PLS 2025 Appendix A – Evidence to Decision Tables

Starting CPR CAB vs. ABC (PLS 4070.02)

QUESTION

Should CPR commence with compressions (30:2) or ventilations (2:30)?	
PROBLEM:	Adults and children in any setting (in-hospital or out-of-hospital) with cardiac arrest
OPTION:	Commencing CPR with compressions first (30:2)
COMPARISON:	Commencing CPR with ventilation first (2:30)
MAIN OUTCOMES:	*Critical*: Survival with favorable neurological outcome at hospital discharge or 30-days, Survival at hospital discharge or 30 days, Survival with favourable neurological outcome to one-year, Survival to one-year, Event survival, Any ROSC. *Important*: Time to commencement of rescue breaths, Time to commencement of first compression, Time to completion of first CPR cycle, Ventilation rate, Compression rate, Chest compression fraction, Minute ventilation
SETTING:	In-hospital or out-of-hospital
PERSPECTIVE:	Traditionally, cardiopulmonary resuscitation (CPR) commenced with opening the airway and ventilations then, chest compressions (i.e. A-B-C). However, airway and breathing are technical skills and previous systematic reviews by the International Liaison Committee on Resuscitation (ILCOR) have found that starting CPR with compressions in simulation studies resulted in faster times to key elements of resuscitation (rescue breaths, chest compressions, completion of first CPR cycle).
BACKGROUND:	CPR compression—ventilation sequences CAB versus ABC represents a compromise between the need to generate blood flow and the need to supply oxygen to the lungs
CONFLICT OF INTERESTS:	No conflicts to declare

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Since the 2020 ILCOR review of this PICOST,[1, 2] there is ongoing debate in the scientific literature regarding the merits of commencing resuscitation with chest compressions prior to ventilations. Internationally, most adult BLS guidelines commence chest compressions prior to ventilations; however, there is variability in pediatrics and aquatic rescue with different approaches in various jurisdictions.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Delivering high-quality chest compressions as early as possible is vital to high-quality CPR and optimizes the chance of ROSC and survival after cardiac arrest. However, patients who suffer cardiac arrest from respiratory or asphyxia causes (eg. children, drowning) will benefit from additional ventilatory support.	Indirect evidence from before-and-after OHCA registry studies in adults, which examined changes in dispatcher telephone CPR instructions[3] and the implementation of guideline changes[4, 5], suggests that switching from the A-B-C to C-A-B approach was associated with increased rates of bystander CPR[3] and improved patient outcomes.[3],[4, 5] Similar data on in-hospital cardiac arrest show conflicting evidence in patient outcomes.[6, 7] One large registry study from Japan demonstrated increased bystander CPR rates in children with bystander-witnessed OHCAs after compression-only CPR was introduced.[8] Whether the change in sequence to CAB by some ILCOR member councils has resulted in more infants and children receiving compression-only CPR overall is unknown, although available data continues to support the combination of compressions and breaths is needed for optimal pediatric CPR.[9, 10]

		ROSC and survival to hospital discharge. Coronary perfusion pressure is generated by effective chest compressions and is cumulative, therefore when chest compressions stop, it falls to near zero. Early effective chest compressions are vital to establishing and maintaining coronary perfusion pressure. [11] Time to first compression is associated with better patient outcomes, including good neurological outcomes in adults.[12]

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Starting CPR with compressions first results in faster times to key elements of resuscitation, such as time to commencement of chest compressions, time to start and complete the first cycle of compressions, and a higher chest compression fraction. One simulated study in pediatric resuscitation found starting with compressions delayed time to commencement of rescue breaths in cardiac arrest, but the differences was of questionable clinical significance.	Opening the airway and delivery of ventilations is technical, and bystanders, especially if untrained or minimally trained, are typically unable to deliver effective ventilations during simulated CPR.[13] Further evidence suggests that delivering the A-B-C approach has more errors in CPR[14]; and that lay-bystanders prefer C-A-B, and it is easier to learn and retain[14]. The delivery of non-mouth-to-mouth ventilation requires the retrieval and preparation of equipment (e.g. bag-valve-mask, pocket mask), which, when multiple rescuers are present, can occur during chest compressions.

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	This systematic review did not identify any human studies, but identified 5 manikin studies; 1 randomized study [15] focused on adult resuscitation, 2 randomized studies focused on pediatric resuscitation, [16, 17]and 2 observational studies focused on adult resuscitation [18, 19].	

Outcome	Relative importance	Certainty of the evidence (GRADE)
Time to commencement of chest compressions – RCTs and non RCTs	IMPORTANT	⊕◯◯◯ VERY LOW
Time to commencement of rescue breaths – RCTs	IMPORTANT	⊕◯◯◯ VERY LOW
Time to completion of first CPR cycle - RCT	IMPORTANT	⊕◯◯◯ VERY LOW
Ventilation rate -RCT	IMPORTANT	⊕◯◯◯ VERY LOW
Compression rate -RCT and non RCTs	IMPORTANT	⊕◯◯◯ VERY LOW
Chest compression fraction (CCF) - RCT and non RCTs	IMPORTANT	⊕◯◯◯ VERY LOW
Minute alveolar ventilation in the first minute of resuscitation	IMPORTANT	⊕◯◯◯ VERY LOW
Time to diagnosis of need for resuscitation (unresponsive, respiratory arrest, cardiac arrest) - RCT	IMPORTANT	⊕◯◯◯ 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	There is no data on critical patient 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	Mankin studies show minimal differences in times to key resuscitation elements, but most favour commencing with compressions.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	No relevant published data was identified that answers this question. In many jurisdictions, CAB is already in place in adult and paedatric BLS so resource requirements are small. In jurisdictions where ABC is used, there are a number of resources required to implement CAB in preference to ABC including investments required to train rescuers, reconfiguration of CPR feedback devices and AEDs, and production of educational materials.	
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	No relevant published data was identified for review so unable to provide any certainty here.	
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 relevant published data was identified that answers this question	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased	No relevant published data was identified that answers this question.	

○ Increased ○ Varies ● Don't know		

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE – CHECK CURRENT FLOW CHARTS**	**ADDITIONAL CONSIDERATIONS**
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	In Europe, the current pediatric guidelines recommend an ABC approach in preference to CAB. In other parts of the world (eg AHA and ANZCOR) the approach of CAB in preference to ABC is in place. Therefore recommendations of one approach in preference to another may have significant impact on education and approach to resuscitation training. In adults a CAB approach in preference to ABC has been in place. In children, there is international variability so a recommendation of CAB in preference to ABC may create some debate.	Due to the public's concerns with mouth-to-mouth ventilations,[20] commencing CPR with airway and ventilations may result in no bystander CPR being provided.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	In adults, many BLS guidelines recommend CAB in preference to ABC thus the intervention (CAB) presents no significant deviation from current practices. In children, feasibility will be more problematic given the degree of international variation in BLS guidelines.	

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

CONCLUSIONS

Recommendation

The following treatment recommendations are for children.
Recommendations for adults are posted separately. https://costr.ilcor.org/document/starting-cpr-abc-vs-cab-bls-2201-tf-sr

There is insufficient evidence to support a treatment recommendation regarding the optimal order of commencing CPR in children (ie ventilation or compressions first).

The task force considers that both an A-B-C (ventilation followed by compression) and a C-A-B (compression followed by ventilation) approach are acceptable and that both ventilation and chest compressions are important components of CPR in children (good practice statement).

Justification

The majority of the existing evidence (5 manikin studies) [17, 21-24] suggests that starting CPR with compressions results in faster times to key elements of resuscitation.

One simulated study in pediatric resuscitation found that starting with compressions delayed the commencement of rescue breaths in cardiac arrest by six seconds.[24] This delay may be clinically acceptable. However, alveolar minute ventilation and the number of ventilations delivered in the first minute of resuscitation were higher with the A-B-C (delivering 5 rescue breaths before commencing chest compressions) sequence.

Indirect evidence from before-and-after OHCA registry studies in adults, examining changes in dispatcher telephone CPR instructions[3] and implementation of guideline changes[4, 5], suggests that switching from the A-B-C to C-A-B approach was associated with increased rates of bystander CPR[3] and improved patient outcomes.[3-5] Similar data on in-hospital cardiac arrest show conflicting evidence in patient outcomes.[6, 7] One large registry study from Japan demonstrated increased bystander CPR rates in children with bystander-witnessed OHCA after compression-only CPR was introduced.[8] Whether the change in sequence to C-A-B by some ILCOR member councils has resulted in more infants and children receiving compression-only CPR overall is unknown, although available data continues to support the combination of compressions and breaths is needed for optimal pediatric CPR.[9, 10]

While important uncertainties regarding timing and delays in initiation of the components of CPR (chest compressions, opening airway, and rescue breaths) remain and may not be readily extrapolated from manikin studies, the BLS and PLS task forces also considered:

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Energy Doses for Pediatric Defibrillation During Resuscitation (PLS 4080.12)

QUESTION

Energy doses for pediatric defibrillation during resuscitation	
POPULATION:	Infants and children (excluding newborn children) who are in ventricular fibrillation or pulseless ventricular tachycardia during out-of-hospital or in-hospital cardiac arrest
INTERVENTION:	Initial defibrillation dose approximating 2J/kg (1.5-2.5 J/kg)
COMPARISON:	Compared with initial defibrillation dose of >2.5J/kg, <1.5J/kg or any other specified dose
MAIN OUTCOMES:	Any clinical outcome including but not limited to: ▪ survival to hospital discharge with good neurologic outcome ▪ survival to hospital discharge ▪ survival to hospital admission ▪ return of circulation (ROC) The PLS TF prefers outcomes defined in the P-COSCA publication[1]
SETTING:	in cardiac arrest

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Shockable ventricular arrhythmias (VF, pVT) are less frequently recorded in pediatric cardiac arrest but are associated with a higher survival rate than non-shockable rhythms (asystole, PEA). Early defibrillation is the foundation of treatment but optimal energy doses for initial and subsequent shocks remain controversial. Differences remain in the first shock dose recommended by ILCOR member councils, with the ERC and ANZCOR recommending 4J/kg for the first and all subsequent shocks and the AHA recommending an initial dose of 2-4 J/kg (for ease of teaching, a dose of 2 J/kg is used in algorithms and training materials). For refractory VF, the AHA guidelines recommend increasing the defibrillation dose to 4 J/kg, suggesting that subsequent energy doses should be at least 4 J/kg and noting that higher levels may be considered, not to exceed 10 J/kg. Current ILCOR treatment recommendations[2] suggest the routine use of an initial dose of 2 to 4 J/kg of monophasic or biphasic defibrillation waveforms for infants or children in VF or pVT cardiac arrest. They recognized that there was insufficient evidence from which to base a recommendation for second and subsequent defibrillation dosages.	A systematic review[3] failed to show a significant benefit of one dosing regimen over another but was hampered by small sample sizes and study heterogeneity. The more recent large pediatric in-hospital registry study[4] provided support for a 2 J/kg dose for initial defibrillation but did not provide guidance for subsequent doses. The current systematic review aims to review all available evidence that may support or change the current recommendations.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Overall, based on current evidence the systematic review results suggest with very low certainty (downgraded for imprecision and risk of bias) that neither defibrillation doses <2 J/kg nor defibrillation doses >2 J/kg are superior to defibrillation doses approximating 2 J/kg for treatment of shockable rhythms in cardiac arrest in children for the critically important outcomes of survival to hospital discharge (SHD) and return of spontaneous circulation (ROSC) and the important outcome of termination of the shockable rhythm (VF or pVT). Very low certainty data from 4 cohort studies, involving 266 patients showed no significant difference to ROSC associated with defibrillation dose <2 J/kg compared to that approximating 2 J/kg (51 more survivors per 1,000 resuscitations; CI 95%: 42 fewer to 152 more). Very low certainty data from 2 cohort studies involving 225 patients also showed no	

	significant difference to SHD associated with defibrillation dose <2 J/kg compared to that approximating 2 J/kg (29 more survivors per 1,000 resuscitations; CI 95%: 96 fewer to 192 more). Additional very low certainty evidence from two observational studies of 265 children found no significant effect on termination of VF/pVT associated with defibrillation dose <2 J/kg compared to that approximating 2 J/kg (179 fewer per 1,000; CI 95%: 415 fewer to 888 more). Very low certainty data from 6 cohort studies, involving 596 patients showed no significant difference to ROSC associated with defibrillation dose >2 J/kg compared to that approximating 2 J/kg (29 fewer survivors per 1,000 resuscitations; CI 95%: 133 fewer to 98 more). Very low certainty data from 2 cohort studies involving 225 patients also showed no significant difference to SHD associated with defibrillation dose >2 J/kg compared to that approximating 2 J/kg (82 more survivors per 1,000 resuscitations; CI 95%: 253 fewer to 1000 more). Additional very low certainty evidence from two observational studies of 265 children found no significant effect on termination of VF/pVT associated with defibrillation dose >2 J/kg compared to that approximating 2 J/kg (22 fewer per 1,000; CI 95%: 99 fewer to 77 more).	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Specific undesirable effects (outside of the lack of ROSC/SHD) were not consistently reported in the studies identified eg. myocardial damage. None of these outcomes were proposed *a priori* as important or critical by the PLS Task Force.	
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	Seven studies[4-10] were included in the systematic review. None of these provided clinical trial data. The 7 identified studies were all cohort studies and provided very low certainty evidence (downgraded for imprecision and risk of bias) for the comparisons with the important and critical outcomes described.	The task force also recognised that most of the studies were conducted in sites where either 2 J/kg or 4 J/kg doses were recommended for initial defibrillation. The variability of dosing was largely attributable to the limited number of energy dose settings on defibrillators. So, although no specific energy dose was found superior, energy selections would generally have been approximating either 2 or 4 J/kg.
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 ILCOR P-COSCA initiative developed a core outcome set specific for pediatric cardiac arrest studies. The design and methods of the initiative included use of a Delphi process to develop consensus on a core domain set.[1] Survival to hospital discharge (SHD), a P-COSCA outcome, and return of spontaneous circulation (ROSC) were chosen as critical outcomes for this review and are highly valued. Termination of the shockable rhythm (VF/pVT) was considered an important measurable outcome. We have not identified any studies that specifically addressed how patients valued the different 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	Acknowledging the very low level of certainty, the current available data suggest that the critical (SHD, ROSC) and important (termination of VF/pVT) outcomes are not significantly better or worse when initial defibrillation doses of <2 J/kg or >2 J/kg are used for children in cardiac arrest with a shockable rhythm (VF or pVT) compared with initial doses approximating 2 J/kg.	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	While no studies evaluated this specifically (including cost effectiveness) there should be no difference in resources/costs involved in delivering different defibrillation doses.	

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	No studies regarding resource requirements were included in this systematic review.	

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	Cost effectiveness data was not identified in this systematic review.	

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		Defibrillation interventions are currently offered in hospitals and in EMS systems with ALS capability. This varies by country and region and may not be readily available in all areas in the developing world. Paediatric defibrillation requires a moderate investment in equipment and a significant investment in training, skills maintenance, and quality control programs to be successful. While defibrillation is supported in essentially all hospital settings in the developed world, advanced life (ALS) support-capable emergency medical services agencies and IHCA teams will need to maintain this capability as well.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	The systematic review search strategy used did not identify any studies that addressed how patients or clinicians valued different outcomes.	Essentially all hospital resuscitation teams and all ALS-based emergency medical services (EMS) systems already provide defibrillation. Guidelines for pediatric defibrillation dosing vary between different resuscitation councils around the world with some recommending an initial dose of 2J/kg and others recommending 4 J/kg. It is likely that local guidance will stay in place unless there is clear evidence to change.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		A change in recommended initial dosing for pediatric defibrillation would be readily implementable.

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

In the absence of evidence to demonstrate a clear preference for any particular energy dose, we suggest the use of an initial defibrillation dose of 2 to 4 J/kg for infants or children in VF or pVT cardiac arrest [weak recommendation, very low certainty evidence].
This review did not investigate the evidence for second and subsequent defibrillation dosages.

Justification

There is currently no supporting evidence that any particular defibrillation dose for initial management of VF/pVT in pediatric cardiac arrest improves ROSC or survival to hospital discharge.

Subgroup considerations

The benefit or harm associated with different defibrillation dosing strategies in paediatric resuscitation may differ across settings. Importantly, the available data do not inform the questions of whether better outcomes might be achieved by different energy dosing strategies in in-hospital compared to out-of-hospital arrest settings, for primary of secondary shockable rhythms or when monophasic or biphasic defibrillator waveforms are used. When AEDs are utilized in pediatric arrest it is more likely that higher defibrillation doses (J/kg) will be used.

Implementation considerations

It is likely that a change in recommended defibrillation dosing would be acceptable to key stakeholders.

Monitoring and evaluation

See below

Research priorities

Shockable ventricular arrhythmias (VF, pVT) are less frequently recorded in pediatric cardiac arrest compared to adult populations. Prehospital and in-hospital studies, ideally comparing existing different dosing strategies with planned subgroup analyses based on patient age and type of shockable rhythm (primary vs secondary) are ethical, necessary, and critically important to help guide clinicians in making these complex decisions. As different resuscitation councils recommend either 2 or 4 J/kg as an initial defibrillation dose, this may provide an opportunity for an international comparative study.

Further examination of the potential adverse effects of higher defibrillation doses when fixed energy doses are provided (AEDs) would also be helpful.

Future studies would benefit from including outcome measures consistent with the P-COSCA recommendations.

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Pads Size and Placement (PLS 4080.17)

Part 1: PAD PLACEMENT

QUESTION

Should different pad orientation (i.e. AP) vs. standard position (AL) be used for children with cardiac arrest and a shockable rhythm at any time during cardiopulmonary resuscitation (CPR)?	
POPULATION:	children with cardiac arrest and a shockable rhythm at any time during cardiopulmonary resuscitation (CPR)
INTERVENTION:	different pad orientation (i.e. AP)
COMPARISON:	standard position (AL)
MAIN OUTCOMES:	Survival to hospital discharge with good neurological outcome; Return of spontaneous circulation; Return of spontaneous circulation; Survival to hospital discharge with good neurological outcome; Survival to hospital discharge; Survival to hospital discharge; VF termination;

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Survival from sudden cardiac arrest is low. Patients who present in an shockable rhythm have a higher rate of good outcome. Approximately 20% of VF adult patients, however, will remain in VF despite standard resuscitation interventions. In addition, transthoracic impedance (TTI) may vary based on pad size and orientation and this may have an impact on shock success. Different pad orientations may also result in a higher voltage gradient in different area of the myocardium from where fibrillation may start/restart.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Improvement in ROSC, long term survival, and neurologic outcome are desirable. However, there are no studies in patients at early-stage VF/pulseless VT directly comparing the effects of different pad positions on defibrillation success, ROSC and long term survival. Indeed, the recent trial from Cheskes, 2022, compared vector change vs. standard pad position, i.e. AP vs. AL position, only in refractory VF patients. Most studies evaluates cardioversion (eg, AF) or secondary endpoints (eg, TTI). There are no studies in children that compare pads different orientation and placement.	In 2022 the topic related to the pads position has been challenged by a cluster-randomized trial with crossover (Cheskes, 2022, 1947) evaluating, among new defibrillation strategies, the vector-change (VC) defibrillation to the anterior-posterior (AP) position, compared with the standard (anterior-lateral (AL)) defibrillation in adult patients with refractory ventricular fibrillation (VF) during out-of-hospital cardiac arrest (OHCA). Refractory VF was defined as an initial presenting rhythm of VF or pulseless ventricular tachycardia (VT) that was still present after three consecutive standard defibrillations. A total of 136 patients were assigned to receive standard defibrillation while 144 received VC defibrillation. Survival to hospital discharge was more common in the VC group than in the standard group (21.7% vs. 13.3%; RR, 1.71; 95% CI, 1.01 to 2.88). No difference in good neurological outcome (RR 1.48 [95% CI, 0.81 to 2.71]) nor in ROSC (RR 1.39 [95% CI, 0.97–1.99]) was reported between VC vs. standard defibrillation. Termination of VF occurred 79.9% of VC defibrillations compared to 67.6% of standard ones (RR 1.18 [95% CI, 1.03 to 1.36]).

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Available evidence is inconclusive.	

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 randomized trial from Cheskes, 2022, compared vector change vs. standard pad position only in refractory VF patients. This is the first showing a benefit from VC compared with SD for VF termination and survival to discharge and only a possible benefit for ROSC and survival with favorable neurologic outcome (not statistically significant). There are no other studies in patients on early-stage VF/pulseless VT directly comparing the effects of various pad positions on patient outcome. There are no studies in pediatric populations.	

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		

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 evidence in favour the intervention or the comparison for the initial treatment of shockable cardiac arrest. However, if we consider the condition of refractory VF, although the certainty of evidence is very low, the existing evidence suggests a beneficial effect with VC compared with standard AL pad position in VF termination and survival with good neurological outcome.	AP positioning in easier to stablish in children.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	If beneficial, stakeholders will likely accept the intervention.	

Feasibility
Is the inervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

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
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

Recommendations for both pad placement and size (see part 2 below) are included here

For Manufacturers

Manufacturers could consider the standardization of pads size for infants, children, and adults (good practice statement).

