QUESTION

Should Targeted temperature management (TTM) with a target temperature of 32-36℃ vs. No TTM or TTM at an alternative target temperature range be used for Post Pediatric Cardiac Arrest?	
POPULATION:	Infants and Children after Cardiac Arrest
INTERVENTION:	Targeted temperature management (TTM) with a target temperature of 32-36C
COMPARISON:	No TTM or TTM at an alternative target temperature range
MAIN OUTCOMES:	Primary Outcomes: · Good neurobehavioral survival (GBS) long-term Secondary Outcomes: · GBS short-term and intermediate-term · Neurobehavioral score change from pre-arrest, intermediate-term and long-term · Survival short-term, intermediate-term, and long-term
SETTING:	Out of Hospital or In Hospital Setting
PERSPECTIVE:	THE LAST PUBLISHED COSTR (2015) ONLY REFERRED TO THE RANDOMISED CONTROLLED TRIAL OF TTM FOR COMATOSE PATIENTS FOLLOWING OHCA. THIS REVIEW SOUGHT TO EVALUATE NEW EVIDENCE REGARDING TTM FOR IHCA.
BACKGROUND:	Since the publication of the ILCOR COSTR in 2015, there have been additional studies that are important to consider in widening the evidence base for the PICOST, particularly for the in-hospital target population.
CONFLICT OF INTERESTS:	Dr Anne-Marie g, Barney, Professor Vinay Nadkarni – involved in the THAPCA trials

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. Targeted temperature management (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	**Good neurobehavioral survival at 1 year:** RR=1.15 95% CI 0.69-1.93; I2=61%) for TTM 32-34°C compared to TTM 36-37.5°C. **Good neurobehavioral survival at 6 months:** aOR=0.50 (95% CI 0.11-2.22; I2=N/A) for TTM <35C compared to no TTM. **Good neurobehavioral survival at hospital discharge**: aOR=1.22 (95% CI 0.59-2.51; I2=N/A) for TTM 32-34°C compared to no TTM **Survival at 1 year:** RR=1.14 (95% CI 0.93-1.39; I2=9%) for TTM 32-34°C compared to TTM 36-37.5°C. **Survival at 6 months:** aOR=0.50 (95% CI 0.11-2.22; I2=N/A) for TTM <35°C compared to no TTM	The effects of avoiding fever during post arrest care may be substantial.

