Original citation:
Kleinman, Monica E., Perkins, Gavin D., Bhanji, Farhan, Billi, John E., Bray, Janet E., Callaway, Clifton W., de Caen, Allan, Finn, Judith C., Hazinski, Mary Fran, Lim, Swee Han, Maconochie, Ian, Nadkarni, Vinay, Neumar, Robert W., Nikolaou, Nikolaos, Nolan, Jerry P., Reis, Amelia, Sierra, Alfredo F., Singletary, Eunice M., Soar, Jasmeet, Stanton, David, Travers, Andrew, Welsford, Michelle and Zideman, David (2018) ILCOR Scientific knowledge gaps and clinical research priorities for cardiopulmonary resuscitation and emergency cardiovascular care : a consensus statement. Circulation . CIR.0000000000000561.
doi:10.1161/CIR.0000000000000561

Knowledge Gaps in Resuscitation Science Identified During and After the 2015 International Liaison Committee on Resuscitation Evidence Evaluation Process: A Consensus Statement

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Abstract

Despite significant advances in the field of resuscitation science, important knowledge gaps persist. Current guidelines for resuscitation are based on the International Liaison Committee on Resuscitation (ILCOR) 2015 Consensus on Science, which includes treatment recommendations supported by the available evidence. The writing group developed this consensus statement with the goal of focusing future research by addressing the knowledge gaps identified during and after the 2015 ILCOR evidence evaluation process. Key publications since the 2015 Consensus on Science are referenced, along with known ongoing clinical trials that are likely to impact future guidelines.

[h1]Introduction

Since 1992, when the International Liaison Committee on Resuscitation (ILCOR) was created, resuscitation experts from around the world have regularly convened to evaluate the existing evidence, achieve consensus on science, and, when appropriate, provide treatment recommendations for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care. Between 2012 and 2015, the 7 ILCOR Task Forces identified 165 resuscitation-related questions by using the PICO (population, intervention, comparator, outcome) format.[1] Topic experts performed systematic reviews based on a formal search of the published literature,[2] and the strength of recommendation and quality of evidence were reported by using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology and the GRADE Guideline Development Tool.[3] A standardized evidence-to-recommendation framework was used to guide the Task Forces when writing treatment recommendations.[4]

The *2015 International Consensus on CPR and Emergency Cardiovascular Care Science With Treatment Recommendations* (CoSTR) publication was a focused update of key topics and, as with prior evidence review cycles, was notable for the limited number of treatment recommendations supported by high-quality science.[5,6] To promote transparency, each systematic review was accompanied by a list of knowledge gaps identified by the Task Forces as they wrote treatment recommendations that were frequently qualified as “weak” on the basis of “low-quality evidence.” When there was insufficient or conflicting evidence that prohibited formulation of a treatment recommendation, the following language was used: “The confidence in effect estimates is so low that the panel feels a recommendation to change current practice is too speculative." The 7 ILCOR member resuscitation councils used the resultant CoSTR to develop council-specific, evidence-based resuscitation guidelines and educational materials.

The objective of this Consensus Statement is to provide the resuscitation science community with a focused account of knowledge gaps identified during and after the 2015 ILCOR evidence evaluation process. Each major content area (Basic Life Support [BLS]; Advanced Life Support [ALS]; Pediatric Life Support; Education, Implementation, and Teams; and First Aid) includes a synopsis of recent data and a summary of current evidence to characterize the existing state of the field. The writing group members recognize that this statement does not exhaustively review the scientific literature since publication of the October 2015 CoSTR, nor does it include every knowledge gap listed, because prioritization by the Task Force members led to the exclusion of some gaps in favor of others. Efforts were made to reference sentinel papers and high-quality investigations in progress (eg, randomized controlled trials [RCTs]).

The statement's writing group members were selected from the ILCOR Task Forces involved in the 2015 evidence evaluation and consensus on science processes. We sought to achieve representation from each of the 7 member councils and included experts from the ILCOR steering committee as well as individuals involved in managing conflict of interest. The writing group was asked to query the remaining Task Force members, and, with the use of a survey process, specific gaps were rated in terms of *impact* and *priority*, reflecting the potential to save lives or years of life, and *feasibility*, indicating the potential to design a study to answer the specific question. The figure represents the selected knowledge gaps as they correspond to the links in the Chain of Survival, reflecting a wide range of opportunities to answer critical questions. It is our hope that directing research efforts toward areas of high priority and impact will drive future progress in resuscitation outcomes.

