B.1 ANTICIPATORY DEFIBRILLATOR CHARGING (ALS 2001: SCOPREV)

Conflict of Interest Declaration

The ILCOR Continuous Evidence Evaluation process is guided by a rigorous ILCOR Conflict of Interest policy. The following Task Force members and other authors were recused from the discussion as they declared a conflict of interest: (insert names or declare none applicable)
The following Task Force members and other authors declared an intellectual conflict of interest and this was acknowledged and managed by the Task Force Chairs and Conflict of Interest committees: (insert names or declare none applicable) **NONE APPLICABLE**

Task Force Scoping Review Citation

Otto Q, Musiol S, Deakin CD, Morley PT, Soar J, on behalf of the International Liaison Committee on Resuscitation Advanced Life Support Task Force.
***Anticipatory defibrillator charging for ALS – manual defibrillation: Scoping Review and Task Force Insights** [Internet] Brussels, Belgium: International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support Task Force, 2020 Jan 3. Available from: http://ilcor.org*

Methodological Preamble and Link to Published Scoping Review

Insert a brief methodological overview and TF chair will adjust specific for the TF Scoping Review Team that did the work:

The continuous evidence evaluation process started with a scoping review of adult life support conducted by the ILCOR ALS Task Force Scoping Review team. Evidence for literature was sought and considered by the Advanced Life Support Adult Task Force.

Scoping Review

Otto Q, Musiol S, Deakin CD, Morley PT, Soar J, on behalf of the International Liaison Committee on Resuscitation Advanced Life Support Task Force. Anticipatory defibrillator charging for ALS – manual defibrillation: A Scoping Review. In preparation.

Header - PICOST

The PICOST (Population, Intervention, Comparator, Outcome, Study Designs and Timeframe)

Population: Adults with cardiac arrest in any setting

Intervention: Charging the (manual) defibrillator prior to rhythm analysis

Comparators: Charging the (manual) defibrillator after rhythm analysis

Outcomes: Survival to hospital discharge, 30 days or greater than days with good neurological outcome, and survival to hospital discharge 30 days or greater than 30 days were ranked as critical outcomes. Return of spontaneous circulation (ROSC) was ranked as an important outcome. Other outcomes considered were defibrillation success, pre-shock pause, hands-off time, post-shock pause, peri-shock pause, compression-fraction, and hands-on time.

Study Designs: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) are eligible for inclusion. Manikin studies were included for this scoping review, as was grey literature.

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 7 October, 2019.

Search Strategies

Developed in liaison with Helen Pullen, Information Specialist at University Hospitals, Bristol

MEDLINE AND EMBASE via HDAS on 7/10/2019
(exp "HEART ARREST"/ OR exp "VENTRICULAR FIBRILLATION"/ OR heart arrest OR cardiac arrest OR asystole OR cardiopulmonary arrest OR cardiovascular arrest OR exp "CARDIOPULMONARY RESUSCITATION"/ OR resuscitation OR CPR OR “advanced life support” OR ALS OR "advanced cardiac life support" OR ACLS OR exp "HEART MASSAGE"/ OR heart massage*OR cardiac massage* OR Basic Life Support OR BLS OR cardiac rhythm) AND (("pre-charg*" OR "pre charg*" OR Anticipatory charg* OR Defibrillator charg* OR Defibrillation strateg* OR Defibrillation Sequence OR defibrillation algorithm OR shocking strateg* OR Shocking Algorithm OR COACHED OR "C.O.A.C.H.E.D." OR (prior ADJ3 charg*)).ti,ab)

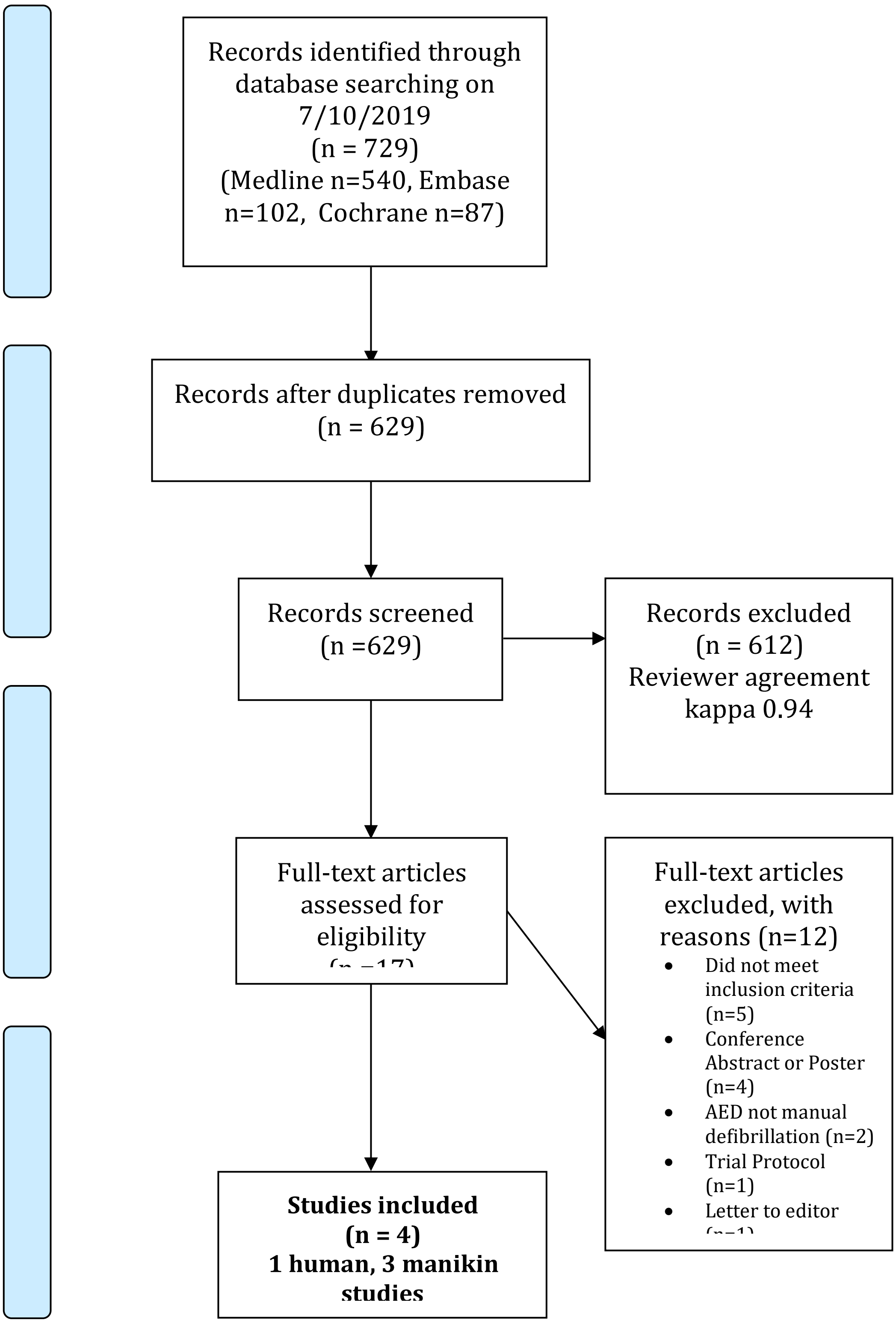
Results

EMBASE 102
MEDLINE 540

COCHRANE on 7/10/2019
([mh “Heart Arrest”] OR [mh “Ventricular Fibrillation”] OR “heart arrest”:ab,ti OR “cardiac arrest”:ab,ti OR asystole:ab,ti OR “cardiopulmonary arrest”:ab,ti OR “cardiovascular arrest”:ab,ti OR [mh “Cardiopulmonary Resuscitation”] OR resuscitation:ab,ti OR CPR:ab,ti OR “advanced life support”:ab,ti OR ALS:ab,ti OR “advanced cardiac life support”:ab,ti OR ACLS:ab,ti OR “basic life support”:ab,ti OR BLS:ab,ti OR [mh “Heart Massage”] OR “heart massage*”:ab,ti OR “cardiac massage*”:ab,ti) AND ("pre-charg*":ab,ti OR "pre charg*":ab,ti OR Anticipatory charg*:ab,ti OR Defibrillator charg*:ab,ti OR Defibrillation strateg*:ab,ti OR Defibrillation Sequence:ab,ti OR defibrillation algorithm:ab,ti OR shocking strateg*:ab,ti OR
Shocking Algorithm:ab,ti OR COACHED:ab,ti OR "C.O.A.C.H.E.D.":ab,ti OR prior NEAR charg*:ab,ti)
Results 87

Header – Inclusion and Exclusion criteria

PRISMA Flow Diagram



Header – Data tables

Anticipatory defibrillator charging for ALS: A Scoping Review

Identified studies: 7/10/2019

<table>
<tr><td colspan="7">HUMAN STUDIES</td></tr>
<tr><td>Reference</td><td>Methods</td><td>Population</td><td>Interventions</td><td>Comparisons</td><td>Outcomes</td><td>Notes</td></tr>
<tr><td>Edelson, 2010</td><td>Multi-centre, retrospective study, three US academic teaching hospitals</td><td>A total of 680 charge cycles from 244 in-hospital cardiac arrests involving 225 distinct patients, April 2006 to April 2009</td><td>Charging defibrillator prior to rhythm analysis [If VF/pVT give shock]

[Anticipatory method]
N= 67 shocks</td><td>Charging defibrillator after rhythm assessment with ongoing chest compressions
[AHA method]
N = 255</td><td>Results from anticipatory subgroup analysis. Median (IQR) in s
Pre-shock Pause:
• AHA: 2.5 (1.8-3.3) vs anticipatory 3.8 (2.4-5.4), p =0.08
Post shock pause
• AHA 1.7 (1.3-2.5) vs anticipatory 2.2 (1.6-3.5) p=0.39
Total hands off time in 30s preceding shock
• AHA 11.5 (9.1-14.5) vs anticipatory 3.9 (2.4-5.6). p<0.001
No difference in inappropriate shocks, one shock to rescuer in anticipatory method, not causing interruption to CPR

Results from anticipatory subgroup analysis.
<table><tr><td></td><td>Anticipatory method</td><td>AHA method</td><td>p-value</td></tr><tr><td>Pre-shock pause, median (IQR), s</td><td>3.8 (2.4-5.4)</td><td>2.5 (1.8-3.3)</td><td>0.08</td></tr><tr><td>Post-shock pause, median (IQR), s</td><td>2.2 (1.6-3.5)</td><td>1.7 (1.3-2.5)</td><td>0.39</td></tr><tr><td>Hand-off time in 30 s preceding shock</td><td>3.9 (2.4-5.6)</td><td>11.5 (9.1-14.5)</td><td><0.001</td></tr><tr><td>Inappropriate shocks, n/total (%)</td><td>13/67 (19.4)</td><td>45/255 (17.6)</td><td>0.74</td></tr><tr><td>Shocks to rescuers, n/total (%)</td><td>1/67 (1.5)</td><td>0/255 (0.0)</td><td>0.05</td></tr></table></td><td>Shock success, ROSC, Survival outcomes not reported from study

Study not designed to establish difference in AHA and anticipatory method, but compressions during charging.
Anticipatory charging had longer pre-shock pause but shorter total hands-off time in preceding 30s.
Lead author contacted for further data</td></tr>
<tr><td colspan="7">MANIKIN STUDIES</td></tr>
<tr><td>Reference</td><td>Methods</td><td>Population</td><td>Interventions</td><td>Comparisons</td><td>Outcomes</td><td>Notes</td></tr>
<tr><td>Hansen, 2013</td><td>Randomized Crossover Simulation</td><td>Volunteer junior physicians confronted with simulated adult cardiac arrest,</td><td>Charging the defibrillator while ongoing compressions, then</td><td>1) ERC 2005 guideline algorithm, pausing for duration of rhythm check</td><td>Hands-off-time (time without chest compressions) mean in s (95%CI).
Overall ERC 2005
• Intervention 6.7 (5.6-7.9) vs ERC 2005 13.0 (100-15.9) p<0.1</td><td>Intervention had shorter overall and shockable rhythm</td></tr>
</table>

