2021 Evidence Update Worksheet

Appendix B2 ALS 1

ALS 444 : Algorithm for transition from shockable to non-shockable rhythm and vice versa (EvUp)

Worksheet author(s): Tonia Nicholson

Date Completed: Jan 2021

PICO / Research Question: Among adults who are in cardiac arrest who were initially in a) a non-shockable rhythm but who develop a shockable rhythm or b) were in a shockable rhythm and develop a non-shockable rhythm, in any setting (P), does any specific alteration in treatment algorithm (I), compared with standard care (according to 2010 treatment algorithm) (C), change (O)?

Outcomes: Primary outcome assessed was *Survival to Hospital Discharge***.**
Secondary outcomes considered were *Survival to Hospital Discharge with Favorable Neurological Functional and Adverse Drug-Related Effects.*

Type (intervention, diagnosis, prognosis): Intervention
Additional Evidence Reviewer(s):
Conflicts of Interest (financial/intellectual, specific to this question): None
Year of last full review: (Not clear to me) 2000. 2010. Worksheet done as EvUp in 2020 (but not included in CoSTR)

Last ILCOR Consensus on Science and Treatment Recommendation: *Unable to identify a specific CoSTR on this topic. The most relevant CoSTR identified from 2010 was that regarding Timing of Drug Delivery (During Cardiac Arrest):*

Consensus on Science There are no studies that addressed the order of drug administration. Subgroup analyses from 2 clinical studies reported decreased survival for every minute drug delivery was delayed, measured from call received at EMS dispatch (LOE 4).[190,191] This finding was likely to be biased by a concomitant delay in onset of ALS. In 1 study the interval from the first shock to the injection of the drug was a significant predictor of survival (LOE 4).[190] One animal study reported lower coronary perfusion pressure when delivery of vasopressor was delayed (LOE 5).[192] Time to drug administration was a predictor of ROSC in a retrospective analysis of cardiac arrest in swine (LOE 5).[193]

Treatment Recommendation There is inadequate evidence to define the optimal timing or order for drug administration. An incomplete review of animal studies suggests that timing of vasopressor administration may affect circulation, and further investigations are important to help guide the timing of drug administration.

Current Search Strategy: Updated 25 Aug 2020 1 year= 54 results

((((((((((asystole [mesh]) OR pulseless electrical activity [tiab]) OR PEA [tiab]) AND ventricular fibrillation [mesh]) OR ventricular tachycardia [mesh]) AND ("2009/01/01"[PDat] : "3000/12/31"[PDat]))) AND ((((((((((((life support care[MeSH Terms]) OR "life support"[Title/Abstract]) OR cardiopulmonary resuscitation[MeSH Terms]) OR "cardiopulmonary resuscitation"[Title/Abstract]) OR "CPR"[Title/Abstract]) OR "return of spontaneous circulation"[Title/Abstract]) OR "ROSC"[Title/Abstract]) OR heart arrest[MeSH Terms]) OR "cardiac arrest"[Title/Abstract])))) AND ("2009/01/01"[PDat] : "3000/12/31"[PDat]))) AND ((((((asystole [mesh]) OR pulseless electrical activity [tiab]) OR PEA [tiab]) AND ventricular fibrillation [mesh]) OR ventricular tachycardia [mesh]) *AND ("2009/01/01"[PDat] : "3000/12/31"[PDat]))) NOT animals Filters: Publication date from 2008/01/01*

Database(s) searched: PubMed

Date Search(es) Completed: Aug 25th 2020

Search Results (Number of articles identified / number identified as relevant): 2020 – 256 Articles identified, 1 relevant
2021 (Search done in Aug 2020) - 54 articles identified – none thought relevant.

Inclusion/Exclusion Criteria: Included only studies published from 2008/01/01

Link to Article Titles and Abstracts (if available on PubMed):

Summary of Evidence Review:

No relevant studies were identified.

(Number of studies identified: SRs . . . , RCTs . . . , Non-RCTs . . .)

Relevant Guidelines or Systematic Reviews: No

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles included in review	Key findings	Treatment recommendations

RCT: Yes

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Antiarrhythmic Drugs for Non-shockable-Turned-Shockable Out- of-Hospital Cardiac Arrest: The Amiodarone, Lidocaine or Placebo Study (ALPS) . Kudenchuk, et al 2017	**<u>Study Aim:</u>** To determine the clinical effects of amiodarone or lidocaine compared to placebo in those with initial non-shockable-turned-shockable OHCA. **<u>Study Type:</u>** Prospective, randomized, double-blind, placebo-controlled multicenter trial. Pre-planned cohort of ALPS trial.	**<u>Inclusion Criteria:</u>** 18 years of age or older with atraumatic, OHCA with established IV or IO access, with an initial non-shockable rhythm that subsequently became shock-refractory VF/VT.	**<u>Intervention:</u>** Administration of antiarrhythmic medication (150mg amiodarone N=389, or 60mg lignocaine N=358) **<u>Comparison:</u>** Normal saline placebo (N=316)	**<u>1° endpoint:</u>** *Survival to hospital discharge, adjusted* (for baseline differences in the shockable vs non-shockable group -See*) For *all* initial non-shockable rhythms, Absolute difference in survival between Amiodarone (4.1%) & Placebo (1.9%) = 2.3% (95%CI -0.3-4.8%, p= 0.08).	2° Endpoint : Survival to hospital discharge with favorable neurological functional (Modified Ranking scale □ 3)-No difference For all initial non-shockable rhythms, Absolute difference in survival to hospital discharge with MRS ≤ 3 between Amiodarone & Placebo = 1.2 (95%CI -0.6-3.0%, p= 0.20); Absolute difference in survival to discharge with MRS ≤ 3 between Lignocaine &Placebo = 0.8% (-0.9-2.5%, p= 0.37) For initial rhythm of PEA, absolute difference in

Circulation. 2017 Nov 28; 136(22): 2119–2131. **PMID: 28904070**	**Study Size (N):** 1,063. (29,986 had an initial non-shockable rhythm. In 1,864 of these the rhythm became shockable. 1,320 of these were randomized to drug Rx 1, 063 remained study eligible (rhythm resistant to ≥ 1 shock). Initial rhythm PEA in 400 (38%), asystole in 587 (55%) and not characterized in 76 patients (7%)			Absolute difference in survival between Lignocaine (3.1%) & Placebo (1.9%) = 1.2% (-1.1-3.6%, p= 0.3). For initial rhythm of *PEA*, absolute difference in survival between Amiodarone(5%) & Placebo (1.9%)= 1.2% (–3.6-6.5%, p= 0.57). Absolute difference in survival between Lignocaine (4.3%)& Placebo (3.4%) = 0.6% (-3.9-5.2%, p= 0.79). For initial rhythm of *asystole*, absolute difference in survival between Amiodarone (3.3%)& Placebo (0.6%)= 2.3% (–0.3-4.9%, p= 0.08). Absolute difference in survival between Lignocaine(2.1%) & Placebo(0.6%) = 1.5% (-0.8-3.8%, p= 0.20).	survival to discharge with MRS ≤ 3 between Amiodarone & Placebo= 0.5% (–3.5-4.4%, p= 0.81). Absolute difference in survival to discharge with MRS ≤ 3 between Lignocaine & Placebo = 0.9% (-2.6-4.4%, p= 0.62). For initial rhythm of asystole, absolute difference in survival to discharge with MRS ≤3 between Amiodarone & Placebo= 0.9% (–0.3-2.1%, p= 0.13). Absolute difference in survival to discharge with MRS≤ 3 between Lignocaine & Placebo = 0.5% (-0.5-1.5%, p= 0.29). Also, whether the initial rhythm was asystole, PEA, or VF/VT did not significantly alter the response to antiarrhythmic treatment. While not statistically different, survival trends all favored use of either antiarrhythmic agent. Adverse Drug-related effects – Effects previously reported with these medications that occurred within 24 hours of their administration, including anaphylaxis, thrombophlebitis requiring treatment, clinical seizures and bradycardia requiring temporary cardiac pacing. No difference in frequency between groups Other prespecified mechanistic outcomes - were also assessed including return of spontaneous circulation (ROSC), survival to hospital admission and responses to treatment

					(number of shocks and need for ancillary therapies). Study Limitations: 1.Underpowered (study was intended to explore but was not robustly powered to prove clinical effects). 2.Comorbid conditions weren't assessed prior to randomization (so treatment groups may not have been balanced in all respects). 3.Hospital care was not controlled (though no significant differences in care were observed between treatment arms).

*Multiple logistic regression was done to evaluate the trial's main endpoints of survival and neurological outcome at hospital discharge, adjusting for age, sex, arrest etiology (presumed cardiac versus not), arrest location (public versus private), bystander or EMS-witnessed status of the OHCA, provision of bystander CPR, the incident call to EMS arrival interval and by trial site.

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	**Study Type/Design; Study Size (N)**	**Patient Population**	**Primary Endpoint and Results (include P value; OR or RR; & 95% CI)**	**Summary/Conclusion Comment(s)**
	Study Type:	**Inclusion Criteria:**	**1° endpoint:**	

Reviewer Comments (including whether meet criteria for formal scoping review or systematic review):

Since 2010, only 1 article (out of an initial 256 & then 54 articles) has been identified as relevant to the topic of transition from non-shockable to shockable rhythms during CA. This article looked to address the effect of amiodarone and lidocaine vs placebo for shock refractory VF/pVT after an initial rhythm of PEA or asystole. Although their findings do suggest that these medications are better than placebo there was no deviation from the standard ACLS protocol. Overall there were no studies found that looked to alter the ACLS algorithm specifically when there is a change from an initial rhythm to another initial rhythm

The Task Force decided there is insufficient evidence to do ascoping review or systematic review on this topic.

	Date
Presented to taskforce	**8/01/2021**
Plan for next presentation	**2021**

Reference list:

1. Kudenchuk PJ, Leroux BG, Daya M, et al. Antiarrhythmic Drugs for Nonshockable-Turned-Shockable Out-of-Hospital Cardiac Arrest: The ALPS Study (Amiodarone, Lidocaine, or Placebo). *Circulation*. 2017;136(22):2119–2131. doi:10.1161/CIRCULATIONAHA.117.02862

2021 Evidence Update Worksheet

Appendix B2 ALS 2

ALS 889: Oxygen dose during CPR

Worksheet author(s): Jasmeet Soar

Date Submitted: 2 November 2020

PICO / Research Question:

(P) In adults with cardiac arrest in any setting,

(I) Does administering a maximal oxygen concentration (e.g. 100% by face mask or closed circuit),

(C) compared with no supplemental oxygen (e.g. 21%) or a reduced oxygen concentration (e.g. 40-50%),

Outcomes: Survival with favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days and/or 1 year, Survival only at discharge, 30 days, 60 days, 180 days and/or 1 year, ROSC?

Type (intervention, diagnosis, prognosis): intervention

Additional Evidence Reviewer(s):

Conflicts of Interest (financial/intellectual, specific to this question): No relevant conflicts

Year of last full review: 2015 and Evidence Update in 2020

Last ILCOR Consensus on Science and Treatment Recommendation:

In 2020 (unchanged from 2015):

We suggest using the highest possible inspired oxygen concentration during CPR (weak recommendation, very-low-certainty evidence).

2021 Search Strategy:

("Oxygen"[Mesh] OR “oxygen concentration”[TIAB] OR “supplemental oxygen”[TIAB] OR “oxygen therapy”[TIAB] OR “titrated oxygen”[TIAB] OR “inspired oxygen”[TIAB] OR paO2[TIAB] OR “100% oxygen”[TIAB] OR “high flow oxygen”[TIAB] OR "Hyperoxia"[Mesh] OR "Oxidative Stress"[Mesh] OR ((Hyperoxi*[TIAB] OR Hypoxi*[TIAB] OR Normoxi*[TIAB]) AND (Ventilat*[TIAB] OR "Oxygen Inhalation Therapy"[Mesh:NoExp] OR "Respiration, Artificial"[Mesh: NoExp]))) AND ("Heart Arrest"[Mesh] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "cardiac arrest"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[TIAB] OR asystole*[TIAB] OR "pulseless electrical activity"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "cardiopulmonary arrests"[TIAB] OR "cardio-pulmonary arrest"[TIAB] OR "cardio-pulmonary arrests"[TIAB] OR "Out-of-Hospital Cardiac Arrest"[Mesh]) AND ("resuscitation"[Mesh] OR resuscitat* OR CPR OR prehospital OR pre-hospital OR “out-of-hospital”[TIAB] OR “out of hospital”[TIAB] OR "Emergency Medical Services"[Mesh]) NOT (neonat*OR newborn*) NOT ("letter"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] or Case Reports[Publication Type])

Database searched: PubMed

Date Search Completed: Up to 2 November 2020

Search Results: 33 new studies new since previous Evidence Update on 2 December 2019

Inclusion/Exclusion Criteria: Adult human studies of inspired oxygen during CPR

No relevant adult human studies of oxygen during CPR identified.

Summary of Evidence Update:

There are no new studies of different inspired oxygen concentration and outcome during CPR. Previous indirect evidence suggests that there is an association between arterial partial pressure of oxygen during CPR and ROSC.

Reviewer Comments (including whether meet criteria for formal review):

ALS TF discussion on 2 November 2020 concluded that there was insufficient new data to pursue ScopRev or SR as data very unlikely to change current TR

Task Force discussions included that most patients are hypoxemic immediately after ROSC and require supplemental oxygen. There is no technology currently available that helps guide optimal titration of inspired oxygen during CPR of after ROSC.

There are no trials in progress

	Approval Date
Evidence Update coordinator	2 November 2020
ILCOR board	

***Once approval has been made by Evidence Update coordinator, worksheet will go to ILCOR Board for acknowledgement.**

Reference list

2021 Evidence Update Worksheet

Appendix B2 ALS 3

Steroids during CPR (ALS433: EvUp)

Worksheet author(s): Tonia Nicholson
Date Submitted: Feb 2021

PICO / Research Question: Among adults who are in cardiac arrest in any setting (P), does the administration of corticosteroids during CPR (I) compared with not using corticosteroids (C), improve outcome (O) (eg. Survival)?

Outcomes: Survival with Favourable neurological outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year; Survival only at discharge, 30 days, 60 days, 180 days AND/OR 1 year; ROSC.

Type (intervention, diagnosis, prognosis): Intervention

Additional Evidence Reviewer(s): N/A

Conflicts of Interest (financial/intellectual, specific to this question): N/A

Year of last full review: 2015**.** EvUp in 2020.

Last ILCOR Consensus on Science and Treatment Recommendation:
Consensus on Science:
In-hospital cardiac arrest. For the critical outcome of **survival to discharge with favorable neurological outcome**, there was low-quality evidence (downgraded for indirectness and for imprecision from 1 RCT in 268 patients with IHCA that showed improved outcome with methylprednisolone, vasopressin and epinephrine during cardiac arrest, and hydrocortisone in those with post-ROSC shock compared with only epinephrine and

placebo (18/130 [13.9%] versus 7/138 [5.1%];RR,2.94;95% CI, 1.16-6.50, which translates to 98 more /1000 surviving with good neurological outcome [95% CI , from 8 to 279 more/1000 surviving with good neurologic outcome]).

For the critical outcome of **survival to discharge**, there was low-quality evidence (downgraded for indirectness and for imprecision) from 1 RCT or 100 patients with IHCA that showed improved outcome with the combination of methylprednisolone, vasopressin and epinephrine during cardiac arrest and hydrocortisone after ROSC for those with shock, compared with the use of only epinephrine and placebo (9/48 [19%] versus 2/52 [4%]; RR,4.87; 95% CI, 1.17-13.79, which translates to 149 more /1000 surviving to discharge [95% CI,7-492 more /1000 surviving to discharge]).

For the important outcome of **ROSC,** there was low-quality evidence (downgraded for indirectness and imprecision) from 2 RCTs involving 368 patients with IHCA showing improved outcome with the use of methylprednisolone and vasopressin in addition to epinephrine, compared with the use of placebo and epinephrine alone (combined RR,1.34; 95% CI,1.21-1.43, which translates to 130-267 more achieving ROSC with the combination of methylprednisolone ,vasopressin and epinephrine during cardiac arrest, compared with the use of only epinephrine and placebo [95% CI, 130-267 more achieving ROSC]).

Out-of-hospital cardiac arrest. For the critical outcome of **survival to discharge,** there was very-low-quality evidence (downgraded for risk of bias, indirectness and imprecision) from 1 RCT and 1 observational study showing no association with benefit with the use of steroids. Paris had no long-term survivors and Tsai showed survival to discharge in 8% (3/36) receiving hydrocortisone compared with 10% (6/61) receiving placebo (p = 0.805).