[h1]Scope of the Problem

Data from the World Health Organization show that ischemic heart disease remains the leading single cause of mortality worldwide, accounting for approximately 13% of all deaths. In 2008, this equated to an estimated 17.3 million lives lost.[7] In Europe alone, there are an estimated 4.1 million deaths from cardiovascular disease annually.[8]

Global estimates of the incidence of out-of-hospital cardiac arrest (OHCA) show marked variation between countries, making the total number of cardiac arrests worldwide difficult to quantify.[9] According to the Resuscitation Outcomes Consortium (ROC) Epistry, approximately 347 000 adults in the United States experienced emergency medical services (EMS)–assessed OHCA in 2015; of the approximately 52% who were treated by EMS, the survival rate to hospital discharge was 11.4%.[10,11] In the Cardiac Arrest Reporting to Enhance Survival (CARES) Registry, among EMS-treated adults with nontraumatic OHCA, the survival rate to hospital discharge was 10.6% and the survival with favorable neurologic outcome was 8.6%.[10] This equates to an estimated US annual loss of 311 000 lives and 3.3 million life-years.[12] In England, 2014 data indicated there were 28 729 EMS-treated cardiac arrests (53 per 100 000 population), and the survival to hospital discharge rate was 7.9%.[13] In Japan, a nationwide OHCA registry is used to track the incidence of cardiac arrest. During calendar years 2005 to

2009, there were 547 143 episodes of OHCA recorded, with the annual incidence rate increasing from 80.7 to 90.4 per 100 000 population during the study period.[14]

Adult in-hospital cardiac arrest (IHCA) rates and outcomes vary widely, and estimates are based on limited data from voluntary registries. In the United States, data from the American Heart Association (AHA) Get With The Guidelines®-Resuscitation program estimated 209 000 hospitalized adults are treated for cardiac arrest annually, with a survival rate of 24.8%.[15] The United Kingdom National Cardiac Arrest Audit found an incidence of IHCA of 1.5 per 1000 admissions across 144 acute-care hospitals, with an unadjusted survival rate of 18.4%.[16]

[h1]BLS and Automated External Defibrillators

Accurate recognition of cardiac arrest, prompt initiation of high-quality CPR, early defibrillation, and rapid activation of EMS are key interventions associated with improved outcome from adult cardiac arrest.[17-25] The 2015 Consensus on Science considered several topics related to the role of emergency dispatchers to improve recognition of, and bystander response to, OHCA. Given the global burden of lives lost and years of life lost from cardiac arrest, studies to address the knowledge gaps associated with cardiac arrest recognition, dispatch-assisted CPR, and public access defibrillation programs are considered to be of high impact and priority and are quite feasible.

[h2]Training/Protocols for Dispatcher-Assisted Recognition of Cardiac Arrest and Interventions to Promote Bystander CPR

Bystander CPR improves survival rates by 2- to 4-fold.[19-22,25] The 2015 Consensus on Science noted a strong association between telephone-assisted CPR instruction and the provision of bystander CPR.[26,27] Specifically, unconsciousness and abnormal (agonal) breathing are the key diagnostic features to enable dispatchers to recognize cardiac arrest. Enhancing dispatcher recognition of cardiac arrest is likely to be one of the most cost-effective solutions to improving survival. Dispatcher training and protocol configuration can assist with cardiac arrest recognition, but further research is required to define the optimal system and processes. Specific knowledge gaps include the influence of a dispatcher's background (clinical/nonclinical), the impact of and solutions to language barriers, and optimal questions/instructional sequence to provide to callers. Future studies should report the diagnostic performance characteristics (eg, sensitivity, specificity), time to key events (recognition of cardiac arrest, initiation of bystander CPR, time of first responder/EMS arrival), and relevant clinical outcomes (survival to hospital discharge and favorable neurologic outcome).