<table>
<tr><td></td><td>Study. Regional hospital, Denmark.</td><td>randomly assigned arrest rhythm of both pulseless VT (pVT) and asystole (AS). 10 physicians for comparison with ERC 2005 and 12 for ERC 2010</td><td>pausing for rhythm check and shocking if indicated (pVT) or disarming if not (AS). 1) paddles used to compare to ERC 2005 2) Pads used to compare to ERC 2010</td><td>through charging/shocking (if pVT) before continuing compressions. Paddles used. 2) ERC 2010 guideline algorithm, pausing for rhythm check, if pVT - compressions during charging and pause for shock before continuation of compressions</td><td>pVT ERC 2005
intervention 7.1 (5.2-8.9) vs ERC 2005 18.2 (15.3-21.1) p<0.1
AS ERC 2005 no difference
Overall ERC 2010 <u>(this is what PICOST addresses)</u>
intervention 3.9 (3.4-4.4) vs ERC 2010 5.6 (4.5-6.8) p<0.1
pVT
intervention 4.5 (3.7-5.3) vs ERC 2010 7.6 (6.0-9.3)
AS ERC 2010 no difference p<0.1
No evidence of dangerous defibrillation</td><td>hands-off time compared to both ERC 2005 and ERC 2010. No difference in safety

MANUAL MONITORING OF HANDS OFF TIME</td></tr>
<tr><td>Kemper, 2019</td><td>Randomized Controlled Single Centre Simulation Study.</td><td>243 Medical Students presented with randomly sequenced pulseless VT (pVT), VF or asystole (AS)</td><td>Anticipatory defibrillator charging (ADC)</td><td>ERC 2010 guideline algorithm (ERC), pausing for rhythm check, if VF or pVT - compressions during charging and pause for shock before continuation of compressions</td><td>No-flow time mean +/- SD
ADC = 25.8 s +/- 7.4 s vs ERC = 27.4 +/- 8.4 s, p = 0.19
No differences in defibrillation safety
Results reported as mean (SD)<table><tr><th></th><th>Anticipatory method</th><th>ERC 2010</th><th>p-value</th></tr><tr><td>No-flow time, s</td><td>25.8 (7.4)</td><td>27.4 (8.4)</td><td>0.19</td></tr><tr><td>Peri-shock pause, s</td><td>9.5 (2.8)</td><td>3.3 (1.9)</td><td><0.001</td></tr><tr><td>Pre-shock pause, s</td><td>6.9 (2.8)</td><td>1.6 (1.3)</td><td><0.001</td></tr><tr><td>Post-shock pause, s</td><td>2.6 (0.9)</td><td>1.7 (1)</td><td><0.001</td></tr><tr><td>Total pause, s</td><td>9.5 (2.8)</td><td>10.9 (3.3)</td><td>0.03</td></tr><tr><td>Number of peri-shock pauses >5s</td><td>1.8 (0.5)</td><td>0.2 (0.5)</td><td><0.001</td></tr></table></td><td>ADC had longer peri-shock pauses, pre-shock pauses and post-shock pauses. ADC had shorter total pauses. No differences in safety</td></tr>
<tr><td>Koch Hansen, 2016</td><td>Randomized Crossover Simulation Study. Danish University Hospital</td><td>29 Volunteer cardiology physicians randomly assigned roles in an arrest team and confronted randomly with different arrest rhythms (pVT, VF, PEA, AS) in 11 simulated adult cardiac arrest scenarios. Oral command</td><td>Stop-Only-While-Shocking (SOWS) - charging the defibrillator before rhythm check, while ongoing chest compressions</td><td>ERC 2010 guideline algorithm (ERC), pausing for rhythm check, if VF or pVT - compressions during charging and pause for shock before continuation of compressions</td><td>Mean hands-off time (expressed as per cent of entire simulation):
ERC = 26.6% +/- 4.8 vs SOWS 22.1% +/- 2.3, p = 0.04
No inappropriate shocks</td><td>SOWS had lesser % hands-off time. No inappropriate shocks</td></tr>
</table>

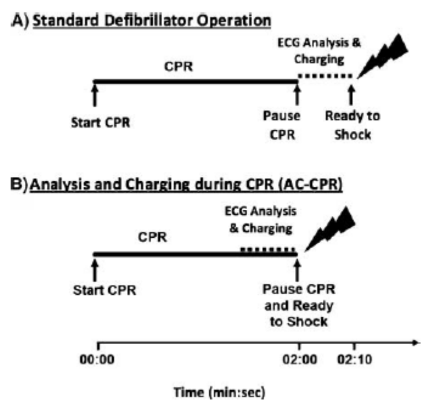
		for control or intervention algorithm.				

REFERENCES

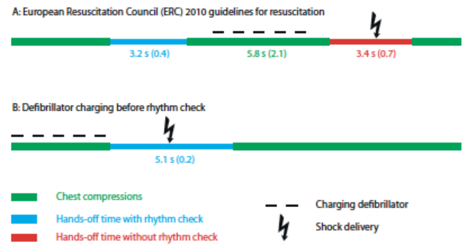
1. Edelson, D.P., Robertson-Dick, B.J., Yuen, T.C., Eilevstjønn, J., Walsh, D., Bareis, C.J., Vanden Hoek, T.L., Abella, B.S., 2010. Safety and efficacy of defibrillator charging during ongoing chest compressions: a multi-center study. Resuscitation 81, 1521–1526.
2. Hansen, L.K., Folkestad, L., Brabrand, M., 2013. Defibrillator charging before rhythm analysis significantly reduces hands-off time during resuscitation: a simulation study. Am J Emerg Med 31, 395–400. https://doi.org/10.1016/j.ajem.2012.08.029.
3. Kemper, M., Zech, A., Lazarovici, M., Zwissler, B., Prückner, S., Meyer, O., 2019. Defibrillator charging before rhythm analysis causes peri-shock pauses exceeding guideline recommended maximum 5 s. Anaesthesist 68, 546–554. https://doi.org/10.1007/s00101-019-0623-x
4. Koch Hansen, L., Mohammed, A., Pedersen, M., Folkestad, L., Brodersen, J., Hey, T., Lyhne Christensen, N., Carter-Storch, R., Bendix, K., Hansen, M.R., Brabrand, M., 2016. The Stop-Only-While-Shocking algorithm reduces hands-off time by 17% during cardiopulmonary resuscitation - a simulation study. Eur J Emerg Med 23, 413–417. https://doi.org/10.1097/MEJ.0000000000000282

Anticipatory defibrillator charging for ALS: A Scoping Review **Possible papers of relevance/Relevant Posters/Abstracts/Letters** **Search on: 7/10/2019**

[will move to appendix]

Reference	Methods	Participants	Interventions	Comparisons	Outcomes	Notes
1) Barash, 2011. **Published Study**	Randomized Crossover Simulation Study. USA	Thirty providers confronted with simulated adult cardiac arrests. 10 ALS Paramedics, 9 BLS medical technicians, 10 BLS lay rescuers and 1 BLS nurse.	Analysis and Charging during CPR mode (AC-CPR) [B in fig below]  Figure 2. Cardiopulmonary resuscitation (CPR) segment composition in the resuscitation intervals with standard defibrillator operation (**A**) and Analysis and Charging during CPR mode (**B**). ECG = electrocardiogram. Time is shown in minutes:seconds.	Manual defibrillation CPR (ALS providers); Automated defibrillation CPR (BLS providers)	Duration of interruptions in chest compressions during whole resuscitation. Mean =/- SD in s: • AC-CPR (ALS) = 43.2 +/- 7.3 vs ALS = 104.2 +/- 30.6; p = 0.005 • *AC-CPR (BLS) = 42.6 +/- 15/9 vs BLS = 108.5 +/- 17.2, p < 0.0001* Pre-shock pause: • AC-CPR (ALS) = 3.0 +/- 1.2 vs ALS = 10.2 +/- 1.9, p < 0.0001 • *AC-CPR (BLS) = 1.7 +/- 0.5 vs BLS 11.3 +/- 0.8, p < 0.0001* Post-shock pause: • AC-CPR (ALS) = 4.4 +/- 2.5 vs ALS 6.8 +/- 4.1, **p = 0.2** • *AC-CPR (BLS) = 5.8 +/- 2.0 vs BLS 4.9 +/- 2.0, p = 0.3* No differences in perceived exertion or pain	WRONG INTERVENTION The intervention also encompasses automated rhythm analysis, and BLS modes. Sponsored by Zoll, two authors employed by Zoll, manufacturers of the technology used. **AC-CPR (ALS) had shorter interruptions in whole arrest and**

						shorter pre-shock pause .
2) Coggins 2018 Published Study	Cohort single-blinded study in Australian University Hospital	112 Hospital ALS providers undergoing manikin training for mechanical CPR, assessed on defibrillation practice (blinded). 109 defibrillations over 6 months	Correct or 'near correct' use of C.O.A.C.H.E.D cognitive aid	Incorrect or absent use of cognitive aid	The C.O.A.C.H.E.D. cognitive aid was applied correctly in 92 of 109 defibrillations. Providers with correct cognitive aid use had a median length of peri-shock pause time of 6.0 s (IQR 5.0–7.0). Providers with 'entirely incorrect or absent' cognitive aid use had a peri-shock pause time of 8.0 s (IQRF 6.6–10.0)($p \leq 0.001$). No unsafe defibrillation practices were observed.	The C.O.A.C.H.E.D aid used correctly reduces peri-shock pause time. **No unsafe defibrillation attempts.**
3) Iversen 2019 **Conference Abstract**	A feasibility study introducing defib Pre-charge through short theoretical and practical lectures, followed by simulated arrest.	Pre-hospital practitioners in simulated adult (assumed) cardiac arrests, after teaching session on pre-charging.	Pre-charging the defibrillator before rhythm check	Any other sequence of action or practice, as judged by two consultant observers	Pre-charge was adequately used in 95 of 99 cases. One 'near-miss' shock in case of a non-shockable rhythm.	Small study of a short training programme to learn new method. Outcomes measured of limited value.
4) Studnek, 2012 **Conference Abstract**	This was a retrospective analysis of data obtained from a single ALS urban EMS system from 1/1/2010 to 12/31/10 and 8/1/11 to 11/6/2011	Paramedics in EMS system treating adult patients who required at least one defibrillation and had the CPR feedback device connected during the defibrillation attempt	Charging the defibrillator after 180 compressions and pausing for rhythm check +/- shock at 200 compressions (anticipatory charging)	Current practice (not described) assumed no compressions during charging. Author contacted.	Pre-shock pause pre-intervention was 35 seconds (95% CI 20-50) post-intervention duration was 9 seconds (95% CI 7-12) $p<0.001$	Continuation of compressions during charging reduces pre-shock pause.

5) Thim, 2012 **Letter to Editor**	Randomised controlled crossover study	Six physician volunteers (ALS) confronted with VF arrests (but told to expect any rhythm)	Defibrillator pre-charging	Standard ERC2010 guidelines	• Absolute difference in time interval between 2 CPR cycles: 7.3 s (95% CI 4.3 - 10.3); Difference in hands-off time 1.5 s (0.4 - 2.5 s); Favouring Pre-charging  **Fig. 1.** Graphical presentation of the rhythm check time course. Panel A: European Resuscitation Council (ERC) 2010 guidelines for resuscitation. Panel B: Defibrillator charging before rhythm check. Average times used for heart rhythm analysis, defibrillator charging, and resuming compressions after shock delivery are given with their standard deviations in parentheses. Difference in total and hands-off time between two CPR cycles estimated with the paired *t*-test were 7.3 s (95% confidence interval 4.3–10.3) and 1.5 s (95% confidence interval 0.4–2.5).	Pre-charging shortened the total time and hands-off time between CPR cycles
6) Boushra 2019 **Conference** ePoster	Retrospective single-centre cohort study	102 patients over a three-year period with OHCA who presented with a shockable rhythm and received at least one shock	Pre-charging the defibrillator before rhythm check	Any other method of defibrillation (author response – 'majority' performed compressions during charging ('back on the chest')	25 of 102 enrolled patients survived to hospital discharge. Pre-charging was associated with decreased time from rhythm analysis to shock delivery by 12.73.5 [typo in original abstract] seconds (p=.0004). No correlation was found between pre-charging and time to ROSC (p=.4518), number of shocks delivered (p=.925), or neurological outcome (R-square=0.025) [blinded modified Rankin score]	Unsurprising relationship between time from rhythm analysis to shock delivery. No other benefit found from this small study. Sample size n=25 Useful outcome data limited. Author contacted. Working on full paper. Not quite sure what comparator group is.