For the important outcome of **ROSC,** we found very-low-quality evidence from 1 RCT and 1 observational study with a combined total of 183 patients. The RCT showed no improvement in ROSC (and ICU admission) with dexamethasone given during cardiac arrest compared with placebo (5.4% [2/37] versus 8.7% [4/46]), but observational study showed an association with improved ROSC with hydrocortisone compared with no hydrocortisone (58% versus 38%; p=0.049).

Treatment Recommendation

For IHCA, the task force was unable to reach a consensus recommendation for or against the use of steroids in cardiac arrest. We suggest against the routine use of steroids during CPR for OHCA (weak recommendation, very-low-quality evidence).

2015 Search Strategy:

The search performed for the 2015 ILCOR CoSTR used the following terms:

Corticosteroid terms: corticosteroid'/exp; corticosteroid*:ti,ab; mineralocorticoids:ti,ab; 'steroid'/exp; steroids:ti,ab; prednisone:ti,ab; prednisolone:ti,ab; methylprednisolone:ti,ab; dexamethasone:ti,ab; fludrocortisone:ti,ab

Cardiac arrest terms: heart arrest'/exp; "cardiac arrest":ti,ab; "cardiac arrests":ti,ab; "cardiovascular arrest":ti,ab; "cardiovascular arrests":ti,ab; "heart arrest":ti,ab; "heart arrests":ti,ab; "asystole":ti,ab; "pulseless electrical activity":ti,ab; "cardiopulmonary arrest":ti,ab; "cardiopulmonary arrests":ti,ab; CPR:ti,ab; 'resuscitation'/exp; resuscitat*:ti; “chest compression”:ti,ab; “chest compressions”:ti,ab; 'heart massage'/exp; “heart massage”:ti,ab; “cardiac massage”:ti,ab; “cardiac compression”:ti,ab; “cardiac compressions”:ti,ab; “thoracic compression”:ti,ab; “thoracic compressions”:ti,ab; “basic life support”:ti,ab

2021 Search Strategy: Explanation of search strategy approach for updating ALS 433

The search for 2015 PICO on steroids during /after cardiac arrest was run on 18 July 2014. It was re-run for the last EvUp on the PICO to capture studies between 2014 and 2019. It was again repeated and time restricted in 2021 (Dec 1st 2019 – Jan 13th 2021) to try and identify any relevant new articles on the topic since the last EvUp.

#	Search string (developed for the EMBASE.com platform, which includes Medline and Embase databases)	Explanation
#1	'heart arrest'/exp 'heart arrest$':ti,ab 'cardiac arrest$':ti,ab 'cardiovascular arrest$':ti,ab 'cardiopulmonary arrest'/exp 'cardiopulmonary arrest$':ti,ab 'cardio-pulmonary arrest$':ti,ab 'resuscitation'/exp rosc:ti,ab 'post-rosc':ti,ab 'post-resuscitation':ti,ab	**Population – Cardiac arrest** Terms related to cardiac arrest and/or ROSC should be the focus of the article, so these terms must appear in either the title or the abstract, or the article must be tagged with EMTREE terms for cardiac arrest or ROSC. Note, general terms for life support such as ‘basic life support’ (as used in prior search) or ‘‘advanced cardiac life support’ were considered too generic, and terms relating to CPR techniques such as chest compressions and heart massage were considered too specifically focusing on the process of CPR rather than the post-ROSC patient.

#	Search string (developed for the EMBASE.com platform, which includes Medline and Embase databases)	Explanation
	'return of spontaneous circulation':ti,ab resuscitat*:ti,ab	
#2	#1 NOT ('animal'/exp NOT 'human'/exp OR 'nonhuman'/exp OR 'rodent'/exp OR 'animal experiment'/exp OR 'experimental animal'/exp OR rat:ti,ab OR rats:ti,ab OR mouse:ti,ab OR mice:ti,ab OR dog$:ti,ab OR pig$:ti,ab OR porcine:ti,ab OR swine:ti,ab OR chick$:ti,ab)	**Exclude non-human studies** The search results must include citations from the newborn population string, so a 'non-human studies' filter was applied to it.
#3	#2 NOT ([conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [book]/lim OR 'case report'/de)	**Exclude publication types** Conference abstracts and other ineligible study types were removed here.
#4	#3 AND [2014-2020]/py	**Date limit** The date of the last ILCOR search was 18 July 2014. This search string can be combined with intervention strings or other population strings to produce a final number of records.
#5	'steroid'/de 'corticosteroid'/de 'mineralocorticoid'/de corticosteroid$:ti,ab mineralocorticoid$:ti,ab steroid$:ti,ab prednisone:ti,ab prednisolone:ti,ab methylprednisolone:ti,ab	**Intervention terms – steroids** To identify steroid studies. These terms must appear in the title or abstract, or the article must be tagged with EMTREE terms for steroids. Note, the EMTREE terms were not exploded as that includes a large number of irrelevant interventions. Instead, studies coded directly to the steroid EMTREE term (or the corticosteroid EMTREE term, etc.) were captured, along with studies that include these terms as free text, or include the specific drugs that were included in the search for the 2015

#	Search string (developed for the EMBASE.com platform, which includes Medline and Embase databases)	Explanation
	fludrocortisone:ti,ab hydrocortisone:ti,ab dexamethasone:ti,ab	ILCOR CoSTR (hydrocortisone was added to this set of specific drugs as it is mentioned in the 2015 Consensus on science).
#6	#4 AND #5	**Population + intervention**
#7	(((after OR post) NEAR/4 (rosc OR spontaneous OR circulation OR resuscitation OR cardiac OR arrest)):ti,ab) OR postarrest:ti,ab OR 'post-arrest':ti,ab OR 'post-rosc':ti,ab OR (surviv* NEAR/3 (cardiac OR arrest OR resuscitation OR ohca OR 'oh ca' OR ihca OR 'ih ca'))	**Post-arrest terms** This string is useful to stratify studies according to whether they include reference to post-ROSC status. However, this string could potentially exclude relevant studies, and should not be relied upon to filter the identified studies.
#8	#6 AND #7	**Population + intervention + post-arrest terms**
#9	#6 NOT #8	**Population + intervention (minus + post-arrest terms)**

Database searched: EMBASE.com platform (includes Medline and EMBASE)/Cochrane Reviews**/**National Clinical Trails database and WHO

Date Search Completed: Jan 13th 2021

Search Results (Number of articles identified / number identified as relevant):

Embase/Medline 214

Cochrane: 26

Trials Registry: 61

Inclusion/Exclusion Criteria:

Inclusion – Adults (>18yrs) with non-traumatic cardiac arrest

Exclusions - Steroids given post-ROSC, paediatric patients, animal studies, letters, commentaries, editorials, case series, poster presentations only, journal club reviews, interim analyses.

Link to Article Titles and Abstracts (if available on PubMed):

1) Liu B, Zhang Q and Li C (2020). Steroid use after cardiac arrest is associated with favourable outcomes: a systematic review and meta-analysis. Journal of International Medical Research. 48(5).[1]

2) Li Y, Zhang J, Cai N & He F. Efficacy and safety of corticosteroid therapy in patients with cardiac arrest: a systematic review of randomised controlled trials. E Journal of Clinical Pharmacology (2020) 76:1631–1638.https://doi.org/10.1007/s00228-020-02964-3

Summary of Evidence Update:

Relevant Guidelines or Systematic Reviews: *Two*

Org (if relevant); Author; Year Published	**Guideline or systematic review**	**Topic addressed or PICO(S)T**	**Number of articles identified**	**Key findings**	**Treatment recommendations**
Liu B, Zhang Q and Li C (2020) [1]	Systematic review and meta-analysis.	To investigate whether steroid use after CA increased the return of spontaneous circulation (ROSC) rate and survival to discharge in patients with CA. Subgroup analysis done based on the	Identified 4 RCTs & 3 observational studies. (3 published in English and 4 in Chinese). Six of these studies examined the association between steroid use and ROSC – 4 of these studies were RCTs and 2 were cohort studies.	The overall effect size (RR 1.44; 95% CI 1.17–1.76; P ¼ 0.02) demonstrated a significant association between steroid use and ROSC. A subgroup analysis (RCTs vs cohort studies) was also conducted. Both study types revealed a significant association between steroid	Current evidence indicates that steroid use increases the rate of ROSC and survival to discharge in patients with CA. Steroid use may remain an acceptable option for patients with CA; however, high-quality and adequately powered RCTs are warranted

		time of drug administration (during CPR or after CA).		use and ROSC (RCT: RR 1.43; 95%CI: 1.10–1.86, P ¼ 0.008; cohort studies: RR 1.54; 95%CI 1.12– 2.12, P ¼ 0.009). In addition, a subgroup analysis based on the time of steroid administration showed that steroid use during CPR (compared with after CA) was significantly associated with an increased rate of ROSC (RR 1.64; 95% CI 1.05–2.58, P < 0.005).	
Li Y, Zhang J, Cai N & He F. (2020)	Systematic Review	Aimed to evaluate the efficacy and safety of corticosteroid therapy in CA patients.	Five studies (551 patients) met the criteria. One of these was of steroids post ROSC & hence not relevant to this PICO (Donnino 2016). The other four studies have all been considered in the development of previous PICOs on this topic +/or EvUps. (Mentzelopoulos 2009,	Given the clinical and methodological heterogeneity across the studies, combining data using meta-analysis methods was not considered appropriate. Hence the SR just summarised the evidence of the individual studies identified.	Due to the inherent limitations of the studies in this review, we have not been able to reach definitive conclusions. Larger-scale and better-designed studies are therefore recommended, to further evaluate the potential and rational use of corticosteroid therapy in CA patients.

			2013 comparing placebo with steroids in combination with vasopressin & epinephrine; Paris 1984 & Bolvardi 2016, both comparing placebo with steroids alone).		

Of the 7 articles identified for inclusion in the systematic review and meta-analysis by Liu, 3 of the studies were published in English (Mentzelopoulos, 2013[(3)]; Tsai, 2019[(4)]; Niimura, 2017[(5)]). All of these were considered in the 2020 ILCOR EvUp on the use of steroids during cardiac arrest.

4 of the studies were published only in Chinese (Zhang, 2015[(6)]; Mu 2014[(7)]; Yang, 2002[(8)]; He 2001[(9)]). The latter 3 studies were all small and were conducted before 2005, so would not be included in an ILCOR SR on this PICO because of the significant differences in other aspects of management of cardiac arrest before this time. The first study (Zhang, 2015) was an RCT conducted in China between 2011 and 2014. From the summary tables in the systematic review it was a small study with only 50 patients in each arm of the study (steroids vs no steroids). The study seems to suggest an association between the use of steroids during CPR and a positive outcome (ROSC in 31/50 with the use of steroids and 8/50 without). However, it is unlikely that this study alone would be considered sufficient evidence to result in a change in the current ILCOR COSTR about the use of steroids post CA.

The second systematic review by Li et al didn't include any studies that had not been identified in the 2020 ILCOR EvUp on the use of steroids during cardiac arrest. However, the Bolvardi study [(10)] was not described in detail in the previous EvUp, so for completeness is included below.

RCT: *None (*but *Bolvardi study is described here as it wasn't described in the 2020 EVUR)*

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**

Bolvardi 2016. Studying the Influence of Epinephrine Mixed with Prednisolone on The Neurologic Side Effects After Recovery in Patients Suffering From Cardiopulmonary Arrest	To establish if administration of methylprednisolone during cardiac arrest reduces the neurologic side effects after CPR. RCT. 50 patients (25 intervention and 25 control)	OHCA	All patients were given 1mg of epinephrine with each cycle of CPR. The study arm were also given 125mg of methylprednisolone during the 1st cycle of resuscitation or the 2nd time epinephrine was given. The control group were given a saline placebo instead of the methylprednisolone.	Overall survival to hospital discharge and survival with positive neurological outcome were the same - 1/25 with methylprednisolone vs 0/25 for controls (4% vs 0%).	There was no measurement of demographic information of patients before arrival at hospital, or factors contributing to CA. There was also a shortage of ICU beds so patients stayed in the ED longer than would generally occur in other centres.

Nonrandomized Trials, Observational Studies: *None*

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

Reviewer Comments (including whether meet criteria for formal review):

Two systematic reviews have been published in the last year regarding the use of steroids during cardiac arrest. The majority of the studies included in these were considered in the development of the 2020 ILCOR EvUp on the use of steroids during cardiac arrest. An additional study in Chinese (Zhang 2015[6]) that wasn't included in the 2020 EvUp has now been reviewed and thought unlikely to add sufficient evidence to change the current ILCOR COSTR. The Bolvardi study, although considered last time without description, has now been described. Though an additional

RCT, it used methylprednisolone rather than hydrocortisone, so it is questionable whether meta-analysis of the results of this study with the Donnino (2016) study would be appropriate.

No new observational studies or RCTs regarding the use of steroids during cardiac arrest have been published in the last year.

The 2020 EvUp on the use of steroids during cardiac arrest identified 3 relevant studies registered with the Clinical National Trials registry.

1) Nct 02790788 Physiological Effects of Stress Dose Corticosteroids in the Management of In-hospital Cardiac Arrest [11] was a randomized controlled trial by Mentzelopoulos SD, et al. It enrolled 100 patients after in-hospital cardiac arrest, with allocation to a treatment arm of IV methylprednisolone during cardiac arrest and IV hydrocortisone if there was shock present 4hrs after ROSC, compared with a saline placebo. The results of this study were made available on the NCT register in Nov 2019.Likely due to the situation with COVID 19, these results have not yet been published in a peer-reviewed journal, but have been presented at the National symposium on Intensive Care Medicine. The results do not suggest a significant benefit for the use of steroids for patients after in-hospital cardiac arrest, either in terms of post-ROSC haemodynamic status, inflammatory response or survival. It is unknown whether publication of this study is still planned, and this may well depend on the COVID workload of the Greek authors of the study.

2) Nct. 03640949 (2018). Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest. https://clinicaltrials.gov/show/NCT03640949 [12]
This is an investigator-initiated, multicenter, randomized, placebo-controlled, parallel group, double-blind, superiority trial of vasopressin and methylprednisolone during adult in-hospital cardiac arrest. There are five enrolling sites in Denmark. 492 adult patients with in-hospital cardiac arrest receiving at least one dose of adrenaline are to be enrolled. The primary outcome is return of spontaneous circulation and key secondary outcomes include survival at 30 days and survival at 30 days with a favourable neurological outcome. COVID has had an impact on enrolment in this study and its projected completion date has been extended from 2021 to 2022. (Principle investigator is Lars Wiuff Andersen, Associate Professor, Aarhus University Hospital, Denmark).

3) Nct. (2017). Effect of Vasopressin, Steroid, and Epinephrine Treatment in Patients with Out-of-hospital Cardiac Arrest. This was registered in 2017 as a Multicentre, Double Blind, Randomized, Placebo-controlled Study to compare the Effect of Vasopressin, Steroid & Epinephrine treatment in patients with OOH Cardiac Arrest. https://clinicaltrials.gov/show/NCT03317197 [13].

The primary outcome to be assessed was to be survival to discharge and to 1yr, with good neurological outcome (CPC 1 or 2). The study was to compare administration of epinephrine and saline placebo during CPR with administration of epinephrine and vasopressin, epinephrine and methylprednisolone and epinephrine, vasopressin and methylprednisolone in combination. (Principle investigator is Assistant Professor Jung-Youn Kim from the Korean University of Guro Hospital.)

The study was registered with an aim of recruiting 839 patients. It had an anticipated completion date of Aug 2020 – at present however, the study has not commenced recruitment, and it is not clear if it will still go ahead.

As there have been 2 recent systematic reviews including many of the available studies on the use of steroids during cardiac arrest, there is one completed study with results that may be presented for peer review in future, and there is at least one large active RCT relevant to the PICO, **it would still seem appropriate to wait further evidence before ILCOR looks to carrying out another Systematic Review on the use of Steroids During Cardiac Arrest.**

	Approval Date
Evidence Update coordinator	**15 February 2021**
ILCOR board	

***Once approval has been made by Evidence Update coordinator, worksheet will go to ILCOR Board for acknowledgement.**

Reference list

1) Liu B, Zhang Q and Li C (2020). Steroid use after cardiac arrest is associated with favourable outcomes: a systematic review and meta-analysis. Journal of International Medical Research. 48(5).