Manufacturers of AEDs should standardize pad placement in an anteroposterior position for infants and young children (with 1 pad anteriorly, over the left precordium, and the other pad posteriorly to the heart just inferior to the left scapula) (good practice statement).

Manufacturers should include instructions to ensure adequate contact between the pad and the skin and ensure that their pad position diagrams clearly indicate the ILCOR-recommended pad position (good practice statement).

For CPR Providers Using an AED

Follow the AED specific guidance and instructions for pads placement in infants and children (good practice statement).

For CPR Providers Trained in Manual Defibrillation

In infants and children, place pads in an anterior-posterior position (good practice statement).

Vector Change Strategy

We cannot make a recommendation for or against the use of vector change strategy for the treatment of refractory VF or pulseless VT in infants and children.

Justification

In making these recommendations, the PLS Task Force considered the following:

- Pulseless shockable rhythms are more common in adults than in children and vary according to the age. The low frequency of these rhythms contributes to the lack of information on pediatric defibrillation. We do not know the incidence of refractory shockable rhythms in children.
- Transthoracic impedance varies based on pad size and position, and this may impact shock success. Different pad orientations/positions may also result in a higher voltage gradient in different areas of the myocardium from where fibrillation may start/restart.
- The four studies included were all adults studies and at serious risk of bias, and only one was a RCT (Cheskes, 2022, 1947).
- No studies directly compare the effects of different pad placement on patient outcomes outside of refractory shockable rhythms in adults.
- A secondary analysis of the DOSE VF trial (Cheskes, 2024, 110186), which explored the relationship between alternative defibrillation strategies employed and the type of VF, i.e. shock-refractory VF or recurrent VF, on patient outcomes, showed that vector-change defibrillation compared to standard pads placement, was not superior for VF termination, ROSC, or survival for shock-refractory VF; for recurrent VF, vector-change defibrillation was superior to standard pads placement only for VF termination, but not for ROSC or survival.
- There are no studies examining defibrillation pad orientation for IHCA. However, this evidence could be applied to the IHCA, with additional downgrading for indirectness.
- Paddles may still be in use in some low-resource settings. However, the Task Force acknowledges that the anterior-posteriorposition is not feasible with paddles and that paddle sizes are those standard as provided by the manufacturer. The Task Force did not foresee future development in the use of paddles.
- In pediatric resuscitation, pads are also used as real-time feedback devices for quality assessment of chest compressions. For chest compression metric measurement pads are generally needed to be positioned in AP.
- Anterio-posterior positioning of pads is easier in children than in adults.
- AEDs have pictoral representation to guide providers in correct pad positioning. Most AEDs for pediatric patients depict AP positioning. However, there is a wide variation in this recommendations and evidence suggests that correct anatomical pad placement is poor, such that a clearer, more effective diagram is urgently needed. In a recent study in adults, untrained bystanders failed to achieve accurate defibrillation pad placement, when guided by current defibrillation pad diagrams (Deakin 2019 282).
- In most cases, bias was assessed per comparison rather than per outcome, since there were no meaningful differences in bias across outcomes. In cases where differences in risk of bias existed between outcomes this was noted.

Subgroup considerations

None.

Implementation considerations

Implementation of a different pad position and/or a VC strategy would require training. Instructions for BLS providers should be clear and easy to be followed.

Monitoring and evaluation

Since current evidence is inconclusive, we suggest the resuscitation systems to collect and analyze data on pad orientation and outcome of shockable cardiac arrest.

Research priorities

- No studies examined the paediatric/in-hospital setting.
- No RCTs have compared different pad positions with standard positions in any patient population, in the first 3 shocks.
- No studies have evaluated pad placement in unique populations.
- No studies evaluated the interaction between pad size and orientation.

GRADE table for Pad Placement

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	different pad orientation (i.e. AP)	standard position (AL)	Relative (95% CI)	Absolute (95% CI)		
Survival to hospital discharge with good neurological outcome												
1	randomised trials	serious[a]	not serious	very serious[b,c]	very serious[d]		51/144 (35.4%)	36/136 (26.5%)	**RR 1.39** (0.97 to 1.99)	**103 more per 1000** (from 8 fewer to 262 more)	Very low ,a,b,c,d	IMPORTANT
Return of spontaneous circulation												
1	non-randomised studies	very serious[e,f,g,h]	not serious	very serious[c,i]	not serious		117/158 (74.1%)	49/97 (50.5%)	**OR 2.64** (1.50 to 4.65)	**224 more per 1000** (from 100 more to 321 more)	Very low c,e,f,g,h,i	IMPORTANT
Return of spontaneous circulation												
1	randomised trials	serious[a]	not serious	very serious[b,c]	very serious[d]		51/144 (35.4%)	36/136 (26.5%)	**RR 1.39** (0.97 to 1.99)	**103 more per 1000** (from 8 fewer to 262 more)	-Very low a,b,c,d	IMPORTANT
Survival to hospital discharge with good neurological outcome												
1	non-randomised studies	very serious[e,f,g,h]	not serious	very serious[c,i]	not serious		54/158 (34.2%)	22/97 (22.7%)	**OR 1.86** (0.98 to 3.51)	**126 more per 1000** (from 4 fewer to 280 more)	Very low c,e,f,g,h,i	CRITICAL
Survival to hospital discharge												
1	randomised trials	serious[a]	not serious	very serious[b,c]	serious[d]		31/143 (21.7%)	18/135 (13.3%)	**RR 1.71** (1.01 to 2.88)	**95 more per 1000** (from 1 more to 251 more)	Very low a,b,c,d	CRITICAL
Survival to hospital discharge												
1	non-randomised studies	very serious[e,f,g,h]	not serious	very serious[c,i]	not serious		54/158 (34.2%)	25/97 (25.8%)	**OR 1.55** (0.83 to 2.90)	**92 more per 1000** (from 34 fewer to 244 more)	Very low c,e,f,g,h,i	CRITICAL
VF termination												
1	randomised trials	serious[a]	not serious	very serious[b,c]	serious[d]		115/144 (79.9%)	92/136 (67.6%)	**RR 1.18** (1.03 to 1.36)	**122 more per 1000** (from 20 more to 244	Very low a,b,c,d	IMPORTANT

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

Explanations

a. . The cluster randomization led to lack of blinding to treatments, rescuers knowing already what group a patient would be in at the time of enrollment. Rescuers also determined some outcomes (VF termination, ROS C)
b. The AP position was tested vs. the standard one only in the instance of refractory VF (thus from the 4th shock)
c. The population studied included no children
d. In the original trial design, the calculated sample size was 310 patients per group; the actual number of patients enrolled was 136 in the standard position and 144 in the vector change group. Thus, due to the smaller sample size, the study was likely underpowered
e. No sample size calculation. Study likely underpowered.
f. Selection bias as pad placement was left to the discretion of individual EMS crews
g. Limits in generalizability as the study involved cases treated by a single fire-based EMS agency
h. ROS C definition by EMS might have been complicated by difficulty in pulse palpation in cardiac arrest
i. Results account for a change in pad position (vector change) midway through the resuscitation.

See Part 2 below for references

Pads Size and Placement (PLS 4080.17)

Part 2: PAD POSITION

QUESTION

Should The use of large pad size vs. small pad size be used for children in any setting (in-hospital or out-of-hospital) with cardiac arrest and a shockable rhythm at any time during cardiopulmonary resuscitation (CPR)?	
POPULATION:	children in any setting (in-hospital or out-of-hospital) with cardiac arrest and a shockable rhythm at any time during cardiopulmonary resuscitation (CPR)
INTERVENTION:	The use of large pad size
COMPARISON:	small pad size
MAIN OUTCOMES:	Survival to hospital discharge with good neurological outcome; Return of spontaneous circulation; Return of spontaneous circulation; Survival to hospital discharge with good neurological outcome; Survival to hospital discharge; Survival to hospital discharge; VF termination;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Survival from sudden cardiac arrest is low. Patients who present in an shockable rhythm have a higher rate of good outcome. Approximately 20% of VF adult patients, however, will remain in VF despite standard resuscitation interventions. In addition, transthoracic impedance (TTI) may vary based on pad size and this may have an impact on shock success.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Improvement in ROSC, long term survival, and neurologic outcome are desirable. However, there are few studies in patients at early-stage VF/pulseless VT directly comparing the effects of different pad size on defibrillation success, ROSC and long term survival.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Available evidence is inconclusive.	

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	Available evidence is inconclusive.	Several old studies have evaluated the role of pad and paddle size in children relationship to thransthoracic impedance (TTI). One prospective before and after observational study in adults found no differences in the first shock defibrillation success between small pads (89%) and large pads (86%), TTI was significantly higher with small pads.

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		

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 evidence in favour of higher or lower size for the treatment of shockable cardiac arrest.	For pad size there are old studies mainly focusing on TTI, showing that smaller pads or paddles are associated with higher TTI. A recent obervational study from 2023, investigating large vs. small pad sizes showed no difference in defibrillation success after a BTE shock.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	If beneficial, stakeholders will likely accept the intervention.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		

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

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 recommend intervention
○	○	●	○

CONCLUSIONS

Recommendation

Recommendations for both pad placement and size (see part 2 below) are included here

For Manufacturers

Manufacturers could consider the standardization of pads size for infants, children, and adults (good practice statement).

Manufacturers of AEDs should standardize pad placement in an anteroposterior position for infants and young children (with 1 pad anteriorly, over the left precordium, and the other pad posteriorly to the heart just inferior to the left scapula) (good practice statement).

Manufacturers should include instructions to ensure adequate contact between the pad and the skin and ensure that their pad position diagrams clearly indicate the ILCOR-recommended pad position (good practice statement).

For CPR Providers Using an AED

Follow the AED specific guidance and instructions for pads placement in infants and children (good practice statement).

For CPR Providers Trained in Manual Defibrillation

In infants and children, place pads in an anterior-posterior position (good practice statement).

Vector Change Strategy

We cannot make a recommendation for or against the use of vector change strategy for the treatment of refractory VF or pulseless VT in infants and children.

Justification

In making these recommendations, the PLS Task Force considered the following:

- Pulseless shockable rhythms are more common in adults than in children and vary according to the age. The low frequency of these rhythms contributes to the lack of information on pediatric defibrillation. We do not know the incidence of refractory shockable rhythms in children.
- Transthoracic impedance varies based on pad size and position, and this may impact shock success. Different pad orientations/positions may also result in a higher voltage gradient in different areas of the myocardium from where fibrillation may start/restart.
- In Yin (2023), transthoracic impedance was higher for smaller electrodes than the larger electrodes, but defibrillation success was equivalent. The study, however, has important biases in its design. It included no data on ROSC or survival and focused only on the biphasic truncated exponential defibrillation waveform. Based on the above assumptions, there is no evidence that any specific pad size/orientation and position differing from the standard anterior-lateral improves any critical or important outcome. However, it is likely that defibrillator manufacturers have proprietary data that are not available in the public sphere.
- Two observational studies in adults (Kerber 1981 676; Yin 2023 109754) and three in children (Atkins 1994 90; Atkins 1988 914; Samson 1995 544) showed that transthoracic impedance was significantly higher with small-sized pads/paddles than large-sizedpads/paddles. Lower transthoracic impedance results in higher current flow, possibly allowing for higher defibrillation success. Another observational study (Kastreva 2006 1009) evaluated transthoracic impedance in volunteers measured according to the interelectrode voltage drop obtained by passage of a low amplitude high-frequency current between the two self-adhesive electrodes in anterior-posterior and anterior-lateral positions without delivering a shock. Lower transthoracic impedance was measured in the anterior-posterior compared to the anterior-lateral position.
- An observational study included 123 cardiac arrests (Dalzell 1989 741). Pad diameters were small (8/8 cm) in 26 cardiac arrests, intermediate (8/12 cm) in 63 arrests and large (12/12 cm) in 34 cardiac arrests. Transthoracic impedance significantly decreased with increasing pad size. A single shock of 200 J (delivered energy) was successful in 8 of 26 (31%) arrests using small pads, in 40 of 63 (63%) with intermediate pads and in 28 of 34 (82%) with large pads (p=0.0003).
- There are no studies examining defibrillation pad size or orientation for IHCA. However, this evidence could be applied to the IHCA, with additional downgrading for indirectness.
- If the same pads size could be used for adult, children and infants, costs would be reduced and training could be improved.
- In most cases, bias was assessed per comparison rather than per outcome, since there were no meaningful differences in bias across outcomes. In cases where differences in risk of bias existed between outcomes this was noted.

Subgroup considerations

N/A

Implementation considerations

Implementation of a different size pad did not require training. Instructions for BLS providers should be clear and easy to be followed.

Monitoring and evaluation

Since current evidence is inconclusive, we suggest the resuscitation systems to collect and analyze data on pad size and outcome of shockable cardiac arrest.

Research priorities

- No studies examined the paediatric/in-hospital setting.
- No RCTs compared different pad sizes in any patient population.
- No studies evaluated the interaction between pad size and orientation.
- Only surrogate outcomes were evaluated for pads size (i.e. transthoracic impedance).

GRADE Table for Pad Size

Author(s):
Question: The use of large pad size compared to small pad size in children in any setting (in-hospital or out-of-hospital) with cardiac arrest and a shockable rhythm at any time during cardiopulmonary resuscitation (CPR)
Setting:
Bibliography: Yin RT, Taylor TG, de Graaf C, Ekkel MM, Chapman FW, Koster RW. Automated external defibrillator electrode size and termination of ventricular fibrillation in out-of-hospital cardiac arrest. Resuscitation. 2023 Apr;185:109754. doi: 10.1016/j.resuscitation.2023.109754. Epub 2023 Feb 25. PMID: 36842678.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	The use of large pad size	small pad size	Relative (95% CI)	Absolute (95% CI)		
Nuevo desenlace												
1	non-randomised studies	extremely serious[a,b,c]	not serious	serious[d]	not serious		135/157 (86.0%)	158/178 (88.8%)	**OR 0.82** (0.42 to 1.60)	**21 fewer per 1000** (from 119 fewer to 39 more)	[a,b,c,d]	IMPORTANTE

CI: confidence interval; **OR:** odds ratio

Explanations

a. Before and after study design with patients cases collected over several years between outcomes. Many factos have changed over time and there are other differences between groups to be accounted for.
b. Only defibrillations with BTE waveforms were investigated
c. Strong involvement of the manufacturer of AEDs used in the study's authorship
d. VF termination was evaluated based on ECG rhythm annotations, i.e. whether the VF was extinguished, which was necessary but not sufficient condition for ROSC and survival

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Pulse Check Accuracy (PLS 4080.18)

QUESTION

Should Pulse check as per current guidelines by healthcare providers be used to diagnose return of spontaneous circulation in infants and children in cardiac arrest?	
POPULATION:	infants and children in cardiac arrest
INTERVENTION:	any other site for pulse check (eg. femoral pulse, etc) OR method (not exclusively, cardiac auscultation, pulse oximetry, ultrasonography, rise in end-tidal CO2 values above specific thresholds, invasive monitoring, etc)
COMPARATOR:	pulse check as per current guidelines by healthcare providers (brachial pulse for infants and carotid pulse for children and adolescents)
MAIN OUTCOMES	Any outcome including but not limited to: • accuracy, defined as sensitivity and specificity of detecting a perfusing rhythm • duration of cardiac compression pauses • any clinical outcome The PLS TF prefers outcomes defined in the P-COSCA publication (Topjian 2021 162)
SETTING	in cardiac arrest
PERSPECTIVE:	
BACKGROUND:	
SUBGROUPS:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	To start CPR, the absence of signs of life is recommended by resuscitation councils. Pulse checks during rhythm analysis should not exceed ten seconds. Pulse checks are recommended to detect a return of spontaneous circulation (ROSC) during rhythm checks. Palpation of a pulse (or its absence) is not reliable as the sole determinant of cardiac arrest and the need for chest compressions. A prolonged duration leads to longer no-flow, compromising patients' outcomes. A false determination of a present pulse will likely result in stopping chest compressions.	

Test accuracy
How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ● Inaccurate ○ Accurate ○ Very accurate ○ Varies	One study evaluated cardiac ultrasound during rhythm analysis compared to simultaneous pulse checks and found a sensitivity of 100% for detecting a return of spontaneous circulation (1). However, specificity could not be reported due to insufficient data. Two studies assessed different pulse check sites in children with ECMO or LVAD. For the detection of a pulse, the sensitivities in the two studies were 76% (95% CI 64 to 86) (2) and 86% (95%CI 79 to 91) (3). Specificities were 79% (95% CI 69 to 86) (2) and 64% (95% CI 53 to 74), respectively.	

○ Don't know		

Test result	Number of results per 1000 patients tested (95% CI)			№ of participants (studies)	Certainty of the evidence (GRADE)
	Prevalence 0%	Prevalence 1%	Prevalence 10%		
True positives patients with return of spontaneous circulation	6 to 8	8 to 10	76 to 100	216 (3)	⨁◯◯◯ Very low[1,2,3,a,b]
False negatives patients incorrectly classified as not having return of spontaneous circulation	0 to 2	0 to 2	0 to 24		
True negatives patients without return of spontaneous circulation	635 to 784	634 to 782	576 to 711	160 (3)	⨁◯◯◯ Very low[2,3,b]
False positives patients incorrectly classified as having return of spontaneous circulation	208 to 357	208 to 356	189 to 324		
Inconclusive	undefined			(0)	-
Complications	undefined			(0)	-

1. Tsung, J. W., Blaivas, M.. Feasibility of correlating the pulse check with focused point-of-care echocardiography during pediatric cardiac arrest: a case series.Resuscitation; May 2008.
2. Tibballs, J., Weeranatna, C.. The influence of time on the accuracy of healthcare personnel to diagnose paediatric cardiac arrest by pulse palpation.Resuscitation; Jun 2010.
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a. One study (Tsung) evaluated patients with knowledge about the reference test.

b. Two studies (Tibballs) evaluated patients on ECMO and LVAD systems. Those were not in cardiac arrest, the mechanical circulatory support system was used to mimic cardiac arrest

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate	One case series assessing ultrasound has resulted in a 100% accuracy with direct comparison to central pulse palpation (1). Two experienced providers performed the ultrasound. Additionally, the small sample size limits generalizability, wherefore the	

○ Large ○ Varies ○ Don't know	desirable effect is small. From two studies with indirect evidence, the overall accuracy was 78% in both studies. Resulting in a wrong interpretation of the pulse check in two out of ten children. **Test accuracy** In the included studies sensitivity ranged from 76% to 100% , while specificity was lower with 64% 79%.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Current guidelines recommend limiting chest compression pauses to ten seconds for rhythm analysis. One study evaluated the time until a decision was made about whether a pulse was present or not (2). In this study, only 39% (60/153) of the participants decided on the presence of a pulse within ten seconds. The median duration until any decision was made was 18 seconds, with an accuracy of 85%. Inexperienced providers took longer to make their decisions. This indirect evidence indicates that there is a reasonable concern about prolonged chest compression pauses, especially in inexperienced clinicians.	Evidence from the 2010 treatment recommendations suggest that the palpation of a pulse in children with cardiac arrest is inaccurate {Kleinman, 2010 #10}. Combined with the indirect evidence found in this systematic review, it was found that a decision on wheater a pulse is present or not cannot be reliably made within ten seconds.
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of test accuracy?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Due to the limited applicability, indirect evidence, and small sample size, the certainty of the evidence is very low.	
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Two observational studies provided indirect evidence for the research question. Pulse check accuracy in a lower acuity setting than in cardiac arrest was moderate, even for experienced providers (3, 2). One study evaluated survival until hospital discharge. Two out of fourteen patients survived (14%) (1). The indirectness and low sample size resulted in the very low certainty of the evidence.	
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Certainty of the evidence of test result/management How certain is the link between test results and management decisions?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Certainty of effects What is the overall certainty of the evidence of effects of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

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	Accuracy is the gold standard in assessing diagnostic interventions. For clinical outcomes the ILCOR P-COSCA initiative developed a core outcome set specific for pediatric cardiac arrest studies. The design and methods of the initiative included use of a Delphi process to develop consensus on a core domain set (4).	

variability		
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	Due to the small evidence, with missing undesirable effects, a statement favoring the comparator or intervention cannot be made.	
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No studies were identified that evaluated the resources required. However, ultrasound devices are considered standard of care and available on all intensive care units or resuscitation rooms. There might be a lack of ultrasound devices in the prehospital system, especially in low- and middle income countries.	
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	No studies regarding resource requirements were included in this systematic review.	

studies		
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	Cost effectiveness data was not identified in this systematic review.	
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	Equity data was not identified in this systematic review	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't	Identifying ROSC in pediatric advanced life support requires evaluating circulation, including manual pulse palpation. While experienced clinicians perform better than inexperienced, the risk of type 1 and type 2 errors and prolonged CPR pauses remains significant. In addition to pulse checks, international guidelines recommend including other intra-arrest parameters such as etCO2, blood pressure, SpO2, and ultrasound to determine ROSC (5, 6).	Where possible, in-hospital medical emergency teams and ALS-based emergency medical service systems use ultrasound during cardiac arrest. For in-hospital cases, the availability of invasive blood pressure monitoring is an already-used alternative.

know		
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A prospective observational trial found that apical or subxiphoid views of the heart to assess contractility can be obtained within 10 seconds in 86% and 94%, respectively. The femoral view showed a slightly worse result, with 74% of the scans being interpretable for pulsatility within 10 seconds (7). A dedicated protocol combined with supervised training may increase the rates of interpretable views within 10 seconds (8).	Implementing ultrasound checks within a pediatric advanced life support algorithm seems feasible. Providers must be trained to perform the assessment quickly and accurately. Medical emergency team leaders are skilled at this task.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	Very inaccurate	**Inaccurate**	Accurate	Very accurate		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 THE EVIDENCE OF TEST ACCURACY	**Very low**	Low	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	**Very low**	Low	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF EFFECTS	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

Treatment recommendations:

We suggest that the palpation of a pulse (or its absence) is unreliable as the sole determinant of cardiac arrest and the need for chest compressions. [weak recommendation, very low certainty on evidence]

In unresponsive children, not breathing normally and without signs of life, lay rescuers and healthcare professionals should begin CPR. (Good Practice Statement)

Justification

Due to the limited evidence and the limited applicability of the included study, the treatment recommendation remains unchanged. The ILCOR PLS Taskforce considered indirect evidence post-hoc and downgraded it for indirectness.