REFERENCES

1) Barash, D.M., Raymond, R.P., Tan, Q., Silver, A.E., 2011. A new defibrillator mode to reduce chest compression interruptions for health care professionals and lay rescuers: a pilot study in manikins. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors 15, 88–97.
2) Coggins A, Nottingham C, Chin M, Warburton S, Han M, Murphy M, et al. A prospective evaluation of the 'C.O.A.C.H.E.D.' cognitive aid for emergency defibrillation. Australas Emerg Care. 2018 Aug;21(3):81–6.
3) Iversen B.N., Alstrup K., Faurby R., Christensen S., Kirkegaard H., 2019. Introducing pre-charge in the pre-hospital setting: A feasibility study. Acta Anaesthesiologica Scandinavica 63.
4) Studnek J., Hawkins E., Vandeventer S., 2012. The impact of an educational intervention on the pre-shock pause interval among patients experiencing an out-of-hospital cardiac arrest. Academic Emergency Medicine 19.
5) Thim, T., Grove, E.L., Løfgren, B., 2012. Charging the defibrillator before rhythm check reduces hands-off time during CPR: A randomised simulation study. Resuscitation 83, e210–e211. https://doi.org/10.1016/j.resuscitation.2012.07.034
6) Boushra M., Dixon M., Coco M., Stahl J., Brewer K.L., Taylor S.E. Defibrillator precharging does not improve survival or neurological outcome in prehospital cardiac arrest. Academic Emergency Medicine. 2019 May;26.

Task Force Insights

1. Statement about why this topic was reviewed.

- This new topic was chosen because some resuscitation systems have adopted the anticipatory charging approach for manual defibrillation.
- There is debate about this topic: [Sam Ghali, "Beyond ACLS: Pre-Charging the Defibrillator", REBEL EM blog, March 24, 2016. Available at: https://rebelem.com/beyond-acls-pre-charging-the-defibrillator/.]
- This scoping review aims to identify the available studies on this topic, and whether a systematic review is required.

2. Narrative summary of evidence identified

- There are currently insufficient studies to support progressing to a systematic review on this topic.
- We identified no randomised controlled clinical trials in humans addressing this topic.
- The single human observational study [Edelson 2010 1521] did not report ROSC or survival outcomes.
- The human [Edelson 2010 1521] and manikin studies [Hansen 2013 395, Kemper 2019 546, Koch-Hansen 2016 413] suggest that charging the defibrillator in anticipation of the rhythm check, and shocking or disarming as appropriate increases the immediate pre-shock pause, and the peri-shock pause, but decreases the total number of pauses and hands off time.
- Anticipatory charging may be a method to reduce the overall compression pause time during cardiac arrest, but may result in longer immediate pre and peri-shock pause times.
- We do not know which combination of these pauses is most important. Peri-shock pause is an important metric associated with key outcomes during resuscitation. Longer pauses worsen outcomes [Cheskes, 2011 124, Cheskes 2014 336]. A shorter pre-shock pause is associated with increased defibrillation success [Edelson 2006 136].
- Direct comparison of peri and pre-shock pauses between current methods are difficult and may not be valid.
- One manikin study showed that the post-shock pause time is longer with anticipatory charging [Kemper 2019 546].
- The available studies did not identify any safety issues between the different defibrillation strategies.
- These defibrillation strategies are primarily for a pads-based approach for manual defibrillation [need to highlight those studies that used paddles]
- We have also reviewed abstracts, posters, letters and related publications and these do not provide any new information.
- Other relevant studies to this subject
    - It appears safe and feasible to charge the defibrillator in anticipation of a rhythm check in and out of hospital, and cognitive aids have been used successfully in resuscitation systems to achieve this [Coggins 2018 81, Iverson, 2019].

  - An observational study in real cardiac arrests reported that long pauses before defibrillation are likely due to human factors during the resuscitation and not due to inherent difficulties with rhythm identification [Abella 2006 S427].
  - A randomised manikin study showed that 'Hands-on time and time to defibrillation' are worse with ad-hoc teams or when leadership is poor [Hunziker 2009 3]. The techniques may work differently for different teams.

- We did not specifically look at:
  - New defibrillator technologies that filter the effect of movement during chest compression – these defibrillators are designed to analyse rhythm without pausing chest compression. They are not part of this question. This type of defibrillator removes the need to analyse rhythm and enables charging during chest compression when the rhythm is identified as shockable.
  - How long it takes for the defibrillator to charge – modern defibrillators charge very rapidly – if chest compressions are given during charging only this leads to very few chest compressions. Should there be a specific period of chest compressions before giving shock in current commonly used approach? This would have to be less than the time for the defibrillation 'dumping the charge' if no shock is delivered after charging.

3. Narrative Reporting of the task force discussions

- The TF decided there was insufficient information at this time to warrant a formal systematic review.
- There are no studies that look at critical or important outcomes.
- This topic is redundant in those settings that use defibrillators that can analyse during chest compression – this function is currently not commonly used.
- The usefulness of approaches depends on skills of individual using the defibrillator.
- The charging prior to rhythm analysis approach is taught in Australia, New Zealand and in some parts of Europe and North America.

Knowledge Gaps

Knowledge Gaps Template for Task Force chairs

There were no RCTs identified, and little in the way of observational clinical data on this topic. The relative importance of different pauses, (e.g. pre-, post-, peri-shock, compression fraction) is not known.

References

Abella, B.S., Kim, S., Edelson, D.P., Huang, K.-N., Merchant, R.M., Myklebust, H., Vanden Hoek, T.L., Becker, L.B., 2006. Difficulty of cardiac arrest rhythm identification does not correlate with length of chest compression pause before defibrillation. Crit. Care Med. 34, S427-431. https://doi.org/10.1097/01.CCM.0000246757.15898.13

Barash, D.M., Raymond, R.P., Tan, Q., Silver, A.E., 2011. A new defibrillator mode to reduce chest compression interruptions for health care professionals and lay rescuers: a pilot study in manikins. Prehosp Emerg Care 15, 88–97. https://doi.org/10.3109/10903127.2010.531375

Boushra M., Dixon M., Coco M., Stahl J., Brewer K.L., Taylor S.E., 2019. Defibrillator precharging does not improve survival or neurological outcome in prehospital cardiac arrest. Academic Emergency Medicine 26.

Cheskes, S., Schmicker, R.H., Christenson, J., Salcido, D.D., Rea, T., Powell, J., Edelson, D.P., Sell, R., May, S., Menegazzi, J.J., Van Ottingham, L., Olsufka, M., Pennington, S., Simonini, J., Berg, R.A., Stiell, I., Idris, A., Bigham, B., Morrison, L., 2011. Peri-shock pause: an independent predictor of survival from out-of-hospital shockable cardiac arrest. Circulation 124, 58–66. https://doi.org/10.1161/CIRCULATIONAHA.110.010736

Cheskes, S., Schmicker, R.H., Verbeek, P.R., Salcido, D.D., Brown, S.P., Brooks, S., Menegazzi, J.J., Vaillancourt, C., Powell, J., May, S., Berg, R.A., Sell, R., Idris, A., Kampp, M., Schmidt, T., Christenson, J., 2014. The impact of peri-shock pause on survival from out-of-hospital shockable cardiac arrest during the Resuscitation Outcomes Consortium PRIMED trial. Resuscitation 85, 336–342. https://doi.org/10.1016/j.resuscitation.2013.10.014

Coggins, A., Nottingham, C., Chin, M., Warburton, S., Han, M., Murphy, M., Sutherland, J., Moore, N., 2018. A prospective evaluation of the “C.O.A.C.H.E.D.” cognitive aid for emergency defibrillation. Australas Emerg Care 21, 81–86. https://doi.org/10.1016/j.auec.2018.08.002

Edelson, D.P., Abella, B.S., Kramer-Johansen, J., Wik, L., Myklebust, H., Barry, A.M., Merchant, R.M., Hoek, T.L.V., Steen, P.A., Becker, L.B., 2006. Effects of compression depth and pre-shock pauses predict defibrillation failure during cardiac arrest. Resuscitation 71, 137–145. https://doi.org/10.1016/j.resuscitation.2006.04.008

Edelson, D.P., Robertson-Dick, B.J., Yuen, T.C., Eilevstjønn, J., Walsh, D., Bareis, C.J., Vanden Hoek, T.L., Abella, B.S., 2010. Safety and efficacy of defibrillator charging during ongoing chest compressions: A multi-center study. Resuscitation 81, 1521–1526. https://doi.org/10.1016/j.resuscitation.2010.07.014

Hansen, L.K., Folkestad, L., Brabrand, M., 2013. Defibrillator charging before rhythm analysis significantly reduces hands-off time during resuscitation: a simulation study. Am J Emerg Med 31, 395–400. https://doi.org/10.1016/j.ajem.2012.08.029

Hunziker, S., Tschan, F., Semmer, N.K., Zobrist, R., Spychiger, M., Breuer, M., Hunziker, P.R., Marsch, S.C., 2009. Hands-on time during cardiopulmonary resuscitation is affected by the process of teambuilding: a prospective randomised simulator-based trial. BMC Emergency Medicine 9, 3. https://doi.org/10.1186/1471-227X-9-3

Iversen B.N., Alstrup K., Faurby R., Christensen S., Kirkegaard H., 2019. Introducing pre-charge in the pre-hospital setting: A feasibility study. Acta Anaesthesiologica Scandinavica 63.

Kemper, M., Zech, A., Lazarovici, M., Zwissler, B., Prückner, S., Meyer, O., 2019. Defibrillator charging before rhythm analysis causes peri-shock pauses exceeding guideline recommended maximum 5 s. Anaesthesist 68, 546–554. https://doi.org/10.1007/s00101-019-0623-x

Koch Hansen, L., Mohammed, A., Pedersen, M., Folkestad, L., Brodersen, J., Hey, T., Lyhne Christensen, N., Carter-Storch, R., Bendix, K., Hansen, M.R., Brabrand, M., 2016. The Stop-Only-While-Shocking algorithm reduces hands-off time by 17% during cardiopulmonary resuscitation - a simulation study. Eur J Emerg Med 23, 413–417. https://doi.org/10.1097/MEJ.0000000000000282

Studnek J., Hawkins E., Vandeventer S., 2012. The impact of an educational intervention on the pre-shock pause interval among patients experiencing an out-of-hospital cardiac arrest. Academic Emergency Medicine 19.

Thim, T., Grove, E.L., Løfgren, B., 2012. Charging the defibrillator before rhythm check reduces hands-off time during CPR: A randomised simulation study. Resuscitation 83, e210–e211. https://doi.org/10.1016/j.resuscitation.2012.07.034

B2a Scoping_Review_BP_intra-arrest variables ALS 656: SCOPREV)

Conflict of Interest Declaration

The ILCOR Continuous Evidence Evaluation process is guided by a rigorous ILCOR Conflict of Interest policy. The following Task Force members and other authors were recused from the discussion as they declared a conflict of interest: none applicable
The following Task Force members and other authors declared an intellectual conflict of interest and this was acknowledged and managed by the Task Force Chairs and Conflict of Interest committees: none applicable

Task Force Scoping Review Citation

Van de Voorde P, Atkins D, Scholefield B, …., on behalf of the International Liaison Committee on Resuscitation Paediatric Life Support Task Force.
Value of measurable intra-arrest variables during pediatric in- and out-of-hospital cardiac arrest: Blood Pressure. Scoping Review and Task Force Insights [Internet] Brussels, Belgium: International Liaison Committee on Resuscitation (ILCOR) Pediatric Life Support Task Force, 2018 May 30. Available from: http://ilcor.org

Methodological Preamble and Link to Published Scoping Review

The continuous evidence evaluation process started with a scoping review of blood pressure and haemodynamic resuscitation in paediatric cardiac arrest, conducted by the ILCOR PLS Task Force Scoping Review team. Evidence from adult and pediatric literature was sought and considered by the PLS Task Force.