2) Li Y, Zhang J, Cai N & He F. Efficacy and safety of corticosteroid therapy in patients with cardiac arrest: a systematic review of randomised controlled trials. E Journal of Clinical Pharmacology (2020) 76:1631–1638.https://doi.org/10.1007/s00228-020-02964-3

3) Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids and epinephrine and neurologically favourable survival after in-hospital cardiac arrest: a randomized clinical trial. JAMA. 2013;310:270-9

4) Tsai, MS, Chuang, PY, Huang, CH, Tang, CH, Yu, PH, Chang, WT and Chen, WJ. (2019). Post-arrest Steroid Use May Improve Outcomes of Cardiac Arrest Survivors. Critical care medicine. 47(2):167-175.

5) Niimura, T, Zamami, Y, Koyama, T, Izawa-Ishizawa, Y, Miyake, M, Koga, T, Harada, K, Ohshima, A, Imai, T, Kondo, Y, Imanishi, M, Takechi, K, Fukushima, K, Horinouchi, Y, Ikeda, Y, Fujino, H, Tsuchiya, K, Tamaki, T, Hinotsu, S, Kano, MR and Ishizawa, K. (2017). Hydrocortisone administration was associated with improved survival in Japanese patients with cardiac arrest. Scientific reports. 7(1):17919.

6) Zhang F, Yang ZJ, Shen J, et al. Adrenaline combined with methylprednisolone sodium succinate Cardiopulmonary resuscitation Chinese Clinical Medicine 2015; 22: 670–671.

7) Mu CJ, Li WQ, Zhou YM, et al. Hydrocortisone sodium succinate for cardio- pulmonary resuscitation the influence of patient prognosis. Chinese Journal of Integrated Traditional and Western Medicine 2014; 21: 229–231.

8) Yang GL and Li CX. Clinical study on comprehensive medication for cardiopulmonary cerebral resuscitation. National Coal Industry Medical Journal 2002; 5: 379–380.

9) He WX and Hong Z. Application of high- dose adrenaline combined with aminophyl- line, of clinical study of cardiopulmonary cerebral resuscitation with dexamethasone. Chinese Emergency Medicine 2001; 21: 224–225.

10) Bolvardi, E, Seyedi, E, Seyedi, M, Abbasi, AA, Golmakani, R and Ahmadi, K. (2016). Studying the influence of epinephrine mixed with prednisolone on the neurologic side effects after recovery in patients suffering from cardiopulmonary arrest. Biomedical and Pharmacology Journal. 9(1):209-214.

11) Nct. (2016). Physiologic Effects of Steroids in Cardiac Arrest.https://clinicaltrials.gov/show/NCT02790788

12) Nct. (2018). Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest. https://clinicaltrials.gov/show/NCT03640949

13) Nct. (2017). Effect of Vasopressin, Steroid, and Epinephrine Treatment in Patients with Out-of-hospital Cardiac Arrest. This was registered in 2017 as a Multicentre, Double Blind, Randomized, Placebo-controlled Study to compare the Effect of Vasopressin, Steroid & Epinephrine treatment in patients with OOH Cardiac Arrest. https://clinicaltrials.gov/show/NCT03317197 [(13).]

2021 Evidence Update Worksheet

Appendix B2 ALS 4

Confirmation of Tracheal Tube Position (ALS469: EvUp)

Worksheet author(s): Markus B Skrifvars
Date Completed: 19.11.2020
PICO / Research Question:

P – Among adults who are in cardiac arrest, needing/with an advanced airway, in any setting,
I – does use of devices (eg, 1. waveform capnography, 2. CO2 detection device, 3. esophageal detector device or 4. tracheal ultrasound),
C – compared with not using devices,
O – change placement of the ET tube between the vocal cords and the carina, success of intubation?

Primary search conducted August 25th 2020
Search author Peter Morley
Outcomes: Verification of placement of an ETT
Type (intervention, diagnosis, prognosis): Diagnostic

Additional Evidence Reviewer(s):
Conflicts of Interest (financial/intellectual, specific to this question): None

Year of last full review: 2015
Last ILCOR Consensus on Science and Treatment Recommendation:
We recommend using waveform capnography to confirm and continuously monitor the position of a tracheal tube during CPR in addition to clinical assessment (strong recommendation, low-quality evidence).

Current Search Strategy:

((((((((((endotracheal tube) OR "Intubation, intratracheal"[MH] OR "tracheal intubation"[TI]OR "endotracheal intubation"[TI] OR"ETT"[TI] OR "advanced airway management"[TI]OR "intubation"[TI] OR "intubation/methods"[MH]) OR "advanced airway management"[TI])))) AND ((((((((((((Heart Arrest[MeSH Major Topic]) OR Cardiopulmonary resuscitation [MeSH Major Topic]) OR Ventricular Fibrillation[MeSH Major Topic]) OR heart Massage [MeSH Major Topic]) OR asystole[Title/Abstract]) OR(cardiac arrest[Title/Abstract]) OR Cardiac compression[Title/Abstract]) OR cardiac massage[Title/Abstract]) OR Cardiac compression[Title/Abstract]) OR cardiac massage[Title/Abstract) OR chest compression*[Title/Abstract]) OR CPR[Title/Abstract])OR heart compression[Title/Abstract])))) AND (((((((capnography) OR Waveform[Title/Abstract]) OR CO2 Detection Device) OR Carbon dioxide device) OR Esophageal detector device) OR edd) OR instrumentation[MeSH Subheading]))) NOT(((animals[mh] NOT humans[mh]))) NOT (("letter"[pt] OR "comment"[pt] OR "editorial"[pt]or Case Reports[ptyp])))

Database(s) searched: PUBMED

Date Final Search(es) Completed: November 15th 2020, January 25th 2021

Search Results (Number of articles identified / number identified as relevant): 123 new paper since 2015

Inclusion/Exclusion Criteria: Clinical studies assessing/comparing means to identify the placement of an endotracheal tube in the trachea (below the vocal cords)

Summary of Evidence Review:

Compared to the evidence review conducted in 2014 for the 2015 Guidelines, two potentially relevant studies were found (1,2). On systematic review was also identified.

Relevant Guidelines or Systematic Reviews: Yes or No

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles included in review	Key findings	Treatment recommendations
Sahu et al. 2020	Systematic review	The accuracy of US for determination of ETT placement. A sub analysis of the CA patients.	5 studies	US less specific in CA than in non-CA patients	Consider US if/when capnography is not available or unreliable.

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Silvestri et al. 2017	Experimental study	Two cadavers	Accuracy of waveform capnography in two cadavers (without pulmonary circulation)	Waveform capnography was found to be 100% specific and sensitive for verification of ETT placement in the trachea.
Karacabey et al. 2016	Observational study	30 patients with cardiac arrest	US was not very accurate for the verification of correct ETT placement in CA	No evidence that US would be superior to waveform capnography in CA patients.

Reviewer Comments (including whether meet criteria for formal scoping review or systematic review):

The ALS task Force Opinion is that there is no new evidence that would suggest a need to change the treatment recommendation from 2015.

The task force discussed that the use of waveform capnography to confirm tracheal tube position during CPR is now the standard of care in many settings.

	Date
Presented to taskforce	November 19th 2020
Plan for next presentation	

Reference list

1. Silvestri S, Ladde JG, Brown JF, Roa JV, Hunter C, Ralls GA, Papa L. Endotracheal tube placement confirmation: 100% sensitivity and specificity with sustained four-phase capnographic waveforms in a cadaveric experimental model. Resuscitation. 2017 Jun;115:192-198. doi: 10.1016/j.resuscitation.2017.01.002. Epub 2017 Jan 19. PMID: 28111195
2. Karacabey S, Sanrı E, Gencer EG, Guneysel O. Tracheal ultrasonography and ultrasonographic lung sliding for confirming endotracheal tube placement: Speed and Reliability. Am J Emerg Med. 2016 Jun;34(6):953-6. doi: 10.1016/j.ajem.2016.01.027. Epub 2016 Jan 26.
3. Sahu AK, Bhoi S, Aggarwal P, Mathew R, Nayer J, T AV, Mishra PR, Sinha TP. Endotracheal Tube Placement Confirmation by Ultrasonography: A Systematic Review and Meta-Analysis of more than 2500 Patients. Journal of Emergency Medicine, 2020-08-01, Volume 59, Issue 2, Pages 254-264

2021 Evidence Update Worksheet

Appendix B2 ALS 5

Automatic ventilators vs manual ventilation during CPR (ALS 490: EvUp)

Worksheet author(s): Joshua Reynolds, MD, MS
Date Submitted: February 17, 2021

PICO / Research Question: In adults and children in cardiac arrest (out-of-hospital [OHCA], in-hospital [IHCA]) and who have advanced airways in place, does the use of automatic ventilators, compared with manual ventilation, improve outcome (e.g. ventilation, oxygenation, reduce hands-off time, allow for continuous compressions and/or improves survival)?

Outcomes: Ventilation, Oxygenation, Hands-off-time, survival
Type (intervention, diagnosis, prognosis): Intervention

Additional Evidence Reviewer(s):
Conflicts of Interest (financial/intellectual, specific to this question):

Year of last full review: 2010 / 2015 / New question: 2010

Last ILCOR Consensus on Science and Treatment Recommendation:

ILCOR Consensus on Science

One pseudorandomized study suggested that the use of an automatic transport ventilator with intubated patients may enable the EMS team to perform more tasks while subjectively providing ventilation similar to that provided by hand with a resuscitation bag (LOE 2). One study suggested that the use of an automatic transport ventilator with intubated patients provides oxygenation and ventilation similar to that achieved with a bag-valve device but with no difference in survival (LOE 2).

ILCOR Treatment Recommendation

There is insufficient evidence to support or refute the use of an automatic transport ventilator over manual ventilation during resuscitation of the cardiac arrest victim with an advanced airway.

ILCOR Knowledge Gaps

Studies evaluating adequacy of oxygenation, difference between volume and pressure cycled ventilation, and survival and complication rates when comparing manual ventilation versus automatic transport ventilator in cardiopulmonary resuscitation with an advanced airway in place are needed to advance the science in this area.

2010/2015/2020 Search Strategy:

2021 Search Strategy:

(Ventilators, Mechanical) AND ((((((((((life support care[MeSH Terms]) OR "life support"[Title/Abstract]) OR cardiopulmonary resuscitation[MeSH Terms]) OR "cardiopulmonary resuscitation"[Title/Abstract]) OR "CPR"[Title/Abstract]) OR "return of spontaneous circulation"[Title/Abstract]) OR "ROSC"[Title/Abstract]) OR heart arrest[MeSH Terms]) OR "cardiac arrest"[Title/Abstract])) NOT ((animals[MH] NOT humans[MH])))

Database searched: MEDLINE, CINAHL

Date Search Completed: February 17, 2021

Search Results (Number of articles identified / number identified as relevant): 340 identified / 5 relevant

Inclusion/Exclusion Criteria:

Inclusion criteria

- Studies of adult OHCA or IHCA (potential for inter-facility transfer)
- Studies with reported subgroups of adult cardiac arrest
- Design: Randomized, observational, registry-based
- Language: At least abstract in English

Exclusion criteria

- Design: Case reports, case series, letters to editor, abstract only

- Exclude simulation studies or animal models unless there is now new clinical data, in which case consider indirect evidence from simulation studies or animal models

Link to Article Titles and Abstracts (if available on PubMed):

<u>From 2010 CoSTR</u>

1. Johannigman JA, Branson RD, Johnson DJ, Davis K, Hurst JM. Out-of-hospital ventilation: bag–valve device vs transport ventilator. Acad Emerg Med. 1995; *2*:719–724.

2. Weiss SJ, Ernst AA, Jones R, Ong M, Filbrun T, Augustin C, Barnum M, Nick TG. Automatic transport ventilator versus bag valve in the EMS setting: a prospective, randomized trial. South Med J. 2005; *98*:970–976.

<u>New articles for 2020 update</u>

3. Allen SG, Brewer L, Gillis ES, Pace NL, Sakata DJ, Orr JA. A Turbine-Driven Ventilator Improves Adherence to Advanced Cardiac Life Support Guidelines During a Cardiopulmonary Resuscitation Simulation. Respir Care. 2017 Sep;62(9):1166-1170. PMID: 28807986

4. Bergrath S, Rossaint R, Biermann H, Skorning M, Beckers SK, Rörtgen D, Brokmann JCh, Flege C, Fitzner C, Czaplik M. Comparison of manually triggered ventilation and bag-valve-mask ventilation during cardiopulmonary resuscitation in a manikin model. Resuscitation. 2012 Apr;83(4):488-93..PMID: 21958929

5. El Sayed MJ, Tamim H, Mailhac A, Mann NC. Impact of prehospital mechanical ventilation: A retrospective matched cohort study of 911 calls in the United States. Medicine (Baltimore). 2019 Jan;98(4):e13990. PMID: 30681557

Summary of Evidence Update:

Evidence Update Process for topics not covered by ILCOR Task Forces

1. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

Organization (if relevant); Author; Year Published	**Guideline or systematic review**	**Topic addressed or PICO(S)T**	**Number of articles identified**	**Key findings**	**Treatment recommendations**

RCT:

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
Weiss 2005 Included for 2010 guidelines	**<u>Study Type</u>**: Open label randomized trial **<u>Study Size</u>**:	**<u>Inclusion Criteria:</u>** Adults with successful endotracheal intubation	**<u>Intervention:</u>** Transport ventilator (n=15) **<u>Comparison:</u>** BVM (n=15)	**<u>1° endpoints:</u>** "Successful management" (Likert scale from provider on use compared to other device; range from -2 to + 2)	**<u>Secondary endpoints</u>** Binary yes/no as to whether O2 or EtCO2 data points were recorded O2 data recorded 4/14 vs. 8/14 EtCO2 data recorded

	N=28 (14 in each study arm) 22/28 were in cardiac arrest No subgroup analyses	**Exclusion Criteria**: Age < 18 years; Weight < 40 kg **Note** Subject demographics not reported		Ease of use -0.9 vs. -0.4 Set-up time -0.6 vs. -0.2 Expediation of transport 0.3 vs. 0.0 Accomplishing additional tasks 0.6 vs. -0.3 Ability to document 0.2 vs. -0.3 Patient comfort 0.0 vs. -0.4 Ability to provide overall patient care 0.4 vs. 0.0	5/14 vs. 8/14 **Study Limitations:** Small sample size Open label design Outcome data difficult to interpret No convincing signal for benefit or harm Might free up providers to perform other after longer set-up time (akin to mechanical CPR)

Bergrath 2012 Simulation study New for 2021 evidence update	**<u>Study Type</u>** Randomized simulation study **<u>Study Size</u>** 74 subjects in 34 2-person teams randomized to either ventilator (20 teams) or BVM (17 teams)	**<u>Inclusion criteria for volunteers</u>**: 3rd year medical students	**<u>Intervention</u>** Ventilator: novel, compact, pressure-limited ventilator with manually triggered ventilations; dynamic adjustment of ventilation pressure to achieve selected Vt based on dynamic changes in lung compliance (MEDUMAT Easy CPR, Weinmann, Hammburg, Germany) **<u>Comparison</u>** BVM: Total volume 1,600 mL with pressure relief valve at 40 mbar	**<u>Primary outcome</u>**: ventilation parameters Mean Vt (mL) Vent: mean 315 (SD 165) BVM: mean 408 (SD 164) P=0.10 Maximum Vt (mL) Vent: mean 565 (SD 178) BVM: mean 620 (SD 143) P=0.31 PAP (mbar) Vent: mean 13.6 (SD 2.2) BVM: mean 13.3 (SD 2.0) P=0.69 Inspiratory time (sec)	

				Vent: mean 1.39 (SD 0.31) BVM: mean 0.80 9SD 0.23) P<0.001 Hands-off time CPR (sec) Vent: mean 162 (SD 11) BVM: mean 134 (SD 18) P=0.001	
Allen 2017 Simulation Study New for 2021 evidence update	**Study Type** Randomized crossover simulation study **Study Size** 24 subjects in 12 teams of 2 performed 4 scenarios each (alternating	**Inclusion Criteria for volunteers**: ACLS certified	**Intervention** Mechanical ventilator (8 breaths/min at 22 cmH20) **Comparator** BVM (Ambubag, AMBU, Glen Burnie, MD)	**Primary outcome**: Ventilation parameters (Vt, RR, PAP) Vt (L) Vent: median 0.5 (IQR 0.5 – 0.5) BVM: median 0.6 (IQR 0.5 – 0.7) P=0.007 Respiratory rate	SimMan 3G manikin (Laerdal) used to collect CPR data Test lung adjacent to manikin (covered by a shield) used to collect ventilation data The ventilator delivered remarkably reliable parameters once it was set Expected variation in parameters with BVM

	roles) in random order			Vent: median 7.98 (IQR 7.98-7.99) BVM: median 9.5 (IQR 8.2 – 10.7) P=0.11 Peak airway pressure (cmH20) Vent: median 22 (IQR 22-22) BVM: median 30 (IQR 2-35) P<0.001 Associated hands-off time CPR (seconds) Vent: mean 5.25 (SD 2.11) BVM: mean 6.41 (SD 1.45) P<0.001	