Subgroup considerations

One study evaluated the difference between femoral and brachial pulse checks without finding a difference in accuracy. Although the current guidelines state that healthcare professionals should check for a pulse, there may be differences between providers in terms of their experience with cardiac arrests, particularly in children. Differences in the level of expertise between different healthcare providers have to be considered.

Implementation considerations

Monitoring and evaluation

Research priorities

Clinical studies should assess different sites for ultrasound-guided pulse checks, such as different sites for vascular and/or cardiac ultrasound, and different methods (doppler-mode vs. visual interpretation).

Prehospital and in-hospital studies, comparing point of care ultrasound (vascular or cardiac) during rhythm analysis are ethical, necessary, and critically important to help guide clinicians in making these complex decisions. As different resuscitation councils recommend varying pulse check locations, this may provide an opportunity for an international comparative study.

Further examination of the potential longer hands-off time and their impact on outcome would also be helpful.

Future studies would benefit from including outcome measures consistent with the P-COSCA recommendations.

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Vasopressors for Cardiac Arrest in Children (PLS 4080.21)

QUESTION

Should No vasopressor vs. vasopressor use be used for cardiac arrest in children?	
POPULATION:	Cardiac arrest in children
INTERVENTION:	Vasopressor use
COMPARISON:	No vasopressor
MAIN OUTCOMES:	Pre-hospital ROSC; 1-month survival; Favorable neurological outcome at 1-month; Survival to Hospital Discharge; Favorable neurological outcome at hospital discharge
SETTING:	Any

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 pediatric 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.	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[6].

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	The systematic review reported 2 pre-hospital retrospective, propensity-score matched cohort studies that addressed our PICOST[1,4]. ***Favorable neurological survival at 1-month (Cerebral Performance Category)*** For this critical outcome, we identified low certainty data (downgraded for serious risk of bias, and serious indirectness), from 1 cohort study which was propensity score matched for children 8 to 17 years old[4], involving 608 patients which showed no significant difference associated when epinephrine was administered compared to when no epinephrine was administered (15 more patients with favorable neurological survival at 1-month per 1,000 resuscitations; 95 CI%: 11 fewer to 92 more). ***Favorable neurological survival at hospital discharge (Modified Rankin Score)*** For this critical outcome, we identified low certainty data (downgraded for serious risk of bias, and serious indirectness), from 1 cohort study which was propensity score matched for children less than 18 years old[1], involving 1426 patients which showed no significant difference associated when epinephrine was administered compared to when no epinephrine was administered (9 more patient with favorable neurological survival at hospital discharge per	While return of spontaneous circulation may not be a patient-centered outcome, the need for additional considerations of maintaining organ viability for potential organ donation needs to be addressed. The 2 pediatric studies did not report less favorable neurological outcomes from the administration of epinephrine. There were consistent signals but non-significant associations with the use of epinephrine (versus when not given) with comparatively more short-term survival and favorable neurological outcomes. Further studies are needed to evaluate long term neurological outcomes of pre-hospital administration of epinephrine for pediatric out-of-hospital cardiac arrest. These patient-centered clinical outcomes should be studied[7].

	1,000 resuscitations; 95 CI%: 13 fewer to 50 more). ***Survival at 1-month*** For this critical outcome, we identified low certainty data (downgraded for serious risk of bias, and serious indirectness), from 1 cohort study which was propensity score matched for children 8 to 17 years old[4], involving 608 patients which showed no significant difference associated when epinephrine was administered compared to when no epinephrine was administered (10 more survivors per 1,000 resuscitations; 95 CI%: 27 fewer to 78 more). ***Survival to hospital discharge*** For this critical outcome, we identified low certainty data (downgraded serious risk of bias, and serious indirectness), from 1 cohort study which was propensity score matched for children less than 18 years old[1], involving 1426 patients which showed no significant associations with survival at hospital discharge when epinephrine was administered compared to when no epinephrine was administered (19 more survivor per 1000 resuscitations; 95 CI%: 7 fewer to 64 more). ***Pre-hospital Return of spontaneous circulation (ROSC)*** For this important outcome, we identified very low certainty data (downgraded for serious risk of bias, very serious inconsistency, and serious indirectness), from the 2 cohort studies[1,4], involving 2034 patients less than 18 years old, which showed significant associations with ROSC when epinephrine was administered, compared to when no epinephrine was administered (63 more patients with ROSC per 1,000 resuscitations; 95 CI%: 28 more to 145 more).	

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 epinephrine in pediatric 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 epinephrine in pediatric cardiac arrest, especially in resource-limited settings. The 2 included studies were from advanced EMS systems that could provide pre-hospital advanced pediatric life support[1,4].	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[2]. The only factor associated with severe adverse safety events was young age.

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 systematic review reported 2 pre-hospital retrospective, propensity-score matched cohort studies that addressed our PICOST. Pooled analysis of the 2 included studies[1,4] demonstrated that the use of epinephrine in the out-of-hospital setting was associated with increased ROSC. The 2 identified studies provided low certainty of evidence with the critical outcomes (downgraded for serious risk of bias and serious indirectness) and very low certainty of evidence with the important outcomes (downgraded for serious risk of bias, very serious inconsistency, and serious indirectness).	
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 may be variability in the perceived clinical value of pre-hospital return of spontaneous circulation.	While return of spontaneous circulation may not be a patient-centered outcome, the need for additional considerations of maintaining organ viability for potential organ donation needs to be considered.
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 pediatric out-of-hospital cardiac arrest to significantly improve ROSC rates. In any healthcare system that has advanced EMS life support teams that are trained and have the necessary resources to administer epinephrine for pediatric 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 the use of epinephrine in advanced EMS systems that are able to provide advanced life support to pediatric cardiac arrest patients in the pre-hospital setting. These should include patient-centered clinical outcomes, especially long-term neurological outcomes[7]. The task force acknowledges that randomized controlled trials on its use in pediatric cardiac arrest would unlikely be studied in the near future.	In EMS systems that can provide advanced pediatric life support, the administration of epinephrine in pediatric out-of-hospital cardiac arrests should 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 paucity of studies looking at resources required to train, maintain skillsets and provide the necessary equipment and drugs need for EMS systems to administer epinephrine in pediatric 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 pediatric 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 pediatric life support.	The advocacy to administer epinephrine in pediatric out-of-hospital cardiac arrests should consider additional training 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 observational 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 pediatric 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 enabling EMS systems to administer epinephrine in pediatric out-of-hospital cardiac arrests.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact	There were no studies identified that looked directly at the health economic impact and benefits of EMS to be able to deliver vasopressors in pediatric out-of-hospital cardiac arrests in all settings, including in resource-limited countries.	

○ Probably increased ○ Increased ○Varies ● Don't know	Further studies should look not only in 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 ○ Yes ○ Varies ○ Don't know	There was sufficient evidence to support administering epinephrine in advanced EMS systems that can or already provide advanced pediatric life support in pediatric out-of-hospital cardiac arrest. In developing EMS systems or healthcare settings with significant resources limitations, the feasibility of administrating epinephrine in pediatric out-of-hospital cardiac arrests is unknown due to 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 pediatric life support for pediatric out-of-hospital cardiac arrests, the evidence suggests that administration of epinephrine improved outcomes of ROSC; favouring the intervention. In developing EMS systems or countries with significant resource limitations, the feasibility of administrating epinephrine in pediatric out-of-hospital cardiac arrests is unknown due to 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].

There is insufficient evidence to generate a treatment recommendation for the use of epinephrine in pediatric in-hospital cardiac arrest. However, the task force considers the indirect evidence from OHCA to *support the administration of epinephrine in pediatric in-hospital cardiac arrest. [Good practice statement]*

Justification

In EMS systems that are already providing or planning to provide advanced pediatric life support while ensuring high quality basic life support, the current evidence while very low-quality, suggest using epinephrine in pediatric out-of-hospital cardiac arrest.

The taskforce acknowledged that the included studies were from settings with advanced Emergency Medical Services. In similar settings, the administration of epinephrine as part of advanced pediatric life support for pediatric out-of-hospital cardiac arrest should be continued but also further evaluated.

However, there is paucity of studies looking at resources required to train, maintain skillsets and provide the necessary equipment for EMS systems to administer epinephrine in pediatric out-of-hospital cardiac arrests. Future studies should be undertaken to evaluate the ability of EMS systems to provide advanced care in pediatric 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)
· LMICs versus Non-LMICs
· 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 survival and neurological outcomes[4].
· Further studies should address if specific sub-populations might potentially benefit from administration of epinephrine in the pre-hospital settings
· Cost-effectiveness and feasibility on the provision of advanced pediatric life support in the pre-hospital settings to facilitate administration of epinephrine, in pediatric out-of-hospital cardiac arrest while ensuring high quality basic life support, should be explored in all healthcare settings, including in LMICs.
· There were no inpatient studies identified. Future studies should include evaluation of use of vasopressors in the inpatient setting, especially in the context of initial resuscitation of pediatric cardiac arrest patients prior to extracorporeal cardiopulmonary resuscitation (ECPR) [3,5].

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)	Certainty	Importance
Favorable neurological outcome at 1-month												
1	non-randomised studies Matsuyama, 2020[4]	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)	⨁⨁◯◯ Low[a,c,d]	CRITICAL
Favorable neurological outcome at hospital discharge												
1	non-randomised studies Amoako, 2023[1]	serious[a]	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)	⨁⨁◯◯ Low[a,c]	CRITICAL
1 month survival												
1	non-randomised studies Matsuyama, 2020[4]	serious[a]	not serious	serious[c,d]	not serious	none	31/304 (10.2%)	24/304 (7.9%)	**RR 1.13** (0.67 to 1.93)	**10 more per 1,000** (from 27 fewer to 78 more)	⨁⨁◯◯ Low[a,c,d]	CRITICAL
Survival to Hospital Discharge												
1	non-randomised studies Amoako, 2023[1]	serious[a]	not serious	serious[c]	not serious	none	45/713 (6.3%)	36/713 (5.0%)	**RR 1.38** (0.87 to 2.19)	**19 more per 1,000** (from 7 fewer to	⨁⨁◯◯ Low[a,c]	CRITICAL

										64 more)		

Pre-hospital ROSC

2	non-randomised studies Amoako, 2023[1]; Matsuyama, 2020[4]	serious[a]	very serious[b]	serious[c]	not serious	none	157/1017 (15.4%)	97/1017 (9.5%)	**RR 1.64** (1.26 to 2.13)	**63 more per 1,000** (from 28 more to 145 more)	⊕◯◯◯ Very low[a,b,c]	IMPORTANT

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

Explanations

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

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Intra-arterial Blood Pressure Monitoring (PLS 4160.08)

QUESTION

Should a blood pressure target vs. no blood pressure target be used for infants and children receiving resuscitation after in-hospital cardiac arrest with intra-arterial blood pressure (IABP) monitoring in place at the time of arrest?	
POPULATION:	infants and children receiving resuscitation after in-hospital cardiac arrest with intra-arterial blood pressure (IABP) monitoring in place at the time of arrest
INTERVENTION:	A specific blood pressure target during arrest
COMPARISON:	no blood pressure target
MAIN OUTCOMES:	Return of spontaneous circulation; Survival to hospital discharge; Survival with favorable neurological outcome (PCPC 1-3 or no change from baseline); Functional status scale increase by 3 or increase by 2 in single domain (in survivors); any outcome included in the P-COSCA

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There are approximately 15,000 pediatric in-hospital cardiac arrests in children in the United States every year, with many occurring in highly monitored settings such as intensive care units (Berg et al., 2013; Holmberg et al., 2019). In these monitored settings, children may have an intra-arterial catheter placed for blood pressure monitoring, which may provide information about the quality of compressions during arrest events (Berg et al., 2016). ILCOR and member resuscitation councils provide recommendations for high-quality CPR but not all provide recommendations regarding intra-arterial blood pressure (IABP) monitoring in pediatric cardiac arrest. Furthermore, there are no prior systematic reviews on IABP in pediatric cardiac arrest and existing guidelines are consensus driven. The American Heart Association Pediatric Advanced Life Support Guidelines state “it is reasonable to for providers to use diastolic blood pressure to assess CPR quality” (Topjian et al., 2020) and the European Resuscitation Council states “the level of certainty of the available evidence is too low to make any recommendation for or against the use of diastolic blood pressure to guide resuscitation efforts in children with cardiac arrest” (Van de Voorde et al., 2021). Providing a review of the existing literature will provide clinicians with more confidence and decrease variability in blood pressure monitoring and/or targets in pediatric in-hospital cardiac arrest. Potential benefits of providing specific guidance include both more survivors to hospital discharge and more survivors with favorable neurological outcome.	This is the first systematic review on this topic for the ILCOR pediatric life support task force. Intra-arrest blood pressure monitoring is invasive and generally limited to high-resource settings, such as intensive care units.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Five studies were included in the systematic review. (1, 2, 3, 4, 5) All five were observational cohort studies, with all being secondary analyses of larger cohorts. Three were analyses of the same cohort, but examined different sub-populations or different outcomes.(2, 3, 5) **Diastolic blood pressure**	The diastolic blood pressure cuttofs of 25 mmHg for infants under 1 and 30 mmHg for children 1 - 18 years were derived from Berg 2018.

	For the critically important outcome of return of spontaneous circulation (ROSC), we identified very low-certainty evidence (downgraded for imprecision and indirectness) from two observational studies enrolling 577 children with in-hospital cardiac arrest and invasive arterial blood pressure monitoring in place at the time of arrest(1, 2). In these infants and children, diastolic blood pressures above the cutoffs for the first 10 minutes of CPR were associated with an unadjusted relative risk of ROSC of 1.33 (95% CI 1.12-1.59). For the critically important outcome of survival to hospital discharge (SHD), we identified very low-certainty evidence (downgraded for imprecision and indirectness) from two observational studies enrolling 577 children with in-hospital cardiac arrest and invasive arterial blood pressure monitoring in place at the time of arrest(1, 2). In these infants and children, diastolic blood pressures above the cutoffs for the first 10 minutes of CPR were associated with a pooled adjusted relative risk of SHD of 1.55 (95% CI 1.18-1.91). For the critically important outcome of survival with favorable neurological outcome (defined as pediatric cerebral performance category of 1-3 or no change from baseline), we identified very low-certainty evidence (downgraded for imprecision and indirectness) from two observational studies enrolling 577 subjects with in-hospital cardiac arrest and invasive blood pressure monitoring in place at the time of arrest(1, 2). In these infants and children, diastolic blood pressures above the cutoffs for the first 10 minutes of CPR were associated with a pooled adjusted relative risk of favorable neurological outcome of 1.37 (95% CI 1.04-1.69). For the critically important outcome of new substantive morbidity in survivors (defined as Functional Status Scale increase of at least 3 points or increase of 2 in a single domain), we identified very low-certainty evidence (downgraded for imprecision and indirectness) from a single study enrolling 77 subjects with in-hospital cardiac arrest and invasive blood pressure monitoring in place at the time of arrest (4). In these infants and children, there was no assocation between diastolic blood pressure cutoffs for the first 10 minutes of CPR and new substantive morbidity in survivors (unadjusted relative risk of 1.7 [95% CI 0.83-3.41]). There was no difference between the median diastolic blood pressures between subjects with new substantive morbidity and those without (30.5 mmHg and 30.9 mmHg, p = 0.5). **Systolic blood pressure** For the critically important outcome of survival to hospital discharge (SHD), we identified very low-certainty evidence (downgraded for imprecision and indirectness) from two observational studies enrolling 577 children with in-hospital cardiac arrest and invasive arterial blood pressure monitoring in place at the time of arrest (1, 2). In these infants and children, systolic blood pressures above the cutoffs for the first 10 minutes of CPR were associated with an unadjusted relative risk of ROSC of 1.12 (95% CI 0.95 - 1.32), showing no benefit.For the critically important outcome of survival with favorable neurological outcome (defined as pediatric cerebral performance category of 1-3 or no change from baseline), we identified very low-certainty evidence (downgraded for imprecision and indirectness) from one observational study enrolling 164 subjects with in-hospital cardiac arrest and invasive blood pressure monitoring in place at the time of arrest(2). In these infants and children, systolic blood pressures above the cutoffs for the first 10 minutes of CPR were associated with an adjusted relative risk of favorable neurological outcome of 1.0 (95% CI 0.7-1.4), suggesting no benefit. For the critically important outcome of new	

substantive morbidity in survivors (defined as Functional Status Scale increase of at least 3 points or increase of 2 in a single domain), we identified very low-certainty evidence from a single study enrolling 77 subjects with in-hospital cardiac arrest and invasive blood pressure monitoring in place at the time of arrest (4). In these infants and children, there was no assocation between systolic blood pressure cutoffs for the first ten minutes of CPR and new substantive morbidity in survivors (unadjusted relative risk of 0.7 [95% CI 0.4-1.24]). There was no difference between the median diastolic blood pressures between subjects with new substantive morbidity and those without (76.3 mmHg and 63 mmHg, p = 0.2).

Presence of monitoring

For the critically important outcomes of ROSC, SHD, FNO, we identified very low-certainty evidence that there was no significant difference between clinician-reported use of invasive monitoring of diastolic blood pressure to monitor CPR performance.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no blood pressure target	Risk with a diastolic blood pressure of 25 for infants <1 and 30 for children >=1				
Return of spontaneous circulation (ROSC)	Study population		**RR 1.33** (1.12 to 1.59)	577 (2 non-randomised studies)[1,2]	⨁◯◯◯ Very low[a]	Favors DBP target of 25mmHg for infants <1yr and 30 for children >=1 in 1st 10 minutes of CPR
	528 per 1,000	**703 per 1,000** (592 to 840)				
Survival to hospital discharge (SHD)	Study population		**RR 1.55** (1.18 to 1.91)	577 (2 non-randomised studies)[1,2]	⨁◯◯◯ Very low[a]	Favors DBP target of 25mmHg for infants <1yr and 30 for children >=1 in 1st 10 minutes of CPR
	407 per 1,000	**630 per 1,000** (480 to 776)				
Survival with favorable neurological outcome (PCPC 1-3 or no change from baseline) (FNO)	Study population		**RR 1.37** (1.04 to 1.69)	577 (2 non-randomised studies)[1,2]	⨁◯◯◯ Very low[a,b]	Favors DBP target of 25mmHg for infants <1yr and 30 for children >=1 in 1st 10 minutes of CPR
	390 per 1,000	**535 per 1,000** (406 to 660)				
	Study population					

Functional status scale increase by 3 or increase by 2 in single domain (in survivors) (FSS)	222 per 1,000	**376 per 1,000** (184 to 760)	**RR 1.69** (0.83 to 3.42)	77 (1 non-randomised study)[3]	⨁◯◯◯ Very low[c]	No difference between the median diastolic blood pressures between subjects with new substantive morbidity and those without

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a. Two secondary analyses of prospective cohorts

b. Berg 2018 showed an improvement to FNO with the intervention, but Berg 2023 did not

c. Secondary analysis of a single cohort with 77 subjects included

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no blood pressure target	Risk with a diastolic blood pressure of 25 for infants <1				

		and 30 for children >=1				
Survival to hospital discharge (SHD)	Study population		**RR 1.64** (1.06 to 2.54)	88 (1 non-randomised study)[1]	⨁◯◯◯ Very low[a]	Showed no difference between exposure to a DBP of ≥25 mmHg for infants <1 and ≥30 mmHg for children ≥1 for the first 10 minutes of CPR
	405 per 1,000	**665 per 1,000** (430 to 1,000)				

1. Yates, Andrew R, Sutton, Robert M, Reeder, Ron W, Meert, Kathleen L, Berger, John T, Fernandez, Richard, Wessel, David, Newth, Christopher J, Carcillo, Joseph A, McQuillen, Patrick S, Harrison, Rick E, Moler, Frank W, Pollack, Murray M, Carpenter, Todd C, Notterman, Daniel A, Dean, J Michael, Nadkarni, Vinay M, Berg, Robert A. Survival and Cardiopulmonary Resuscitation Hemodynamics Following Cardiac Arrest in Children With Surgical Compared to Medical Heart Disease..Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies; 2019.