Scoping Review

PICOST

The PICOST (Population, Intervention, Comparator, Outcome, Study Designs and Timeframe)

Population: Infants & Children in any setting (in-hospital or out-of-hospital) with cardiac arrest

Intervention: the presence of variables -images, cut-off values or trends- during CPR (intra-arrest) that can provide physiologic feedback to guide resuscitation efforts, namely:

2/ Arterial blood pressure

Comparators: the absence of such factors -images, cut-off values or trends.

Outcomes: Any clinical outcome.

Study Designs: STEP 1: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) that concern directly the population and intervention described above are eligible for inclusion. If it is anticipated that there will be insufficient studies from which to draw a conclusion, case series may be included in the initial search. The minimum number of cases for a case series to be included was set by the taskforce at 5 cases. Unpublished studies (e.g., conference abstracts, trial protocols) are excluded.
STEP 2: the same study designs and/or existing systematic or scoping reviews not directly concerning the population or intervention defined above but considered informative as additional evidence for the development of the final taskforce insights.

Timeframe: For STEP 1, all languages are included, as long as there is an English abstract. We searched articles from 2015 onwards. For STEP 2, if a systematic or scoping review of high quality (as per AMSTAR 2 tool) is identified, search can be limited to beyond data and/or scope of that review.

Active and Reposed PICOs Related to scope of work for this PICOST: P 826 Invasive Blood Pressure Monitoring During CPR

2015 Consensus on Science*:*

For the critical outcome of survival to 180 days and good neurologic outcome, we identified no studies. For the critical outcome of survival to 60 days and good neurologic outcome, we identified no studies. For the critical outcome of survival to hospital discharge and good neurologic outcome, we identified no studies. For the critical outcome of the likelihood of survival to discharge, we identified very-low-quality evidence (downgraded for risk of bias, very serious inconsistency, indirectness, and imprecision) from 2 pediatric animal RCTs(Friess 2013, 2698-2704; Sutton 2013, 696-701) involving 43 subjects, which showed benefit. For the important outcome of ROSC, we identified very-low-quality evidence (downgraded for risk of bias, inconsistency, very serious indirectness, and imprecision) from 2 pediatric animal RCTs(Friess 2013, 2698-2704; Sutton 2013, 696-701) involving 43 subjects, which showed benefit.

2015 Treatment Recommendation*:*

The confidence in effect estimates is so low that the panel decided a recommendation was too speculative.

Search Strategies

We searched PUBMED and Embase with the predefined inclusion criteria (13/09/2019) and combined the following terms using Bolean operators*: life support care, cardiopulmonary resuscitation, ROSC, heart arrest, cardiac arrest* using both individual (ti,ab,kw) and related MESH terms, as well as exploded terms within Embase. We combined these with the terms: *blood pressure, diastolic, systolic, (mean) arterial pressure, coronary perfusion pressure, hemodynamic-directed, haemodynamic-directed* (again both individual and MESH terms, and Embase exploded terms).

We identified 259 articles after elimination of duplicates. We excluded only those studies that clearly did not have blood pressure as study focus, were strictly animal data (separately included for step 2), or had one of the other pre-defined exclusion criteria.
We accepted 13 abstracts for review. 100% consensus was reached after a first blinded individual review (Rayyan.qrci.org) and a subsequent discussion about 1 abstract.

Inclusion and Exclusion criteria

This review is part of a cluster of scoping reviews (see general description) focussing on those variables that can be measured or monitored during the provision of ALS and before ROSC. The variables under consideration are those that have potential to provide (physiologic and/or haemodynamic) feedback to the resuscitating team, potentially guiding their actions to improve outcome, and which might predict outcome. Inclusion criteria as per PICOST.
Exclusions include:
1/ Newborn at Delivery
2/ Pre-arrest features, not influenced by ALS: time of day, location, bystander CPR, gasping, age, etiology, initial rhythm, unwitnessed…
3/ Standard ALS interventions e.g. ventilation strategies, fluids, firm surface, medications given, eCPR, length and Quality of CPR….

4/ Post-ROSC parameters such as lactate clearance, post-arrest rhythm, hypotension nor any actions to provide neuroprotective care post-ROSC.

Adult data are only considered in step 2 as both the etiology and pathophysiology of paediatric arrest differs substantially leading to serious indirectness. Moreover, the complexity or impact of obtaining the variable under study will likely differ e.g. placing an arterial line… Finally, animal data are considered in step 2 but -as human data are available- mostly to inform the knowledge gaps and possible future research agenda.

Outcome might include: Quality of CPR, ROSC, survival to discharge, (changes in) functional outcome at discharge or other time points.

Data tables

Non-RCT OR OBSERVATIONAL *(acronym); Author; Year Published*	*Study type/design; Study size (N)*	*Patient Population (inclusion criteria)*
1. Wolfe 2019 57	*Prospect. multicentre observat. N=164, with 77 survivors*	*IHCA (PICU-PCICU) compressions>1' and invasive BP in place; US, 2013-2016, same reference population as Berg 2018 1784 but only survivors*
Results primary endpoints (P value; OR or RR; & 95% CI)	*77 survivors (69% <1y, 71% congenital heart disease), baseline PCPC normal to mild in 76%. New substantive morbidity NSM (increase of >2 in total functional state scale FSS or 2 in any FSS domain) in 42%. NSM not associated with median SBP or DBP value nor for % above target (diastolic above 30 child/25 infant mmHg; systolic 80/60 mmHg),*	
Summary/Conclusion - Comments	*In this preselected population, no association between any intra-arrest BP and neurological outcome of survivors was identified.*	
2. Berg 2018 1784	*Prospect. multicentre observat. N= 244 CPR events of which 164 could be analysed*	*IHCA (PICU-PCICU) compressions>1' and invasive BP in place; US, 2013-2016, The mean age of the sample was 0.7y old (IQR 0.1-3.1), 60% had a congenital heart disease.*
Results primary endpoints (P value; OR or RR; & 95% CI)	The hypothesised cut-off levels for mean diastolic BP (first 10 minutes of CPR or length of CPR if less): ≥25 mm Hg in infants and ≥30 mm Hg in children ≥1-year-old were reached in 62% of events. Using Multivariable Poisson regression, the adjusted RR for survival was 1.7 [1.22.6] and 1.6 for favourable neurological outcome [1.1; 2.5]. For ROSC it was 1.2 [0.9;1.5]. Stepwise backward models showed similar results. No significant association could be found for systolic blood pressure cut-off values.	
Summary/Conclusion - Comments	*In general, the CA events described were of short duration (55% less than 10 minutes) and the quality of CPR was presumed to be high (dedicated teams all in ICU). This resulted in a ROSC of 68% and another 22% surviving the event by providing e-CPR. 47% survived to discharge and 43% had a favourable neurological outcome (defined as PCPC of 1 to 3 or no change from baseline).* *In this very much preselected population, Berg et al found significant association between the mean diastolic BP during the first 10 minutes of CPR (or less) and outcome. Although the test performance as such was less than optimal, Berg et al were able to define ROC curve threshold optimums (restricted cubic splines). The optimal ROC curve thresholds without covariable consideration were 27 mmHg (infants) and 31.75 mmHg (children). These correlated with predicted survival rates of 63% [35,84] and 67% [48,82]. Survival rapidly dropped with thresholds below 20 mmHg (infant) resp. 25 mmHg (child). The lowest*	

	mean DBP with survival to discharge was 16mmHg (infants) resp. 18 mmHg (children).	
3. Yates 2019 1126	*Prospect. multicentre observat.* *N= 164 CPR events of which 113 were included*	*IHCA (PICU-PCICU) compressions>1' and invasive BP in place; US, 2013-2016, tertiary centres PCCRN; 37w gestation till 19y old* *88 surgical cardiac, 25 medical cardiac*
Results primary endpoints (P value; OR or RR; & 95% CI)	The hypothesised cut-off levels for mean diastolic BP (first 10 minutes of CPR or length of CPR if less): ≥25 mm Hg in infants and ≥30 mm Hg in children ≥1-year-old were reached in 58% of surgical and 68% of medical cardiac cases. The achievement of BP goals was associated with survival to discharge in surgical but not medical cardiac etiology (p0.018). The performance of CPR within the guidelines was not associated with any outcome (compression rate, mean ventilatory rate, compression fraction). The median ventilation rate significantly differed from the guidelines defined 10/minute (between 24.7 and 34.9 depending on subgroup). In addition, the number of cases with compression rates between 100 and 120 or compression fraction above 90% was less than half of all cases.	
Summary/Conclusion - Comments	*During resuscitation in an ICU, with invasive monitoring in place, diastolic blood pressure targets of greater than or equal to 25 mm Hg in infants and greater than or equal to 30 mm Hg in children can be achieved in patients with both surgical and medical heart disease. Achievement of diastolic blood pressure target was associated with improved survival to hospital discharge in surgical cardiac patients, but not medical cardiac patients. Diastolic blood pressure targets were feasible to achieve in 1) single ventricle patients, 2) open chest physiology, and 3) extracorporeal cardiopulmonary resuscitation patients.*	

Task Force Insights

1. Why this topic was reviewed.

Ideally, physiologic monitoring and feedback to the clinician during cardiac arrest resuscitation would allow rescuers to monitor (and adjust) quality of CPR, and to predict (and influence) the likelihood of return of spontaneous circulation and subsequent neurologic recovery. As such, this physiologic monitoring could lead to a form of 'individualised' CPR, where actions are altered to match with individual needs and responses of the victim in cardiac arrest.

Arterial Blood Pressure (systolic (SBP), diastolic (DBP) or mean blood pressure (MBP)) drives coronary and brain perfusion and therefore a certain level of S-D-M blood pressure might be associated with improved outcome. This observation has been supported by both pre-clinical data and expert experience. However, it is unknown if CPR with an individualized BP-goal directed protocol rather than the standard one-size-fits-all protocol could change outcome. Given the need for arterial access this question is currently limited to the IHCA population, and more specifically to those in an intensive care environment.

2. Narrative summary of evidence identified

We identified 3 observational studies from the same group (and describing overlapping populations, be it that Wolfe et al looked only at the survivors). Wolfe et al (Wolfe 2019 57) did not find any association between any BP and neurological outcome in a cohort of survivors from (PICU-PCICU) IHCA.
Berg et al (Berg 2018 174) did find, in a very much preselected population, a significant association between the mean diastolic BP during the first 10 minutes of CPR (or less) and outcome. Although the test performance as such was less than optimal, Berg et al were able to define ROC curve threshold optimums. The optimal ROC curve thresholds without

adjustment with covariables were 27 mmHg (infants) and 31.75 mmHg (children). These correlated with predicted survival rates of 63% [35,84] and 67% [48,82]. Survival rapidly dropped with thresholds below 20 mmHg (infant) resp. 25 mmHg (child). The lowest mean DBP with survival to discharge was 16mmHg (infants) resp. 18 mmHg (children).
Yates et al (Yates 2019 1126) argumented in their cohort study the feasibility of attaining certain diastolic blood pressure targets in patients with surgical and medical cardiac etiology of CA. Achievement of these targets was associated with improved survival to hospital discharge in surgical cardiac patients, but not medical cardiac patients.