	Survival (to hospital discharge: RR=1.14 (95% CI 0.96-1.36; I2=18%) for TTM 32-34°C compared to TTM 36-37.5°C **Survival at 30 days or hospital discharge:** aOR=1.08 (95% CI 0.53-2.17; I2=34%) for TTM 32-36°C compared to TTM 36-37.5°C or no TTM. There was insufficient information available to provide specific information on neurobehavioral score change, health-related quality of life (HRQoL) scores or HRQoL score change. **Subgroup Location of Cardiac Arrest** **Out-of-Hospital Cardiac Arrest (OHCA)** **Good neurobehavioral survival at 1 year:** RR=1.59 (95% CI 0.89-2.85; I2=N/A) for TTM 32-34°C compared to TTM 36-37.5°C **Good neurobehavioral survival at 6 months:** RR=10.92 (95% CI 1.43-83.50; I2=N/A) for TTM 32-34°C compared to TTM 36-37.5°C **Good neurobehavioral survival at 6 months**: RR=1.19 (95% CI 0.76-1.84; I2=N/A) for TTM 32-34°C compared to TTM 36-37.5 or no TTM **Survival at 1 year:** RR=1.32 (95% CI 0.94-1.84; I2=N/A) for TTM 32-34°C compared to TTM 36-37.5°C **Survival at 6 months:** RR=2.18 (95% CI 1.15-4.13; I2=N/A) for TTM 32-34°C compared to TTM 36-37.5°C **Survival at hospital discharge:** RR=1.30 95% (CI 0.97-1.76; I2=N/A) for TTM 32-34°C compared to TTM 36-37.5°C **Survival at 30 days or hospital discharge):** the evidence from **3 unadjusted observational cohort studies** could not be pooled, but **two of the individual studies showed no statistical benefit or harm and the third showed statistical benefit** of TTM 32-34°C compared to TTM 36-37.5°C or no TTM RR = 0.93 (95% CI 0.68-1.28) **In-Hospital Cardiac Arrest (IHCA)** **Good neurobehavioral survival at 1 year:** RR=0.93 (95% CI 0.68-1.28; I2=N/A) for TTM 32-34°C compared to TTM 36-37.5°C **Good neurobehavioral survival at 3-6 months:** RR=0.54 95% CI 0.30-0.97; I2=N/A) for TTM 32-36°C compared to TTM 36-37.5°C or no TTM **Survival at 1 year:** RR=1.06 (95% CI 0.84-1.33; I2=N/A) for TTM 32-34°C compared to TTM 36-37.5°C **Survival at 3-6 months**: RR=0.50 95% CI 0.28-0.90; I2=N/A) for TTM 32-36C compared to TTM 36-37.5°C or no TTM **Survival at hospital discharge**: RR=1.08 (95% CI 0.91-1.28; I2=N/A) for TTM 32-34°C compared to TTM 36-37.5°C **Survival at 30 days or hospital discharge:** the evidence from **3 unadjusted observational cohort studies** could not be pooled, but **none of the individual studies showed a statistical benefit or harm** of TTM 32-34°C compared to TTM 36-37.5°C or no TTM **Subgroup Presumed Etiology of Cardiac Arrest**	

	Presumed Cardiac Cause of Arrest Survival: **Survival at 1 year:** evidence from **2 unadjusted observational studies** could **not be pooled** due to significant clinical heterogeneity, but the individual studies showed **no statistical benefit or harm** of TTM 32-34°C compared to TTM 36-37.5°C **Presumed Asphyxial Cause of Arrest** **Good neurobehavioral survival at 6 months:** RR=10.92 (95% CI 1.43-83.50; I2=N/A) for TTM 32-34°Ccompared to TTM 36-37.5°C or no TTM **Good neurobehavioral survival at hospital discharge):** RR= 1.77 (95% CI 10.93-3.4) for TTM 32-34°C compared to TTM 36-37.5°C **Survival at 6 months:** RR=2.18 (95% CI 1.15-4.13; I2=N/A) for TTM 32-34°C compared to TTM 36-37.5°C **Survival** at 30 days or hospital discharge: evidence from **3 unadjusted observational studies** could not be pooled, but **two of the individual studies showed no statistical benefit or harm and the third showed statistical benefit** of TTM 32-34°C compared to TTM 36-37.5°C, RR 1.95 (95% CI 1.1-3.45) **Presumed Drowning Cause of Arrest** **Good neurobehavioral survival at 1 year:** RR=1.76 (95% CI 0.64-4.84; I2=N/A) for TTM 32-34°C compared to TTM 36-37.5°C **Survival at 1 year:** RR=1.15 95% CI 0.67-1.99; I2=N/A) for TTM 32-34°C compared to TTM 36-37.5°C **Survival** to hospital discharge: RR=1.04 95% CI 0.66-1.66; I2=N/A) for TTM 32-34°C compared to TTM 36-37.5°C **Subgroup Extracorporeal Membrane Oxygenation (ECMO)** **Good neurobehavioral survival at 1 year:** RR = 0.8 (95% CI 0.48-1.32) **Survival to hospital discharge:** RR1.19 (95% CI 0.82-1.73)	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		TTM 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 certainty of evidence for all outcomes was very low, with the exception of: · Good neurobehavioral outcome at 1 year: for the pooled results of the 2 (IHCA and OHCA) RCTs: low certainty · Good neurobehavioral outcome at 1 year for OHCA survivors: moderate certainty · Survival at 1 year for OHCA survivors: moderate certainty · Survival to hospital discharge for OHCA survivors: moderate certainty · Good neurobehavioral outcome at 1 year for IHCA survivors: moderate certainty · Survival at 1 year for IHCA survivors: moderate certainty · Survival to hospital discharge for IHCA survivors: moderate certainty · Good neurobehavioral outcome at 1 year for presumed drowning as cause of arrest survivors: moderate certainty · Survival at 1 year for presumed drowning as cause of arrest survivors: moderate certainty · Survival to hospital discharge for presumed drowning as cause of arrest survivors: moderate certainty	1. The two RCTs were conducted by the same research group and designed to have the same methodology except for the 2 different settings (in-hospital cardiac arrest and out-of-hospital cardiac arrest). The inclusion and exclusion criteria were extensive and included those patients who achieved return of circulation but remained comatose with Glasgow Coma Scale Motor Score of < 5, as well as being mechanically ventilated, CPR >2mins, over 48hrs old and admitted to PICU . These studies fail to clarify whether there is benefit to either approach of TTM for patients that do not meet these inclusion criteria. 2. The observational studies (mostly retrospective cohort studies), had varying methods as evidenced by different inclusions and exclusions, different comparison groups (some were actively maintained normothermia TTM (preventing fever) and others had no TTM), different length of TTM, and different definitions for some of the harm outcomes. 3. None of the high certainty data addresses whether the other components of post ROC bundle of care (e.g. BP targets, ventilation/ oxygenation targets) were targeted as part of the study protocols. Neither RCT trial allowed patients to be treated with TTM temperature >34.0°C, 35°C or <36.0°C. Therefore, we have no RCT evidence with ANY patients in this temperature range. None of the 5 adult RCT used anything other than 33 or 32-34°C targets for the hypothermia group, so there is no indirect adult evidence using these temperatures. On these grounds, there would be concern about a treatment recommendation where the temperatures >34/35/<36.0°C are given as an option as this temperature range has not explicitly been tested for its efficacy or safety. (Of note: From a clinical perspective this temperature range is the most difficult to control with external cooling as patients have the strongest shivering response between 34-36°C. When <34°C, the shivering response is supressed so when it is easier to control).