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Johannigman 1995 Included for 2010 guidelines	**<u>Study Type:</u>** Prospective convenience sample N=160 subjects Metropolitan area with 3 neighboring counties; large receiving university hospital	**<u>Inclusion Criteria:</u>** Subjects requiring out-of-hospital ventilation Male 60% Mean age 61 years Endotracheal intubation 83% Data are for subset of 122/160 with cardiac arrest (defined as SBP < 50 mmHg)	**<u>1° endpoint:</u>** ABG on ED arrival (within 5 min) *missing for 70 subjects Subset of cardiac arrest (122/160) Manual ventilation (n=20) pH 7.20 (SD 0.16) pCO2 42 (SD 21) pO2 217 (SD 138) HCO3 15 (SD 5) Mechanical ventilation (n=32) pH 7.17 (SD 0.17) pCO2 37 (SD 20) pO2 257 (SD 142) HCO3 13 (SD 4) Esophageal Obturator Airway + manual ventilation (n=11)	Some EMS units carried a transport ventilator, while others carried a BVM; pseudo-randomization through usual dispatch operations BVM: minimum volume 2.0 L and O2 flow rate at 15 L/min Transport ventilator: Portable, pneumatically powered, electronically controlled, time-cycled machine (Impact Uni-Vent 706, Impact Instrumentation Inc, West Caldwell, NJ). Option for 5 respiratory frequencies and inspiratory time settings. Inspiratory flow adjustable from 10 – 60 L/min. Tidal volumes

			pH 7.09 (SD 0.13) pCO2 76 (SD 30) pO2 75 (SD 35) HOC3 22 (SD 5) **Secondary Endpoints** Survival to [not specified by authors…either ED arrival or hospital admission] Manual ventilation 3/46 (6.5%) Mechanical ventilation 3/64 (4.7%) EOA + manual ventilation 0.12 (0%)	range from 100 – 1,500 mL. I-time fixed at 1.5 seconds (adults) or 0.75 seconds (pediatrics). No clinically meaningful differences in ABG between manual and mechanical ventilation Esophageal obturator airway (EOA) is currently obsolete Small sample size limits interpretation of survival data No convincing signal for benefit or harm
El Sayed 2019 New for 2021 evidence update	**<u>Study Type</u>** Secondary analysis of NEMSIS (United States) dataset (2011-2014) N=5,740 EMS activations	**<u>Inclusion criteria:</u>** 911 response, ventilator use coded in dataset, ED vital status in dataset, complete data	**<u>Primary outcome</u>**: Mortality at ED discharge Vent: 8.4% No vent: 7.4% P=0.19 **<u>Secondary outcomes</u>**: Total on-scene time Vent: mean 20.7 (SD 12.1)	Only 7% of sample was in cardiac arrest No subgroup analyses Longer on-scene and total prehospital duration with use of a mechanical ventilator – this might be clinically meaningful in

	(could be multiple activations per subject) 1:1 case matching on age (+/- 2 years, sex, EMS diagnostic impression, urbanicity, level of service) 2,870 ventilator (vent without PEEP, vent with PEEP, BiPAP, or CPAP) 2,870 non-ventilator	for matched variables **<u>Exclusion criteria</u>**: "call cancelled", patient refused treatment, destination other than "hospital" Case breakdown: 78% respiratory distress 7% cardiac arrest 3% trauma 3% altered LOC	No vent: mean 17.2 (SD 8.9) P<0.0001 Total prehospital time Vent: mean 45.2 (SD 23.1) No vent: mean 41.1 (SD 21.2) P<0.0001 Mortality at hospital discharge Vent: 29% No Vent: 21% P=0.01	cases of OHCA (akin to mechanical CPR devices)

Reviewer Comments (including whether meet criteria for formal review):

Since the 2010 CoSTR, there is no new direct evidence from clinical data in the target population (adult cardiac arrest). New indirect evidence from two simulation studies (specific to cardiac arrest) and one registry-based observational study (not specific to cardiac arrest) suggest that mechanical ventilation delivers consistent and reliable ventilation parameters compared to manual ventilation. This same indirect evidence also suggests that there is a greater burden of equipment set-up and greater risk of hands-off time during chest compressions when using mechanical ventilation compared to manual ventilation. These findings are similar to those related to mechanical chest compression devices.

Altogether, this topic does not have sufficient new direct evidence to proceed to a formal systematic review.

	Approval Date
Evidence Update coordinator	**15 February 2021**
ILCOR board	

***Once approval has been made by Evidence Update coordinator, worksheet will go to ILCOR Board for acknowledgement.**

Reference list

Previously identified studies for 2010 CoSTR

1. Weiss SJ, Ernst AA, Jones R, Ong M, Filbrun T, Augustin C, Barnum M, Nick TG. Automatic transport ventilator versus bag valve in the EMS setting: a prospective, randomized trial. South Med J. 2005; *98*:970–976. PMID: 16295811

2. Johannigman JA, Branson RD, Johnson DJ, Davis K, Hurst JM. Out-of-hospital ventilation: bag–valve device vs transport ventilator. Acad Emerg Med. 1995; *2*:719–724. PMID: XXXX

<u>New studies for 2021 evidence update</u>

3. Allen SG, Brewer L, Gillis ES, Pace NL, Sakata DJ, Orr JA. A Turbine-Driven Ventilator Improves Adherence to Advanced Cardiac Life Support Guidelines During a Cardiopulmonary Resuscitation Simulation. Respir Care. 2017 Sep;62(9):1166-1170. PMID: 28807986

4. Bergrath S, Rossaint R, Biermann H, Skorning M, Beckers SK, Rörtgen D, Brokmann JCh, Flege C, Fitzner C, Czaplik M. Comparison of manually triggered ventilation and bag-valve-mask ventilation during cardiopulmonary resuscitation in a manikin model. Resuscitation. 2012 Apr;83(4):488-93..PMID: 21958929

5. El Sayed MJ, Tamim H, Mailhac A, Mann NC. Impact of prehospital mechanical ventilation: A retrospective matched cohort study of 911 calls in the United States. Medicine (Baltimore). 2019 Jan;98(4):e13990. PMID: 30681557

<u>Potential studies identified and ultimately excluded</u>

6. Fuchs P, Obermeier J, Kamysek S, Degner M, Nierath H, Jürß H, Ewald H, Schwarz J, Becker M, Schubert JK. Safety and applicability of a pre-stage public access ventilator for trained laypersons: a proof of principle study. BMC Emerg Med. 2017 Dec 4;17(1):37. PMID: 29202698

   - Pilot, prospective observational study of using a transport ventilator in healthy volunteers. Measured ventilator mechanics and air leak.

7. El Sayed M, Tamim H, Mailhac A, N Clay M. Ventilator use by emergency medical services during 911 calls in the United States. Am J Emerg Med. 2018 May;36(5):763-768. PMID: 29032875

- Secondary analysis of NEMSIS database (United States) 2011-2014. A descriptive study of ventilator use by EMS in the United States. Primary outcome was use of a mechanical ventilator. Authors modeled clinical variables associated with ventilator use. There were no clinical outcomes and this study is not specific to cardiac arrest.

8. Nitzschke R, Doehn C, Kersten JF, Blanz J, Kalwa TJ, Scotti NA, Kubitz JC. Effect of an interactive cardiopulmonary resuscitation assist device with an automated external defibrillator synchronised with a ventilator on the CPR performance of emergency medical service staff: a randomised simulation study. Scand J Trauma Resusc Emerg Med. 2017 Apr 4;25(1):36. PMID: 28376849

   - Simulation study. Both study arms used an automatic ventilator.

9. Sherren PB, Lewinsohn A, Jovaisa T, Wijayatilake DS. Comparison of the Mapleson C system and adult and paediatric self-inflating bags for delivering guideline-consistent ventilation during simulated adult cardiopulmonary resuscitation. Anaesthesia. 2011 Jul;66(7):563-7. PMID: 21668912

   - Simulation study. This study compares two different BVM systems and does not involve use of an automatic ventilator.
   -

10. Cordioli RL, Brochard L, Suppan L, Lyazidi A, Templier F, Khoury A, Delisle S, Savary D, Richard JC. How Ventilation Is Delivered During Cardiopulmonary Resuscitation: An International Survey. Respir Care. 2018 Oct;63(10):1293-1301. PMID: 29739857

    - Survey study

11. Winkler BE, Muellenbach RM, Wurmb T, Struck MF, Roewer N, Kranke P. Passive continuous positive airway pressure ventilation during cardiopulmonary resuscitation: a randomized cross-over manikin simulation study. Journal of Clinical Monitoring and Computing. 2017 31:93-101. PMID: 26861639

    - Simulation study. This study compares the tidal volumes generated by various mechanical ventilators set to a range of CPAP levels during passive ventilation from mechanical chest compressions.

12. Greenslade GL. Single operator cardiopulmonary resuscitation in ambulances: which ventilation device? Anaesthesia. 1991 46:391-4. PMID: 2035790

    - Simulation study. Randomized cross-over study of single rescuer CPR. Measured minute ventilation and compressions/minute during a control period of mouth-to-mouth ventilation, followed by mouth-to-mask, BVM, and an automatic ventilator attached to BVM mask. No advanced airways were placed for any of the ventilation modes.

13. Orso D, Vetrugno L, Federici N, Borselli M, Spadaro S, Cammarota G, Bove T. Mechanical ventilation management during mechanical chest compressions. Respiratory Care. 2021 66(2):334-46. PMID: 32934100

    - Narrative review of animal and human literature that summarizes different strategies of mechanical ventilation during mechanical chest compressions. They authors pay particular attention to reviewing strategies to optimize the ventilation mode, tidal volume, PEEP, ventilation rate, I:E ratio, inspiratory trigger, and FiO2.

2021 Evidence Update Worksheet

Appendix B2 ALS 6

Cardiac arrest and asthma (ALS492: EvUp)

Worksheet author(s): Katherine Berg

Date Submitted: Jan 4, 2021

PICO / Research Question: In adult cardiac arrest due to asthma, does any modification of treatment, as opposed to standard care (according to treatment algorithm), improve outcome? **(as worded in 2010 CoSTR)**

Outcomes: ROSC, survival to hospital discharge, 30 days or longer, survival with favorable neurologic outcome at hospital discharge, 30 days or longer.

Type (intervention, diagnosis, prognosis): Intervention

Additional Evidence Reviewer(s):

Conflicts of Interest (financial/intellectual, specific to this question): None

Year of last full review: 2010 / 2015 / New question: 2010

Last ILCOR Consensus on Science and Treatment Recommendation:

Consensus on Science

There are no RCTs that specifically evaluate or compare adjuvant treatment with standard treatment for cardiac arrest in asthmatic patients. Most of the literature comprises case reports and case series.

Evidence from 3 non–cardiac arrest case series involving 35 patients suggests that asthmatic patients are at risk for gas trapping during cardiac arrest, especially if their lungs are ventilated with high tidal volumes and/or rapid rates (LOE 5).[466–468] One volunteer adult study demonstrated that increasing PEEP caused increased transthoracic impedance (LOE 5).[469]

Seven case series involving 37 patients suggested increased ease of ventilation and ROSC with lateral chest compressions at the base of the ribs (LOE 4).[470–476] In a single case report, lateral chest compressions were associated with cardiac arrest and poor cardiac output (LOE 4).[477] Three single case reports (2 intraoperative and 1 ED) involving cardiac arrest caused by asthma suggested improvement in ease of ventilation and ROSC with thoracotomy and manual lung compression (LOE 4).[471,475,476]

Treatment Recommendation

There is insufficient evidence to suggest any routine change to cardiac arrest resuscitation treatment algorithms for patients with cardiac arrest caused by asthma.

2010/2015 Search Strategy:

2021 Search Strategy: ("asthma"[MeSH Terms] OR "asthma"[All Fields] OR "asthmas"[All Fields] OR "asthma s"[All Fields]) AND ("heart arrest"[MeSH Terms] OR ("heart"[All Fields] AND "arrest"[All Fields]) OR "heart arrest"[All Fields] OR ("cardiac"[All Fields] AND "arrest"[All Fields]) OR "cardiac arrest"[All Fields])

Database searched: PubMed

Date Search Completed: January 4, 2021, search limited to January 1, 2009-January 4, 2021

Search Results (Number of articles identified / number identified as relevant): 137 identified, 1 relevant

Inclusion/Exclusion Criteria: Included controlled and uncontrolled studies of treatments/strategies for resuscitation of cardiac arrest related to asthma with a comparison group, case series. Excluded pediatric studies, case reports, animal studies. Also excluded studies looking only at post-ROSC management or studies that did not include cardiac arrest.

Link to Article Titles and Abstracts (if available on PubMed):

Tsai MS, Chuang PY, Yu PH, Huang CH, Tang CH, Chang WT, Chen WJ.Int J Cardiol. Glucocorticoid use during cardiopulmonary resuscitation may be beneficial for cardiac arrest. Nov 1, 2016;222:629-635. PMID: 27517652

Summary of Evidence Update: No controlled studies were identified. A single retrospective observational study use propensity matching to compare outcomes in patients presenting to the ED with cardiac arrest who did receive steroids during CPR to those patients who did not receive steroids during CPR. The authors report better adjusted odds of survival in the patients who received intra-arrest steroids, and the effect appeared larger in patients with asthma or COPD. Two case reports describing patients with cardiac arrest due to asthma were also identified but were not included due to the very critical risk of bias from relaying on case reports.

Relevant Guidelines or Systematic Reviews

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations

RCT:

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
	Study Aim:	**Inclusion Criteria:**	**Intervention:**	**1° endpoint:**	**Study Limitations:**

	Study Type:		**Comparison:**		

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Tsai et al, Glucocorticoid use during cardiopulmonary resuscitation may be beneficial for cardiac arrest, 2016	**Study Type:** Retrospective observational study using propensity matching. Patients were matched by multiple variables including age, gender, presenting complaint, comorbidities, previous steroid use, drugs and electric shocks delivered during CPR, treatment setting (tertiary medical center or not), socioeconomic status, geographic distribution and year that cardiac arrest occurred	**Inclusion Criteria:** adult (18 or older) patients brought to emergency departments for CPR and who received resuscitation attempt in the emergency department. **Exclusion criteria:** trauma, patients in ED >6 hours prior to arrest, patients not triaged as level 1, patients with a history of steroid use	**1° endpoint:** Survival to admission, survival to discharge, 1-year survival	Study included patients from 2004-2011, so this is older data although study was published in 2016. Cohort was over 140,000 patients, but the matched cohort consisted of 2876 who received steroids and 8628 who did not. The findings were that receiving steroids during CPR was associated with an adjusted OR of 2.97 (2.69-3.29) for survival to admission and 1.71 (1.42-2.05) for survival to discharge. In the subgroup of patients with a history of asthma the adjusted OR for survival to admission was 4.56 (3.59-5.81), compare to 2.66 (2.37-2.97) in patients without asthma, with a p-value for the interaction being <0.0001. ROSC was not reported.

Reviewer Comments (including whether meet criteria for formal review):

As only a single observational study was identified since this topic was last reviewed in 2010, I do not think a systematic review on this topic is of high priority.

Although quite limited by bias inherent in the study design, the study findings are suggestive, and a formal review of both adult and pediatric data within the next few years may be warranted.

ALS Task Force discussion – insufficient evidence for systematic review.