To further explore the topic, we also looked at indirect evidence from adult and animal studies (STEP 2). Chopra et all (Chopra 2016 102) performed a systematic review on hemodynamic-directed feedback during resuscitation and identified 6 animal studies (from 2 research groups and published between 2011 and 2014; only studies with a control group were included). The 4 studies looking at survival showed a significant advantage of hemodynamic [HD]-directed CPR, but given the limited sample sizes, the review authors did not feel the evidence to be sufficient to draw any conclusions.
This identified trend was also confirmed in more recent pediatric animal studies (mostly form the same research group).
Morgan et al (Morgan 2016 6) compared HD-directed CPR with standard CPR in a 3-month swine model of either asphyxia-associated or primary VF. They had 37/60 animals (61.7%) surviving to 45 minutes. Diastolic blood pressure was superior to ETCO2 in discriminating survivors (AUC 0.82 vs 0.6) with an optimal cut-off of 34.1 mmHg. Still the test performance was only moderate (sensitivity 0.78, specificity 0.81, PPV 0.64, NPV 0.89).
Naim et al (Naim 2016 e1111) also compared HD-directed CPR with standard CPR in a 3-month old swine model. Again, survival was higher in the HD-directed CPR group (24h survival 5 out of 8 vs. no survivors 0/8 in the standard group). The mean coronary perfusion pressure was higher, and the HD-directed group received more doses of vasopressor and had slightly less compression depth than the standard group.
Morgan et al (Morgan 2017 41) compared HD-directed CPR with standard CPR in an asphyxia VF piglet model. The 4-hour survival was 100% in the HD-directed group, vs. 6 / 10 for the standard group. Tthe mean coronary perfusion pressure was higher and the HD-directed group received more doses of vasopressor and had less compression depth (-14mm) than the standard group.
Lautz et al (Lautz 2019 e241) compared HD-directed CPR with standard CPR in a piglet model of asphyxia VF (N=28, with 6 sham animals). Favourable neurological outcome was observed in 7/10 HD-directed CPR animals, compared to 1/12 with standard CPR). Coronary perfusion pressure and brain tissue oxygenation were markedly higher in the piglets with HD-directed CPR.

Finally, there is one adult study using data from the AHA's Get with the Guidelines-Resuscitation™ registry. Sutton et al (Sutton 2016 76) performed a prospective observational propensity-matched cohort study of adult IHCA. 3032 physiologic monitored patients (either by ETCO2 or diastolic BP) were compared to 6064 patients without monitoring. Those monitored showed a higher rate of ROSC (OR 1.22 [1.04; 1.43]) but not survival to discharge (OR 1.04 [0.91; 1.18]) nor survival with favourable neurological outcome. The study did not specifically look at diastolic BP and even for those with an arterial line in place only about 1/3 reported using the diastolic BP to guide their CPR efforts. Importantly most of the data in this registry were collected before 2010.

3. Narrative Reporting of the task force discussions
Cardiac arrest still not has a good prognosis. High quality CPR improves outcome, but what constitutes the best possible CPR for an individual patient is still based on limited evidence and may be different for different etiological factors. Having parameters to guide CPR and

adjust it to the need of the individual patient is therefore essential.
Adequate myocardial and brain tissue perfusion is fundamental to outcome and (diastolic) blood pressure could be useful as a clinically measurable surrogate for this. The current evidence, be it of very low certainty (due to study design, sample size and selection bias), suggests a possible relation between diastolic BP and patient outcome. Only IHCA events were studied because of the need for invasive BP monitoring.
Although Berg et al were able to identify optimal ROC curve thresholds with regard to test performance, and also identified thresholds below which no child survived, the evidence is too limited to consider diastolic BP in itself sufficient to identify CPR futility.
The taskforce considers the level of certainty of the available evidence too low to make any recommendation for or against the use of diastolic blood pressure to guide resuscitation efforts in children with cardiac arrest. More specifically, there is no single diastolic BP value that can be used to predict a favourable outcome, nor as an indicator of futility. There is not a single diastolic BP value that can be used as a target during CPR. The existing evidence is also too limited to advocate for any more thorough evidence evaluation by systematic review. For those children with IHCA where an arterial line is already in place and within settings that allow for proper implementation, hemodynamic-directed CPR might be considered.

Knowledge Gaps

The potential value of truly personalised hemodynamic-directed CPR, where CPR efforts (chest compressions, vasopressor doses, etiological treatments) are adjusted in view of pre-defined (diastolic) BP goals and not limited by current 'standard' guidelines, has yet to be defined. Animal studies suggest a positive impact on outcome of such an approach but can only be seen as exploratory and hypothesis-generating. An RCT seems warranted.

References

1. Berg RA, Sutton RM, Reeder RW, Berger JT, Newth CJ, Carcillo JA, McQuillen PS, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) PICqCPR (Pediatric Intensive Care Quality of Cardio-Pulmonary Resuscitation) Investigators. Association Between Diastolic Blood Pressure During Pediatric In-Hospital Cardiopulmonary Resuscitation and Survival. Circulation. 2018 24; 137:1784-1795
2. Chopra AS, Wong N, Ziegler CP, Morrison LJ. Systematic review and meta-analysis of hemodynamic-directed feedback during cardiopulmonary resuscitation in cardiac arrest. Resuscitation. 2016; 101:102-7
3. Lautz AJ, Morgan RW, Karlsson M, Mavroudis CD, Ko TS, Licht DJ, Nadkarni VM, Berg RA, Sutton RM, Kilbaugh TJ. Hemodynamic-Directed Cardiopulmonary Resuscitation Improves Neurologic Outcomes and Mitochondrial Function in the Heart and Brain. Crit Care Med. 2019; 47(3):e241-e249
4. Morgan RW, French B, Kilbaugh TJ, Naim MY, Wolfe H, Bratinov G, Shoap W, Hsieh TC, Nadkarni VM, Berg RA, Sutton RM. A quantitative comparison of physiologic indicators of cardiopulmonary resuscitation quality: Diastolic blood pressure versus end-tidal carbon dioxide. Resuscitation. 2016; 104:6-11
5. Morgan RW, Kilbaugh TJ, Shoap W, Bratinov G, Lin Y, Hsieh TC, Nadkarni VM, et al; Pediatric Cardiac Arrest Survival Outcomes PiCASO Laboratory Investigators. A hemodynamic-directed approach to pediatric cardiopulmonary resuscitation (HD-CPR) improves survival. Resuscitation. 2017; 111:41-47
6. Naim MY, Sutton RM, Friess SH, Bratinov G, Bhalala U, Kilbaugh TJ, Lampe JW,

Nadkarni VM, Becker LB, Berg RA. Blood Pressure- and Coronary Perfusion Pressure-Targeted Cardiopulmonary Resuscitation Improves 24-Hour Survival From Ventricular Fibrillation Cardiac Arrest. Crit Care Med. 2016; 44(11): e1111-e1117

7. Sutton RM, French B, Meaney PA, Topjian AA, Parshuram CS, Edelson DP, Schexnayder S, et al; American Heart Association's Get With The Guidelines–Resuscitation Investigators.
Physiologic monitoring of CPR quality during adult cardiac arrest: A propensity-matched cohort study. Resuscitation. 2016; 106:76-82
8. Wolfe HA, Sutton RM, Reeder RW, Meert KL, Pollack MM, Yates AR, Berger JT, et al; Eunice Kennedy Shriver National Institute of Child Health; Human Development Collaborative Pediatric Critical Care Research Network; Pediatric Intensive Care Quality of Cardiopulmonary Resuscitation Investigators. Functional outcomes among survivors of pediatric in-hospital cardiac arrest are associated with baseline neurologic and functional status, but not with diastolic blood pressure during CPR. Resuscitation. 2019; 143:57-65

B2b Scoping_Review_ETCO2_intra-arrest variables ALS 656: SCOPREV)

This review is a final version prepared by ILCOR and is labelled "draft" to comply with copyright rules of journals. The 'draft label' will be removed from this website once a summary article has been published in a scientific journal.

Conflict of Interest Declaration

The ILCOR Continuous Evidence Evaluation process is guided by a rigorous ILCOR Conflict of Interest policy. The following Task Force members and other authors were recused from the discussion as they declared a conflict of interest: none applicable

The following Task Force members and other authors declared an intellectual conflict of interest and this was acknowledged and managed by the Task Force Chairs and Conflict of Interest committees: none applicable

Task Force Scoping Review Citation

Van de Voorde P, Atkins D, Scholefield B, …., on behalf of the International Liaison Committee on Resuscitation Paediatric Life Support Task Force.

Value of measurable intra-arrest variables during pediatric in- and out-of-hospital cardiac arrest: end-tidal CO2. Scoping Review and Task Force Insights [Internet] Brussels, Belgium: International Liaison Committee on Resuscitation (ILCOR) Pediatric Life Support Task Force, 2018 May 30. Available from: http://ilcor.org

Methodological Preamble and Link to Published Scoping Review

The continuous evidence evaluation process started with a scoping review of etCO2 and etCO2-directed resuscitation in paediatric cardiac arrest, conducted by the ILCOR PLS Task Force Scoping Review team. Evidence from adult and pediatric literature was sought and considered by the PLS Task Force.

Scoping Review

PICOST

The PICOST (Population, Intervention, Comparator, Outcome, Study Designs and Timeframe)

Population: Infants & Children in any setting (in-hospital or out-of-hospital) with cardiac arrest

Intervention: the presence of variables -images, cut-off values or trends- during CPR (intra-arrest) that can provide physiologic feedback to guide resuscitation efforts, namely:

2/ end-tidal CO2

Comparators: the absence of such factors -images, cut-off values or trends.

Outcomes: Any clinical outcome.

Study Designs: STEP 1: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) that concern directly the population and intervention described above are eligible for inclusion. If it is anticipated that there will be insufficient studies from which to draw a conclusion, case series may be included in the initial search. The minimum number of cases for a case series to be included was set by the taskforce at 5. Unpublished

studies (e.g., conference abstracts, trial protocols) are excluded.
STEP 2: the same study designs and/or existing systematic or scoping reviews not directly concerning the population or intervention defined above but considered informative as additional evidence – taking into account severe indirectness- for the development of the final taskforce insights.

Timeframe: For STEP 1, all languages are included, as long as there is an English abstract. We searched articles from 2015 onwards. For STEP 2, if a systematic or scoping review of high quality (as per AMSTAR 2 tool) is identified, search can be limited to beyond data and/or scope of that review.

Active and Reposed PICOs Related to scope of work for this PICOST:
P 827 etCO2 Monitoring During CPR

2015 Consensus on Science:
We did not identify any evidence to address the important outcome of survival to hospital discharge or the critical outcome of neurologically intact survival. For the important outcome of ROSC, we identified very-low-quality evidence (downgraded for very serious indirectness and imprecision) from 1 pediatric animal RCT study that showed ETCO2-guided chest compressions are as effective as standard chest compressions optimized by marker, video, and verbal feedback.(Hamrick 2014 e000450)

2015 Treatment Recommendation:
The confidence in effect estimates is so low that the panel decided a recommendation was too speculative.

Search Strategies
We searched PUBMED, Embase and CENTRAL with consideration of the predefined inclusion criteria (13/08/2019), from 2015 onwards (i.e. beyond previous COSTR). We combined the following terms using Bolean operators: life support care, cardiopulmonary resuscitation, ROSC, heart arrest, cardiac arrest using both individual (ti,ab,kw) and related MESH terms, as well as exploded terms within Embase. We combined these with the terms: end tidal carbon dioxide, carbon dioxide end tidal, end tidal pCO2, etCO2, capnography (again both individual and MESH terms, and Embase exploded terms).

We identified 553 articles after elimination of duplicates. For the subsequent screening by title we excluded only those studies that clearly did not have ETCO2 as study focus, were strictly animal data (separately included for step 2), or obviously had one of the other pre-defined exclusion criteria.
We reviewed 110 abstracts. 6 were eliminated because of being duplicates. Two reviewers then evaluated the 104 abstracts for final inclusion. 100% consensus was reached after a first blinded individual review (Rayyan.qrci.org) and a subsequent discussion about 1 abstract.