a. Secondary analysis of a multi center prospective cohort

Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with no blood pressure target	**Risk with a diastolic blood pressure of 25 for infants <1 and 30 for children >=1**				
Survival to hospital discharge (SHD)	Study population		**RR 0.47** (0.15 to 1.41)	25 (1 non-randomised study)[1]	⨁◯◯◯ Very low[a]	Showed benefit from exposure to a DBP of ≥25 mmHg for infants <1 and ≥30 mmHg for children ≥1 for the first 10 minutes of CPR
	500 per 1,000	**235 per 1,000** (75 to 705)				

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Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies; 2019.

a. Secondary analysis of a multi center prospective cohort

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no blood pressure target	Risk with a systolic blood pressure of 60 for infants < 1 and 80 for children >=1				
Survival to hospital discharge (SHD)	Study population		**RR 1.12** (0.95 to 1.32)	577 (2 non-randomised studies)[1,2]	⨁◯◯◯ Very low[a]	Showed no difference between exposure to a SBP of ≥60 mmHg for infants <1 and ≥80 mmHg for children ≥1 for the first 10 minutes of CPR
	507 per 1,000	**568 per 1,000** (482 to 670)				
Survival with favorable neurological outcome (PCPC 1-3 or no change) (FNO)	Study population		**RR 1.0** (0.7 to 1.4)	164 (1 non-randomised study)[2]	⨁◯◯◯ Very low[b]	Showed no difference between exposure to a SBP of ≥60 mmHg for infants <1 and ≥80 mmHg for children ≥1 for the first 10 minutes of CPR
	0 per 1,000	**0 per 1,000** (0 to 0)				
Functional status scale increase by 3 or increase by 2 in single domain (in survivors) (FSS)	Study population		**RR 0.70** (0.40 to 1.24)	77 (1 non-randomised study)[3]	⨁◯◯◯ Very low[c]	No difference between the median diastolic blood pressures between subjects with new substantive morbidity and those without
	489 per 1,000	**342 per 1,000** (196 to 606)				

1. Berg, Robert A., Morgan, Ryan W., Reeder, Ron W., Ahmed, Tageldin, Bell, Michael J., Bishop, Robert, Bochkoris, Matthew, Burns,

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a. Two secondary analyses of prospective cohorts
b. Secondary analysis of a single cohort
c. Secondary analysis of a single cohort with 77 subjects included

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no blood pressure monitoring	Risk with the use of blood pressure monitoring				
Return of spontaneous circulation (ROSC)	Study population		**OR 0.93** (0.79 to 1.10)	(1 non-randomised study)[1]	⨁◯◯◯ Very low[a]	Showed no difference between exposure to reported use of invasive blood pressure monitoring of CPR quality
	0 per 1,000	**0 per 1,000** (0 to 0)				
Survival to 24 hours (24hS)	Study population		**OR 1.02** (0.84 to 1.22)	(1 non-randomised study)[1]	⨁◯◯◯ Very low[a]	Showed no difference between exposure to reported
	0 per 1,000	**0 per 1,000** (0 to 0)				

							use of invasive blood pressure monitoring of CPR quality
	Survival to hospital discharge (SHD)	Study population		**OR 0.97** (0.81 to 1.16)	(1 non-randomised study)[1]	⨁◯◯◯ Very low[a]	Showed no difference between exposure to reported use of invasive blood pressure monitoring of CPR quality
		0 per 1,000	**0 per 1,000** (0 to 0)				
	Survival with favorable neurological outcome (PCP 1-2 or no worsening) (FNO1-2)	Study population		**OR 0.91** (0.72 to 1.17)	(1 non-randomised study)[1]	⨁◯◯◯ Very low[a]	Showed no difference between exposure to reported use of invasive blood pressure monitoring of CPR quality
		0 per 1,000	**0 per 1,000** (0 to 0)				

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a. Single registry study

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	None of the studies examined undesirable effects of the treatment. There are risks and complications from invasive arterial monitoring, such as infection and bleeding, and all subjects enrolled in these studies had invasive monitoring in place prior to arrest.	It was felt by the task force that the evidence applied only to children with invasive blood pressure monitoring in place at the time of arrest, particularly given the challenges and risks associated with initiation of invasive monitoring during arrest.

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	Five studies were included in the systematic review. (1, 2, 3, 4, 5) All five were observational cohort studies, with all being secondary analyses. **Diastolic and systolic blood pressure** Berg 2023 was a secondary analysis of a prospective multicenter cohort study (ICU-RESUScitation, Sutton 2022). Berg 2018 and Wolfe 2019 were secondary analyses of the PICqCPR cohort, but examined different outcomes. The studies were performed at large academic pediatric hospitals in the United States, which limits generalizability but is representative of the population of in-hospital cardiac arrests in highly resourced settings. The pooled aRR for favorable neurological outcome (FNO) showed a modest benefit (aRR 1.37), but this predominantly came from Berg 2018, with Berg 2023 showing no difference in FNO. Furthermore, using the same cohort as Berg 2018, Wolfe et al. found no difference in new substantive morbidity. **Presence of monitoring** The intervention of clinician-reported use of diastolic blood pressure to monitor CPR performance intra-arrest was reported in only one study. (4) The study was large, with 2,886 patients, but relied on clinician-reported use of monitoring (collected post-hoc) and was limited to institutions enrolled in the American Heart Association Get With the Guidelines Registry. The heterogeneity of subjects required propensity score matching.	
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 ILCOR P-COSCA initiative developed a core outcome set specific for pediatric cardiac arrest studies. The P-COSCA outcomes of return of spontaneous circulation, survival to discharge, and survival with favorable neurological outcome were chosen as critical, highly-valued outcomes for this review.	
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	**Diastolic blood pressure** Overall, the benefit of targeting a diastolic blood pressure of 25 mmHg for infants ≤1 and 30 mmHg for children 1 to 18 years, for the first 10 minutes of cardiac arrest for subjects with invasive blood pressure monitoring in place at the time of arrest, is associated with better outcomes when compared to a different diastolic blood pressure. Acknowledging the very low certainty of evidence, the currently available data support higher rates of ROSC, SHD, and FNO for subjects with the intervention. **Systolic blood pressure** Overall, there was no significant difference in outcomes in subjects with systolic blood pressures of 60 mmHg (infants <1) or 80 mmHg (children 1-18 years). **Presence of monitoring** Overall, there was no difference in outcomes for subjects who had clinician-reported use of diastolic blood pressure monitoring of CPR quality. **Overall** Given the benefits of studies examining diastolic blood pressure, the balance of effects favors targeting diastolic blood pressures in infants and children with invasive BP monitoring in place at the time of arrest.	Studies only included subjects with invasive monitoring in place at the time of arrest, and the task force considered it important to highlight the applicability of the evidence to only those with invasive blood pressure monitoring in place at the time of cardiac arrest. The task force also acknowledged that the presence of invasive blood pressure monitoring is challenging in resource-limited settings, and that no studies were found examining the use of other methods of blood pressure monitoring, including non-invasive monitoring.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No specific studies examining the acceptability of targeting a specific blood pressure using invasive monitoring were found. But, in settings where invasive monitoring is available and in place at the time of arrest, it is likely acceptable to continue monitoring blood pressures during arrest.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes	For patients with invasive monitoring in place at the time of arrest, it is feasible to monitor the blood pressure during the arrest. However, it is likely not feasible to initiate invasive monitoring intra-arrest, and no studies examined this. The task force acknowledged that some settings may not have the resources for invasive blood pressure monitoring.	

○ Yes ○ Varies ○ Don't know		

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
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 targeting an intra-arrest diastolic blood pressure of ≥25mmHg for infants <1 year and ≥30mmHg for children 1 to 18 years with invasive blood pressure monitoring in place at the time of cardiac arrest (weak recommendation, very low certainty of evidence).

Justification

The task force considered that in high-resource settings, invasive arterial blood pressure monitoring may be present at the time of arrest, and that current targets have been suggested through individual studies and expert consensus. The ILCOR pediatric life support task force undertook a systematic review of the evidence.

The review found no randomized controlled studies comparing two blood pressure targets during pediatric cardiac arrest. The available evidence consisted solely of observational data demonstrating the effect of exposure to various targets on critically important outcomes.

The consensus of the task force was that for the specific population examined in the studies (ie, infants and children with invasive monitoring in place at the time of arrest), that the evidence from a pooled sample size of 577 was adequate to make a recommendation for diastolic blood pressure targets of 25 mmHg for infants <1 and 30 mmHg for children 1-18 years, understanding that adolescents are under-represented in the studies. Pooled estimates showed better ROSC, SHD, and FNO, but the task force recognized that the FNO outcome was driven primarily by a single study (Berg 2018), and two other individual studies looking at different populations or definitions of FNO, found no difference.

The same studies demonstrated no difference when systolic blood pressures were targeted, so the task force recommended solely diastolic targets. Mean arterial pressure was not examined. A single study examining the clinician-reported presence of arterial monitoring at the time of arrest showed no difference in outcomes (Kienzle 2023), however, we felt that its indirectness was outweighed by the specific targets in other studies (Berg 2018, Berg 2023).

Subgroup considerations

Specific etiologies of arrest and their association with outcomes were not examined given the small number of patients in each subgroup. The subgroup of children heart disease was examined, with children with surgical heart disease having better outcomes but medical disease having no difference in outcomes, with significant limitations given the size of the cohorts.

Implementation considerations

Studies only included subjects with invasive monitoring in place at the time of arrest, and the task force considered it important to highlight the applicability of the evidence to only those with invasive blood pressure monitoring in place at the time of cardiac arrest.

The task force also acknowledged that the presence of invasive blood pressure monitoring is challenging in resource-limited settings, and that no studies were found examining the use of other methods of blood pressure monitoring, including non-invasive monitoring.

Monitoring and evaluation

See below

Research priorities

There are no interventional, randomized controlled trials comparing the benefits or harms of specific blood pressure targets during arrest
There are no studies examining the use of non-invasive methods to measure blood pressure during arrest
There are no studies examining whether different blood pressure targets would be more appropriate for adolescents
There are no studies examining the utility of initiating invasive blood pressure monitoring intra-arrest

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Pediatric Cardiac Arrest due to Pulmonary Embolism (PLS 4160.10)

QUESTION

Should Any specific alteration in the pediatric cardiac arrest algorithm vs. standard pediatric cardiac arrest algorithm be used for infants or children in cardiac arrest due to confirmed or suspected pulmonary embolism?	
POPULATION:	infants or children in cardiac arrest due to confirmed or suspected pulmonary embolism
INTERVENTION:	Any specific alteration in the pediatric cardiac arrest algorithm
COMPARISON:	Standard pediatric cardiac arrest algorithm
MAIN OUTCOMES:	Any clinical outcome
SETTING:	In-hospital or Out-of-hospital

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There are many studies on the magnitude and outcome of massive and sub-massive pulmonary embolism (PE) in children. PE is one of the listed reversible causes of cardiac arrest among Hs and Ts. Single institution case series identified PE as the cause of IHCA in 5 (6.3%) of 79 children who received at least 5 minutes of CPR for an IHCA. (1)	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	PE is a potential reversible cause of cardiac arrest. Specific interventions, in addition to routine cardiac arrest treatment, may improve the chance of achieving return of spontaneous circulation and survival with a good neurological outcome.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	If PE is not confirmed or there are other risk factors for bleeding, thrombolysis (one of the interventions to treat PE) can increase the risk of bleeding. However, understanding the possible reversal of cardiac arrest with specific interventions the impact of undesirable anticipated effects is small.	Mortality rate is very high without any intervention at all from PE leading to cardiac arrest.

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	Two small institutional case series described a total of 10 infants and children where individual or combined interventions (fibrinolysis, embolectomy, thrombectomy, with or without ECPR) were used in addition to standard cardiac arrest algorithms for cardiac arrest associated with confirmed or suspected pulmonary embolism. (1) (2) The number of patients reported and nature of the data presented precluded any meaningful statistical	

	comparison of these supplemental interventions to standard cardiac arrest care when assessing any patient outcomes.	
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 possibly important uncertainty in how much people value the main outcome. However, the importance of supplemental intervention to standard cardiac arrest care is unknown in infants and children.	
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	Thrombolysis (one of the interventions to treat PE) can theoretically increase the risk of bleeding. However, understanding the possible reversal of cardiac arrest with specific interventions, the impact of undesirable anticipated effects is small and favours interventions	
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	Systemic thrombolysis administration during a cardiac arrest requires medication storage, access and delivery mechanisms to be in place. The resources required to have access and delivery of this medication were not assessed in any study. Embolectomy and extracorporeal life support (ECLS) for E-CPR require significant additional surgical, radiological and equipment resources and expertise. Health care settings may not have access to these resources. However, resource requirement was not assessed in the included studies.	
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	No such studies included in this SR	

studies		
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 included in this SR	
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	Non-availability of specific resources and expertise may be limiting factor for certain population.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	PE is a potential reversible cause of cardiac arrest. However, the acceptability of fibrinolysis, embolectomy and thrombectomy, with or without extracorporeal cardiopulmonary resuscitation was not assessed in any studies. The included studies report the use of these interventions and the TF made the judgment that they are probably acceptable in the setting of paediatric cardiac arrest	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Systemic thrombolysis or fibrinolysis drug administration during a cardiac arrest requires medication storage, access and delivery mechanisms to be in place. The included studies describe the delivery of this intervention, although feasibility assessment was not described. Embolectomy and extracorporeal life support (ECLS) for E-CPR also require significant additional surgical, radiological and equipment resources and expertise. Its use has been described in the included studies and therefore it is assumed that the treatments are probably feasible.	

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

There is insufficient evidence to make a treatment recommendation for or against the use of any specific alteration to the cardiac arrest algorithm for pediatric cardiac arrest due to suspected or confirmed pulmonary embolism.

Justification

This question has never been evaluated by the PLS task force. ILCOR treatment Recommendations (TR) for adults are in place (unchanged since 2015) and suggest administering fibrinolytic drugs for cardiac arrest when PE is the suspected cause of cardiac arrest (weak recommendation, very low-certainty evidence). TR suggest the use of fibrinolytic drugs or surgical embolectomy or percutaneous mechanical thrombectomy for cardiac arrest when PE is the known cause of cardiac arrest (3) (4).

The PLS task force acknowledges an absence of good quality pediatric evidence.
The task force considered additional data that did not meet the SR inclusion criteria. A single centre retrospective study of 33 pediatric patients with massive and sub massive PE reported 4 patients that suffered cardiac arrest. One patient died despite standard cardiac arrest care, while 1 of 3 additionally treated with one of or a combination of systemic fibrinolysis, catheter directed fibrinolysis, Embolectomy or ECMO survived (5).
The task force also identified 15 pediatric case reports that did not meet the SR inclusion criteria. Four patients were treated as per standard cardiac arrest algorithm, none of whom survived. Eleven patients were treated with alterations to the algorithm (Fibrinolysis, Embolectomy, ECMO), 7 of whom survived to hospital discharge.

Subgroup considerations

Treatment decisions are likely to vary with confirmed and presumed PE and in patients with known contraindication to systemic thrombolysis.

Implementation considerations

Confirmation of PE based on specific acute changes and settings, such as in-hospital CA and out-of-hospital CA is likely

Monitoring and evaluation

Confirmation of PE in children with CA and RCTs on the impact of supplemental interventions

Research priorities

Identification of PE as an underlying cause of cardiac arrest in children

Studies on use of fibrinolysis, embolectomy, thrombectomy with or without extracorporeal cardiopulmonary resuscitation in patients under 18 years who experienced an in-hospital cardiac arrest due to apparent or confirmed pulmonary embolism

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Treatment of Hyperkalaemia in Children with Cardiac Arrest (PLS 4160.17)

Part 1: Calcium

QUESTION

Should calcium vs. no calcium be used for paediatric CA caused by hyperkalaemia?	
POPULATION:	Paediatric CA caused by hyperkalaemia
INTERVENTION:	Calcium
COMPARISON:	No calcium
MAIN OUTCOMES:	Survival to discharge; Survival to discharge with favourable outcome (PCPC1-3 or no change from baseline); Survival to discharge with PCPC 1 or 2 or no change from baseline;
SETTING:	Any setting

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Paediatric cardiac arrest is rare and patients with hyperkalaemia are only a minority of these patients. So it is not a problem on population level. However, the optimal management strategy is indeed a priority for the individual patients who might arrest due to acute hyperkalaemia such as patients with renal failure, tumor lysis syndrome, massive tissue damage (crush syndrome), malignant hypertermia etc.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The use of calcium was not associated with harm in the subgroup of patients with hyperkalaemia but the desired outcomes were not significantly different for the use of calcium vs. no calcium. (1)	The use of calcium was generally associated with worse outcomes in the overall cohort of paediatric patients with cardiac arrest.

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Calcium use was associated with worse outcomes in the overall population of paediatric patients with cardiac arrest. The effect of calcium in patients with hyperkalaemia is is unclear (e.g. in patients with cardiac arrest and lactacidemia) but possibly can be associated with worse outcomes. (1)	Calcium use in OHCA adult patients with hyperkalaemia was associated with worse outcomes (Wang, 2016)

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate	The data were only from one registry-based study and the certainty of evidence was considered very low.	One animal study showed no benefit of calcium in cardiac arrest caused by hyperkalaemia. One adult study showed calcium use was associated

○ High ○ No included studies		with worse outcomes in OHCA with hyperkalaemia (2).
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 p-COSCA outcomes were assessed as the most important outcomes. It is not clear whether the parents of the children after cardiac arrest value those specific outcomes equally as the researchers and clinicians. However, for the p-COSCA critical outcomes (survival with favourable neurological outcome and survival with PCPCP 1-2 or no change from baselineit is likely that there is minimal uncertainty that these are desired outcomes for parents as well as for clinicians and also on the population level.	
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 calcium if used is relatively low. The other resources will not differ between the groups with or without the calcium.	
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		

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		

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		Calcium is inexpensive. But one need to consider the negative effects on cardiac arrest in general which are negative.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Calcium is commonly used during pediatric cardiac arrest although its effect is questionable and generally is associated with worse outcomes. (1)	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes		

○ Yes ○ Varies ○ Don't know		

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

For the children in cardiac arrest suspected to be caused by hyperkalaemia, there is insufficient evidence to suggest for or against the use of calcium.

Justification

The very low certainty evidence suggests association of calcium with worse outcomes but there are critical risks of bias and high uncertainty of associated effects mainly due to resuscitation time (duration of resuscitative efforts) bias. However, even in patients without cardiac arrest, any evidence of calcium having effect on ECG pathology was not shown in the systematic review performed. Therefore, the rationale behind the use of calcium for the assumed myocardium protecting effect is being questioned.

Research priorities

The role of calcium as a protection of myocardial cells from hyperkalaemia is recently questioned and the published studies do not support its presumed usefulness. More studies are needed to better understand this topic.

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Treatment of Hyperkalaemia in Children with Cardiac Arrest (PLS 4160.17)

Part 2: Bicarbonate

QUESTION

Should bicarbonate vs. no bicarbonate be used for pediatric CA caused by hyperkalaemia?	
POPULATION:	Pediatric CA caused by hyperkalaemia
INTERVENTION:	Bicarbonate
COMPARISON:	No bicarbonate
MAIN OUTCOMES:	All outcomes
SETTING:	Any setting

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No evidence exist for paediatric patients.	Paediatric cardiac arrest is rare and patients with hyperkalaemia are only a minority of these patients. So it is not a problem on population level. However, the optimal management strategy is indeed a priority for the individual patients who might arrest due to acute hyperkalaemia such as patients with renal failure, tumor lysis syndrome, massive tissue damage (crush syndrome), malignant hypertermia etc.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	No research evidence for paediatric patients.	Altogether, there is no evidence even in adult patients that the sodium bicarbonate alone is effective in lowering potassium levels (in the meta-analysis performed in the original SR for adult patients there was no effect on potassium levels).

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	No evidence for paediatric patients.	Sodium bicarbonate is generaly associated with worse patients outcomes. The causal effect however was not established and there are possible confounder biases for this effect.

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	No evidence for pediatric patients.	
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 predefined patient outcomes are similar to those defined in P-COSCA dataset, except that quality of life that was not predefined as an outcome. Other clinical outcomes in the original SR performed are standard clinical outcomes in cardiac arrest studies, however, it is not clear which of these outcomes are the most important for the patients and their parents themselves.
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	No evidence for the population in question.	
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies		Sodium bicarbonate is an inexpensive drug. There may be countries where it is not available for all.

○ Don't know		
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		Sodium bicarbonate is an inexpensive drug.
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		Negligible saving costs if sodium bicarbonate is not used.
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 may be countries where the availability might differ.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		Sodium bicarbonate was widely used in cardiac arrest and it was also recommended for use in cardiac arrest caused by hyperkalaemia based on patophysiological judgment of its properties. However, there is no scientific evidence for its use in the paediatric population and it was associated with worse outcomes in pediatric cardiac arrest patients.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know		

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

For children in cardiac arrest associated with hyperkalaemia, there is insufficient evidence to make a treatment recommendation for or against the use of sodium bicarbonate.

Justification

There is an absence of evidence on which to base the recommedation. The PLS TF did not feel there are additional considerations on which to make the decision.

Research priorities

The high quality RCTs are difficult to perform for such a rare condition or the acquisition of patients into the study to reach the statistical significance would take a very long time. Therefore, our best evidence in the future will probably come from the paediatric cardiac arrest registries preferably with high numbers of patients. However, such evidence will inevitably be downgraded for confounder and other bias.