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	Main outcome is survival, and being neurologically intact survival. No published evidence regarding this intervention for quality of life in survivors, and in general the population varies in how much they value survival (at all costs) vs neurologically-intact survival. Unlikely that people would perceive neurologically intact outcome from enhanced post-ROC care as not being important. Prolonged ICU length of stay stemming from TTM (delayed withdrawal of life sustaining therapy) hopefully offset by greater clarity surrounding prognostication as well as improved family-centered care'. This will stem from either option of TTM care.	There are many components within the TTM bundle of care for comatose children post cardiac arrest and ROSC. Further research is required on the effect of individual elements of these protocols.

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		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The clinicians' concern surrounding post-ROC cooling and potential undesirable side effects should have been reduced by the absence of negative effects of cooling noted in either THAPCA trial. Unfortunately, the publication of the 2 (negative) THAPCA trials has led to some practitioners believing that TTM (either normothermia or hypothermia treatment arm) is not effective and unnecessary, inadvertently allowing for post-ROC pyrexia in some patients.	Cooling post-ROC does entail a post-ROC period before prognostication can be performed accurately. This may lead to challenges with longer ICU length of stay, and associated costs to families, and timely access to ICU resources if they are at all limited

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		TTM is in use in many institutions. This approach requires considerable investment in personnel, training and other resources. Feasible in larger centres 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
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 using TTM 32-34°C or TTM 36-37.5°C for pediatric patients (> 24 hours to 18 years of age) who achieve ROSC after OHCA and remain comatose (weak recommendation, very low certainty of evidence).

We suggest using TTM 32-34°C or TTM 36-37.5°C for pediatric patients (> 24 hours to 18 years of age) who achieve ROSC after IHCA and remain comatose (weak recommendation, very low certainty of evidence).