Inclusion and Exclusion criteria
This review is part of a cluster of scoping reviews focussing on those variables that can be measured or monitored during the provision of ALS and before ROSC. The variables under consideration are those that have potential to provide (physiologic and/or haemodynamic) feedback to the resuscitating team, potentially guiding their actions to improve outcome, and which might predict outcome. Inclusion criteria as per PICOST.
Exclusions include:

1/ Newborn at Delivery
2/ Pre-arrest features, not influenced by ALS: time of day, location, bystander CPR, gasping, age, etiology, initial rhythm, unwitnessed…
3/ Standard ALS interventions e.g. ventilation strategies, fluids, firm surface, medications given, eCPR, length and Quality of CPR….
4/ Post-ROSC parameters such as lactate clearance, post-arrest rhythm, hypotension nor any actions to provide neuroprotective care post-ROSC.

Adult data are only considered in step 2 as both the etiology and pathophysiology of paediatric arrest differs substantially (serious indirectness). Moreover, the complexity or impact of obtaining the variable under study will likely differ e.g. advanced airway for capnography… Finally, animal data are considered in step 2 but -as human data are available- mostly to inform the knowledge gaps and possible future research agenda.

Outcome might include: Quality of CPR, ROSC, survival to discharge, (changes in) functional outcome at discharge or other time points.

Data tables

Non-RCT OR OBSERVATIONAL *(acronym); Author; Year Published*	*Study type/design; Study size (N)*	*Patient Population (inclusion criteria)*
1. Stine 2019 e01871	*Retrospect. single-centre observat.; N=49*	*IHCA (PICU-PCICU) infants ≤ 6m; US, 2008-2012*
Results primary endpoints (P value; OR or RR; & 95% CI)	*Ability of etCO2 to predict ROSC: The highest positive predictive values were seen for ETCO2 values between 17 and 18 mmHg, reaching a PPV of 0.885*	
Summary/Conclusion - Comments	*The authors point out the importance of this as an alternative to the still existing practice of evaluation by auscultation (which may cause a long hands-off time). However, auscultation is (or should be) clearly only part of practice in infants at delivery (transition at birth) and not in infant CPR anyhow.*	
2. Berg 2018 173	*Prospect. multicentre observat. N= 43 with 48 CPR events*	*IHCA (60% <1y old) US, 2013-2016*
Results primary endpoints (P value; OR or RR; & 95% CI)	*No association was found between any mean ETCO2 (as such or per CPR minute epoch) and any outcome (ROSC, survival, etc.)*	
Summary/Conclusion - Comments	*In general, the CA events described were of short duration (mean 5 minutes, 65% less than 10 minutes) and the quality of CPR was presumed to be high (dedicated teams, mostly on ICU). This resulted in a ROSC fraction of 73% (and a survival to discharge in 37.2%). Importantly Berg et al found no association between any mean ETCO2 (as such or per CPR minute epoch) and any outcome. From the three patients with ETCO2 below 10 mmHg for every minute of epoch, there was one survivor. There was a relation of ETCO2 with ventilation rate in that the mean ETCO2 decreased 3.6 mmHg [1.3-6] for every 10/minute increase in ventilation. Surprisingly, the mean ventilation rate for these children in CA was 29/minute [24-35] (being mechanically ventilated). On the other hand, there was no correlation of ETCO2 with diastolic blood pressure targets, which drives coronary perfusion. Three patients who reached proper diastolic targets, did so despite a mean etC02 below 15 mmHg. In two it was < 10 mmHg.*	

Task Force Insights

1. Why this topic was reviewed.

Ideally, physiologic monitoring and feedback to the clinician during cardiac arrest resuscitation would allow rescuers to monitor (and adjust) quality of CPR, and to predict (and *influence) the likelihood of return of spontaneous circulation and subsequent neurologic recovery. As such, this physiologic monitoring could lead to a form of 'individualised' CPR, where actions are altered to match with individual needs and responses of the victim in cardiac arrest.*

End-tidal carbon dioxide (EtCO2) monitoring was initially recommended to confirm tracheal tube placement, but also seemed to offer an estimate of chest compression effectiveness and indirectly of cardiac output, pulmonary blood flow, and coronary perfusion pressure. A rapid increase in EtCO2 may be associated with ROSC, and sustained decline or persistently low values may be associated with the absence of ROSC (and potentially poor quality CPR).

2. Narrative summary of evidence identified

We identified two observational studies (with very low certainty of evidence, having among others small sample sizes, and selective study populations). Only the study of Berg et al seems to really inform our PICOST question, as Stine et al used protocols for newborns within the delivery room. Berg et al found no association between any mean ETCO2 (as such or per CPR minute epoch) and any outcome. From the three patients with ETCO2 below 10 mmHg for every minute of epoch, there was one survivor. There was a relation of ETCO2 with ventilation rate in that the mean ETCO2 decreased 3.6 mmHg [1.3-6] for every 10/minute increase in ventilation. Surprisingly, the mean ventilation rate for these children in CA was 29/minute [24-35]. On the other hand, there was no correlation of ETCO2 with diastolic blood pressure targets, which drives coronary perfusion. Three patients who reached proper diastolic targets, did so despite a mean etC02 below 15 mmHg. In two it was < 10 mmHg.

*To further explore the topic, we also looked at indirect evidence from adult and animal studies (**STEP 2**). As part of the ILCOR 2015 evidence evaluation process a systematic review (and meta-analysis) of the use of ETCO2 in adult cardiac arrest was performed. It was published in 2018 (Paiva 2018 1). The systematic review included 17 observational studies (n=6198; studies up till December 2016), of which five were appropriate for meta-analysis. The majority concerned OHCA. There were no paediatric studies found. They found only limited evidence (of at most low certainty) to suggest a relation of ETCO2 above 10 mmHg and 20 mmHg respectively with increased likelihood for ROSC. Values of ETCO2 below 10 mmHg after 20' of CPR had a 0.5% likelihood of ROSC, and this might inform – according to the authors- discussions about futility.*
In addition, Sheak et al (Sheak 2015 149) described a multicentre cohort of 583 adult patients (constituting 29028 fifteen second epochs). For every 10 mm compression depth increase, ETCO2 increased with 1.4 mmHg. For every increase of ventilation rate with 10 breaths/minute, ETCO2 decreased with 3mmHg.
Sutton et al (Sutton 2016 76) described 803 adult OHCA (as part of a much larger cohort looking at physiologic variables to monitor CPR quality). Survival to discharge and favourable neurological outcome were significantly higher if the ETCO2 during CPR was above 10 mmHg. The Odds Ratio for survival to discharge was 2.41 [1.35-4.3].
Savastano et al (Savastano 2017 71) described 207 shock events in 62 patients with VF-cardiac arrest. Shock success was clearly different for those events with 'mean ETCO2 in the minute before shock' values below 20mmHg (50%) versus above 30mmHg (78%). None of the shocks with ETCO2 values below 7 while all of the shocks with ETCO2 >45 were successful.

Finally, we also reviewed recent animal research data (from 2015 onwards). The identified data came from three research groups.
Lampe et al (Lampe 2015 69) found in a swine model of VF arrest no significant correlation between ETCO2 and compression depth nor blood flow.
Hamrick et al (Hamrick 2017 e575) compared in a piglet-model RCT video/verbal feedback with ETCO2-directed CPR. In the latter group there were 7 survivors (out of 14 piglets),

compared to only 2 in the verbal feedback group. There was no effect of epinephrine observed. Interestingly, compression rates largely exceeding current guidelines (143+- 10/') were needed in the ETCO2 directed group.
O'Brien et al (O'Brien 2018 e009728) in 10 piglets also identified this faster compression rate was necessary to meet ETCO2 goals but saw no changes in myocardial perfusion pressure when CPR was ETCO2-directed.
Hamrick et al (Hamrick 2019 e352) in an asphyxia arrest piglet model found a clear difference in ROSC rate for ETCO2-directed resuscitation (9 vs. 3 survivors out of 14) for an asphyxia duration of 17 minutes. This difference was lost if asphyxia time prolonged to 23 minutes.
Morgan et al (Morgan 2016 6) did an RCT in 60 3month old swine, with primary VF or asphyxia-associated arrests. The Area-under-curve AUC for diastolic blood pressure was superior to ETCO2 for survival (0.82 vs 0.6).
Ryu et al (Ryu 2016 1012) found in 16 piglets a clear association between compression depth and both systolic blood pressure (immediate effect, AUC 0.895-0.939) and ETCO2 (similar AUC but delay of about 30 seconds). Epinephrine changed blood pressure but not ETCO2 values.

3. Narrative Reporting of the task force discussions
Cardiac arrest, and especially OHCA, still has an infaust prognosis. High quality CPR improves outcome, but what constitutes the best possible CPR for an individual patient is still based on limited evidence and probably differs between patients and etiologies. Having better parameters to guide CPR and adjust it to the need of the individual patient is therefore essential.

Importantly, an advanced airway is required to accurately monitor ETCO2. In children, as in adults, the desirable effects of placing an advanced airway during CPR needs to be balanced by the potential undesirable effects (for this we refer to the specific COSTR on advanced airway placement in paediatric cardiac arrest). Both identified paediatric studies only focused on patients in the intensive care unit, many of whom are already intubated before arrest.

The level of certainty is very low when considering the available evidence. The adult literature is more extensive but even then, the level of certainty remains low. Pathophysiological differences between adults and children are such that extrapolation from this literature should be done with caution (serious indirectness presumed).

ETCO2 is thought to relate to cardiac output and perfusion. However, it was not associated with diastolic blood pressure nor with any pre-defined outcomes in the Berg et al study. This might be because ETCO2 is also affected by minute volume and ventilation:perfusion matching. It is important to recognise that the study by Berg et al was only descriptive in nature and thus at no point evaluated the outcomes associated with ETCO2-directed CPR (regardless of current guidelines).

In view of the above, the taskforce currently considers the level of certainty of the available paediatric evidence too low to make any recommendation for or against the use of ETCO2 to guide resuscitation efforts in children with cardiac arrest. More specifically, there is no single ETCO2 value that can be used as an indicator to terminate CPR, nor is there a single ETCO2 value that can be used as a target during CPR or an argument to continue CPR. The existing evidence is also too limited to advocate for any more thorough evidence evaluation by systematic review.

The use of etCO2 to indicate the correctness of endotracheal tube positioning is beyond the scope of the current review.

Knowledge Gaps

The true value of ETCO2-directed resuscitation stills needs to be clarified in future research. Animal data suggest ETCO2-directed resuscitation might make a difference in outcome but only if deviation from existing guidelines is allowed at the same time. Importantly its place will also have to be evaluated in relation to other intra-arrest factors like arterial diastolic blood pressure.

Furthermore, the interpretation and use of ETCO2 might be different for different cardiac arrest circumstances and aetiologies (asphyxia-related versus primary VF, initial rhythm…) and this too should be focus of future research.