Part 3: Insulin with Glucose or Salbutamol

QUESTION

Should insulin with glucose or salbutamol vs. no insulin with glucose and no salbutamol be used for paediatric patients in CA suspected to be caused by hyperkalaemia?	
POPULATION:	Paediatric patients in CA suspected to be caused by hyperkalaemia
INTERVENTION:	Insulin with glucose or salbutamol
COMPARISON:	No insulin with glucose and no salbutamol
MAIN OUTCOMES:	Survival to discharge; Survival to discharge with favourable outcome (PCPC1-3 or no change from baseline); Survival to discharge with PCPC 1 or 2 or no change from baseline;
SETTING:	Any setting

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Paediatric cardiac arrest is rare and patients with hyperkalaemia are only a minority of these patients. So it is not a problem on population level. However, the optimal management strategy is indeed a priority for the individual patients who might arrest due to acute hyperkalaemia such as patients with renal failure, tumor lysis syndrome, massive tissue damage (crush syndrome), malignant hypertermia etc.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The salbutamol was proven to have potassium lowering effect in the performed meta-analysis of the patients not in cardiac arrest(1, 2, 3, 4, 5, 6, 7, 8). It was not possible to perform meta-analysis of the studies with insulin with glucose because of the heterogeneity(9, 10, 11). However, the potassium lowering effect was proven in meta-analysis in adult patients for different doses. The magnitude of the potassium lowering effect in the cardiac arrest patient population is unclear.	The potassium lowering effect of the insulin with glucose as well as of the salbutamol IV requires up to 30-60 minutes in patients not in cardiac arrest.

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Since the population of patients in cardiac arrest due to hyperkalemia is small, the undersirable effects are trivial. There might be theoretical cumulative effect of salbutamol with adrenaline on the beta-receptors and insulin which could cause hypoglycemia.	

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low	No pediatric studies were identified.	

○ Moderate ○ High ● No included studies		
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 p-COSCA outcomes were assessed as the most important outcomes. It is not clear whether the parents of the children after cardiac arrest value those specific outcomes equally as the researchers and clinicians. However, for the p-COSCA critical outcomes (survival with favourable neurological outcome and survival with PCPCP 1-2 or no change from baseline) there probably is not be uncertainty that these are desired outcomes for parents as well as for clinicians, as well as desired outcomes on the population level.	
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 potassium lowering effect was proven in the population of pediatric patients not in cardiac arrest in the systematic review performed for salbutamol. For insulin with glucose, the meta-analysis could not be performed but the potassium lowering effect was consistent in adult population. The safety profile of these interventions was good. Adverse events included mainly tachycardia for salbutamol and hypo- or hyperglycemia for insulin with glucose. All were usually mild and non life-threatening.	
Resources required		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	Insulin with glucose and salbutamol are both inexpensive medications. However, there might be places where they are not easily available to everyone and the implementation of the good practice statement might add additional costs.	
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		
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		
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 might be places where the insulin with glucose or salbutamol IV might not be easily available to everyone and the implementation might add additional costs.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know		Although the intervention is likely well accepted in high-resource settings, it can be more difficult in the limited-resource setting (costs, personnel).
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes		Same as above.

○ Yes ○ Varies ○ Don't know		

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 using intravenous salbutamol or insulin with glucose (or a combination of both) in children with cardiac arrest associated with hyperkalaemia with the aim to lower the potassium levels during concurrently ongoing high-quality resuscitation efforts (Good Practice Statement).

Justification

The effects on potassium levels in the cardiac arrest patients were not studied so it is not clear whether the potassium-lowering effect would be present also in cardiac arrest patients. However, the Task Force agreed that the potential benefits of these pharmacological interventions outweigh potential risks in the cardiac arrest patients and their use is therefore justified. Despite limited evidence for clinical outcomes, an initial treatment strategy aiming at acutely lowering extracellular potassium levels simultaneously with more permanent potassium lowering strategies seems logical when hyperkalaemia is a suspected reversible cause of cardiac arrest. Only beta2-agonists were proven to have potassium lowering effect in paediatric patients by meta-analysis in the systematic review. Inhalation administration is generally not recommended in cardiac arrest. Insulin with glucose for the potassium lowering effect was studied in the pediatric patients but the high heterogeneity of the studies precluded the meta-analysis. PLS TF agreed that they would use insulin with glucose in case of suspected hyperkalemia despite the lack of high quality studies in pediatric patients. The insulin with glucose was used in this indication and it has proven potassium lowering effect in adult population.

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BP Targets after Return of Spontaneous Circulation (PLS 4190.01)

QUESTION

Should does >5th, 10th centile systolic blood pressure (SBP) , or > 5th, 10th or 25th centile mean arterial blood pressure (MAP) target within 6 hours (I) vs. compared with <5th, 10th centile SBP or < 5th, 10th or 25th centile MAP be used for infants and children in any setting (in-hospital or out-of-hospital cardiac arrest) after return of spontaneous circulation (ROSC), or return of circulation (ROC) (P) ?	
POPULATION:	Infants and children in any setting (in-hospital or out-of-hospital cardiac arrest) after return of spontaneous circulation (ROSC), or return of circulation (ROC) (P),
INTERVENTION:	Does >5th, >10th centile systolic blood pressure (SBP) target, or > 5th, 10th or 25th centile mean arterial blood pressure (MAP) within 6 hours (I)
COMPARISON:	Compared with <5th, 10th centile SBP or < 5th, 10th, 25th centile MAP
MAIN OUTCOMES:	Survival to hospital discharge; Survival with favourable neurological outcome;
SETTING:	In-hospital or out of hospital cardiac arrest (IHCA, OHCA)

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Many more infants and children get return of spontaneous circulation (ROSC), or return of circulation with the aid of ECMO (ROC), after cardiac arrest than those who survive to hospital discharge. Even fewer of those who do survive do so with favourable neurological outcomes. Once ROSC/ROC is achieved, the focus shifts towards ensuring adequate organ perfusion and reducing the risk of further neurological injury. Among the critical factors influencing post-cardiac arrest care, blood pressure control may play a pivotal role in maintaining adequate tissue perfusion and optimizing patient outcomes. Determining the optimal blood pressure targets in infants and children after ROSC/ROC poses a significant challenge due to lack of evidence. Clinical practice in this area is largely based upon a few pediatric studies, extrapolation from studies conducted in adult populations or expert consensus recommendations. While individual studies seem to suggest there is an association between hypotension post ROSC/ROC in infants and children, these studies are small and observational. It is also difficult to know if the association is causal or is a surrogate marker of more severe cardiac arrest. Potential benefits include both more survivors to hospital discharge, and also more survivors with favourable neurological outcomes. The present studies are all observational, while all studies, except Topjian 2019b (p88), provide information about vasopressor use, none of the studies describe if aiming for a specific blood target changes outcome, or how often it is achievable post ROSC/ROC. Use of higher blood pressure targets may have undesirable patient effects, such as longer length of stay and complications of requiring central access, but these are likely to be less important than the undesirable outcomes of patient death or survival with poor neurological outcome.	This is the second systematic review on this topic for the pediatric task force. The first was done in 2023, and it was repeated this year as there was a large new publication to add to the SR.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Based upon the evidence in this systematic review, the evidence suggests with very low certainty that a systolic blood pressure (SBP) target of > 5th centile norms within the first 6 hours post ROSC is better than < 5th centile norms for the critical outcomes of both survival to hospital discharge and favourable neurological outcomes at discharge. **Studies comparing SBP > or < 5th centile within the first 6 hours of ROC** For the critically important outcome (O) of survival, we have identified very-low-certainty evidence (downgraded for inconsistency and indirectness) from 4 observational studies (Topjian 2014 (Page 1518), Topjian 2018 (page 143), Topjian 2019b (p 24), Laverriere 2020 (page 143)) enrolling 931 children after in-hospital or out-of-hospital cardiac arrests (P), showing benefit from exposure to a systolic blood pressure greater than 5th centile (I) when compared with SBP less than 5th centile (C) (RR, 1.41; 95%CI, 1.2 to 1.60); P = 0.01); 173 more patients/1000 survived with the intervention [95% CI, 84 more patients/1000 to 253 more patients/1000 survived with the intervention]) For the critically important outcome (O) of survival with good neurological outcome, we have identified very-low-certainty evidence (downgraded for inconsistency and indirectness) from 3 observational studies (Topjian 2014 (page 1518), Laverriere 2020 (page 143), Ushpol 2024 (page 1)) enrolling 1193 children after in-hospital or out-of-hospital cardiac arrests (P), showing benefit from exposure to a systolic blood pressure greater than 5th centile (I) when compared with SBP less than 5th centile (C) (RR, 1.3; 95%CI, 1.06 to 1.6); P = 0.01); 132 more patients/1000 survived with the intervention [95% CI, 26 more patients/1000 to 264 more patients/1000 survived with the intervention]) **Outcomes** / **№ of participants (studies) Follow-up** / **Certainty of the evidence (GRADE)** / **Relative effect (95% CI)** Survival to hospital discharge assessed with: survival — 931 (4 non-randomised studies)[1,2,3,4] — ⨁◯◯◯ Very low[a,b] — **RR 1.41** (1.20 to 1.60) Survival with favourable neurological outcome assessed with: PCPC 1-2 or no change from baseline,(Topjian 2014 143, Ushpol 1) or PCPC 1-3 or no change from baseline (Gardiner 388) — 1193 (3 non-randomised studies)[1,4,5] — ⨁◯◯◯ Very low[c,d] — **RR 1.30** (1.06 to 1.60)	Although the effect size from the combined studies is small, the value of the outcomes is of high value and the potential impact on infants and children globally who get ROSC following a CA is large. The Gardner paper 2023 (p 388), Topjian 2019a (p 88) and Topjian 2019b (p 24) use BP norms adjusted for age, sex and **height,** Topjian 2018 (p 1518) and Ushpol (p 1) use age, and the other papers used BP norms adjusted for age and sex. The task force felt it was most appropriate to use BP norms **adjusted for age, sex and height**.

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	identified low-certainty evidence (downgraded for indirectness and imprecision) from 1 observational study (Gardner 2023, 388), (P), enrolling 693 patients with IHCA, from 18 PICU's, showing benefit from exposure to a SBP greater than 10th centile (I) when compared with SBP ≤10th centile (C) (RR, 1.210; 95%CI, 1.000 to 1.331); P =0.001); 138 more patients/1000 survived with the intervention [95% CI, 66 more patients/1000 to 213 more patients/1000 survived with the intervention]). For the critically important outcome (O) of survival with good neurological outcome, we have identified low-certainty evidence (downgraded for study design) from 2 studies, (Gardner 2023, 388; Ushpol 2024, 1) following ROC ,(P), enrolling 1325 patients, with IHCA and OHCA from 17 countries, showing benefit from exposure to a SBP greater than 10th centile (I) when compared with SBP ≤10th centile (C) (RR, 1.22; 95%CI, 1.10 to 1.35); P = 0.001); 116 more patients/1000 survived with the intervention [95% CI, 53 more patients/1000 to 185 more patients/1000 survived with the intervention]). 6. Gardner, Monique M, Hehir, David A, Reeder, Ron W, Ahmed, Tageldin, Bell, Michael J, Berg, Robert A, Bishop, Robert, Bochkoris, Matthew, Burns, Candice, Carcillo, Joseph A, Carpenter, Todd C, Dean, J Michael, Diddle, J Wesley, Federman, Myke, Fernandez, Richard, Fink, Ericka L, Franzon, Deborah, Frazier, Aisha H, Friess, Stuart H, Graham, Kathryn, Hall, Mark, Harding, Monica L, Horvat, Christopher M, Huard, Leanna L, Maa, Tensing, Manga, Arushi, McQuillen, Patrick S, Meert, Kathleen L, Morgan, Ryan W, Mourani, Peter M, Nadkarni, Vinay M, Naim, Maryam Y, Notterman, Daniel, Pollack, Murray M, Sapru, Anil, Schneiter, Carleen, Sharron, Matthew P, Srivastava, Neeraj, Tilford, Bradley, Viteri, Shirley, Wessel, David, Wolfe, Heather A, Yates, Andrew R, Zuppa, Athena F, Sutton, Robert M, Topjian, Alexis A. Identification of post-cardiac arrest blood pressure thresholds associated with outcomes in children: an ICU-Resuscitation study..Critical Care; 2023. 7. Ushpol A, Je SNiles D,Majmudar T,Kirschen M,del Castillo J,Buysse C,Topjian A,Nadkarni V,Gangadharan S,for the PediRES-Q investigators. Association of blood pressure with neurologic outcome at hospital discharge after pediatric cardiac arrest resuscitation.Resuscitation; 2024. a. IHCA only b. Only one study available c. Only two studies available, but multiple centres and countries **Studies comparing MAP > or < 5th centile within the first 6 hours of ROC** For the critically important outcome (O) of survival with good neurological outcome, we identified low-certainty evidence (downgraded for study design) from 1 study, (Ushpol 2024,1) following ROC, enrolling 787 patients with IHCA and OHCA, from 60 sites and 17 countries, showing benefit from exposure to a mean arterial blood pressure (MAP) greater than 5th centile (I) when	

compared to MAP < 5th centile (C) 1.36 (95%CI, 1.18 to 1.58); P<0.01) 158 more patients/1000 survived with the intervention [95% CI, 79 more patients/1000 to 254 more patients/1000 survived with the intervention]).

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)
favourable neurological survival (PCPC 1 or 2 or no change) at discharge assessed with: PCPC at discharge	787 (1 non-randomised study)[8,a]	⊕⊕◯◯ Low[a]	**RR 1.36** (1.18 to 1.58)

8. Ushpol A, Je SNiles D,Majmudar T,Kirschen M,del Castillo J,Buysse C,Topjian A,Nadkarni V,Gangadharan S,for the PediRES-Q investigators. Association of blood pressure with neurologic outcome at hospital discharge after pediatric cardiac arrest resuscitation.Resuscitation; 2024.

a. Single study but 60 sites and 17 countries

Studies comparing MAP > or < 10th centile within the first 6 hours of ROC

For the critically important outcome (O) of survival with good neurological outcome, we identified low-certainty evidence (downgraded for study design) from 1 study, (Ushpol 2024,1) following ROC, enrolling 787 patients with IHCA and OHCA, from 60 sites and 17 countries, showing benefit from exposure to a mean arterial blood pressure (MAP) greater than 10th centile (I) when compared to MAP < 10th centile (C) (RR 1.21: 95%CI, 1.05 to 1.32); P = 0.001); 102 more patients/1000 survived with the intervention [95% CI, 24 more patients/1000 to 156 more patients/1000 survived with the intervention]).

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)
favourable neurological outcome (PCPC 1 or 2 or no change) at discharge assessed with: PCPC at discharge	787 (1 non-randomised study)[9,a]	⊕⊕◯◯ Low	**RR 1.21** (1.05 to 1.32)

9. Ushpol A, Je SNiles D,Majmudar T,Kirschen M,del Castillo J,Buysse C,Topjian A,Nadkarni V,Gangadharan S,for the PediRES-Q investigators. Association of blood pressure with neurologic outcome at hospital discharge after pediatric cardiac arrest resuscitation.Resuscitation; 2024.

a. Single study, but 60 centers and 17 countries

Studies comparing MAP > or < 25th centile within the first 6 hours of ROC

For the critically important outcome (O) of survival with good neurological outcome, we identified low-certainty evidence (downgraded for study design) from 1 study, (Ushpol 2024,1) following ROC, enrolling 787 patients with IHCA and OHCA, from 60 sites and 17 countries, showing benefit from exposure to a mean arterial blood pressure (MAP) greater than 25thth centile (I) when compared to MAP < 25th centile (C) (RR 1.29: 95%CI, 0.96 to 1.74); P = 0.001); 150 more patients/1000 survived with the intervention [95% CI, 21 fewer patients/1000 to 382 more patients/1000 survived with the intervention]).

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Favorable neurological outcome at discharge (PCPC 1 or 2 or no change from baseline) assessed with: PCPC	787 (1 non-randomised study)[9,a]	⨁⨁◯◯ Low	**RR 1.29** (0.96 to 1.74)

10. Ushpol A, Je SNiles D,Majmudar T,Kirschen M,del Castillo J,Buysse C,Topjian A,Nadkarni V,Gangadharan S,for the PediRES-Q investigators. Association of blood pressure with neurologic outcome at hospital discharge after pediatric cardiac arrest resuscitation.Resuscitation; 2024.

a. Single study but 60 centers and 17 countries.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The undesirable effects of not surviving to hospital discharge and surviving with unfavourable neurological outcomes are significant. However, we did not look at reasons for non-survival as an *a priori* outcome, and the studies do not report value to families of survival with un-favourable neurological outcomes vs death.	There might be specific sub-groups, such as an outcome with GCOS of 5, where the undesirable anticipated effects are very substantial, especially in some populations.

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	Seven studies were included in the systematic review. All studies were non-randomised cohort studies, with five out of the seven being secondary analyses of other studies. Two of these (Topjian 2018 (p 1518)) and Topjian 2019b (p 24)) were secondary analysis of multicentre RCT's (THAPCA In Hospital Cardiac Arrest (IHCA)), and THAPCA Out of Hospital Cardiac Arrest (OHCA)). Topjian 2019a (p 88), was a secondary analysis of a prospective multicentre cohort study, Topjian 2014 (p 143) was a retrospective cohort study from a	

	multicentre database of cardiac arrest, the Pediatric Emergency Care Applied Research Network (PECARN). The only single centre study, Laverriere 2020 (p 143) (Children's Hospital of Philadelphia), was a retrospective cohort study of both IHCA and OHCA from a prospectively collected database. The two largest studies, Gardiner 2023 (p 388), with 693 infants and children, was a secondary analysis of prospectively collected data for the ICU-RESUCitation trial and involved 18 US centres. The blood pressure cut offs of systolic blood pressure greater than 10th centile and diastolic blood pressure of greater than 50th centile were generated from receiver operator characteristic curves and spline curves. While Ushpol 2024 (p 1), which included 787 infants and children, was a retrospective analysis of data collected prospectively by the Pediatric Resuscitation Quality Collaborative (pediRES-Q), from 60 sites and 17 countries, they reported on the association of mean blood pressures and neurological outcomes after cardiac arrest. The authors provided, unpublished data on systolic blood pressure. They plan to publish this data as a post publication supplement to the original publication. **Studies comparing SBP or MAP by centile within the first 6 hours of ROC** To summarize, in our final analysis, we included four observational studies (Topjian 2014, 1518; Topjian 2018, 143; Topjian 2019a, 88; Laverriere 2020, 143) examining the BP targets of systolic BP >5th percentile for age compared with systolic BP ≤5th percentile within the first six hours post ROC (including 8 patients on ECMO). The pooled sample included 463/930 (49.8%) patients following in-hospital cardiac arrest (IHCA), and 467/930 (50.2%) after out-of-hospital cardiac arrest (OHCA). We included two studies (Gardner 2023, p388; Ushpol 2024, 1) which enrolled 1,180 infants and children after IHCA (excluding patients requiring extra-corporeal life support). These studies compared systolic BP >10th centile with systolic BP ≤10th centile within the first six hours post ROC. Lastly, we included one observational study, from 60 centers and 17 countries (Ushpol 2024,1), that included 787 patients (IHCA 625, OHCA 161), and looked at the association between the lowest MAP in the first 6 hours post ROC and neurologic outcome at discharge.	
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 ILCOR P-COSCA initiative developed a core outcome set specific for pediatric cardiac arrest studies. The design and methods of the initiative included use of a Delphi process to develop consensus on a core domain set. (Topjian 2020 e246) The P-COSCA outcomes of survival to discharge and survival to discharge with favourable neurological outcomes were chosen as critical outcomes for this review and are highly valued.	
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	While acknowledging the very low level of certainty, the current available data suggests that a mean arterial or systolic blood pressure (SBP) target of greater than 10th centile norms within the first 6 hours post ROC is better than less than 10th centile norms for the critical outcomes of both survival to hospital discharge and favourable neurological outcomes at discharge. As outlined in the knowledge gaps, we do not know if a higher mean arterial or systolic pressure would result in greater improvements in both the critical outcomes of survival to hospital discharge and favourable neurological outcomes at discharge, as the data is not available. The recent paper by Ushpol (2024,1) included in this review, has data comparing a mean arterial blood pressure in the first 6 hours post ROC of greater than 25th centile with less than 25th centile, showing benefit of a target greater than 25th centile, but with wide confidence intervals (RR 1.29: 95%CI, 0.96 to 1.74); P = 0.001); 150 more patients/1000 survived with the intervention [95% CI, 21 fewer patients/1000 to 382 more patients/1000 survived with the intervention]).	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There are no specific studies looking at this, but in settings where ICU level of care is available, measuring and managing blood pressure is standard of care. In 6 studies information was provided around inotrope use, but this was not analysed as it was not an *a priori* question or subgroup. There was heterogeneity between the studies as to how they reported inotrope use.	In places where ICU level of care is not available for infants and children post cardiac arrest this will be more difficult to achieve, but the principle is likely to still be acceptable to stakeholders. It was felt by the task force that a good practice statement should be stated that in infants and children who have cardiac arrest followed by ROSC, blood pressure should always be measured as part of their post cardiac arrest care.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There is no specific research evidence to support the intervention being feasible to implement, but management of blood pressure is part of standard post cardiac arrest care, and the blood pressure is routinely measure and managed as standard of care for all pediatric intensive care patients.	In places where ICU level of care is not available for infants and children post cardiac arrest this will be more difficult to achieve, but the principle is likely to still be acceptable to stakeholders.

