., Bell, Michael J., Kochanek, Patrick M.. 24 vs. 72 hours of hypothermia for pediatric cardiac arrest: A pilot, randomized controlled trial.Resuscitation; 2018.

APPENDICES

Appendix 1

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ATM for another duration (e.g. 72 hrs.)	Risk with ATM for one duration (e.g. 24 hrs.)				
Favorable neurological outcome. RCT. Short term outcome	Study population		**RR 0.86** (0.36 to 2.02)	34 (1 RCT)[4]	⨁◯◯◯ Very low[a,b,c,d,e]	
	412 per 1,000	**354 per 1,000** (832 to 148)				
Survival RCT. Short term outcome 24H vs 72H	Study population		**RR 0.69** (0.41 to 1.16)	34 (1 RCT)[4]	⨁◯◯◯ Very low[a,b,c,d,f]	
	765 per 1,000	**528 per 1,000** (887 to 314)				

a. very small sample size, pilot study
b. Hypothermia was initiated for clinical reasons prior to the consent process and randomization, this raises concerns about true randomization and selection bias
c. Two children in the 72-hour group did not receive the entire assigned treatment: one was rewarmed after 43 hours and progressed to brain death, another had supportive care withdrawn without rewarming during the treatment period These deviations were not clearly accounted for in the analysis
d. Single study
e. Wide confidence intervals 0.36-2.02
f. Wide confidence interval 0.41-1.16