References

1. Berg RA, Reeder RW, Meert KL, Yates AR, Berger JT, Newth CJ, Carcillo JA, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) Pediatric Intensive Care Quality of Cardio-Pulmonary Resuscitation (PICqCPR) investigators. End-tidal carbon dioxide during pediatric in-hospital cardiopulmonary resuscitation. Resuscitation. 2018; 133:173-179
2. Hamrick JL, Hamrick JT, O'Brien CE, Reyes M, Santos PT, Heitmiller SE, Kulikowicz E, et al. The Effect of Asphyxia Arrest Duration on a Pediatric End-Tidal CO2-Guided Chest Compression Delivery Model. Pediatr Crit Care Med. 2019; 20(7):e352-e361.
3. Hamrick JT, Hamrick JL, Bhalala U, Armstrong JS, Lee JH, Kulikowicz E, Lee JK, et al. End-Tidal CO2-Guided Chest Compression Delivery Improves Survival in a Neonatal Asphyxial Cardiac Arrest Model. Pediatr Crit Care Med. 2017; 18(11):e575-e584.
4. Lampe JW, Tai Y, Bratinov G, Shoap W, Lin Y, Kaufman CL, Becker LB. End tidal carbon dioxide is not a good predictor of compression depth or blood flow during CPR. Resuscitation 2015; 96 Suppl1:69
5. Morgan RW, French B, Kilbaugh TJ, Naim MY, Wolfe H, Bratinov G, Shoap W, Hsieh TC, Nadkarni VM, Berg RA, Sutton RM. A quantitative comparison of physiologic indicators of cardiopulmonary resuscitation quality: Diastolic blood pressure versus end-tidal carbon dioxide. Resuscitation. 2016; 104:6-11
6. O'Brien CE, Reyes M, Santos PT, Heitmiller SE, Kulikowicz E, Kudchadkar SR, Lee JK, et al. Pilot Study to Compare the Use of End-Tidal Carbon Dioxide-Guided and Diastolic Blood Pressure-Guided Chest Compression Delivery in a Swine Model of Neonatal Asphyxial Cardiac Arrest. J Am Heart Assoc. 2018; 7(19):e009728
7. Ryu SJ, Lee SJ, Park CH, Lee SM, Lee DH, Cho YS, Jung YH, Lee BK, Jeung KW. Arterial pressure, end-tidal carbon dioxide, and central venous oxygen saturation in reflecting compression depth. Acta Anaesthesiol Scand. 2016; 60(7):1012-3
8. Savastano S, Baldi E, Raimondi M, Palo A, Belliato M, Cacciatore E, Corazza V, et al. End-tidal carbon dioxide and defibrillation success in out-of-hospital cardiac arrest. Resuscitation 2017; 121: 71-75
9. Sheak KR, Wiebe DJ, Leary M, Babaeizadeh S, Yuen TC, Zive D, Owens PC, et al. Quantitative relationship between end-tidal carbon dioxide and CPR quality during both in-hospital and out-of-hospital cardiac arrest. Resuscitation. 2015; 89:149-54.
10. Stine CN, Koch J, Brown LS, Chalak L, Kapadia V, Wyckoff MH. Quantitative end-tidal CO(2) can predict increase in heart rate during infant cardiopulmonary resuscitation. Heliyon. 2019; 5(6): e01871

11. Sutton RM, French B, Meaney PA, Topjian AA, Parshuram CS, Edelson DP, Schexnayder S, et al; American Heart Association's Get With The Guidelines–Resuscitation Investigators. Physiologic monitoring of CPR quality during adult cardiac arrest: A propensity-matched cohort study. Resuscitation. 2016; 106:76-82

B2c Scoping_Review_NIRS_intra-arrest variables ALS 656: SCOPREV)

Scoping review: value of measurable intra-arrest variables during pediatric in- and out-of-hospital cardiac arrest

Conflict of Interest Declaration

The ILCOR Continuous Evidence Evaluation process is guided by a rigorous ILCOR Conflict of Interest policy. The following Task Force members and other authors were recused from the discussion as they declared a conflict of interest: none applicable

The following Task Force members and other authors declared an intellectual conflict of interest and this was acknowledged and managed by the Task Force Chairs and Conflict of Interest committees: none applicable

Task Force Scoping Review Citation

Kool M, Atkins D, Van de Voorde P, Maconochie I, …. Scholefield B on behalf of the International Liaison Committee on Resuscitation Paediatric Life Support Task Force. *Value of measurable intra-arrest variables during pediatric in- and out-of-hospital cardiac arrest: Near Infrared Spectroscopy. Scoping Review and Task Force Insights.*

Methodological Preamble and Link to Published Scoping Review

The continuous evidence evaluation process started with a scoping review of near-infrared spectroscopy (NIRS) and NIRS directed resuscitation in pediatric cardiac arrest, conducted by the ILCOR PLS Task Force Scoping Review team. Evidence from adult and pediatric literature was sought and considered by the PLS Task Force.

Scoping Review

PICOST

The PICOST (Population, Intervention, Comparator, Outcome, Study Designs and Timeframe)

Population: Infants & Children in any setting (in-hospital or out-of-hospital) with cardiac arrest

Intervention: the presence of variables -images, cut-off values or trends- during CPR (intra-arrest) that can provide physiologic feedback to guide resuscitation efforts, namely:

1/ Near-infrared spectroscopy / cerebral oxygen saturation monitoring

Comparators: the absence of such factors -images, cut-off values or trends.

Outcomes: Any clinical outcome.

Study Designs: STEP 1: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) that concern directly the population and intervention described above are eligible for inclusion. As we anticipate that there will be insufficient studies from which to draw a conclusion, case series with greater than 5 cases will be included in the initial search. Unpublished studies (e.g., conference abstracts, trial protocols) are excluded.

STEP 2: the same study designs and/or existing systematic or scoping reviews not directly concerning the population or intervention defined above but considered informative as additional evidence – taking into account severe indirectness- for the development of the final taskforce insights.

Timeframe: For STEP 1, all years and all languages are included, as long as there is an English abstract. For STEP 2, if a systematic or scoping review of high quality (as per AMSTAR 2 tool) is identified, search can be limited to beyond data and/or scope of that review. Literature search updated to October 14, 2019.

Previous Treatment Recommendation

NIRS/Cerebral oxygen saturation monitoring is not included in the 2010 or 2015 pediatric or adult COSTR or AHA/ERC resuscitation guideline.

Adult 2015 COSTR (appendix A) mentions cerebral oxygen saturation monitoring within the 'Physiological monitoring during cardiac arrest'. However no treatment recommendations are made due to limited studies of very low quality evidence (Callaway et al., 2015, s84).

Search Strategies

We searched PUBMED, Embase, CINAHL and Medline with consideration of the predefined inclusion criteria (14/10/2019). We combined the following terms using Bolean operators: life support care, cardiopulmonary resuscitation, ROSC, heart arrest, cardiac arrest using both individual (ti,ab,kw) and related MESH terms, as well as exploded terms within Embase and CINAHL. We combined these with the terms: near-infrared spectroscopy, cerebral oximetry, regional cerebral oxygenation, regional cerebral oxygen saturation (again both individual and MESH terms, and Embase and CINAHL exploded terms). The full search strategies are included in Appendix B1.

We identified 132 articles after duplications were removed. The titles and abstracts were independently screened by two reviewers for inclusion (Rayyan.qrci.org). Disagreements were resolved by consensus and 8 studies were selected. After full text review, six further studies were eliminated; one study was excluded as the population reviewed was only adults, another study was excluded as there was no full text available, but was included in an adult systematic review and therefore excluded. In the last excluded study, the population with cardiac arrest within the study was small and no subgroup analyses were done in this group. The other three were case reports of <5 patients and therefore excluded. A flow diagram of the systematic search and selection is provided in Appendix B2.

Inclusion and Exclusion criteria

These scoping review series focusses on those variables that are measured or monitored during the provision of ALS and before return of spontaneous circulation (ROSC). These variables might provide etiologic, physiologic and/or hemodynamic feedback to the resuscitating team, potentially guiding their actions to improve outcome, and might predict outcome. Inclusion criteria are as per PICOST.

Exclusions include:

1/ Newborn at Delivery
2/ Pre-arrest 'case' features, not influenced by ALS: time of day, location, bystander CPR, gasping, age, etiology, initial rhythm, unwitnessed…
3/ The ALS interventions themselves, performed to influence the parameters mentioned e.g. ventilation strategies, fluids, firm surface, medications given, eCPR, length and Quality of CPR….
4/ Post-ROSC parameters such as lactate clearance, post-arrest rhythm, hypotension nor any actions to provide neuroprotective care post-ROSC.

Adult data are only considered in step 2 as both the etiology and pathophysiology of pediatric arrest differs substantially (serious indirectness).

Outcome might include: Feasibility of obtaining measurements, ROSC, survival to discharge, (changes in) functional outcome at discharge or other time points.

Data tables

Relevant Guidelines or Systematic Reviews: None available
RCT: None available

Table 1: NIRS observations during CPR in children with CA Non-randomized controlled trials, Observational Studies;				
Author; Year	Design, country	Population	Intervention/Comparator	Main findings
1. Abramo et al. 2014, 1439.e1	Case series United States of America	CSF shunt patients in cardiac arrest or with severe bradycardia who had rcSO2 with BVI monitoring, admitted to ED (*n*=14)	Compared NIRS monitoring with ETCO2 and cerebral BVI	Cerebral physiology changes can be detected using rcSO2 with BVI during cardiac arrest, ICP reduction, arrest resolution, and post arrest.
2. Çağlar et al. 2017, 642	Prospective cohort study Turkey	<u>**Inclusion Criteria:**</u> All patients younger than 18 years of age with OHCA, admitted to ED between March 2014 to March 2016 <u>**Exclusion Criteria:**</u> Patients with chronic cyanotic cardiac disease, pulmonary disease, frontal head trauma or intracranial injury. (*n*=10)	NIRS monitoring was compared with pulse oximetry and ECG in all patients, ETCO2 in three out of ten patients	Minimum rcSO2 values during CPR were significantly higher in ROSC patient group (median (IQR) 30±1in ROSC vs. 20.7±5.7 in non-ROSC population, *p*=0.02). Only 3 out of 10 patients achieved sustained ROSC, only 1 survived to hospital discharge. rcSO2 increased with ROSC and following blood transfusion.
OHCA=Out-of-Hospital Cardiac Arrest, CA=Cardiac Arrest, ED=emergency department, BVI= blood volume index, EtCO2=end-tidal CO2, rcSO2 = regional cerebral tissue oxygen saturation, NIRS=Near-infrared spectroscopy, CPR= cardiopulmonary resuscitation, CSF= cerebrospinal fluid, ROSC = return of spontaneous circulation, ICP = Intracranial pressure, ECG=electrocardiogram				

Task Force Insights

1. Why this topic was reviewed.

Ideally, physiologic monitoring and feedback to the clinician during cardiac arrest resuscitation would allow rescuers to monitor (and adjust) quality of cardiopulmonary resuscitation (CPR), and to predict (and influence) the likelihood of return of spontaneous circulation and subsequent neurologic recovery. As such, this physiologic monitoring could lead to a form of 'individualized' CPR, where actions are altered to match with individual needs and responses of the victim in cardiac arrest.

<u>Near-infrared spectroscopy</u> is a non-invasive way of estimating regional cerebral oxygen saturations (rcSO2) and can be detected in cardiac arrest state when flow is absent. There are several different non-invasive devices on the market that report either the cerebral tissue oxygenation index (TOI), or

rcSO2. Both are expressed as ratio of oxygenated hemoglobin (Hb) to total Hb using a modification of the Beer-Lambert law (Green et al., 2017, 48; Nagdyman et al., 2008, 160) Nagdyman et al. published a comparison between two NIRS devices, NIRO 200 (measuring TOI) and INVOS 5100 (measuring rcSO2), and two invasive measurements of venous oxygen saturation: jugular venous bulb saturation and central venous oxygen saturation in 31 children undergoing cardiac catheterization. Although a significant correlation was shown between non-invasive and invasive venous oxygen measurements, a considerable bias was also found in both NIRS devices. Furthermore, the study demonstrated a significant difference between the two NIRS devices, with lower mean percentages in TOI as compared to rcSO2 (Nagdyman et al., 2008, 160).

2. Narrative summary of evidence identified

STEP 1 We identified five pediatric studies after full text review. Three of those were case reports with only one or two cases, so only two studies were selected in the final review (Table 1). Abramo et al. published a case series of 14 patients with CSF shunts and raised intracranial pressure presenting in CA and describes NIRS values reflecting changes in observations e.g. end tidal CO2, cerebral blood volume index (T. Abramo et al., 2014, 1439.e1). The cohort study by Çağlar et al. of 10 OHCA patients, suggests minimum rcSO2 were lower in the population who did not achieve ROSC (Çağlar et al. 2017, 642). There were insufficient studies identified to support a more specific systematic review.
Due to the limited evidence available in pediatric studies, we also looked at indirect evidence from adult studies (**STEP 2**).

RCTs

No RCT's were identified to evaluate the association between NIRS and quality of CPR or ROSC in adults or children. Nevertheless, an adult RCT is pending which will review if NIRS guided CPR (with the aim to optimize NIRS values) is superior compared to the current standard practice according to published CPR guidelines (NCT03911908), which is due to finish July 2021.