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
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 in infants and children post return of circulation, following an in-hospital or out-of-hospital cardiac arrest, that a systolic or mean arterial pressure blood pressure >10th centile for age should be targeted (weak recommendation, very low certainty evidence).

Justification

The Pediatric Task Force considered that the measurement and treatment of blood pressure is a standard component of the post-resuscitation bundle of care after cardiac arrest. However, current post-cardiac arrest blood pressure treatment targets and thresholds for treatment have been suggested through expert consensus and evidence extrapolated from individual studies. The Pediatric Task Force therefore undertook an ILCOR led systematic review of the current evidence in 2023 and 2024.

Measurement of blood pressure is a low-cost intervention and available in nearly all resource settings. However, the taskforce did not review the cost-effectiveness of intermittent, non-invasive blood pressure measurement with invasive arterial or continuous BP measurement.

There were no randomized controlled studies comparing two treatment approaches, or two BP targets following cardiac arrest. The available evidence consisted of observational data demonstrating the impact of exposure to different blood pressure thresholds on clinically important outcomes. However, the blood pressure thresholds were chosen either a-priori by investigators as a clinically important threshold (eg ≤5th centile), or the cut off value was derived statistically from the population data, as the most significant inflection point (≤10th centile). The Pediatric Task Force focused on the impact of hypotension on clinical outcome and did not include studies assessing the impact of normotension or hypertension on outcomes.

The Pediatric Task Force considered the exposure overlap of the two thresholds of systolic blood pressure <5th centile and <10th centile. It was not statistically possible to perform meta-regression to compare the two treatment targets. The consensus of the TF was that higher threshold cut off target (<10th centile) included the population included in the <5th centile group. In addition, acknowledging the low certainty of evidence, the target of >10th centile systolic BP was the more acceptable systolic

BP goal and ensured avoidance of the 5th to 10th BP centiles that were associated with worse outcome in the larger study by Gardner (2023, 388).
Based on one retrospective observational study, the task force considered the multivariable logistical regression data evaluating the association of mean arterial pressure (MAP) with favorable neurologic outcome. The evidence suggests that in the first 6 hours post ROC a lowest documented MAP between 5th -74th percentile for age was associated with favorable neurologic outcome. (Ushpol 2024, 1) The consensus of the TF was that MAP centiles less than 10th centile for age were associated with worse outcomes.
The Pediatric Task Force felt, that although the effect size from the pooled studies is small, the value of the outcome is high and the potential impact on infants and child survivors globally is therefore large

Subgroup considerations

Two papers Topijan 2019b (p 24) and Topijan 2014 (p 143) targeted temperature management was applied. The SBP measurements were obtained during the 0-6 hour time frame from when the targeted temperature management was applied and not from the time of sustained ROSC. In both studies targeted temperature management was initiated within the first 6 hours of sustained ROSC.

Implementation considerations

Management of blood pressure is a component of standard pediatric care treatment.

Monitoring and evaluation

See research priorities below.

Research priorities

• There are no interventional randomized controlled trials comparing benefit or harm of targeting specific BP targets.
• Information on impact of pre-hospital BP measurement or treatment for OHCA is missing.
• It is unclear if specific sub-groups (e.g. medical and cardiac surgical patient's vs medical patients) of pediatric patients post return of circulation require different BP targets (systolic, MAP or diastolic).
• Observational data demonstrate an association between exposure to lower BP targets and worse outcome; however, more data are required to demonstrate a causal relationship between treatment interventions to achieve higher BP targets and improved outcomes. In addition, the TF was unable to assess the benefits or harm of exposure to hypertension in the period after cardiac arrest.
• We encourage, consistent reporting of BP monitoring definitions (e.g. site, repeated measurement, component of BP (systolic, diastolic, mean BP) and definitions of exposure to hypotension (e.g. single episode versus percentage of time), and collaboration between sites and investigators to provide answers.
• Most of the observational data is based upon a single episode of hypotension in the first 6 hours post ROC, rather than a burden of hypotension in the post arrest period.
• Majority of included data report exposure to BP thresholds within six hours; impact of BP interventions outside this timeframe may be important and remain untested.
• It is unclear which strategy is optimal to achieve a BP above the threshold level (e.g. fluids, vasopressor support, mechanical support), and interventions themselves may be associated with harm.
• There is limited data if a BP target or another marker of end organ perfusion is the most appropriate target.
    - Optimal BP targets during extracorporeal life support (ECLS) post-cardiac arrest are unknown. Some patients on ECLS may have a lack of heart pulsatility which also limits the use of systolic BP in this patient group
    - There is limited data available on the optimal strategy to use when cerebral autoregulation is impaired.

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Biomarkers for Prognostication of Survival with Poor Neurological Outcome after Cardiac Arrest (PLS 4220.01)

QUESTION

Should blood based biomarker measurement be used for predicting poor neurological outcomes in children after cardiac arrest?	
POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Blood Lactate, pH and other blood-based biomarkers (eg S100b, NSE, NfL, GFAP)
COMPARISON:	none
MAIN OUTCOMES:	Prediction of survival with poor neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of >3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score >2, or change in PCPC score from baseline >2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Aug 27th 2024.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prediction of poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Lactate** Lactate was evaluated in 6 studies.[1-6]. Only two studies identified a FPR <1% for poor outcome prediction. The first used a lactate threshold >28.8 mmols/L at <1 hour [6] with a corresponding sensitivity of 11%. The second, used failure of lactate clearance to <2mmol/L by 48 hours with a sensitivity of 23%. [1] All other tests with a lactate level >2mmols at 6-12, 24 and 48 hours had a reported FPR of 14-84%. [1, 3-5] A lactate >5mmol/L at <1 hour or 24 hours had a FPR of 34% and 11% respectively. [2] Lactate was not a reliable prognostic test. **pH** pH was evaluated in 4 studies. [1, 4-6] pH thresholds were <6.6, <7.0, <7.3, and >7.5 at resuscitation and within 1 hour,	

	6-12 hours and 24 hours of return of circulation. Extremes of pH <6.6 and >7.5 had a FPR for poor outcome prediction of <5% but very low <14% sensitivity. Blood pH of <7.0 measured 6-12 hours from ROC also had a FPR of 3-4% and a low sensitivity of 3-14% for predicting poor neurological outcome. [4, 5] pH was not a reliable prognostic test. **Neuronal biomarkers** Three study reported NSE and S100b in 156 children [6-8]. Cut off values were calculated and reported to classify low FPR for poor neurological outcome. Values were calculated at <1, 6-12, 24, 48 and 72 hours. Wide (10+ fold) variation in cutoff values were reported. At 24 hours s100b levels of 0.128 µg/L [8], 2.0 µg/L [7] and 2.24 µg/L [6] were reported to predict a poor neurological outcome with a FPR of 0% (95% CI 0-20%) and a sensitivity of 29-38%. Similarly, NSE level of both 53.1 µg/L [8], 56 µg/L [7] and 132.7 µg/L [6] predicted a poor neurological outcome with a FPR of 0% (95% CI 0-20%) and a sensitivity of 19-26%. MBP was assessed in one study at 24 and 48 hours with cut off threshold of 5.83 µg/L predicting poor neurological outcome with low FPR 0% (95%CI 0-20%). NSE, S100b and MBP all fulfilled reliable test criteria but with wide range of cutoff thresholds in the individual studies. Only one study reported UCH-L1, NfL, Tau and GFAP biomarker prediction of poor neurological outcome at 24, 48 and 72 hours.[9] Cut off threshold values were calculated to produce an optimal FPR of 4-5% (95%CI 1 to 15%) and corresponding sensitivity of 12-61%.	

Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large o Moderate o Small o Trivial o Varies o Don't know	A false positive prediction of a poor outcome based on lactate, pH of blood biomarker levels above the cut off level may lead to and premature withdrawal of life sustaining therapy in a patient who would have a good neurological outcome. This is likely to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from non-neurological causes of a raised lactate.	

Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low o Low o Moderate o High o No included studies	The certainty of evidence from lactate and pH is very low (down graded for study design, risk of bias, inconsistency, indirectness, and imprecision). Risk of bias is high especially self-fulfilling prophecy and non-specific nature of lactate and acidosis metabolism. Other blood-based biomarkers are more specific for neurological injury; however the certainty of evidence is low (downgraded for risk of bias and publication bias) due to the wide variability in the cut off values demonstrating imprecision in the use of this test and potential for other studies, not reporting dichotomous results to have been excluded.	

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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA).[10] However, tools and definitions to measure poor neurological outcome in our studies were the PCPC >2 and >3, or >1 change in PCPC and the VABS II <70. Change from baseline neurological status may be more important than the neurological functional level, especially in infants and children with pre-existing neurological impairment. We defined poor neurological outcome prediction as imprecise when the false positive rate (FPR) was >1%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. We defined the reliability of the evidence as reliable if the FPR was <1% and the upper 95% confidence intervals <10%; and moderately reliable if FPR was <1% with without a restriction on width of 95% confidence interval. A low false positive rate means that a low proportion of patients, predicted to have a poor outcome will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). The task force felt that when focused on accuracy of predicting a poor outcome - a low false positive rate (e.g. <1%) is more desirable to avoid falsely pessimistic prediction than a high sensitivity. The cut off of <1% FPR (equivalent to >99% specificity) was chosen as the consequences of false pessimism is substantial. False pessimism may result in discontinuation of life sustaining therapy in a patient who will eventually have a good outcome. Continuing treatment may involve increased resources; however, this may also allow more time for further prognostic evaluation and further additional tests. Reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment.	
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	Lactate and pH were non-specific markers of hypoxic-ischemia following cardiac arrest. Extreme values (very high lactate, very low pH) have a low FPR in the included studies, but frequent outliers and very low sensitivity were reported. Four studies identified cut-offs across a range of blood-based biomarkers (S100b, NSE, MBP, UCH-L1, NfL, Tau and GFAP) that are known to represent brain injury and are associated with poor neurological outcome with a low FPR. However, sensitivity was low and the wide range of reported cut off thresholds preclude any accurate description of clinical utility. Furthermore, these tests require specialized laboratory equipment and are not widely available, even though they only require the patient's blood.	
Resources required		

How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	Lactate and pH is measured on blood gas analysers and is easily accessible in most settings. However, other blood-based biomarkers require specialist equipment and are currently not available in many health care settings. However, no study evaluated cost in our study.	
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	We did not identify any studies specifically assessing costs of blood-based biomarkers for prognostication after cardiac arrest.	
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	We did not identify any studies addressing cost-effectiveness.	
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	A problem of inequity is possible, since assessment of biomarkers implies resources that cannot be universally available.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any study assessing acceptability, but acceptability is likely.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Although may not be available in resource limited settings.	

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 that no single blood-based biomarker examination test be used in isolation to predict poor neurological outcome in children after cardiac arrest (strong recommendation, very-low certainty evidence).

Clinicians should use multiple tests in combination for poor neurological outcome prediction (good practice statement).

We suggest against using lactate and pH after return of circulation (ROC), for predicting poor neurological outcome in children after cardiac arrest at any time point (weak recommendation, very-low-certainty evidence).

There is insufficient evidence to make a recommendation for or against the use of other blood-based biomarkers (e.g. S100beta, Neuron Specific Enolase, Neurofilament Light Chain (NfL) etc.) after ROC for predicting poor neurological outcome in children after cardiac arrest at any time point.

Justification

- The Task Force considered the use of single biomarker tests in predicting a poor neurological outcome.
- The available evidence had a high risk of bias based on high heterogeneity across studies, small number of studies and small number of patients included in addition to lack of blinding, variation in test assessment and performance, and variability in outcome measurement. Therefore, no meta-analysis was performed. Overall assessment of test performance was based on visual assessment of forest plots.
- Included studies were observational studies and randomized controlled trials, but not primarily designed to test prognosis of blood biomarkers.
- Lactate and pH were non-specific markers of hypoxic-ischaemia following cardiac arrest. Extreme values (very high lactate, very low pH) have a low FPR in the included studies, but frequent outliers and very low sensitivity were reported.
- Four studies identified cut-offs across a range of blood-based biomarkers (S100b, NSE, MBP, UCH-L1, NfL, Tau and GFAP) that are known to represent brain injury and are associated with poor neurological outcome with a low FPR. However, sensitivity was low and the wide range of reported cut off thresholds preclude any accurate description of clinical utility. Furthermore, these tests require specialized laboratory equipment and are not widely available, even though they only require the patient's blood.
- No studies reported any assessment of the confounding influence of medication. None of the included studies specifically excluded the presence of residual sedation at the time clinical examination was assessed.
- Lack of blinding is a major limitation of biomarker tests, even if the withdrawal of life-sustaining therapy based on test results has not been documented in any of the studies included in our review. No studies included blinding of test results from treating clinicians and only one study had blinded outcome assessment.

Subgroup considerations

none

Implementation considerations

Lactate levels and lactate clearance is widely used to guide therapy, thus only relevant implementation considerations are for settings without access to this biomarker and interpreting in context of whole patient because of the many potential confounders.
Until blood-based biomarkers become more widely used (i.e., more indications with higher certainty of evidence), this test will likely be used for research purposes primarily. The field is growing quickly and equipment is becoming more accessible so that the clinician may adopt this test in the future.

Research priorities

- This is a relatively new field of research and holds considerable promise. There are a range of potential candidate biomarkers more specific for neurological injury (e.g. NSE, s100b, NFL, GFAP, Tau, UCH-L1) that should be explored.
- Economic cost evaluation and cost-effectiveness studies are required as biomarker testing can be expensive.
- Further research is required on multi-modal prognostication, timing, definitions of testing, accurate outcome timing and outcome definition.
- We encourage wider research and consultation with patients, children, parents, guardians and caregivers, health care professionals and members of the wider society on understanding survivorship after pediatric cardiac arrest to inform correct definitions and framework of neurological outcome for prediction research.

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Clinical Examination (GCS and Motor) for Prognostication of Survival with Poor Neurological Outcome after Cardiac Arrest (PLS 4220.02)

QUESTION

Should coma score, absence of motor response or brain stem reflex vs. none or presence of reflex be used for predicting poor neurological outcomes in children after cardiac arrest?	
POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Coma score, absence of motor response or absence of brain stem reflex assessed within 10 days after cardiac arrest.
COMPARISON:	None or presence of response or reflex
MAIN OUTCOMES:	Prediction of death or survival with poor neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of >3, or Vineland Adaptive Behavioural scale-II < 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death).
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Aug 27th 2024.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, it has a low rate of survival and high chance of neurological injury. Prediction of good or poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	*Coma Level* The relationship between coma assessment using the GCS motor score alone or total GCS and poor neurological outcome was evaluated in 3 studies[1-3] including 296 patients. Outcomes were assessed at intensive care unit discharge, hospital discharge, and 6 months. GCS motor score of less than 4 within 1 hour and at 4 to 6 hours after ROC had a sensitivity of 94% and 93% for predicting poor neurological outcome at 6 months, with a high corresponding FPR of 83% and 50% respectively.[1] Using total GCS measured at resuscitation or within 1 hour, a score of 4 or less predicted poor neurological outcome with a high sensitivity of 86% but a high FPR of 70%.[3] A total GCS score of 7 or less had a slightly higher sensitivity of 92%, with a FPR of 69%.[2] However, only 1 study was available	

	to assess each test using total GCS or GCS motor score cutoff or at each testing time point. GCS and coma was only assessed up to 24 hour. Later coma, or delayed awakening was not assessed in any study. GCS was an unreliable test up to 24 hours for poor outcome prediction. *Motor Response* The absence of a motor response to any stimulus was evaluated in 1 study.[4] Sensitivity for prediction was 70%, 73% and 61% at <1 hour, 48 hours, and 72 hours after ROC with up to 27 patients. FPR only reached <1% (95% CI 0-28%) at 72 hours testing timepoint. Motor response was moderately reliable in only one study at 72 hours. *Brainstem Reflex* The presence of brainstem reflexes to predict poor neurological outcome at intensive care unit or hospital discharge was evaluated in 3 studies[5-7] including 118 patients. Evoked responses to pain, gag reflex, and cough reflex were assessed at 6 to 12 hours, 24 hours and 72 hours. Predictive sensitivity of absence of pain response at 6 to 12 hours was 33% with an FPR of 0% (95%CI 0-15%).[5] The absence of a gag and cough reflex at 24 hours both predicted a poor neurological outcome with a sensitivity of 65-68% and FPR of 60% respectively.[6] Brainstem reflex was moderately reliable in only one test at 6-12 hours.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large o Moderate o Small o Trivial o Varies o Don't know	A false positive prediction of a poor outcome and discontinuing treatment based on pupillary reactivity may lead to inappropriate treatment withdrawal in a patient with a god neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from non-neurological causes of pupil reactivity (e.g. medication).	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low o Low o Moderate o High o No included studies	The certainty of evidence from coma, motor response and brainstem reflex is very low because of the risk of bias, especially risk of confounding from concurrent medication (sedative drug) use and risk of self-fulfilling prophecy. Evidence was also downgraded for impression.	
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 o Possibly important uncertainty or variability o Probably no important uncertainty or variability o No important uncertainty or variability	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA).[8] However, tools and definitions to measure poor neurological outcome in our studies were the PCPC >2 and >3, or >1 change in PCPC and the VABS II <70. Change from baseline neurological status may be more important than the neurological functional level, especially in infants and children with pre-existing neurological impairment.	

	We defined poor neurological outcome prediction as imprecise when the false positive rate (FPR) was >1%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. We defined the reliability of the evidence as reliable if the FPR was <1% and the upper 95% confidence intervals <10%) and moderately reliable if FPR was <1% with without a restriction on width of 95% confidence interval. A low false positive rate means that a low proportion of patients, predicted to have a poor outcome will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). The task force felt that when focused on accuracy of predicting a poor outcome - a low false positive rate (e.g. <1%) is more desirable to avoid falsely pessimistic prediction than a high sensitivity. The cut off of <1% FPR (equivalent to 99% specificity) was chosen as the consequences of false pessimism is substantial. False pessimism may result in discontinuation of life sustaining therapy in a patient who will eventually have a good outcome. Continuing treatment may involve increased resources; however, this may also allow more time for further prognostic evaluation and further additional tests. Reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment..	
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	Considering the low sensitivity of pupillary light reflex and high and unreliable false positive rate in the first 24 hours, the balance of effects favours not using pupillary light reflex as a predictor of poor neurological outcome in the early period after ROC. However, at 48 and 72 hours, the low FPR (<1%) and moderately reliable 95% CI, the balance of effect favours the use of pupillary light reflex as a predictor of poor neurological in this later period.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Costs for the clinical assessment of coma, motor response and brain stem reflex are negligible. However, no study assessing savings from prognostication based on these clinical examinations has been included in our review.	
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	We did not identify any studies assessing cost of clinical examination.	

○ High ● No included studies		

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	We did not identify any studies addressing cost-effectiveness.	

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	Considering the negligible costs of clinical examination, a problem of inequity is unlikely.	

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any study assessing acceptability, but acceptability is likely.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Although feasibility was not specifically addressed in any of the studies included in this review, the assessment of coma, motor response and brain stem reflex does not require special skills. The key requirement is training and education of the clinician performing the exam. The examiner needs to be familiar with the basics of clinical neurological examination.	

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 (GCS / Coma ≤ 24 hours)**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

We recommend that no single clinical examination test be used in isolation to predict poor neurological outcome in children after cardiac arrest (strong recommendation, very-low certainty evidence).

Clinicians should use multiple tests in combination for poor neurological outcome prediction (good practice statement).

We suggest against using GCS within 24 hours after ROC to predict poor neurological outcome in children after cardiac arrest (weak recommendation, low-certainty evidence).

There is insufficient evidence to make a recommendation for or against the use of other brainstem or motor response tests to predict poor neurological outcome in children after cardiac arrest at any time point.

Justification

Coma assessment using GCS was unreliable with high FPR rates in all assessments up to 24hours after ROC following cardiac arrest. It was not reported in studies after 24 hours, and use of GCS or coma assessment at a later time point (e.g. assessment of delayed awakening) can not be judged.
For overall motor response, and brain stem test, only one study was available (with small patient sample size) for each test and time point, with variable FPR and sensitivity and therefore due to insufficient evidence no treatment recommendation could not be made.
No studies reported any assessment of confounding influence of medication. No studies included blinding of test results from treating clinician and only one study had blinded outcome assessment.
None of the included studies specifically excluded the presence of residual sedation at the time coma score was assessed. Lack of blinding is a major limitation of coma score, even if WLST based on coma score only has not been documented in any of the studies included in our review.
Despite its limitations, given the ease of assessment and the minimal equipment required, the balance between the costs and benefits favours benefits.

Subgroup considerations

None

Implementation considerations

Coma and motor response is an easy clinical assessment; however, the examiner requires knowledge of basic neurological examination.

Monitoring and evaluation

None

Research priorities

Use of coma score, including GCS motor score and other reported scores (e.g. FOUR score), require assessment in the paediatric population. FPR at 72 hours was identified using absence of motor response; however, only in single studies with small sample sizes. Further assessment is encouraged.