	Approval Date
Evidence Update coordinator	15 February 2021
ILCOR board	

***Once approval has been made by Evidence Update coordinator, worksheet will go to ILCOR Board for acknowledgement.**

Reference list

Tsai MS, Chuang PY, Yu PH, Huang CH, Tang CH, Chang WT, Chen WJ.Int J Cardiol. Glucocorticoid use during cardiopulmonary resuscitation may be beneficial for cardiac arrest. 2016 Nov 1;222:629-635. doi: 10.1016/j.ijcard.2016.08.017. Epub 2016 Aug 4.PMID: 27517652

Case reports (not included)

Lang Y, Zheng Y, Hu X, Xu L, Luo Z, Duan D, Wu P, Huang L, Gao W, Ma Q, Ning M, Li T.J
Extracorporeal membrane oxygenation for near fatal asthma with sudden cardiac arrest.
Asthma. 2020 Jun 30:1-5. doi: 10.1080/02770903.2020.1781164. PMID: 32543251

Hui Guo , Qian Zhao , Su-Yan Li , Xin Xu , Ning Xu , Chang Lv , Zhang-Shun Shen, Jian-Guo Li Successful treatment of fatal asthma combined with a silent chest: A case report. Int Med Res, 2020 May;48(5):300060520925683. PMID: 32466702

2021 Evidence Update Worksheet

Appendix B2 ALS 7

ECPR versus manual or mechanical CPR (ALS 723: EvUp)

Worksheet author(s): Lars W. Andersen

Date Submitted: Jan. 20, 2021

PICO / Research Question:

Population: Adults (≥ 18 years) and children (<18 years) with cardiac arrest in any setting (out-of-hospital or in-hospital)

Interventions: ECPR, including extracorporeal membrane oxygenation or cardiopulmonary bypass, during cardiac arrest

Control: Manual CPR and/or mechanical CPR

Outcomes: Clinical outcomes, including, but not necessarily limited to, return of spontaneous circulation, survival/survival with a favorable neurological outcome at hospital discharge/30 days, and survival/survival with a favorable neurological outcome after hospital discharge/30 days (e.g. 90 days, 180 days, 1 year).

Type (intervention, diagnosis, prognosis): Intervention

Additional Evidence Reviewer(s): NA

Conflicts of Interest (financial/intellectual, specific to this question): NA

Year of last full review: 2010 / 2015 / New question: 2017, 2019 CoSTR

Last ILCOR Consensus on Science and Treatment Recommendation:

We suggest that ECPR may be considered as a rescue therapy for selected patients with cardiac arrest when conventional CPR is failing in settings in which it can be implemented (weak recommendation, very low-certainty evidence).

2010/2015/2020 Search Strategy:

Provided in:

Resuscitation 2018 Oct;131:91-100.
Extracorporeal Cardiopulmonary Resuscitation for Cardiac Arrest: A Systematic Review
Holmberg M, Geri G, Wiberg S, Guerguerian AM, Donnino M, Nolan J, Deakin C, and Andersen LW

2021 Search Strategy:

(extracorporeal OR “cardiopulmonary bypass” OR “heart bypass” OR ECPR OR CPB OR ECMO OR ECLS) AND (cardiopulmonary resuscitation[MH] OR cardiac arrest*[TW]) AND (randomized controlled trial[PT] OR controlled clinical trial[PT] OR randomized[TIAB] OR randomly[TIAB] OR trial[TIAB] OR groups[TIAB] OR placebo[TIAB] OR drug therapy[SH]) NOT (animals[MH] NOT humans[MH]) NOT (case reports[PT] OR review[PT])

Database searched: PubMed

Date Search Completed: Nov. 1, 2017 - Nov. 18, 2020

Search Results: One relevant article identified.

Inclusion/Exclusion Criteria: Only RCTs.

Link to Article Titles and Abstracts (if available on PubMed):

https://pubmed.ncbi.nlm.nih.gov/33197396/

Summary of Evidence Update:

RCT:

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
ARREST; Yannopoulos; 2020	**<u>Study Aim:</u>** EPCR vs. standard CPR	**<u>Inclusion Criteria:</u>** Refractory VF, age 18 – 75, estimated transfer time < 30 min.	**<u>Intervention:</u>** ECPR **<u>Comparison:</u>** Standard CPR	**<u>1° endpoint:</u>** Survival to hospital discharge: 1/15 (7%) vs. 6/14 (43%) RD: 36% (95%CI: 4, 59)	**<u>Study Limitations:</u>** Small study

Reviewer Comments (including whether meet criteria for formal review):

This small new study, while the first RCT, does not change the current recommendation. The ALS task force therefore decided that no formal review is needed at this time. A systematic review is planned at a later stage when more ongoing RCTs are published.

	Approval Date
Evidence Update coordinator	**15 February 2021**
ILCOR board	

***Once approval has been made by Evidence Update coordinator, worksheet will go to ILCOR Board for acknowledgement.**

Reference list

Yannopoulos D, Bartos J, Raveendran G, Walser E, Connett J, Murray TA, Collins G, Zhang L, Kalra R, Kosmopoulos M, John R, Shaffer A, Frascone RJ, Wesley K, Conterato M, Biros M, Tolar J, Aufderheide TP. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. Lancet. 2020 Dec 5;396(10265):1807-1816.

2021 Evidence Update Worksheet

Appendix B2 ALS 8

Steroids after ROSC (ALS446: EvUp)

Worksheet author(s): Tonia Nicholson

Date Submitted: Feb 2021

PICO / Research Question: In adult patients with ROSC after cardiac arrest (prehospital or in-hospital) (P), does treatment with corticosteroids (I) as opposed to standard care (C), improve outcome (O) (eg. survival)?

Outcomes: Survival to Hospital discharge with good neurological outcome / Survival to hospital discharge (+/- Time to Shock Reversal / Shock Reversal)

Type (intervention, diagnosis, prognosis): Intervention

Additional Evidence Reviewer(s): N/A

Conflicts of Interest (financial/intellectual, specific to this question): N/A

Year of last full review: 2010 (but similar literature search done to address 2015 PICOT 433)

Last ILCOR Consensus on Science and Treatment Recommendation: *Consensus on Science* : There were no human or animal studies that directly ad- dressed the use of the estrogen, progesterone, insulin, or insulin-like growth factor in cardiac arrest. Early observational studies of the use corticosteroids during cardiac arrest suggested possible benefit (LOE 4).[229,230] One complex randomized pilot study (LOE 1)[231] and 1 nonrandomized human study (LOE 2)[232] suggested benefit with corticosteroids, whereas 1 small, older, human prehospital controlled clinical trial suggested no benefit (LOE 1).[233] One animal study of corticosteroids suggested possible benefit (LOE 5).[234]

Treatment Recommendation : There is insufficient evidence to support or refute the use of corticosteroids alone or in combination with other drugs during cardiac arrest.

2010 Search Strategy: Cochrane Library search:
("Heart Arrest"[Mesh] OR "Cardiopulmonary Resuscitation"[Mesh]) AND ("Pituitary-Adrenal System"[Mesh] OR "Adrenal Insufficiency"[Mesh] OR "Adrenal Cortex Hormones"[Mesh] OR "Glucocorticoids"[Mesh] OR "Hydrocortisone"[Mesh] OR "Cortisone"[Mesh] OR "Prednisolone"[Mesh] OR "Prednisone"[Mesh] OR "Methylprednisolone"[Mesh] OR "Dexamethasone"[Mesh] OR "Betamethasone"[Mesh]). 5 results.

PubMed search:
("Heart Arrest"[Mesh] OR "Cardiopulmonary Resuscitation"[Mesh]) AND ("Pituitary-Adrenal System"[Mesh] OR "Adrenal Insufficiency"[Mesh] OR "Adrenal Cortex Hormones"[Mesh] OR "Adrenal Cortex Hormones "[Pharmacological Action] OR "Glucocorticoids"[Mesh] OR "Hydrocortisone"[Mesh] OR "Cortisone"[Mesh] OR "Prednisolone"[Mesh] OR "Prednisone"[Mesh] OR "Methylprednisolone"[Mesh] OR "Dexamethasone"[Mesh] OR "Betamethasone"[Mesh]). 184 results.

EMBASE search:
('heart arrest'/exp/mj OR 'resuscitation'/exp/mj) AND 'corticosteroid'/exp/mj 347 results.

AHA Endnote database search: (“arrest” OR “CPR”) AND (“adrenal” OR “glucocorticoids” OR ”steroid” OR “hydrocortisone” OR “cortisone” OR “prednisolone” OR “prednisone” OR “methylprednisolone” OR “dexamethasone” OR “betamethasone”): 379 results. Titles and abstracts (where appropriate) of all results were examined for relevance. Where doubt existed the full papers were reviewed to identify relevant papers.

The reference lists of relevant papers were searched for other relevant papers. Forward searching of relevant papers was performed using SCOPUS.

2021 Search Strategy: Table Error! No text of specified style in document.**.1** **Explanation of search strategy approach**
This search is a re-run of the last search performed for the EVUR done on this PICO in 2019. It was time restricted (Dec 1st 2019 – Jan 13th 2021) to try and identify any relevant new articles on the topic in the past year.

#	Search string (developed for the EMBASE.com platform, which includes Medline and Embase databases)	Explanation
#1	'heart arrest'/exp 'heart arrest$':ti,ab 'cardiac arrest$':ti,ab 'cardiovascular arrest$':ti,ab 'cardiopulmonary arrest'/exp 'cardiopulmonary arrest$':ti,ab 'cardio-pulmonary arrest$':ti,ab 'resuscitation'/exp rosc:ti,ab 'post-rosc':ti,ab 'post-resuscitation':ti,ab 'return of spontaneous circulation':ti,ab resuscitat*:ti,ab	**Population – Cardiac arrest** Terms related to cardiac arrest and/or ROSC should be the focus of the article, so these terms must appear in either the title or the abstract, or the article must be tagged with EMTREE terms for cardiac arrest or ROSC. Note, general terms for life support such as 'basic life support' (as used in prior search) or ''advanced cardiac life support' were considered too generic, and terms relating to CPR techniques such as chest compressions and heart massage were considered too specifically focusing on the process of CPR rather than the post-ROSC patient.
#2	#1 NOT ('animal'/exp NOT 'human'/exp OR 'nonhuman'/exp OR 'rodent'/exp OR 'animal experiment'/exp OR 'experimental animal'/exp OR rat:ti,ab OR rats:ti,ab OR mouse:ti,ab OR mice:ti,ab OR dog$:ti,ab OR pig$:ti,ab OR porcine:ti,ab OR swine:ti,ab OR chick$:ti,ab)	**Exclude non-human studies** The search results must include citations from the newborn population string, so a 'non-human studies' filter was applied to it.
#3	#2 NOT ([conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR	**Exclude publication types** Conference abstracts and other ineligible study types were removed here.

#	Search string (developed for the EMBASE.com platform, which includes Medline and Embase databases)	Explanation
	[erratum]/lim OR [letter]/lim OR [note]/lim OR [book]/lim OR 'case report'/de)	
#4	#3 AND [2014-2020]/py	**Date limit** The date of the last ILCOR search was 18 July 2014. This search string can be combined with intervention strings or other population strings to produce a final number of records.
#5	'steroid'/de 'corticosteroid'/de 'mineralocorticoid'/de corticosteroid$:ti,ab mineralocorticoid$:ti,ab steroid$:ti,ab prednisone:ti,ab prednisolone:ti,ab methylprednisolone:ti,ab fludrocortisone:ti,ab hydrocortisone:ti,ab dexamethasone:ti,ab	**Intervention terms – steroids** To identify steroid studies. These terms must appear in the title or abstract, or the article must be tagged with EMTREE terms for steroids. Note, the EMTREE terms were not exploded as that includes a large number of irrelevant interventions. Instead, studies coded directly to the steroid EMTREE term (or the corticosteroid EMTREE term, etc.) were captured, along with studies that include these terms as free text, or include the specific drugs that were included in the search for the 2015 ILCOR CoSTR (hydrocortisone was added to this set of specific drugs as it is mentioned in the 2015 Consensus on science).
#6	#4 AND #5	**Population + intervention**
#7	(((after OR post) NEAR/4 (rosc OR spontaneous OR circulation OR resuscitation	**Post-arrest terms**

#	Search string (developed for the EMBASE.com platform, which includes Medline and Embase databases)	Explanation
	OR cardiac OR arrest)):ti,ab) OR postarrest:ti,ab OR 'post-arrest':ti,ab OR 'post-rosc':ti,ab OR (surviv* NEAR/3 (cardiac OR arrest OR resuscitation OR ohca OR 'oh ca' OR ihca OR 'ih ca'))	This string is useful to stratify studies according to whether they include reference to post-ROSC status. However, this string could potentially exclude relevant studies, and should not be relied upon to filter the identified studies.
#8	#6 AND #7	**Population + intervention + post-arrest terms**
#9	#6 NOT #8	**Population + intervention (minus + post-arrest terms)**

Database searched: EMBASE.com platform (includes Medline and EMBASE)/Cochrane Reviews**/**National Clinical Trials Database and WHO International Clinical Trials Registry

Date Search Completed: Jan 13th 2021

Search Results (Number of articles identified / number identified as relevant):
Embase/Medline 10
Cochrane: 26
Trials Registry 61

Inclusion/Exclusion Criteria:
Inclusion – Adults (>18yrs) with non-traumatic cardiac arrest
Exclusions - Steroids given during CPR (ie. Prior to ROSC), paediatric patients, animal studies, letters, commentaries, editorials, case series, poster presentations only, journal club reviews, interim analyses.

Link to Article Titles and Abstracts (if available on PubMed):

Summary of Evidence Update:

Evidence Update Process for topics not covered by ILCOR Task Forces

Relevant Guidelines or Systematic Reviews – *One*

Organisation (if relevant); Author; Year Published	**Guideline or systematic review**	**Topic addressed or PICO(S)T**	**Number of articles identified**	**Key findings**	**Treatment recommendations**
Liu B, Zhang Q and Li C. (2020). Steroid use after cardiac arrest is associated with favourable outcomes: a systematic review and meta-analysis. Journal of International Medical Research. 48(5).[1]	Systematic review and meta-analysis.	To investigate whether steroid use after CA increased the return of spontaneous circulation (ROSC) rate and survival to discharge in patients with CA. Subgroup analysis done based on the time of drug administration (during CPR or after CA).	Identified 4 RCTs & 3 observational studies. 3 of the studies were published in English and 4 in Chinese. 4 of the studies included administration of steroids post cardiac arrest and the data from these studies was pooled. However, this pooling is questionable, since in all but one of the studies (Tsai 2019), steroids were also administered during CA not just post ROSC, and in one study vasopressin was also given during CA.	Subgroup analysis of patients given steroids after cardiac arrest found a significant association with increased rate of survival to discharge (RR 1.35; 95% CI 1.23-1.48, $p < 0.05$). However, it is not clear from the data whether these patients ALSO received steroids during cardiac arrest or ONLY received them after ROSC.	The conclusion of the article was that current evidence indicates that steroid use increases the rate of ROSC & survival to discharge in patients with CA. However, though steroid use may remain an acceptable option for patients with CA, high-quality and adequately powered RCTs are warranted.

Of the 7 articles identified for inclusion in this systematic review and meta-analysis, 3 of the studies were published in English (Mentzelopoulos, 2013[2]; Tsai, 2019[3]; Niimura, 2017[4]). All of these were considered in the 2020 ILCOR EvUp on the use of steroids post cardiac arrest.

4 of the studies were published only in Chinese (Zhang, 2015[(5)]; Mu 2014[(6)]; Yang, 2002[(7)]; He 2001[(8)]). The latter 3 studies were all small and were conducted before 2005, so would not be included in an ILCOR SR on this PICO because of the significant differences in other aspects of management of cardiac arrest before this time.

The first study (Zhang, 2015) was an RCT conducted in China between 2011 and 2014. From the summary tables in the systematic review it was a small study with only 50 patients in each arm of the study (steroids vs no steroids). It is clear that those patients who achieved ROSC after steroids must have been given them during cardiac arrest, and although the systematic review reports a subgroup analysis of those receiving steroids after cardiac arrest, it is probable that those patients receiving steroids post arrest also received them *during* arrest, since the total number of subjects in each group is the same (50). Therefore, inclusion of this study into a SR would be unlikely alone to result in a modification of the current ILCOR COSTR.

RCT: *None*

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR;& 95%CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events

Nonrandomized Trials, Observational Studies – *None*

1 article was identified as possibly relevant at initial abstract screening, but due to a small time overlap in the search strategies for 2019 & 2020, this had already been considered and included in the development of the 2020 EVUR (Tsai, 2019).

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

Clinical trials registry: *Nine*

Nine studies were identified in the Clinical trials registry of potentially being relevant to this PICO.
Four of these were subsequently identified as completed studies, which had been considered in either the generation of the last COSTR on the topic, or the EVUR in 2020 (Botnaru, 2015[9] ; Mentzelopoulos 2009 and 2013; Donnino 2016 [10]).