Systematic reviews

Two systematic reviews were identified: the latest was published in 2018 and comprised of studies published before February 2017. The systematic reviews concluded that a higher NIRS is associated with a higher chance of ROSC and survival and a lower NIRS is linked with an increased mortality (Schnaubelt et al.,2018, 39, Cournoyer et al., 2016, 851). However, there seems to be no consensus on specific thresholds of rcSO2 at which a prediction can be made regarding different outcomes: ROSC, survival or neurologic outcome (Schnaubelt et al.,2018, 39). Furthermore, there was a wide overlap of mean or median rcSO2 values between patients with ROSC and patients where ROSC was not achieved. This is also reflected in the cohort studies (Prosen et al., 2018, 141; Tsukuda et al., 2019, 33; Yazar et al. 2019, 311). However, an increasing trend in rcSO2 seems more reliable as a predicting factor for ROSC, with suggested increase of at least 7 – 15% from baseline (Genbrugge et al., 2018, 107; Schnaubelt et al.,2018, 39 ; Takegawa et al., 2019, 201).

Observational studies

Only one study compared the rates of ROSC in the use of NIRS versus no NIRS monitoring and found no differences in the occurrence of ROSC (Singer et al., 2018, 403). All the other studies compared NIRS in patients who achieved ROSC versus no ROSC achieved. Many different NIRS devices were used throughout the studies which complicates comparisons as the saturation indices are not interchangeable (Nagdyman et al., 2008, 160) . The findings of the observational studies since February 2017 correlate with those published in both systematic reviews.

3. Narrative Reporting of the task force discussions

Cardiac arrest, and especially OHCA, still has a very poor prognosis. High quality CPR improves outcome, but what constitutes the best possible CPR for an individual patient is still based on limited evidence and probably differs between patients and etiologies. Having better parameters to guide CPR and adjust it to the need of the individual patient is therefore essential.

The level of certainty is very low when considering the available identified evidence. The adult literature is more extensive but even then, the level of certainty remains low. Pathophysiological differences between adults and children are such that extrapolation from this literature should be done with caution (serious indirectness presumed). At present, there is no consensus on a cut off threshold of rcSO2 that can be used as an indicator to terminate CPR, nor is there a single rcSO2 value that can be used as a target during CPR or an argument to continue CPR. The adult literature suggests a trend of rcSO2 to be the most useful prognostic indicator, although this has not yet been validated in adults or pediatrics.

In view of the above, the taskforce agrees that the existing evidence is too limited to advocate for any more thorough evidence evaluation by systematic review.

Knowledge Gaps

Large observational studies evaluating rcSO2 directed resuscitation in children are lacking. The value of rcSO2 in evaluating CPR quality and modifications in CPR technique still needs to be clarified in future research. Furthermore studies are needed that measure the effect of rcSO2 monitoring to guide resuscitation on ROSC and survival with good neurological outcome. Importantly its place will also have to be evaluated in relation to other intra-arrest factors and monitoring techniques.

References

Abramo, T. J., Meredith, M., Jaeger, M., Schneider, B., Bagwell, H., Ocal, E., & Albert, G. (2014). Cerebral oximetry with blood volume index in asystolic pediatric cerebrospinal fluid malfunctioning shunt patients. American Journal of Emergency Medicine. https://doi.org/10.1016/j.ajem.2014.04.007

Caglar, A., Er, A., Ulusoy, E., Akgul, F., Citlenbik, H., Yilmaz, D., & Duman, M. (2017). Cerebral oxygen saturation monitoring in pediatric cardiopulmonary resuscitation patients in the emergency settings: A small descriptive study. The Turkish Journal of Pediatrics, 59(6), 642–647. https://doi.org/10.24953/turkjped.2017.06.004

Callaway, C. W., Soar, J., Aibiki, M., Böttiger, B. W., Brooks, S. C., Deakin, C. D., … Zimmerman, J. (2015). Part 4: Advanced life support: 2015 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Circulation. https://doi.org/10.1161/CIR.0000000000000273

Cournoyer, A., Iseppon, M., Chauny, J.-M., Denault, A., Cossette, S., & Notebaert, E. (2016). Near-infrared Spectroscopy Monitoring During Cardiac Arrest: A Systematic Review and Meta-analysis. Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine, 23(8), 851–862. https://doi.org/10.1111/acem.12980

Genbrugge, C., De Deyne, C., Eertmans, W., Anseeuw, K., Voet, D., Mertens, I., … Dens, J. (2018). Cerebral saturation in cardiac arrest patients measured with near-infrared technology during pre-hospital advanced life support. Results from Copernicus I cohort study. Resuscitation, 129, 107–113. https://doi.org/10.1016/j.resuscitation.2018.03.031

Green, D. W., & Kunst, G. (2017). Cerebral oximetry and its role in adult cardiac, non-cardiac surgery and resuscitation from cardiac arrest. Anaesthesia, 72, 48–57. Retrieved from http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1365-2044

Nagdyman, Nicole, Ewert, P., Peters, B., Miera, O., Fleck, T., & Berger, F. (2008). Comparison of different near-infrared spectroscopic cerebral oxygenation indices with central venous and jugular venous oxygenation saturation in children. Paediatric Anaesthesia. https://doi.org/10.1111/j.1460-9592.2007.02365.x

Prosen, G., Strnad, M., Doniger, S. J., Markota, A., Stozer, A., Borovnik-Lesjak, V., & Mekis, D. (2018). Cerebral tissue oximetry levels during prehospital management of cardiac arrest - A prospective observational study. Resuscitation, 129, 141–145. https://doi.org/10.1016/j.resuscitation.2018.05.014

Schnaubelt, S., Sulzgruber, P., Menger, J., Skhirtladze-Dworschak, K., Sterz, F., & Dworschak, M. (2018). Regional cerebral oxygen saturation during cardiopulmonary resuscitation as a predictor of return of spontaneous circulation and favourable neurological outcome - A review of the current literature. Resuscitation, 125, 39–47. https://doi.org/10.1016/j.resuscitation.2018.01.028

Singer, A. J., Nguyen, R. T., Ravishankar, S. T., Schoenfeld, E. R., Thode Jr, H. C., Henry, M. C., … Thode, H. C. J. (2018). Cerebral oximetry versus end tidal CO2 in predicting ROSC after cardiac arrest. American Journal of Emergency Medicine, 36(3), 403–407. https://doi.org/10.1016/j.ajem.2017.08.046

Takegawa, R., Shiozaki, T., Ogawa, Y., Hirose, T., Mori, N., Ohnishi, M., … Shimazu, T. (2019). Usefulness of cerebral rSO2 monitoring during CPR to predict the probability of return of

spontaneous circulation. Resuscitation, 139, 201–207. https://doi.org/10.1016/j.resuscitation.2019.04.015
Tsukuda, J., Fujitani, S., Morisawa, K., Shimozawa, N., Lohman, B. D., Okamoto, K., … Taira, Y. (2019). Near-infrared spectroscopy monitoring during out-of-hospital cardiac arrest: can the initial cerebral tissue oxygenation index predict ROSC? Emergency Medicine Journal : EMJ, 36(1), 33–38. https://doi.org/10.1136/emermed-2018-207533
Yazar, M. A., Acikgoz, M. B., & Bayram, A. (2019). Does chest compression during cardiopulmonary resuscitation provide sufficient cerebral oxygenation?. Turkish Journal of Medical Sciences, 49(1), 311–317.

Appendix A

ADULT ADVANCED LIFE SUPPORT – COSTR 2015

Consensus on Science

We found no studies that addressed the critical and important outcomes. For the outcome of change in physiologic values by modifications in CPR, we identified 13 observational studies that provided very-low-quality evidence (downgraded for serious risk of bias, serious inconsistency, serious indirectness, and serious imprecision) comparing different CPR techniques (standard, lower sternal, active compression-decompression, intra-abdominal compression, mechanical thumper, ITD, band chest compression, load-distributing band, vest CPR) with the use of physiologic monitoring (arterial line, ETCO2 , oxygen saturation as measured by pulse oximetry , coronary perfusion pressure, cerebral oximetry, near-infrared spectroscopy) in 469 subjects. Differences were detected between different CPR techniques, although this was not consistent across different modalities. Given the heterogeneity of CPR techniques used across studies, data could not be pooled. There were no studies that were found that used physiologic feedback to evaluate CPR quality.

Treatment Recommendation

We make no treatment recommendation for any particular physiological measure to guide CPR, because the available evidence would make any estimate of effect speculative.

Appendix B1: Search strategies by database

1. Database: Embase

Search on 14/10/2019

Search Strategy:

1 *near infrared spectroscopy/ (7968)

2 (cerebral oximetry or regional cerebral oxygenation or regional cerebral oxygen saturation).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1662)

3 1 or 2 (9387)

4 exp resuscitation/ (106363)

5 exp heart arrest/ or exp cardiopulmonary arrest/ or exp "out of hospital cardiac arrest"/ or exp sudden cardiac death/ (88696)

6 (life support care or life support or cardiopulmonary resuscitation or ROSC or return of spontaneous circulation or cardiac arrest).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (76672)

7 4 or 5 or 6 (183295)

8 exp child/ or boy/ or girl/ or infant/ or toddler/ (2514206)

9 exp adolescent/ (1465397)

10 (infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (4008109)

11 8 or 9 or 10 (4233208)

12 3 and 7 and 11 (64)

2. Database: Ovid MEDLINE

Search on 14/10/2019

Search Strategy:

1 exp Spectroscopy, Near-Infrared/ (12541)

2 (cerebral oximetry or regional cerebral oxygenation or regional cerebral oxygen saturation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (857)

3 1 or 2 (13035)

4 exp Cardiopulmonary Resuscitation/ (17027)

5 exp Heart Arrest/ (45895)

6 exp Life Support Care/ (8689)

7 (life support or cardiopulmonary resuscitation or ROSC or return of spontaneous circulation or cardiac arrest).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (54506)

8 4 or 5 or 6 or 7 (77890)

9 exp adolescent/ or exp child/ or *infant/ (2922830)

10 (infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3933096)

11 9 or 10 (3933096)

12 3 and 8 and 11 (30)

13 limit 12 to humans (26)

3. **Database: Pubmed**

Search on 14/10/2019

Search Strategy:

1 "Spectroscopy, Near-Infrared"[Mesh] (12558)

2 ((cerebral oximetry) OR regional cerebral oxygenation) OR regional cerebral oxygen saturation (4242)

3 1 or 2 (15786)

4 "Life Support Care"[Mesh] (8692)

5 "Cardiopulmonary Resuscitation"[Mesh] (17057)

6 "Heart Arrest"[Mesh] (45984)

7 ((((life support) OR cardiopulmonary resuscitation) OR ROSC) OR return of spontaneous circulation) OR cardiac arrest (749608)

8 4 or 5 or 6 or 7 (749608)

9 (("Infant"[Mesh]) OR "Adolescent"[Mesh]) OR "Child"[Mesh] (3454029)

10 (infan* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab])] (4506159)

11 9 or 10 (4506281)

12 (animals [mh]) NOT humans [mh] (4628218)

13 (newborn* OR new-born* OR perinat* OR neonat* OR prematur* OR preterm*) (1003665)

14 3 and 8 and 11 not 12 not 13 (79)

4. **Database: CINAHL**

Search on 14/10/2019

Search Strategy:

1 (MM "Spectroscopy, Near-Infrared") (788)

2 (cerebral oximetry or regional cerebral oxygenation or regional cerebral oxygen saturation) (356)

3 1 or 2 (1,092)

4 (MH "Resuscitation, Cardiopulmonary+") (13,264)

5 (MH "Heart Arrest+") (17,802)

6 (MH "Life Support Care+") (3,937)

7 life support or cardiopulmonary resuscitation or ROSC or return of spontaneous circulation or cardiac arrest (27,911)

8 4 or 5 or 6 or 7 (183295)

9 (MM "Child") OR (MH "Adolescence+") OR (MM "Infant") OR (MM "Child, Preschool") (468,744)

10 (infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school*) (1,178,752)

11 9 or 10 (1,178,752)

12 3 and 7 and 11 (12)

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