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Clinical Examination (Pupillary Response) for Prognostication of Survival with Poor Neurological Outcome after Cardiac Arrest (PLS 4220.02)

(PLS 4220.02)

QUESTION

Should absence of pupillary light reflex (PLR) vs. presence be used for predicting poor neurological outcomes in children after cardiac arrest?	
POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Pupillary light reflex (PLR), bilaterally absent, within 10 days after cardiac arrest.
COMPARISON:	Present pupillary light reflex response
MAIN OUTCOMES:	Prediction of death or survival with poor neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of >3, or Vineland Adaptive Behavioural scale-II < 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death).
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Aug 27th 2024.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, it has a low rate of survival and high chance of neurological injury. Prediction of poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The predictive ability of absence of pupillary light reflex to classify poor neurological outcome was evaluated in 9 studies [1-9] in 402 patients within 1 hour, 6 to 12 hours, 24 hours, and 72 hours after resuscitation. Between <1 hour and 24 hours, 6/7 studies reported FPR >10% (up to 60%) for predicting poor neurological outcome. [1,4-8] At 48 and 72 hours after ROC, FPR was less than 1% but with wide confidence interval (95% CI 0-40%) and corresponding sensitivity for predicting poor outcome was 12-46%. [1,5,9] Poor neurological outcome was assessed at PICU or hospital discharge in 6 studies [1-3,7,8,10] and at 6 months in 3.[4-6] No studies evaluated automated pupillometer monitoring devices. Pupil reactivity prior to 24	

	hours was not a reliable prognostic test. At 48 and 72 hours pupil reactivity was a moderately reliable test.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large o Moderate o Small o Trivial o Varies o Don't know	A false positive prediction of a poor outcome and discontinuing treatment based on pupillary reactivity may lead to inappropriate treatment withdrawal in a patient with a god neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from non-neurological causes of pupil reactivity (e.g. medication).	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low o Low o Moderate o High o No included studies	The certainty of evidence from pupil light reflect is very low because of the risk of bias, especially self-fulfilling prophecy.	
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 o Possibly important uncertainty or variability o Probably no important uncertainty or variability o No important uncertainty or variability	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA).[11] However, tools and definitions to measure poor neurological outcome in our studies were the PCPC >2 and >3, or >1 change in PCPC and the VABS II <70. Change from baseline neurological status may be more important than the neurological functional level, especially in infants and children with pre-existing neurological impairment. We defined poor neurological outcome prediction as imprecise when the false positive rate (FPR) was >1%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. We defined the reliability of the evidence as reliable if the FPR was <1% and the upper 95% confidence intervals <10%) and moderately reliable if FPR was <1% with without a restriction on width of 95% confidence interval. A low false positive rate means that a low proportion of patients, predicted to have a poor outcome will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). The task force felt that when focused on accuracy of predicting a poor outcome - a low false positive rate (e.g. <1%) is more desirable to avoid falsely pessimistic prediction than a high sensitivity. The cut off of <1% FPR (equivalent to 99% specificity) was chosen as the consequences of false pessimism is substantial. False pessimism may result in discontinuation of life sustaining therapy in a patient who will eventually have a good outcome. Continuing treatment may involve increased resources; however, this may also allow more time for further prognostic evaluation and further additional tests. Reasons for not	

	achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment..	

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	Considering the low sensitivity of pupillary light reflex and high and unreliable false positive rate in the first 24 hours, the balance of effects favours **not** using pupillary light reflex as a predictor of poor neurological outcome in the early period after ROC. However, at 48 and 72 hours, the low FPR (<1%) and moderately reliable 95% CI, the balance of effect favours the use of pupillary light reflex as a predictor of poor neurological in this later period.	

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Costs for the assessment of pupillary reflex are negligible. However, no study assessing savings from prognostication based on pupillary reflex has been included in our review.	

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	We did not identify any studies assessing cost of pupillary light reflex.	

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	We did not identify any studies addressing cost-effectiveness.	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced	Considering the negligible costs of pupillary light reflex, a problem of inequity is unlikely.	

● Probably no impact ○ Probably increased ○ Increased ○ 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	We have not identified any study assessing acceptability, but acceptability is likely.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Although feasibility was not specifically addressed in any of the studies included in this review, the assessment of pupillary light reflex does not require special skills. The key requirement is a light source. The examiner needs to be familiar with the basics of clinical neurological examination.	

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	Probably favors the intervention	Favors the intervention	Varies	**No included studies**

			the comparison				
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 (PLR ≤ 24 hours)**	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention** (PLR 48 & 72 hours)	Strong recommendation for the intervention
○	●	○	●	○

CONCLUSIONS

Recommendation

We recommend that no single clinical examination test be used in isolation to predict poor neurological outcome in children after cardiac arrest (strong recommendation, very-low certainty evidence).

Clinicians should use multiple tests in combination for poor neurological outcome prediction (good practice statement).

The absence of pupil reactivity to light at 48 and 72 hours after ROC may be considered as part of multi-modal testing to predict poor neurological outcome in children after cardiac arrest (good practice statement).

We suggest against using absence of pupil reactivity to light within 24 hours after ROC to predict poor neurological outcome in children after cardiac arrest (weak recommendation, low-certainty evidence).

Justification

For pupillary light reflex, limited evidence suggests that the specificity for prediction of poor neurological outcome is improved at later time points >48hr.
This may be partly due to confounding from the effect of sedatives used for delivery of neuroprotective interventions (e.g., targeted temperature management) or to facilitate ventilation.
No studies reported any assessment of confounding influence of medication. No studies included blinding of test results from treating clinician and only one study had blinded outcome assessment.
Only part of the included studies specifically excluded the presence of residual sedation at the time PLR was assessed. Lack of blinding is a major limitation of PLR, even if WLST based on PLR only has not been documented in any of the studies included in our review.
Despite its limitations, given the ease of assessment and the minimal equipment required, the balance between the costs and benefits favours benefits.

Subgroup considerations

None

Implementation considerations

Pupillary light reflect is an easy clinical assessment; however, the examiner requires knowledge of basic neurological examination.

Monitoring and evaluation

None

Research priorities

The examination of the impact of residual medication on pupillary light reflex assessment in infants and children is needed. No studies evaluated automated pupillometer monitoring devices, research is needed to assess cost and benefits of the use of pupillometry compared to pupillary light reflex assessment.

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Electrophysiology Testing for Prognostication of Survival with Poor Neurological Outcome after Cardiac Arrest (PLS 4220.03)

Part 1: Abnormal background

QUESTION

Should absence of a benign (continuous) EEG pattern or presence of malignant background (attenuated or burst suppression) EEG pattern vs. presence or absence be used for predicting poor neurological outcomes in children after cardiac arrest?	
POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Absence of a continuous or normal background EEG, or Presence of 1) attenuated, isoelectric or flat EEG background or 2) burst suppression, burst attenuation or generalized periodic epileptiform discharges (GPEDS) on EEG background
COMPARISON:	Absence of these features
MAIN OUTCOMES:	Prediction of death or survival with poor neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of >3, or Vineland Adaptive Behavioural scale-II < 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death).
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Aug 27th 2024.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, it has a low rate of survival and high chance of neurological injury. Prediction of poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Absence of continuous or normal background EEG** The absence of a normal/continuous EEG background pattern (defined as normal, continuous and reactive, continuous and unreactive, and nearly continuous by ACNS definitions[1]) were reported in 14 studies at 6 different time points, and included 563 patients.[2-15] There was a wide variability of FPR and sensitivity reported across all timepoints for predicting poor neurological outcome. Only 4/14 studies identified a FPR <10%. The range of FPR across studies was 0-90%. Sensitivity ranged 7 to 96% with 4 studies having a sensitivity >90%. Overall,	

	absence of a continuous EEG was an inaccurate and unreliable method for predicting poor neurological outcome. **Presence of attenuated, isoelectric or flat EEG background** The absence of an attenuated, isoelectric, or flat EEG was reported in 12 studies including up to 526 patients (although there was a risk of some patients appearing in multiple studies).[2-15] In 7/9 studies, which reported prediction of poor neurological at 24 hours to 6 days, there was a FPR <10% (95%CI upper limit ranges 4-52%) and sensitivity of 18-58%.[2-4,7-10] In 4/9 studies, the FPR was <1% (95%CI upper limit ranges 4-52%).[3,4,9,10] At time points earlier than 24 hours, FPR was much higher (ranged 10-90%).[6,7,13,14] Therefore, the absence of an attenuated, isoelectric, or flat EEG FPR was imprecise (at the FPR<1% cut off) in more than 50% of included studies to predict a poor neurological outcome. **Presence of burst suppression, burst attenuation or generalized periodic epileptiform discharges (GPEDS) on EEG background** Absence of burst suppression, burst attenuation or GPEDS were reported in 7 studies including 395 patients.[2,3,6,10,13-15] Prior to 24 hours, in 4 studies, the FPR ranged 0-19% and sensitivity 9-30%. From 24 hours onwards, the accuracy improved. A FPR <1% (95%CI upper limit range 16-54%) was reported in 3 of 4 studies at 24, 48 and 72 hours with a sensitivity of 0-67%.[3,11,15] Therefore, prediction of poor neurological outcome was moderately reliable from 24 to 72 hours.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	A false positive prediction of a poor outcome and discontinuing treatment based on electrophysiological tests may lead to inappropriate treatment withdrawal in a patient with a good neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from sedation and medication affects of electrophysiological parameters.	
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 from clinical and electrophysiological tests is very low because of the risk of bias, lack of blinding, imprecision and self-fulfilling prophecy.	
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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA).[16] However, tools and definitions to measure poor neurological outcome in our studies were the PCPC >2 and >3, or >1 change in PCPC and the VABS II <70. Change from baseline neurological status may be more important than the	

● No important uncertainty or variability	neurological functional level, especially in infants and children with pre-existing neurological impairment. We defined poor neurological outcome prediction as imprecise when the false positive rate (FPR) was >1%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. We defined the reliability of the evidence as reliable if the FPR was <1% and the upper 95% confidence intervals <10%) and moderately reliable if FPR was <1% with without a restriction on width of 95% confidence interval. A low false positive rate means that a low proportion of patients, predicted to have a poor outcome will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). The task force felt that when focused on accuracy of predicting a poor outcome - a low false positive rate (e.g. <1%) is more desirable to avoid falsely pessimistic prediction than a high sensitivity. The cut off of <1% FPR (equivalent to 99% specificity) was chosen as the consequences of false pessimism is substantial. False pessimism may result in discontinuation of life sustaining therapy in a patient who will eventually have a good outcome. Continuing treatment may involve increased resources; however, this may also allow more time for further prognostic evaluation and further additional tests. Reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment.	
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	Overall, absence of a continuous EEG was an inaccurate and unreliable method for predicting poor neurological outcome. The absence of an attenuated, isoelectric, or flat EEG FPR was imprecise (at the FPR<1% cut off) in more than 50% of included studies to predict a poor neurological outcome. However, for absence of burst suppression, burst attenuation or GPEDS a FPR <1% (95%CI upper limit range 16-54%) was reported in 3 of 4 studies at 24, 48 and 72 hours with a sensitivity of 0-67%.[3,11,15] Therefore, prediction of poor neurological outcome was moderately reliable from 24 to 72 hours.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not identify any specific studies assessing costs of assessing background EEG for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in resource-limited settings.	
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	We did not identify any studies specifically assessing costs of performing continuous or intermittent electroencephalography for assessing background EEG.	

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	We did not identify any studies addressing cost-effectiveness.	

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 specific equipment and skills needed to obtain EEG recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity.	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any study assessing acceptability, but acceptability is likely.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Evaluating background EEG pattern on a continuous critical care EEG recording for prognostication purposes requires specific equipment for recording continuous EEG and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day.	

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 (continuous or normal background EEG)	Conditional recommendation for either the intervention or the comparison (presence of attenuated, isoelectric or flat EEG)	Conditional recommendation for the intervention (presence of burst suppression, burst attenuation or GPEDs)	Strong recommendation for the intervention
○	●	●	●	○

CONCLUSIONS

Recommendation

We recommend that no single electrophysiology test be used in isolation to predict poor neurological outcome in children after cardiac arrest at any time point (strong recommendation, very-low certainty evidence).

Clinicians should use multiple tests in combination for poor neurological outcome prediction (good practice statement).

The presence of status epilepticus between 24-72 hours after ROC, presence of burst suppression, burst attenuation or GPEDs between 24-72 hours after ROC, all had moderate reliability and may be considered as part of multi-modal testing to predict poor neurological outcome in children after cardiac arrest (good practice statement).

We suggest against using the following EEG features for predicting poor neurological outcome: presence of clinical or electrographic seizures; absence of sleep spindle and sleep II architecture on EEG, continuous or normal background EEG, EEG reactivity and EEG variability, at any time point (weak recommendation, very low–certainty evidence).

There was insufficient evidence to make a recommendation for or against the use of presence of attenuated, isoelectric, or flat EEG, absence of N20 response on SSEPs, presence of myoclonic status epilepticus, or quantitative EEG score to predict poor neurological outcome in children after cardiac arrest at any time point.

Justification

Overall justification

Overall, absence of a continuous EEG was an inaccurate and unreliable method for predicting poor neurological outcome. The absence of an attenuated, isoelectric, or flat EEG FPR was imprecise (at the FPR<1% cut off) in more than 50% of included studies to predict a poor neurological outcome. However, for absence of burst suppression, burst attenuation or GPEDS a FPR <1% (95%CI upper limit range 16-54%) was reported in 3 of 4 studies at 24, 48 and 72 hours with a sensitivity of 0-67%.[3,11,15] Therefore, prediction of poor neurological outcome was moderately reliable from 24 to 72 hours.

Detailed justification

Certainty of evidence

None of the studies adjusted for the confounding effect of sedation or targeted temperature management on background EEG.

Resources required

Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources.

Equity

Resources required for continuous EEG monitoring and interpretation may not be available in resource-limited settings.

The available scientific evidence had a high risk of bias based on high heterogeneity across studies, small number of studies and small number of patients included in addition to lack of blinding, variation in test assessment and performance, and variability in outcome measurement. Therefore, no meta-analysis was performed. Overall assessment of test performance was based on visual assessment of forest plots.

In addition to providing prognostic information, electrophysiology monitoring may allow identification of reversible events e.g. seizures. Treatment of seizures may prevent additional secondary injury following a hypoxic-ischemic insult. The role of electrophysiology monitoring was not assessed for this purpose.

American Clinical Neurophysiology Society (ACNS) definitions for background EEG patterns were followed in some studies. EEG and SSEP prognostic criteria require clear and reproducible definitions and require validation in the pediatric ICU environment.

Subgroup considerations

None

Implementation considerations

Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings.

Monitoring and evaluation

None

Research priorities

Electrophysiology tests for prognostication after cardiac arrest appear promising but more research is required in infants and children.

More research is required on type of monitoring, intermittent or continuous EEG, use of reduced channel monitoring, quantitative EEG systems, duration and timing of prognostic assessment.

Validation of ACNS or other international definitions of EEG indices within the pediatric ICU environment for infants and children after cardiac arrest.

Further work on multi-modal prognostication, timing, definitions of testing, accurate outcome timing and definition.

We encourage wider research and consultation with patients, children, parents, guardians and caregivers, health care professionals and members of the wider society on understanding survivorship after pediatric cardiac arrest to inform correct definitions and framework of good neurological outcome for prediction research. Status epilepticus represents increased

seizure burden in comparison to individual seizures. Evaluation of association between seizure burden during the first 72 hours post cardiac arrest and neurodevelopmental outcomes is needed.
Future studies should also more carefully adjust for the confounding effect of medications, targeted temperature management and other critical care interventions.

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An Advisory Statement From the International Liaison Committee on Resuscitation. *Resuscitation*. 2021;162:351-364. doi: 10.1016/j.resuscitation.2021.01.023

Electrophysiology Testing for Prognostication of Survival with Poor Neurological Outcome after Cardiac Arrest (PLS 4220.03)

Part 2: Reactivity, Sleep Spindles and SSEPs

QUESTION

Should absence of a reactivity, sleep II architecture or sleep spindles, or variability on EEG vs. presence be used for predicting poor neurological outcomes in children after cardiac arrest?	
POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Absence of a reactivity, sleep II architecture or sleep spindles, or variability on EEG or presence of a specific quantitative EEG score, or absence of N20 responses on SSEPs
COMPARISON:	Presence or absence (as appropriate) of these features
MAIN OUTCOMES:	Prediction of death or survival with poor neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of >3, or Vineland Adaptive Behavioural scale-II < 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death).
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Aug 27th 2024.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, it has a low rate of survival and high chance of neurological injury. Prediction of poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Absence of reactivity, sleep II architecture or sleep spindles, or variability on EEG** The absence of reactivity within an EEG trace was reported in 3 studies,[1-3] absence of sleep II architecture in 2 studies,[4,5] and absence of variability in 2 studies.[1,2] No test had a prediction accuracy with a FPR <1%. Absence of reactivity had a FPR 0-93%, and sensitivity 36-100%; absence of sleep II architecture had a FPR 20-43%, and sensitivity 84-92%; absence of variability	

	in EEG had FPR 0-80% and sensitivity 21 to 82% for poor neurological outcome prediction. These were inaccurate and unreliable tests for poor outcome prediction. **Quantitative EEG scoring** A composite score assessing EEG background from a 24-hour monitoring period, obtained from quantitative EEG using the amplitude integrated EEG trace, was assessed in only one study which included 30 patients.[6] A score of >15 had a predicted FPR of 6% (95%CI 0-27%) and sensitivity of 33% for poor neurological outcome. **Somatosensory evoked potential (SSEPs)** SSEPs, evaluating bilateral absence of N20 waves, were reported in only one study, with a small sample size (n=12), reporting poor neurological outcome (PCPC >3) at 24, 48 and 72 hours.[7] Clinicians were blinded to test results and the SSEP assessor was blinded to outcome. The predicted FPR was 0% (95%CI 0-52%) at 24 and 48 hours and 17% at 72 hours, with a sensitivity of 100% (95%CI 29-100) at all time points. Absence of N20 response on SSEP was moderately reliable to predict poor neurological outcome, but only assessed in one small study.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	A false positive prediction of a poor outcome and discontinuing treatment based on electrophysiological tests may lead to inappropriate treatment withdrawal in a patient with a good neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from sedation and medication affects of electrophysiological parameters.	
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 from clinical and electrophysiological tests is very low because of the risk of bias, lack of blinding, imprecision and self-fulfilling prophecy. There was only one study assessing SSEPs and quantitative EEG.	
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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA).[8] However, tools and definitions to measure poor neurological outcome in our studies were the PCPC >2 and >3, or >1 change in PCPC and the VABS II <70. Change from baseline neurological status may be more important than the neurological functional level, especially in infants and children with pre-existing neurological impairment. We defined poor neurological outcome prediction as imprecise when the false positive rate (FPR) was >1%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. We defined the reliability of the evidence	

	as reliable if the FPR was <1% and the upper 95% confidence intervals <10%) and moderately reliable if FPR was <1% with without a restriction on width of 95% confidence interval. A low false positive rate means that a low proportion of patients, predicted to have a poor outcome will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). The task force felt that when focused on accuracy of predicting a poor outcome - a low false positive rate (e.g. <1%) is more desirable to avoid falsely pessimistic prediction than a high sensitivity. The cut off of <1% FPR (equivalent to 99% specificity) was chosen as the consequences of false pessimism is substantial. False pessimism may result in discontinuation of life sustaining therapy in a patient who will eventually have a good outcome. Continuing treatment may involve increased resources; however, this may also allow more time for further prognostic evaluation and further additional tests. Reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment.	
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	Reactivity, variability and sleep II architecture features on EEG were imprecise for poor outcome prediction. These were therefore inaccurate and unreliable tests for poor outcome prediction. Quantitative EEG and SSEPs showed promise as potential tests, but there was insufficient data and number of studies to make an assessment.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not include any specific studies assessing costs of assessing background EEG or SSEPs for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in resource-limited settings.	
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	We did not identify any studies specifically assessing costs of performing continuous or intermittent electroencephalography for assessing EEG or SSEPs.	
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	We did not identify any studies addressing cost-effectiveness.	

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 specific equipment and skills needed to obtain EEG and SSEP recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity.	

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any study assessing acceptability, but acceptability is likely.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Evaluating SSEPs or EEG pattern on a continuous critical care EEG recording for prognostication purposes requires specific equipment for recording continuous EEG and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day.	

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 (reactivity, Sleep II architect ure, variability on EEG)	Conditional recommendation for either the intervention or the comparison (quantitative EEG score or SSEPs)	Conditional recommendation for the intervention (presence of burst suppression, burst attenuation or GPEDs)	Strong recommendation for the intervention
○	●	●	○	○

CONCLUSIONS

Recommendation

We recommend that no single electrophysiology test be used in isolation to predict poor neurological outcome in children after cardiac arrest at any time point (strong recommendation, very-low certainty evidence).

Clinicians should use multiple tests in combination for poor neurological outcome prediction (good practice statement).

We suggest against using the following EEG features for predicting poor neurological outcome: presence of clinical or electrographic seizures; absence of sleep spindle and sleep II architecture on EEG, continuous or normal background EEG, EEG reactivity and EEG variability, at any time point (weak recommendation, very low–certainty evidence).