Two of the studies are registered on the WHO data base (one in 2019, the other in 2020). No details regarding these studies are currently available as the WHO website is dedicated to issues related to COVID-19.

One study (Pappa, 2020[11]) has been completed and was presented at the 40 th International Symposium on Intensive Care in March 2020. It has not yet however, been presented in a format subject to peer review. This was an RCT involving 100 patients with IHCA, conducted by the CORTICA study group (Mentzelopoulos et al). Forty-six patients were randomly assigned to receive methylprednisolone 40 mg during resuscitation, and 54 to receive saline (placebo). After resuscitation, steroid-treated patients received hydrocortisone 240 mg daily for up to 7 days, followed by tapering over the next 2 days. The study concluded that steroids post cardiac arrest had no significant physiological benefit, including no effect on neurological survival at discharge. Detailed data is not included in the Symposium summary. Of note however, this is the first study by this group that has not suggested a beneficial effect with steroids post cardiac arrest.

Trail Nct4591990 [12] was registered in Oct 2020 but has not commenced recruitment of patients yet. This study has been planned to be conducted across 17 ICUs in France with the primary objective of demonstrating the superiority of arginine-vasopressin (AVP) and hydrocortisone compared with norepinephrine regarding day-30 survival and neurological recovery in post-cardiac arrest patients with hemodynamic failure.

Trial Nct 4624776 [13] was registered in Nov 2020 and is currently recruiting patients. This is a randomized, multicenter, double-blind, placebo-controlled clinical trial (lead by C. Hassager in Denmark). A minimum of 120 unconscious OHCA patients are to be randomized 1:1 after 5 minutes of sustained ROSC to a bolus infusion of 250 mg (4 mL) methylprednisolone in the pre-hospital setting. Patients allocated to placebo will receive 4 mL of isotonic saline (NaCl 0.9%). Secondary outcomes to be assessed include survival to discharge and neurological outcome.

Reviewer Comments (including whether meet criteria for formal review):

Since the 2020 Evidence update review on the use of steroids post ROSC after cardiac arrest, no new RCTs or observational studies have been identified as being published. One systematic review has been conducted, but this did not include any recent, methodologically sound studies that would be likely to result in a change of the current ILCOR COSTR regarding the use of steroids post cardiac arrest.

Review of the Clinical Trials registry suggests that the results of one study on this topic were presented in a non-peer reviewed format last year. The 2020 EvUp on this topic suggested waiting peer review and publication of this study (Nct 02790788) before conducting a new systematic review. It is likely that the current situation with COVID has delayed the submission of the study for publication, and it was presented at a symposium instead.

Additionally, in the last year however, one new study has been registered with a plan to start recruiting soon, and another is already recruiting. Therefore, at this time it would seem sensible to delay a formal systematic review regarding the utility of steroids following ROSC after cardiac arrest, to allow peer-review assessment of the completed study by the CORTICA group, and completion of the two new active trials registered on the topic.

	Approval Date
Evidence Update coordinator	**15 February 2021**
ILCOR board	

***Once approval has been made by Evidence Update coordinator, worksheet will go to ILCOR Board for acknowledgement.**

Reference list

1) Liu, B, Zhang, Q and Li, C. (2020). Steroid use after cardiac arrest is associated with favourable outcomes: a systematic review and meta-analysis. Journal of International Medical Research. 48(5).

2) Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids and epinephrine and neurologically favourable survival after in-hospital cardiac arrest: a randomized clinical trial. JAMA. 2013;310:270-9.

3) Tsai, MS, Chuang, PY, Huang, CH, Tang, CH, Yu, PH, Chang, WT and Chen, WJ. (2019). Post-arrest Steroid Use May Improve Outcomes of Cardiac Arrest Survivors. Critical care medicine. 47(2):167-1

4) Niimura, T, Zamami, Y, Koyama, T, Izawa-Ishizawa, Y, Miyake, M, Koga, T, Harada, K, Ohshima, A, Imai, T, Kondo, Y, Imanishi, M, Takechi, K, Fukushima, K, Horinouchi, Y, Ikeda, Y, Fujino, H, Tsuchiya, K, Tamaki, T, Hinotsu, S, Kano, MR and Ishizawa, K. (2017). Hydrocortisone administration was associated with improved survival in Japanese patients with cardiac arrest. Scientific reports. 7(1):17919.

5) Zhang F, Yang ZJ, Shen J, et al. Adrenaline combined with methylprednisolone sodium succinate Cardiopulmonary resuscitation Chinese Clinical Medicine 2015; 22: 670–671.

6) Mu CJ, Li WQ, Zhou YM, et al. Hydrocortisone sodium succinate for cardio- pulmonary resuscitation the influence of patient prognosis. Chinese Journal of Integrated Traditional and Western Medicine 2014; 21: 229–231.

7) Yang GL and Li CX. Clinical study on com- prehensive medication for cardiopulmonary cerebral resuscitation. National Coal Industry Medical Journal 2002; 5: 379–380.

8) He WX and Hong Z. Application of high- dose adrenaline combined with aminophyl- line, of clinical study of cardiopulmonary cerebral resuscitation with dexamethasone. Chinese Emergency Medicine 2001; 21: 224–225.

9) Botnaru, T, Altherwi, T and Dankoff, J. (2015). Improved neurologic outcomes after cardiac arrest with combined administration of vasopressin, steroids, and epinephrine compared to epinephrine alone. Canadian Journal of Emergency Medicine. 17(2):202-205.

10) Donnino, MW, Andersen, LW, Berg, KM, Chase, M, Sherwin, R, Smithline, H, Carney, E, Ngo, L, Patel, PV, Liu, X and et al. Corticosteroid therapy in refractory shock following cardiac arrest: a randomized, double-blind, placebo-controlled, trial. Critical care (London, England). 2016; 20(1)

11) Pappa, E, Ischaki, E, Malachias, S, Giannopoulos, A, Vrettou, K, Karlis, G, Pantazopoulos, I, Makris, D, Zakynthinos, S and Mentzelopoulos, S. (2020). Physiologic effects of steroids in in-hospital cardiac arrest (CORTICA study group1,2). Critical care (London, England). 24

12) HYdrocortisone and VAsopressin in Post-RESuscitation Syndrome. https://clinicaltrials.gov/show/NCT04591990

13) Steroid Treatment After Resuscitated Out-of-Hospital Cardiac Arrest. https://clinicaltrials.gov/show/NCT04624776.

2021 Evidence Update Worksheet
Appendix B2 ALS 9

Oxygen dose after ROSC (ALS 448: EvUp)

Worksheet author(s): Mathias J. Holmberg
Date Submitted: February 9, 2021

PICO / Research Question:

Population: Unresponsive adults and children with sustained return of spontaneous circulation (ROSC) after cardiac arrest in any setting.

Interventions: A ventilation strategy targeting specific SpO2, PaO2, and/or PaCO2 targets.

Control: Treatment without specific targets or with an alternate target to the intervention.

Outcomes: Clinical outcome including survival/survival with a favorable neurological outcome at hospital discharge/30 days, and survival/survival with a favorable neurological outcome after hospital discharge/30 days (e.g., 90 days, 180 days, 1 year).

Type (intervention, diagnosis, prognosis): Intervention

Additional Evidence Reviewer(s): NA

Conflicts of Interest (financial/intellectual, specific to this question): NA

Year of last full review: 2010 / 2015 / New question: 2020

Last ILCOR Consensus on Science and Treatment Recommendation:

Treatment Recommendation in Adult Patients:

We suggest the use of 100% inspired oxygen until the arterial oxygen saturation or the partial pressure of arterial oxygen can be measured reliably in adults with ROSC after cardiac arrest in any setting (weak recommendation, very low-certainty evidence).

We recommend avoiding hypoxemia in adults with ROSC after cardiac arrest in any setting (strong recommendation, very low-certainty evidence).

We suggest avoiding hyperoxemia in adults with ROSC after cardiac arrest in any setting (weak recommendation, low-certainty evidence).

2010/2015/2020 Search Strategy:

Provided in:

Resuscitation 2020, Jul;152:107-115
Oxygenation and ventilation targets after cardiac arrest: A systematic review and meta-analysis
Holmberg MJ, Nicholson T, Nolan JP, Schexnayder S, Reynolds J, Nation K, Welsford M, Morley P, Soar J, Berg KM

2021 Search Strategy:

((heart arrest[MH] OR cardiopulmonary resuscitation[MH] OR heart massage[MH] OR advanced cardiac life support[MH] OR ventricular fibrillation[MH] OR heart massage[TW] OR heart arrest*[TW] OR cardiac arrest*[TW] OR OHCA[TW] OR IHCA[TW] OR CPR[TW] OR advanced cardiac life support[TW] OR ACLS[TW] OR asystole[TW] OR pulseless electrical activity[TW] OR pulseless ventricular tachycardia[TW] OR ventricular fibrillation[TW] OR return of circulation[TW] OR return of spontaneous circulation[TW] OR ROSC[TW] OR chest compression*[TW] OR cardiopulmonary resuscitation[TW]) AND (oxygen[MH] or carbon dioxide[MH] OR hypoxia[MH] OR hypercapnia[MH] OR hyperoxia[MH] OR hypocapnia[MH] OR oxygen inhalation therapy[MH] OR respiration, artificial[MH] OR ventilators, mechanical[MH] OR oxygen[TW] OR carbon dioxide[TW] OR hypoxi*[TW] OR hyperoxi*[TW] OR hypercapni*[TW] OR hypocapni* [TW] OR normoxi*[TW] or normocarbi*[TW] OR reoxygenation[TW] OR ventilation strategy[TW] OR CO2[TW] OR O2[TW] OR PaO2[TW] OR SpO2[TW] OR PaCO2[TW] OR FiO2[TW] OR inspired oxygen[TW]) NOT (animals[MH] NOT humans[MH]) NOT (case reports[PT] OR review[PT]))

Database searched: PubMed

Date Search Completed: Aug. 22, 2019 – Feb. 01, 2021

Search Results: 469 records screened; 1 systematic review, 1 RCT subgroup analysis, and 12 observational studies were identified as relevant

Inclusion/Exclusion Criteria: RCTs, non-randomized trials, and observational studies.

Link to Article Titles and Abstracts (if available on PubMed):

Young, Resuscitation, 2020
https://pubmed.ncbi.nlm.nih.gov/33058991/

Schjørring, NEJM, 2021
https://pubmed.ncbi.nlm.nih.gov/33471452/

Mckenzie, Resuscitation, 2021
https://pubmed.ncbi.nlm.nih.gov/33232752/

Zhou, American Journal of Emergency Medicine, 2021
https://pubmed.ncbi.nlm.nih.gov/32001056/

Humaloja, Neurocritical Care, 2021
https://pubmed.ncbi.nlm.nih.gov/33403587/

Young, Intensive Care Medicine, 2020
https://pubmed.ncbi.nlm.nih.gov/32809136/

McGuigan, Critical Care, 2020
https://pubmed.ncbi.nlm.nih.gov/32532312/

Zhou, Resuscitation, 2020
https://pubmed.ncbi.nlm.nih.gov/32057947/

Peluso, Resuscitation, 2020
https://pubmed.ncbi.nlm.nih.gov/32169607/

Ebner, Scandinavian Journal or Trauma, Resuscitation, and Emergency Medicine, 2020
https://pubmed.ncbi.nlm.nih.gov/32664989/

Diehl, Critical Care Medicine, 2020
https://pubmed.ncbi.nlm.nih.gov/32574466/

Kang, Resuscitation, 2020
https://pubmed.ncbi.nlm.nih.gov/32531406/

Halter, American Journal of Emergency Medicine, 2020
https://pubmed.ncbi.nlm.nih.gov/31303537/

Chang, Critical Care Medicine, 2019
https://pubmed.ncbi.nlm.nih.gov/31356478/

Summary of Evidence Update:

Relevant Guidelines or Systematic Reviews

Author; Year Published	**Guideline or systematic review**	**Topic addressed or PICO(S)T**	**Number of articles identified**	**Key findings**	**Treatment recommendations**
Young; 2020	Systematic review, meta-analysis, and analysis of patient-level data	Comparison of conservative vs liberal oxygen in post-cardiac arrest patients	8 RCTs; patient-level data from 7 RCTs	In analysis of patient-level data, conservative oxygen was associated with reduced mortality at last follow-up compared with liberal oxygen: 90/221 (41%) vs 103/206 (50%); adjusted OR, 0.58; 95%CI, 0.35-0.96; P = 0.04. Secondary outcomes (30, 90, 180-days mortality, and neurological outcome at 180 days) were not different in adjusted analyses (all P >0.05). Findings in aggregate meta-analyses were similar to analyses of patient-level data.	Certainty of evidence low or very low due to bias, imprecision, and indirectness.

RCTs

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
HOT-ICU; Schjørring; 2021	**<u>Study Aim:</u>** Low vs high oxygen targets; 2017-2020;	**<u>Inclusion Criteria:</u>** Age <u>></u>18 years, ICU admission,	**<u>Intervention:</u>** PaO2 60 mmHg **<u>Comparison:</u>** PaO2 90 mmHg	**<u>1° endpoint:</u>** No difference in 90-day mortality between groups:	**<u>Study Limitations:</u>** Subgroup analysis of post-cardiac arrest

	N = 332	FiO2 ≥0.50 or receiving ≥10 L O2/min		96/147 (65%) vs 111/185 (60%); RR, 1.09 (95%CI, 0.92-1.28); RD, 5.58 (95%CI, -4.88-16.05)	

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	**Study Type/Design; Study Size (N)**	**Patient Population**	**Primary Endpoint and Results (include P value; OR or RR; & 95% CI)**	**Summary/Conclusion Comment(s)**
Mckenzie; 2021	**<u>Study Type:</u>** Observational; 2012-2017; N = 491	**<u>Inclusion Criteria:</u>** Age ≥18 years, OHCA, mechanical ventilation upon ICU admission	**<u>1° endpoint:</u>** Survival to hospital discharge: PaO2 <100 vs 100-180 mmHg; adjusted OR, 0.50; 95%CI, 0.30-0.84 PaO2 >180 vs 100-180 mmHg; adjusted OR, 0.41; 95%CI, 0.18-0.92 **<u>2° endpoint:</u>** 12-month survival:	Exposure defined as mean PaO2 within 24 hours of ICU admission. Mild/moderate hyperoxemia was associated with higher survival compared to normoxemia or severe hyperoxemia.

			PaO2 <100 vs 100-180 mmHg; adjusted OR, 0.46; 95%CI, 0.27-0.77 PaO2 >180 vs 100-180 mmHg; adjusted OR, 0.43; 95%CI, 0.19-0.99	
Zhou; 2021	**Study Type:** Observational; 2014-2015; N = 2836	**Inclusion Criteria:** Adult patients, cardiac arrest, index ICU admission	**1° endpoint:** Hospital mortality	The proportion of time spent in SpO2 of ≤89%, 90%, 91%, and 92% during first 24 hours of ICU admission were associated with higher hospital mortality in adjusted analyses.
Humaloja; 2021	**Study Type:** Observational; 2003-2013; N = 3446	**Inclusion Criteria:** Age ≥18 years, cardiac arrest, mechanical ventilation during first 24 hours in ICU	**1° endpoint:** 1-year mortality: PaO2 >18.3 vs 8.2-18.3 kPa; OR, 1.21; 95%CI, 0.76-1.93 PaO2 <8.2 vs 8.2-18.3 kPa; OR, 1.17; 95%CI, 0.86-1.58	Exposure defined as lowest PaO2 within 24 hours of ICU admission. There was no association between hyperoxemia or hypoxemia and mortality as compared to normoxemia.
Young; 2020	**Study Type:** Post-hoc analysis of ICU-ROX; 2015-2018;	**Inclusion Criteria:** Age ≥18 years, less than 2h of invasive or non-invasive ventilation in ICU, OHCA/IHCA, any rhythm	**1° endpoint:** Hospital mortality: Conservative oxygen therapy (SAT 90-97%) vs usual oxygen therapy	Conservative oxygen therapy was not associated with a reduction in in-hospital mortality compared to usual oxygen therapy in post-cardiac arrest.