Justification

The causes, pathophysiology and outcomes for pediatric cardiac arrests are significantly different to cardiac arrests in adults and in newborns. The PLS TF places a higher value on pediatric study data and believes that it is not appropriate to extrapolate from studies in other age groups given that 2 pediatric RCTs have now been published.
The available pediatric data includes2 controlled trials of comatose survivors of cardiac arrest. Both of these studies used a comparison of TTM 32-34°C vs TTM 36-37.5°C. Temperature was measured centrally. The THAPCA randomized trials compared a duration of TTM 32-34°C for 2 days followed by TTM of 36-37.5°C for 3 days with a TTM of 36-37.5°C for 5 days. Because these trials did not evaluate the effects of other durations of TTM, the Task Force agreed that a recommendation regarding the duration of TTM would be too speculative at this point. The reader is referred to the original publications for details of the protocol.
All of the other pediatric studies included in this review were observational cohort studies which used a variety of TTM temperature range definitions. The TF believes that it is appropriate to base our recommendations on the protocols described in the 2 controlled studies given the variability and uncertainty in approaches described in the cohort studies.
Avoiding and aggressively treating fever is an important part of post resuscitation care. Targeted temperature management protocols may reduce the risk of fever. Active targeted temperature management protocols may also include multiple interventions other than temperature monitoring which could influence neurological outcomes.
This CoSTR compared different temperature ranges, but not techniques of temperature control, rewarming or other aspects of post resuscitation care. As a result, there are no recommendation on these aspects of TTM which may nonetheless have important effects.

The actual temperature applied in the trials was used/studied (e.g. 32-34°C or 36-37.5°C) rather than the 32-36°C temperature interval as this 4-degree spread was not applied in the intervention studies. It is an interval from the Doherty study (multicenter retrospective chart extraction).

The authors of the SR chose not to pool the estimate of the observational studies (that were highly heterogeneous) that collectively span this interval. It would be of concern if patients were treated with a wide 32-36°C range, as usually a 2 degree span is considered feasible (and studied in animals and humans).

Subgroup considerations

The subgroup of children who were managed with ECMO require special consideration. Although some patients in several of the studies underwent ECMO, outcome data was only available from 2 studies. The THAPCA IHCA RCT (non-randomized co-intervention, Moler 2017, 318) reported a statistically significant reduced long-term GBS (at 1 year) for TTM at 32-34°C compared to TTM at 36-37.5°C (RR: 0.51; 95% CI: 0.32-0.81, I2= N/A, n=133). In one observational cohort study (Torres Andres 2018, 451), all patients received ECMO; they reported no statistical benefit in short-term survival.

Implementation considerations

TTM requires investment in personnel, training and other resources. It may not be feasible in low resource settings. TTM has been successfully implemented in many tertiary pediatric centres internationally.

Monitoring and evaluation

Methods of Temperature measurement is not standardized nor emphasized. CORE temperature monitoring is believed to be very important to avoid temperatures above the normal range.

Research priorities

- None of the high certainty data address whether there may be benefit to TTM to T of between 34-36°C, the rate of cooling/ rewarming, and the duration of hypothermia or TTM.
- The impact of treatment by location of arrest and the cause of arrest.
- This PICOST included comparators with both active normothermia TTM (the 2 RCTs and 2 of the observational studies) and no documentation of active TTM. Active management of normothermia is inherently different than permissive fever and should be studied.
- No information available about the effectiveness of TTM on health-related quality of life or cost-effectiveness.
- The role of TTM in children on ECMO post cardiac arrest.

Systematic Review: *Buick J, Wallner C, Aickin R, Meaney P, de Caen A, Maconochie IK, Skifars M, Welsford M et al. on behalf of the International Liaison Committee on Resuscitation Pediatric Life Support Task Force. Pediatric targeted temperature management post cardiac arrest: a systematic review with meta-analysis. Journal TBA. Accepted TBA.*