There was insufficient evidence to make a recommendation for or against the use of presence of attenuated, isoelectric, or flat EEG, absence of N20 response on SSEPs, presence of myoclonic status epilepticus, or quantitative EEG score to predict poor neurological outcome in children after cardiac arrest at any time point.

Justification

Overall justification

Overall, Absence of reactivity, sleep II architecture or sleep spindles, or variability on EEG were inaccurate and unreliable method for predicting poor neurological outcome.

For quantitative EEG score and SSEPs there was insufficient evidence (one study for each test) to make a recommendation.

Detailed justification

Certainty of evidence

None of the studies adjusted for the confounding effect of sedation or targeted temperature management on EEG or SSEPs.

Resources required

Performance and interpretation of SSEPs and continuous EEG in the pediatric critical care environment requires resources.

Equity

Resources required for SSEPSs and continuous EEG monitoring and interpretation may not be available in resource-limited settings.

The available scientific evidence had a high risk of bias based on high heterogeneity across studies, small number of studies and small number of patients included in addition to lack of blinding, variation in test assessment and performance, and variability in outcome measurement. Therefore, no meta-analysis was performed. Overall assessment of test performance was based on visual assessment of forest plots.

In addition to providing prognostic information, electrophysiology monitoring may allow identification of reversible events e.g. seizures. Treatment of seizures may prevent additional secondary injury following a hypoxic-ischemic insult. The role of electrophysiology monitoring was not assessed for this purpose.

American Clinical Neurophysiology Society (ACNS) definitions for background EEG patterns were followed in some studies. EEG and SSEP prognostic criteria require clear and reproducible definitions and require validation in the pediatric ICU environment.

Subgroup considerations

None

Implementation considerations

Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings.

Monitoring and evaluation

None

Research priorities

Electrophysiology tests for prognostication after cardiac arrest appear promising but more research is required in infants and children.

More research is required on type of monitoring, intermittent or continuous EEG, use of reduced channel monitoring, quantitative EEG systems, duration and timing of prognostic assessment.

Validation of ACNS or other international definitions of EEG indices within the pediatric ICU environment for infants and children after cardiac arrest.

Further work on multi-modal prognostication, timing, definitions of testing, accurate outcome timing and definition.

We encourage wider research and consultation with patients, children, parents, guardians and caregivers, health care professionals and members of the wider society on understanding survivorship after pediatric cardiac arrest to inform correct definitions and framework of good neurological outcome for prediction research. Status epilepticus represents increased seizure burden in comparison to individual seizures. Evaluation of association between seizure burden during the first 72 hours post cardiac arrest and neurodevelopmental outcomes is needed.

Future studies should also more carefully adjust for the confounding effect of medications, targeted temperature management and other critical care interventions.

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Electrophysiology Testing for Prognostication of Survival with Poor Neurological Outcome after Cardiac Arrest (PLS 4220.03)

Part 3: Seizures, Status Epilepticus and Status Myoclonus

QUESTION

Should presence of clinical or electrographic seizures, status epilepticus, or myoclonic status epilepticus vs. absence be used for predicting poor neurological outcomes in children after cardiac arrest?	
POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Presence of clinical or electrographic seizures, status epilepticus, or myoclonic status epilepticus within 10 days after cardiac arrest.
COMPARISON:	Absence of these features
MAIN OUTCOMES:	Prediction of death or survival with poor neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of >3, or Vineland Adaptive Behavioural scale-II < 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death).
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Aug 27th 2024.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, it has a low rate of survival and high chance of neurological injury. Prediction of poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Presence of clinical or electrographic seizure** Fourteen studies reported the relationship between presence of clinical and/or electrographic seizures in children post-cardiac arrest and poor neurological outcomes at PICU/hospital discharge, 6 months and 12 month.[1-14] These studies included 1165 children, of which 6/12 studies reported using the ACNS criteria.[1,3,4,7,11,14]	

	Presence of seizures between 4-6 hours and 24 hours post-ROC were reported in 10 studies and had a FPR of 0-20% and a sensitivity of 2-38% for predicting poor neurological outcome. Three studies had a FPR <1% but with wide 95%CI.[4,7,11] At 48 hours and onwards only 3/11 studies reported a FPR for predicting poor outcome of <10%,[5,8,11] the majority reported an imprecise FPR 19-50%. Overall presence of seizures was not a reliable prognostic test for poor outcome prediction; although early (≤24hours) had improved accuracy compared to ≥48hours. **Presence of status epilepticus on EEG** Presence of status epilepticus was reported in five studies including 299 children. [4,12-15] Poor neurological outcome at PIC/hospital discharge were predicted with a low FPR of 0-5% (upper limit of 95%CI ranged 13-41%) and sensitivity was 9-25%. Presence of status epilepticus had moderate reliability as a prognostic test. **Presence of myoclonic status epilepticus on EEG** In two studies, including 61 patients, myoclonic status epilepticus was identified in 8 patients. Presence of myoclonic status epilepticus on EEG predicted poor neurological outcomes with a FPR 0% (95% CI 0-34%) and sensitivity of 17-21% at PICU/hospital discharge.[2,11] Status myoclonus on EEG had moderate reliability as a prognostic test although there was a very small sample size.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	A false positive prediction of a poor outcome and discontinuing treatment based on electrophysiological tests may lead to inappropriate treatment withdrawal in a patient with a good neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from sedation and medication affects of electrophysiological parameters.	
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 from clinical and electrophysiological tests is very low because of the risk of bias, lack of blinding, imprecision and self-fulfilling prophecy.	
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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA).[16] However, tools and definitions to measure poor neurological outcome in our studies were the PCPC >2 and >3, or >1 change in PCPC and the VABS II <70. Change from baseline neurological status may be more important than the neurological functional level, especially in infants and children with pre-existing neurological impairment.	

variability	We defined poor neurological outcome prediction as imprecise when the false positive rate (FPR) was >1%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. We defined the reliability of the evidence as reliable if the FPR was <1% and the upper 95% confidence intervals <10%) and moderately reliable if FPR was <1% with without a restriction on width of 95% confidence interval. A low false positive rate means that a low proportion of patients, predicted to have a poor outcome will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). The task force felt that when focused on accuracy of predicting a poor outcome - a low false positive rate (e.g. <1%) is more desirable to avoid falsely pessimistic prediction than a high sensitivity. The cut off of <1% FPR (equivalent to 99% specificity) was chosen as the consequences of false pessimism is substantial. False pessimism may result in discontinuation of life sustaining therapy in a patient who will eventually have a good outcome. Continuing treatment may involve increased resources; however, this may also allow more time for further prognostic evaluation and further additional tests. Reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment.	
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	Overall presence of clinical or electrographic seizures was not a reliable prognostic test for poor outcome prediction; although early (≤24hours) had improved accuracy compared to ≥48hours; However, FPR was <1% in only 3/10 studies. Presence of status epilepticus had moderate reliability as a prognostic test with FPR 0-5% in five studies, but precision did not reach the specified FPR <1% cutoff. Status myoclonus on EEG had moderate reliability as a prognostic test although there was a very small sample size in two studies.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not include any specific studies assessing costs of ruling out seziures, status epilepticus or myoclonic status epilepticus on EEG for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in resource-limited settings.	
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	We did not identify any studies specifically assessing costs of performing continuous or intermittent electroencephalography and/or ruling out seizures.	

● No included studies		
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	We did not identify any studies addressing cost-effectiveness.	
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 specific equipment and skills needed to obtain EEG recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any study assessing acceptability, but acceptability is likely.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Evaluating seizures and status epilepticus on a continuous critical care EEG recording for prognostication purposes requires specific equipment for recording continuous EEG and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day.	

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 (Clinical/ electrographic seizure)**	**Conditional recommendation for either the intervention or the comparison (myoclonic status epilepticus)**	**Conditional recommendation for the intervention (Status epilepticus)**	Strong recommendation for the intervention
○	●	●	●	○

CONCLUSIONS

Recommendation

We recommend that no single electrophysiology test be used in isolation to predict poor neurological outcome in children after cardiac arrest at any time point (strong recommendation, very-low certainty evidence).

Clinicians should use multiple tests in combination for poor neurological outcome prediction (good practice statement).

The presence of status epilepticus between 24-72 hours after ROC, presence of burst suppression, burst attenuation or GPEDs between 24-72 hours after ROC, all had moderate reliability and may be considered as part of multi-modal testing to predict poor neurological outcome in children after cardiac arrest (good practice statement).

We suggest against using the following EEG features for predicting poor neurological outcome: presence of clinical or electrographic seizures; absence of sleep spindle and sleep II architecture on EEG, continuous or normal background EEG, EEG reactivity and EEG variability, at any time point (weak recommendation, very low–certainty evidence).

There was insufficient evidence to make a recommendation for or against the use of presence of attenuated, isoelectric, or flat EEG, absence of N20 response on SSEPs, presence of myoclonic status epilepticus, or quantitative EEG score to predict poor neurological outcome in children after cardiac arrest at any time point.

Justification

Overall justification

Overall presence of clinical or electrographic seizures was not a reliable prognostic test for poor outcome prediction; although early (≤24hours) had improved accuracy compared to ≥48hours; However, FRP was <1% in only 3/10 studies. We therefore suggest not using this test as for prediction of poor neurological outcome.

Presence of status epilepticus had moderate reliability as a prognostic test with FPR 0-5% in five studies, but precision did not reach our <1% FPR cutoff. This test may therefore be useful as part of multi-modal testing but should not be used in isolation.

Status myoclonus on EEG had moderate reliability as a prognostic test although there was a very small sample size in two studies. We could therefore not make a suggestion for or against its use due to insufficient evidence.

Detailed justification

Certainty of evidence

None of the studies adjusted for the confounding effect of sedation or targeted temperature management on the absence of seizures

Resources required

Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources.

Equity

Resources required for continuous EEG monitoring and interpretation may not be available in resource-limited settings.

The available scientific evidence had a high risk of bias based on high heterogeneity across studies, small number of studies and small number of patients included in addition to lack of blinding, variation in test assessment and performance, and variability in outcome measurement. Therefore, no meta-analysis was performed. Overall assessment of test performance was based on visual assessment of forest plots.

In addition to providing prognostic information, electrophysiology monitoring may allow identification of reversible events e.g. seizures. Treatment of seizures may prevent additional secondary injury following a hypoxic-ischemic insult. The role of electrophysiology monitoring was not assessed for this purpose.

If only one study was available (with small patient sample size) then a suggestion or recommendation could not be made.

There was limited or no context of when tests were undertaken in relation to concurrent pharmacological exposure, sedation and ongoing treatment (e.g., TTM) in patients following cardiac arrest.

American Clinical Neurophysiology Society (ACNS) definitions for seizures and EEG indices were followed in some studies. EEG and SSEP prognostic criteria require clear and reproducible definitions and require validation in the pediatric ICU environment.

Subgroup considerations

None

Implementation considerations

Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings.

Monitoring and evaluation

None

Research priorities

Electrophysiology tests for prognostication after cardiac arrest appear promising but more research is required in infants and children.

More research is required on type of monitoring, intermittent or continuous EEG, use of reduced channel monitoring, quantitative EEG systems, duration and timing of prognostic assessment.
Validation of ACNS or other international definitions of EEG indices within the pediatric ICU environment for infants and children after cardiac arrest.
Further work on multi-modal prognostication, timing, definitions of testing, accurate outcome timing and definition.
We encourage wider research and consultation with patients, children, parents, guardians and caregivers, health care professionals and members of the wider society on understanding survivorship after pediatric cardiac arrest to inform correct definitions and framework of good neurological outcome for prediction research. Status epilepticus represents increased seizure burden in comparison to individual seizures. Evaluation of association between seizure burden during the first 72 hours post cardiac arrest and neurodevelopmental outcomes is needed.
Future studies should also more carefully adjust for the confounding effect of medications, targeted temperature management and other critical care interventions.

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Imaging for Prognostication of Survival with Poor Neurological Outcome after Cardiac Arrest (PLS 4220.04)

QUESTION

Should presence of abnormality on cranial Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) vs. absence be used for predicting poor neurological outcomes in children after cardiac arrest?	
POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Abnormality on cranial MRI or CT
COMPARISON:	No abnormality
MAIN OUTCOMES:	Prediction of death or survival with poor neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of >3, or Vineland Adaptive Behavioural scale-II < 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining poor neurological outcomes with other assessment tools, or as a PCPC score >2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Aug 27th 2024.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, it has a low rate of survival and high chance of neurological injury. Prediction of good or poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Head CT was evaluated in three studies and reported the relationship to poor neurological outcome (PCPC >3) in 173 patients. [1-3] The majority of CT imaging was acquired at 24 h or 48 h after the cardiac arrest. Neurological outcome was assessed on discharge from the intensive care unit or hospital in two studies [1,2] and at six months in one.[3] The absence of Grey-white matter (GWM) differentiation was reported in one study with a FPR 0% (95%CI 0-12%) and sensitivity 65% for poor outcome prediction. Presence of	

	reversal sign on CT at 24 hours was reported in two studies with a range of FPR of 0% to 36%,and corresponding sensitivity of 20 to 30% for poor outcome prediction.[2,3] Presence of effacement of sulci or basal cisterns at 24 hours predicted poor neurological outcome with a low FPR (0-7%; range of 95% CI 0-30%).[2,3] Presence of CT lesions, oedema, or intracranial hemorrhage predicted poor neurological outcome with a FPR 7-17%; however, sensitivity ranged 11 to 68%. Clinicians were not blinded to the CT results in any study. CT reported GWM differentiation at 24 hours was a moderately reliable test, but only reported in a single study. All other CT reported tests were unreliable for poor neurological outcome prediction at 24 and 48 hours. MRI imaging was reported in five studies, including 305 patients, to predict poor neurological outcomes. [4-8] Median time from ROC to MRI ranged 3 to 6 days across all studies with inclusion of patients MRI up to 14 days reported in three studies. [5,7,8] An Apparent diffusion coefficient (ADC) threshold <650x10^{-6} mm^2/s in ≥10% of brain volume (indicating high ischemic burden), at a median of 4 days after ROC, predicted poor neurological outcome with a sensitivity of 49-52% and FPR 0-6% (95% 1-21%) in 3 studies.[4,7,8] One study using ADC thresholds to identify high ischemic burden fulfilled the low FPR <1% with moderate reliability for poor neurological outcome prediction.[8] Any region of abnormality on restricted diffusion, at a median of 4 days after ROC, predicted poor neurological outcome with a range of FPR 12% to 58% and corresponding sensitivity of 98% to 100%. [7,9] An abnormal MRI by qualitative reporting of presence of hypoxic ischemic injury, predicted a poor neurological outcome at 6 months with a FPR of 19% and sensitivity of 90%.[8] Three studies reported up to 14 different individual regions of the brain, at 4-6 days post ROC with DWI, T1 and T2 weighted imaging.[5,6,9] FPR for outcome prediction was predominately 0-10% but upper limits of the 95% CI ranged widely from 20-50%. Overall, only one study using ADC thresholds fulfilled the low FPR <1% with moderate reliability for poor neurological outcome prediction.	

Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	A false positive prediction of a poor outcome and discontinuing treatment based on MRI or CT may lead to inappropriate treatment withdrawal in a patient with a god neurological outcome. The low false positive rate (high specificity) for abnormal MRI on global assessment for predicting poor neurological outcome reduces the chance of false pessimism if an abnormal MRI predicts a poor neurological outcome. FPR <1% was only recording for one study for global assessment of brain injury. Low FPR was identified during regional brain assessment,	

	however only in a small number of cases, with wide confidence limits on the point estimate.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low o Low o Moderate o High o No included studies	The certainty of evidence from CT & MRI abnormalities are low (downgraded for imprecision, and risk of bias). because of the risk of bias, especially self-fulfilling prophecy and wide confidence intervals around the point estimates.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Important uncertainty or variability o Possibly important uncertainty or variability ● Probably no important uncertainty or variability o No important uncertainty or variability	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA).[10] However, tools and definitions to measure poor neurological outcome in our studies were the PCPC >2 and >3, or >1 change in PCPC and the VABS II <70. Change from baseline neurological status may be more important than the neurological functional level, especially in infants and children with pre-existing neurological impairment. We defined poor neurological outcome prediction as imprecise when the false positive rate (FPR) was >1%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. We defined the reliability of the evidence as reliable if the FPR was <1% and the upper 95% confidence intervals <10%) and moderately reliable if FPR was <1% with without a restriction on width of 95% confidence interval. A low false positive rate means that a low proportion of patients, predicted to have a poor outcome will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). The task force felt that when focused on accuracy of predicting a poor outcome - a low false positive rate (e.g. <1%) is more desirable to avoid falsely pessimistic prediction than a high sensitivity. The cut off of <1% FPR (equivalent to 99% specificity) was chosen as the consequences of false pessimism is substantial. False pessimism may result in discontinuation of life sustaining therapy in a patient who will eventually have a good outcome. Continuing treatment may involve increased resources; however, this may also allow more time for further prognostic evaluation and further additional tests. Reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment..	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison	The sensitivity of abnormal MRI or CT to predict a poor neurological outcome is moderate to high, most tests had a low FPR 0-10%, but in some cases up to 40% may be falsely categorized and a falsely pessimistic prediction made. Therefore,	A CT or MRI scan may be performed for other diagnostic indications (e.g. identify the cause of

○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know	with the very-low certainty of evidence, we cannot make a treatment recommendation for or against the use of abnormal MRI or CT for predicting poor neurological outcomes as single tests. However, we encourage further research in this area as these modalities appear promising. In the context of multi-modal monitoring, an abnormal MRI showing high ischemic burden on ADC mapping (≥72 hours) or CT scan showing loss of Grey-White Differentiation (at 24 hours) may be utilized as part of multi-modal testing for poor neurological outcome prediction	cardiac arrest) and the information may be combined with other prognostic tests.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Specialist equipment and training in interpretation to perform CT & MRI is required. Costs and access to CT & MRI may be variable depending on the health care setting. In some settings imaging may not be available or costs prohibitive. However, no study assessing cost of CT & MRI imaging has been included in our review	
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	We did not identify any studies assessing cost.	
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	We did not identify any studies addressing cost-effectiveness.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies	No study assessed the impact on health equity. However, due to the high cost of CT & MRI, there may be health inequity in receiving this investigation and prognostic test.	

○ 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	We have not identified any study assessing acceptability, but acceptability is likely.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	Although feasibility was not specifically addressed in any of the studies included in this review. However, requires significant resources, personnel and training and this may limit the feasibility in all health care settings. Imaging studies used for neuroprognostication after cardiac arrest cannot be performed at the bedside, and require transportation to a Radiology Department, with additional clinical and safety risks.	

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 no single imaging test be used alone to predict poor neurological outcome in children after cardiac arrest at any time point (strong recommendation, very-low certainty evidence).

Clinicians should use multiple tests in combination for poor neurological outcome prediction (good practice statement).

An abnormal MRI showing high ischemic burden on apparent diffusion coefficient mapping at 72 hours and beyond after ROC or CT scan showing loss of Grey-White Matter Differentiation within 24 hours after ROC may be considered as part of multi-modal testing to predict poor neurological outcome in children after cardiac arrest (good practice statement).

Justification

- The available scientific evidence had a high risk of bias based on high heterogeneity across studies, small number of studies and small number of patients included in addition to lack of blinding, variation in test assessment and performance, and variability in outcome measurement. Therefore, no meta-analysis was performed. Overall assessment of test performance was based on visual assessment of forest plots.
- If only one study was available (with small patient sample size) then a suggestion or recommendation could not be made. Only part of the included studies specifically excluded the presence of residual sedation at the time PLR was assessed. Lack of blinding is a major limitation of PLR, even if WLST based on PLR only has not been documented in any of the studies included in our review.
- The low false positive rate (high specificity) for abnormal MRI on global assessment for predicting poor neurological outcome reduces the chance of false pessimism if an abnormal MRI predicts a poor neurological outcome. FPR <1% was only recording for one study for global assessment of brain injury. Low FPR was identified during regional brain assessment, however only in a small number of cases, with wide confidence limits on the point estimate.
- The sensitivity of abnormal MRI or CT to predict a poor neurological outcome is moderate to high, but up to 40% may be falsely categorized and a falsely pessimistic prediction made. Therefore, with the very-low certainty of evidence, we cannot make a treatment recommendation for or against the use of abnormal MRI or CT for predicting poor neurological outcomes as single tests. However, we encourage further research in this area as these modalities appear promising.
- The precision of MRI and CT is affected by the timing of the investigation and is at risk of pseudonormalization.
- The definition of a presence DWI or cut off values for ADC level on MRI, or GWR on CT was inconsistent in the included studies.
- MRI and CT are both expensive tests and require specialist equipment, training, interpretation and most often, patient transport to obtain the information. This may be prohibitive in physiologically unstable patients, or some health care settings..

Subgroup considerations

None

Implementation considerations

CT & MRI are expensive tests and requires specialist equipment, training, interpretation, and patient transport to obtain the information. This may be prohibitive in physiologically unstable patients, or some health care settings.

Monitoring and evaluation

None

Research priorities

The criteria for defining a positive DWI MRI after cardiac arrest need to be standardised.
The role of regional areas of brain for predicting outcome, or the use of Magnetic resonance spectroscopy requires further research.

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