	N = 166		(SAT >90%); 37/87 (43%) vs 43/79 (54%); adjusted OR, 0.65; 95%CI, 0.30-1.42; P = 0.28	Longer-term outcomes were reported in the original RCT and included in the previous 2020 ILCOR review.
McGuigan; 2020	**Study Type:** Observational; 2011-2018; N = 22,765	**Inclusion Criteria:** Age >16 years, OHCA, survival over 24 hours	**1° endpoint:** Hospital mortality: PaO2/FiO2 <100 vs 300 mmHg; adjusted OR, 1.79; 95%CI, 1.48-2.15; P <0.001 PaO2 <60 vs >100 mmHg; adjusted OR 1.35; 95%CI, 1.10-1.65; P <0.001 PaCO2 <35 vs 36-45 mmHg; adjusted OR, 1.91; 95%CI, 1.63-2.24); P <0.001 PaCO2 >55 vs 36-45 mmHg; adjusted OR 0.40; 95%CI, 0.23-0.70; P = 0.001	PaO2, PaCO2, FiO2 were recorded from the ABG with lowest PaO2 within 24 hours after ICU admission. Low PaO2/FiO2 ratio, hypoxemia, and hypocapnia were associated with higher mortality; Hypercapnia was associated with lower mortality.
Zhou; 2020	**Study Type:** Observational; 2014-2015; N = 2783	**Inclusion Criteria:** Adult patients, cardiac arrest, index ICU admission	**1° endpoint:** Hospital mortality:	PaCO2 defined as time-weighted means within 24 hours of ICU admission.

			PaCO2 <35 vs 35-45 mmHg; adjusted OR, 1.37; 95%CI, 1.12-1.67; P = 0.002 PaCO2 45-55 vs 35-45 mmHg; adjusted OR, 1.08; 95%CI, 0.84-1.38; P = 0.56 PaCO2 >55 vs 35-45 mmHg; adjusted OR, 1.98; 95%CI, 1.43-2.74; P <0.001	PaCO2 had U-shaped association with hospital mortality.
Peluso; 2020	**Study Type:** Observational; 2009-2017; N = 356	**Inclusion Criteria:** Age >18 years, IHCA/OHCA, survival >24 hours	**1° endpoint:** CPC score at 3 months	There were no differences in highest/lowest PaO2/PaCO2, AUC, or times over various thresholds of PaO2/PaCO2 within 24 hours after ICU admission between patients with favorable and unfavorable outcomes (effect estimates not reported).
Ebner; 2020	**Study Type:** Observational; 2008-2018; N = 2135	**Inclusion Criteria:** Age >18 years, GCS <8, OHCA, sustained ROSC	**1° endpoint:** CPC 3-5 at hospital discharge: PaO2 >40 vs 8.0-40 kPa; adjusted OR, 1.33; 95%CI, 0.92-1.92; P = 0.13	PaO2 and PaCO2 measured 7 times per patient within 24 hours after ROSC. Exposure to extreme PaO2 or PaCO2 was not associated with poor neurological outcome in adjusted analyses.

			PaO2 <8.0 vs 8.0-40 kPa; adjusted OR, 1.26; 95%CI, 0.87-1.82; P = 0.22 PaCO2 >6.7 vs 4.0-6.7 kPa; adjusted OR, 0.0.89; 95%CI, 0.64-1.24; P = 0.49 PaCO2 <4.0 vs 4.0-6.7 kPa; adjusted OR, 1.28; 95%CI, 0.90-1.83; P = 0.18	
Kang; 2020	**Study Type:** Observational; 2018-2019; N = 42	**Inclusion Criteria:** Adult patients, OHCA	**1° endpoint:** CPC 3-5 at 3 months: PaCO2 <35.3 vs >43.5 mmHg; 9/10 (90%) vs 3/13 (23%); P <0.01	Exposure defined as time-weighted means within 24 hours after ROSC. Proportion of patients with unfavorable neurological outcome was higher in those with low CO2 compared to high CO2.
Halter; 2020	**Study Type:** Observational; 2011-2017; N = 66	**Inclusion Criteria:** OHCA, ECPR in prehospital or ICU setting	**1° endpoint:** Mortality at 28 days: PaO2 >300 vs 60-300 mmHg; adjusted OR, 1.89; 95%CI, 1.74-2.07	Exposure defined as PaO2 within 30 minutes of ECPR. Hyperoxemia was associated with higher mortality at 28 days compared to normoxemia.
Diehl; 2020	**Study Type:** Observational; 2003-2016;	**Inclusion Criteria:** Age ≥18 years, ECPR	**1° endpoint:** Hospital mortality:	Exposure defined as PaCO2 within 6 hours prior to ECPR

	N = 1590		PaCO2 <30 vs 35-44 mmHg; adjusted OR, 1.12; 95%CI, 0.79-1.59; P = 0.52 PaCO2 30-34 vs 35-44 mmHg; adjusted OR, 1.33; 95%CI, 0.87-2.05; P = 0.19 PaCO2 45-60 vs 35-44 mmHg; adjusted OR, 1.40; 95%CI, 1.01-1.94; P = 0.05 PaCO2 >60 vs 35-44 mmHg; adjusted OR, 2.01; 95%CI, 1.46-2.76; P <0.001	Mild and moderate hypercarbia was associated with higher mortality compared to normocarbia.
Chang; 2019	**<u>Study Type:</u>** Observational; 2000-2014; N = 291	**<u>Inclusion Criteria:</u>** Age <u>></u>18 years, IHCA or OHCA, cardiac cause, ECPR	**<u>1° endpoint:</u>** CPC 1-2 at hospital discharge: PaO2 77-220 vs <77 or >220 mmHg; adjusted OR, 2.29; 95%CI, 1.01-5.22; P = 0.05 Survival to hospital discharge: PaO2 77-220 vs <77 or >220 mmHg; adjusted OR, 2.10; 95%CI, 1.08-4.14; P = 0.03	Exposure defined as first PaO2 within 24 hours after ROSC. PaO2 77-220 mmHg was associated with favorable neurological outcome and survival to hospital discharge.

Reviewer Comments (including whether meet criteria for formal review):

This update includes 1 systematic review, 1 subgroup analysis of an RCT, and 12 observational studies. The studies are limited by risk of bias, the inherent study designs, and heterogeneity in measurements and exposures. These studies are, therefore, unlikely to change the current recommendations. A formal systematic review may be warranted at a later stage when ongoing RCTs are published.

	Approval Date
Evidence Update coordinator	**15 February 2021**
ILCOR board	

***Once approval has been made by Evidence Update coordinator, worksheet will go to ILCOR Board for acknowledgement.**

Reference list

Young, P.J., et al., Conservative or liberal oxygen therapy in adults after cardiac arrest: An individual-level patient data meta-analysis of randomised controlled trials. Resuscitation, 2020. 157: p. 15-22.

Schjørring, O.L., et al., Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure. N Engl J Med, 2021.

Mckenzie, N., et al., Non-linear association between arterial oxygen tension and survival after out-of-hospital cardiac arrest: A multicentre observational study. Resuscitation, 2021. 158: p. 130-138.

Zhou, D.W., et al., The optimal peripheral oxygen saturation may be 95-97% for post-cardiac arrest patients: A retrospective observational study. Am J Emerg Med, 2021. 40: p. 120-126.

Humaloja, J., et al., The Association Between Arterial Oxygen Level and Outcome in Neurocritically Ill Patients is not Affected by Blood Pressure. Neurocrit Care, 2021.

Young, P., et al., Conservative oxygen therapy for mechanically ventilated adults with suspected hypoxic ischaemic encephalopathy. Intensive Care Med, 2020. 46(12): p. 2411-2422.

McGuigan, P.J., et al., The interaction between arterial oxygenation and carbon dioxide and hospital mortality following out of hospital cardiac arrest: a cohort study. Crit Care, 2020. 24(1): p. 336.

Zhou, D., et al., Association between mild hypercapnia and hospital mortality in patients admitted to the intensive care unit after cardiac arrest: A retrospective study. Resuscitation, 2020. 149: p. 30-38.

Peluso, L., et al., Oxygen and carbon dioxide levels in patients after cardiac arrest. Resuscitation, 2020. 150: p. 1-7.

Ebner, F., et al., The association of partial pressures of oxygen and carbon dioxide with neurological outcome after out-of-hospital cardiac arrest: an explorative International Cardiac Arrest Registry 2.0 study. Scand J Trauma Resusc Emerg Med, 2020. 28(1): p. 67.

Diehl, A., et al., Association Between Arterial Carbon Dioxide Tension and Clinical Outcomes in Venoarterial Extracorporeal Membrane Oxygenation. Crit Care Med, 2020. 48(7): p. 977-984.

Kang, C., et al., Impact of low and high partial pressure of carbon dioxide on neuron-specific enolase derived from serum and cerebrospinal fluid in patients who underwent targeted temperature management after out-of-hospital cardiac arrest: A retrospective study. Resuscitation, 2020. 153: p. 79-87.

Halter, M., et al., Association between hyperoxemia and mortality in patients treated by eCPR after out-of-hospital cardiac arrest. Am J Emerg Med, 2020. 38(5): p. 900-905.

Chang, W.T., et al., Optimal Arterial Blood Oxygen Tension in the Early Postresuscitation Phase of Extracorporeal Cardiopulmonary Resuscitation: A 15-Year Retrospective Observational Study. Crit Care Med, 2019. 47(11): p. 1549-1556.

2021 Evidence Update Worksheet

Appendix B2 ALS 10

Neuroprognostication following ROSC (ALS 450, 458, 460, 484, 487, 713: EvUp)

Worksheet author(s): Claudio Sandroni, Sofia Cacciola, Sonia D'Arrigo

Date Submitted: 11 February 2021

PICO / Research Question:

Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.

Interventions: index tests based on clinical examination, electrophysiology, serum biomarkers and neuroimaging recorded within 7 days from return of spontaneous circulation (ROSC)

Comparison: the accuracy of the index test was assessed by comparing the predicted outcome with the final outcome.

Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.

Type (intervention, diagnosis, prognosis): prognosis.

Additional Evidence Reviewer(s): none

Conflicts of Interest (financial/intellectual, specific to this question):

- Sofia Cacciola, Sonia D'Arrigo and Claudio Sandroni are co-authors of a systematic review on predictors of poor neurological outcome in comatose survivors of cardiac arrest (Sandroni 2020 1803-1851).
- Claudio Sandroni is member of editorial board, *Resuscitation*, and associate editor, *Intensive Care Medicine*.

Year of last full review: 2020

Last ILCOR Consensus on Science and Treatment Recommendation: 2020

We recommend that neuroprognostication always be undertaken by using a multimodal approach because no single test has sufficient specificity to eliminate false positives (strong recommendation, very low-certainty evidence).

Clinical examination: We suggest using pupillary light reflex (PLR) at 72 hours or more after ROSC for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence). We suggest using quantitative pupillometry at 72 hours or more after ROSC for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, low-certainty evidence).We suggest using bilateral absence of corneal reflex at 72 hours or more after ROSC for predicting poor neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).We suggest using presence of myoclonus or status myoclonus within 7 days after ROSC, in combination with other tests, for predicting poor neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).We also suggest recording EEG in the presence of myoclonic jerks to detect any associated epileptiform activity (weak recommendation, very low-certainty evidence).

Electrophysiology: We suggest using a bilaterally absent N20 wave of SSEP in combination with other indices to predict poor outcome in adult patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

We suggest against using the absence of EEG background reactivity alone to predict poor outcome in adult patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

We suggest using the presence of seizure activity on EEG in combination with other indices to predict poor outcome in adult patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

We suggest using burst suppression on EEG in combination with other indices to predict poor outcome in adult patients who are comatose and effects of sedation after cardiac arrest have cleared (weak recommendation, very low-certainty evidence).

Serum biomarkers: We suggest using neuron-specific enolase (NSE) within 72 hours after ROSC, in combination with other tests, for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence). There is no consensus on a threshold value. We suggest against using S-100B protein for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, low-certainty evidence). We suggest against using serum levels of glial fibrillary acidic protein, serum tau protein, or neurofilament light chain (Nfl) for predicting poor neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence)

Neuroimaging: We suggest using GWR on brain computed tomography for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence). However, no GWR threshold for 100% specificity can be recommended. We suggest using diffusion-weighted brain MRI for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence). We suggest using ADC on brain MRI for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence)

2010/2015/2020 Search Strategy: (("Heart Arrest"[Mesh]) OR ("Cardiopulmonary Resuscitation"[Mesh]) OR ("Death, Sudden, Cardiac"[Mesh]) OR("Hypoxia-Ischemia, Brain"[Mesh])) AND (("Coma"[Mesh]) AND ("Prognosis"[Mesh])).
2021 Search Strategy: “Cardiac arrest [all fields]” AND “Coma” [all fields] AND “Prognosis” [all fields].

Database searched: PubMed. In addition, the websites of the most relevant Journals and the reference list of relevant papers were searched for additional studies.

Date Search Completed: 10 Feb 2021

Search Results (Number of articles identified / number identified as relevant): 36/10

Inclusion/Exclusion Criteria:

- **Inclusion:** adult (≥16 years); resuscitated from cardiac arrest (either in-hospital or out-of-hospital). Comatose (unconscious, unresponsive, and/or having a Glasgow Coma Score (GCS)≤8 at the time of study enrolment). Predictor assessed within 7 days from CA. We included only studies where sensitivity and FPR could be calculated, i.e., those where the 2×2 contingency table of true/false negatives and positives for prediction of poor outcome was reported or could be calculated from reported data.
- **Exclusion:** Studies including non-comatose patients or patients in hypoxic coma from causes other than cardiac arrest (e.g., respiratory arrest, carbon monoxide intoxication, drowning, and hanging).

Link to Article Titles and Abstracts (if available on PubMed):
https://pubmed.ncbi.nlm.nih.gov/?term=%22Cardiac+arrest+%5Ball+fields%5D%22+AND+%22Coma%22+%5Ball+fields%5D+AND+%22Prognosis%22+%5Ball+fields%5D.&filter=years.2020-2021&size=50

Summary of Evidence Update:
This update identified 10 relevant studies that were not included in the 2020 ILCOR evidence review.

Concerning **clinical examination**, one study (Nakstad 2020 170-179) showed that absence of PLR later than four days after ROSC predicts poor neurological outcome with 100% specificity. A study by Obinata et al. (Obinata 2020 77-84) showed that absence of PLR detected using automated pupillometry within 72h from arrest also predicted poor neurological outcome with 100% specificity, confirming previous results from the ILCOR 2020 evidence review. Unlike the studies included in that review, however, the study from Obinata et al. showed that the most accurate predictor among the parameters of pupillometry was constriction velocity (area under the receiver operating characteristic [AUROC[curve = 0.82) while the values of neurological pupil index (NPi) were not significantly different across outcome groups. Pupillometry had greater sensitivity for prediction of poor neurological outcome at a 100%-specificity threshold than absence of the wave V of the auditory brainstem response (51% vs. 44%).

Concerning **electrophysiology**, a study by Nakstad et al. confirmed that bilateral absence of the N20 SSEP wave after 72h from arrest predicts poor neurological outcome with 100% specificity. A *post-hoc* analysis from Glimmerveen et al of a previous cohort study (Glimmerveen 2020 335) provided a quantitative analysis of SSEPs and showed that a SSEP N20 wave amplitude <0.4 μV within 48–72 h predicted poor neurological outcome with 100% specificity. The same study also showed that a suppressed EEG background or a synchronous EEG pattern on a suppressed background at 12h or 24h from ROSC is accurate for prediction of poor neurological outcome (specificity 100%; sensitivity from 30% to 58%). The definitions of these EEG patterns were consistent with the terminology recommended by the American Society of Clinical Neurophysiology (ACNS) in 2013 (Hirsch 2013 1-27) and recently updated (Hirsch 2021 1-29).

Concerning **biomarkers**, a study by Wihersaari et al (Wihersaari 2021 39-48) confirmed that increased blood levels of Nfl measured at 24h, 48h, and 72h from arrest accurately predicts poor outcome in comatose resuscitated patients (AUROC 0.98 at all time points). In that study, no patients with Nfl blood levels higher than 390 pg/ml at any time point had a good outcome. However, the Nfl thresholds associated with 100% specificity for prediction of poor outcome were lower than those described in the major study included in the 2020 ILCOR evidence review (Moseby-Knappe 2019 64-71). In a study by You et al (You 2019 185-191), NSE measured in the cerebrospinal fluid (CSF) was more accurate for prediction of poor neurological outcome than NSE measured in the blood. Similar results were shown in a study by Son et al. (Son 2020 744). This study also showed that CSF NSE combined with diffusion changes on magnetic resonance imaging (MRI) had better performance in terms of AUC than each individual methods.

Concerning **imaging**, a study by Hirsch et al. (Hirsch 2020 e1684-e1692) assessed the accuracy of a previously identified threshold of apparent diffusion coefficient (ADC), a quantitative measure of diffusion changes on MRI. The study showed that the prespecified threshold of >10% of brain tissue with an ADC <650 $\times 10^{-6}$ mm^2/s predicted poor outcome with a sensitivity of 0.63 [0.42–0.80], a specificity of 0.96[0.77–0.99].

A series of studies (Bongiovanni 2020 963-972; Moseby-Knappe 2020 1852-1862; Scarpino 2021) retrospectively measured the accuracy of the multimodal **combination of predictors** recommended in the 2015 ERC-ESICM guidelines for Post-resuscitation Care (Nolan 2015 2039-2056). This had been assessed for the first time in a previous study by Zhou et al (Zhou 2019 343-350) included in the ILCOR evidence review. Two of these studies (Bongiovanni 2020 963-972; Moseby-Knappe 2020 1852-1862) showed that the ERC-ESICM prognostication algorithm had 100% specificity for poor outcome. The sensitivity of the algorithm was similar (54% and 57%). In the study by Scarpino et al (Scarpino, 2021), the ERC-ESICM algorithm had 7 [1-18]% false positive rate for prediction of poor outcome. However, a strategy consisting of combining ≥2 abnormal test results as a criterion for poor neurological outcome yielded a 0% false positive rate. This supports the current ILCOR recommendation to use multiple predictors for neurologic prognostication. The study by Scarpino et al. also showed that the sensitivity of malignant EEG patterns interpreted according to the 2013 ACNS was higher than that of the EEG patterns recommended in the 2015 ERC-ESICM Guidelines, which were not defined according to ACNS. This result was confirmed by the paper by Moseby-Knappe et al (Moseby-Knappe 2020 1852-1862). The study from Bongiovanni et al (Bongiovanni 2020 963-972) showed that standardized malignant EEG patterns had equal specificity but higher sensitivity than NSE for poor outcome prediction in patients who were not identified by clinical examination or SSEPs in the first step of the ERC-ESICM algorithm. The study by Moseby-Knappe also showed that using a Glasgow Coma Scale motor score (GCS-M)≤3 instead of a GCS-M≤2 as an entry point for the 2015 ERC-ESICM prognostication algorithm increased algorithm sensitivity with no decrease in specificity.

Relevant Guidelines or Systematic Reviews

Organization (if relevant); Author; Year Published	**Guideline or systematic review**	**Topic addressed or PICO(S)T**	**Number of articles identified**	**Key findings**	**Treatment recommendations**
Sandroni C et al., 2020	Systematic review	Same as this Evidence Update	94	Bilaterally absent pupillary or corneal reflexes after day 4 from ROSC, high blood values of neuron-specific enolase from 24 h after ROSC, absent N20 waves of short-latency somatosensory-evoked potentials (SSEPs) or unequivocal seizures on electroencephalogram (EEG) from the day of ROSC, EEG background suppression or burst-suppression from 24 h after ROSC, diffuse cerebral oedema on brain CT from 2 h after ROSC, or reduced diffusion on brain MRI at 2–5 days after ROSC had 0% FPR for poor outcome in most studies. Risk of bias assessed using the QUIPS tool was high for all predictors.	In comatose resuscitated patients, clinical, biochemical, neurophysiological, and radiological tests have a potential to predict poor neurological outcome with no false-positive predictions within the first week after CA. Guidelines should consider the methodological concerns and limited sensitivity for individual modalities.

***Note**: the results of this systematic review largely coincided with these of the ILCOR evidence update 2020 on the same topic. Four additional studies (Hirsch 2020 e1684-e1692, Nakstad 2020 170-179, Son 2020 744, You 2019 185-191) were not present in the ILCOR evidence update, since the relevant literature search was conducted up to December 2019, while for the systematic review the last search was conducted on April 10, 2020.*

RCT: None

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Bongiovanni et al, 2020	**Study Type:** single-center prospective observational study. Four-hundred-eighty-five patients included.	**Inclusion Criteria:** Consecutive, adult, comatose patients after cardiac arrest admitted to the ICU. **Exclusion criteria:** Brain death within 24 h, incomplete data about SSEPs and/or brainstem reflexes, EEG and/or NSE, and outcome.	**1st endpoint:** to quantify the rate of patients remaining with an initial indeterminate outcome at 3 months after applying the 2015 ERC/ESICM guidelines. **Results:** 330/485 (68%) of comatose cardiac arrest patients had an indeterminate prognosis after application of the 2015 ERC/ESICM guidelines. **2nd endpoint**: to evaluate whether specific electroencephalogram (EEG) patterns, based on a standardized analysis, and serum neuron-specific enolase (NSE) levels, can be used to reduce prognostic uncertainty in this patient population. **Results:** the absence of a highly malignant EEG by day 3 had 99.5 [97.4–99.9]% sensitivity for good recovery, which was superior to NSE < 33	In the majority of comatose CA patients, the outcome remains indeterminate after application of ERC/ESICM prognostication algorithm. Standardized EEG analysis allows accurate prediction of good and poor recovery, thereby reducing early prognostic uncertainty.

			μg/L (84.9 [79.3–89.4]% when used alone; 84.4 [78.8–89]% when combined with EEG, both $p < 0.001$). Highly malignant EEG had equal specificity (99.5 [97.4–99.9] %) but higher sensitivity than NSE for poor recovery.	
Glimmerveen et al, 2020	**Study Type:** *post hoc* analysis of a multicenter prospective cohort study. One-hundred-thirty-eight patients included.	**Inclusion Criteria:** Consecutive, adult, comatose patients after cardiac arrest (Glasgow Coma Scale score ≤ 8), admitted to the ICU. **Exclusion criteria:** concomitant acute stroke, traumatic brain injury, preexisting dependency in daily life, or progressive neurodegenerative disease.	**1st endpoint:** to analyze the association between SSEP amplitude and neurological outcome (CPC 3-5) at 6 months. **Results:** SSEP N20 wave amplitude <0.4 μV within 48–72 h predicted poor neurological outcome with 100% specificity.	Absent SSEP response, a N20 wave amplitude <0.4 μV within 48–72 h, and suppressed or synchronous EEG with suppressed background at 12 or 24 h after CA were associated with a poor outcome with 100% specificity. Combined, these tests reached a sensitivity for prediction of poor outcome up to 58 at 100% specificity.
Hirsch et al, 2020	**Study Type:** Prospective, clinician-blinded. Fifty-	**Inclusion Criteria:** Consecutive comatose post-cardiac arrest adult (≥18 y) patients who	**1st endpoint:** to determine whether the previously identified threshold of having >10% of brain tissue with an ADC value <650 $\times 10^{-6}$ mm^2/s identified patients with poor outcome (GOS 1-2) at 6 months.	An ADC <650 ×10−6 mm2/s in >10% of brain tissue in an MRI obtained by post arrest day 7 is highly specific for poor

	one patients included.	underwent MRI within 7 days after CA. **Exclusion criteria**: preexisting “do not resuscitate” status, prearrest modified Rankin Scale score ≥3, severe coexisting or terminal disease that would be expected to interfere with long-term outcome assessments, pregnancy, brain death determined before MRI.	**Results:** the prespecified threshold of >10% of brain tissue with an ADC <650 ×10-6 mm2/s predicted poor outcome with a sensitivity of 0.63 [0.42–0.80], a specificity of 0.96[0.77–0.99], and a positive predictive value (PPV) of 0.94[0.71–0.997].	outcome in comatose patients after cardiac arrest.
Moseby-Knappe et al, 2020	**Study Type:** Retrospective descriptive analysis with data from the Target Temperature Management	**Inclusion Criteria:** Adult comatose patients after out-of-hospital cardiac arrest. **Exclusion criteria:**	**1st endpoint:** to assess the performance of the 2015 ERC/ESICM algorithm to predict poor neurological outcome (CPC 3-5) at 6 months. **Results:** the ERC/ESICM algorithm identified poor outcome patients with 54% sensitivity and 100% specificity, and patients who were not	All exploratory multimodal variations thereof investigated in this study predicted poor outcome without false positive predictions. Despite explorative versions to simplify the algorithm

	(TTM) Trial, in a cohort of 585 patients.	Residual sedation and muscle-relaxants, presence of flexor or better motor response (GCS-M), no outcome, missing data.	identified often had a non-neurological presumed cause of death. **2nd endpoint**: to identify strengths and weaknesses of the current algorithm, using an alternative cut-off for serum neuron-specific enolase, an alternative EEG-classification and variations of the GCS-M (GCS-M≤3 instead of a GCS-M≤2). **Results**: the use of exploratory variations as an entry point for the 2015 ERC-ESICM prognostication algorithm increased algorithm sensitivity with no decrease in specificity.	also correctly predicted poor outcome with 100% specificity, these results should be validated, preferably in patients where withdrawal of life-sustaining therapy is uncommon, to reduce the risk of self-fulfilling prophecies.
Nakstad et al, 2020	**Study Type:** Prospective, observational. Two hundred and fifty-nine patients included.	**Inclusion Criteria:** adult (>18 years) comatose (GCS <9) OHCA patients of cardiac and non-cardiac causes with stable ROSC (>20 min). **Exclusion criteria:** OHCA following trauma/acute onset intra-cerebral	**1st endpoint:** to assess the ability of currently recommended diagnostic tools (clinical, neurophysiological, and biochemical) to identify patients with a poor prognosis (CPC 3-5) at 6 months. **Results:** the absence of PLR and N20 wave SSEPs as well as an increased serum NSE values later than 24 h to >80ng/ml predicted poor neurological outcome with 100% specificity. A GCS-M 1-3 had 73% specificity. Malignant EEG (BS/epileptic activity/flat) predicted poor neurological outcome with 95% specificity.	The absence of pupillary light reflex (PLR) later than four days after ROSC and the bilaterally absent N20 SSEP wave after 72h from cardiac arrest predicted poor neurological outcome with 100% specificity.

		pathology, CPR <5 min followed by spontaneous awakening, admission >6h after OHCA, and treatment withdrawal in the emergency room.		
Obinata et al, 2020	**<u>Study Type:</u>** Retrospective, observational. One hundred twenty-four patients included.	**<u>Inclusion Criteria:</u>** Adult comatose patients after cardiac arrest. **<u>Exclusion criteria:</u>** age <18 y; known factors that interfered with AIP or ABR assessments (cataracts, cerebrovascular disease, had injuries, or drug intoxication).	**<u>1st endpoint:</u>** to assess the ability of Automated Infrared Pupillometry (AIP) and auditory brainstem response (ABR), recorded simultaneously at ≤72h to predict CPC 3-5 at discharge. **<u>Results:</u>** the absence of PLR (AIP) had 51% sensitivity and 100% specificity to predict poor neurological outcome, while absence of ABR V wave had 44% sensitivity and 100% specificity.	AIP was significantly superior as compared with ABR (pupil constriction velocity AUC 0.819 vs. ABR AUC 0.560). NPi did not differ among outcome groups.
Scarpino et al, 2021	**<u>Study Type:</u>** secondary analysis of	**<u>Inclusion Criteria:</u>** consecutive comatose adult	**<u>1st endpoint:</u>** to compare the sensitivity and specificity for predicting poor neurological outcome (CPC 3-5) at 6 months of the stepwise	In this study the ERC-ESICM algorithm had 7 [1-18]% false positive rate for

	data from the ProNeCA prospective multicentre study. Two hundred and ten patients included.	patients admitted to the ICUs following resuscitation from cardiac arrest. **<u>Exclusion criteria</u>:** traumatic/surgical cause of arrest, pre-arrest neurological disability, a life expectancy shorter than six months, and brain death.	approach recommended in the 2015 ERC/ESICM prognostication algorithm vs. a prognostic strategy combining at least 2 abnormal results of any of the tests recommended in the algorithm without distinguishing between first-line and second-line predictors. **<u>Results:</u>** The ERC-ESICM prognostication algorithm had 63[56-71]% sensitivity and 7[1-18]% FPR for predicting poor neurological outcome. A ≥2 abnormal test strategy had lower sensitivity 49[41-57] but 0[0-8]% FPR. **<u>2nd endpoint:</u>** to investigate if the prognostic accuracy of EEG and SSEPs could be improved by using more recent classifications to define the abnormality of these tests. **<u>Results:</u>** using an ACNS-based EEG classification increased EEG sensitivity from 14 [9-20]% when using the ERC-ESICM criteria to 49[39-55]%. The same occurred for SSEP using an absent/low voltage criterion for abnormality vs. the ERC-ESICM criterion (52 [44-60]% vs. 43 [36-51]% respectively).	prediction of poor outcome. However, a strategy consisting of combining ≥2 abnormal test results as a criterion for poor neurological outcome yielded a 0% false positive rate. The study also showed that the sensitivity of malignant EEG patterns interpreted according to the ACNS 2013 terminology (Hirsch, 2013) was higher than that of the EEG patterns recommended in the 2015 ERC-ESICM Guidelines.
Son et al, 2020	**<u>Study Type:</u>** retrospective analysis of	**<u>Inclusion Criteria:</u>** adult comatose	**<u>1st endpoint:</u>** to investigate if combining CSF NSE levels and MRI immediately after ROSC may	Combining CSF/serum NSE levels and HSI in DWI before TTM improved the

	prospectively collected data. Fifty-eight patients included.	OHCA survivors treated with TTM. **Exclusion criteria**: <18 years; traumatic CA; interrupted TTM; patients not eligible for TTM; extracorporeal membrane oxygenation; and patients ineligible for lumbar puncture.	better predict CPC 3-5 at 6 months in TTM-treated patients than any single analysis. **Results:** CSF NSE levels showed better prognostic performance than serum NSE levels (AUC 0.873 vs. 0.792). Combining CSF NSE levels and High Signal Intensity (HIS) in DWI had better prognostic performance (AUC 0.925) than each individual methods. The combination between serum NSE levels and HSI on DWI had AUC 0.901.	prognostic performance compared to either each individual method or other combinations.
Wihersaari et al, 2021	**Study Type:** prospective, randomised pilot study of 120 patients.	**Inclusion Criteria:** adult comatose OHCA patients resuscitated from an initial shockable rhythm, treated with TTM. **Exclusion criteria:** no blood samples available.	**1st endpoint:** to assess the ability of plasma NfL to predict outcome (CPC 1-2 vs. 3-5) at 6 months. **Results:** Forty-eight hours after OHCA, the median [IQR] NfL concentration was significantly lower in patients with good outcome vs. poor outcome (19 [11–31] pg/ml vs. 2343 [587–5829] pg/ml, $p < 0.001$). NfL predicted poor outcome with an area under the receiver operating characteristic curve (AUROC) of 0.98 at 24, 48 and 72h.	Compared to NSE, NfL seems to be a more accurate biomarker for prognostication after CA, and if validated in further samples, it has potential to replace NSE in the multimodal prognostication algorithms.

You et al, 2019	**<u>Study Type:</u>** single-centre, prospective, observational. Thirty-four patients included.	**<u>Inclusion Criteria:</u>** adult comatose OHCA survivors treated with TTM. **<u>Exclusion criteria:</u>** traumatic CA; ineligible for lumbar puncture (LP); extracorporeal membrane oxygenation; responsible relatives from the patient's family unable to consent to an LP, and; the provision of further patient treatment declined by the next of kin.	**<u>1st endpoint:</u>** to investigate the prognostic performance between serum NSE and CSF NSE for 6-month poor neurologic outcome (CPC 3-5) in OHCA survivors who had undergone TTM. **<u>Results:</u>** CSF NSE values showed better performance than serum NSE at any time investigated (day 0, 1, 2, 3) with 100% specificity. The best predictive value (81.3% sensitivity and 100% specificity) for serum NSE was found at day 2 with a cut-off of 54.6 ng/ml.	NSE measured in the cerebrospinal fluid (CSF) was more accurate for prediction of poor neurological outcome than NSE measured in the blood.

Reviewer Comments (including whether meet criteria for formal review):

The ten studies included in this evidence update largely confirmed the results of both the ILCOR 2020 evidence review and the 2020 systematic review. The evidence found does not justify a new systematic review at present. We did not find any evidence that would suggest a need to change the 2020 ILCOR recommendations.

	Approval Date
Evidence Update coordinator	**15 February 2021**
ILCOR board	

***Once approval has been made by Evidence Update coordinator, worksheet will go to ILCOR Board for acknowledgement.**

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