[h2]Conventional vs Compression-Only CPR During Dispatch-Assisted CPR

The 2015 Consensus on Science recommends that dispatchers provide direction for chest compression–only CPR for adults with suspected OHCA.[26,27] These recommendations were drawn largely from randomized and observational studies of adults with cardiac arrest from a presumed *cardiac* cause. A recent systematic review supported that use of telephone-assisted continuous chest compressions by bystanders, compared with interruption of compressions for rescue breathing, improved survival to discharge for nonasphyxial OHCA.[28] The 2015 CoSTR noted a paucity of evidence on the most effective strategy (conventional or compression-only CPR by bystanders) when the cause of arrest is believed to be noncardiac. Specific knowledge gaps include the optimal dispatch-assisted CPR recommendations for OHCA victims (compression-only or conventional CPR) and, if conventional CPR is to be given, the optimal instruction sequence for coaching callers. If conventional CPR is advised, the number of chest compressions to provide before ventilations are introduced also needs to be determined.

[h2]System Configuration for Public Access Defibrillation and Automated External Defibrillator Program Characteristics

Defibrillation within the first few minutes after cardiac arrest can lead to survival rates of 50% to 70%.[22] Systems enabling the public to have access to defibrillation have been developed and are associated with improved survival.[23] Training first responders (volunteers, police, fire services) to use an automated external defibrillator (AED) can also reduce time to defibrillation and positively impact survival.[24,25] While evidence supports the clinical effectiveness of these approaches, there is relatively little evidence informing the optimal system configuration or the most cost-effective approach. Specific knowledge gaps include effect of strategies to improve public access defibrillation usage and where best to place AEDs for public access. The role of digital/social media tools and applications to enhance volunteers' and first responders' ability to deliver timely defibrillation appear promising and warrant further evaluation.[29,30]

[h2]CPR Quality

High-quality chest compressions are associated with better patient outcomes. Evidence from observational studies supported the 2015 CoSTR recommendations on optimal chest compression depth and rate, minimizing interruptions in chest compressions, and avoidance of leaning.[26,27] The various components of chest compressions were noted, however, to be interrelated. For example, faster chest compression rates are associated with lower chest compression depth and greater leaning.[31] Further research is needed to identify which of the individual components of chest compressions should be prioritized when delivering CPR. At present, CPR feedback and prompt devices, which measure the quality of CPR delivered, are the most frequently used systems.[32] Some studies have suggested that optimizing CPR to achieve specific physiologic endpoints such as diastolic blood pressure, end-tidal carbon dioxide ($ETCO_2$), or cerebral oximetry may be beneficial.[33-35] These studies highlight a key knowledge gap—identifying the best target(s) for optimizing CPR performance.

[h1]Advanced Life Support

The success of ALS interventions is dependent on the early recognition of cardiac arrest and use of BLS/AED treatments for cardiac arrest. ALS interventions that interfere with provision of high-quality chest compressions may reduce the likelihood of return of spontaneous circulation (ROSC). Postresuscitation care is increasingly recognized as a critical factor in outcome for patients achieving ROSC after cardiac arrest.

[h2]Tracheal Intubation During CPR

The 2015 Consensus on Science recommended use of bag-mask ventilations, a supraglottic airway, or an advanced airway for initial airway management during CPR and noted that selection and efficacy of an airway intervention depends on rescuer skills.[36,37] The role of tracheal intubation during CPR for both IHCA and OHCA remains uncertain with the possibility of both benefit and harm. A recent retrospective review from the Get With The Guidelines-Resuscitation registry found that for IHCA, tracheal intubation anytime during the first 15 minutes of resuscitation, compared with no intubation during that minute, was associated with decreased survival to hospital discharge.[38] In contrast, another large retrospective series showed an inverse relationship between time to intubation during IHCA and survival to discharge and favorable neurologic outcome.[39] Specific knowledge gaps include the type and duration of training required for performing advanced airway management during CPR.

Because most patients receive more than 1 type of airway intervention during CPR, the study of the effect of tracheal intubation on outcome is difficult.[40] Two large RCTs are in progress to compare tracheal intubation with supraglottic airway devices during OHCA and should further inform our understanding of the role of an advanced airway during CPR.[41,42] The 2 trials use different devices and end points: AIRWAYS-2 (ISRCTN08256118), being conducted in the United Kingdom, is using the i-gel supraglottic airway and modified Rankin Scale score at hospital discharge, while the Pragmatic Airway Resuscitation Trial (PART) (NCT02419573), in progress in North America, is using the laryngeal tube and 72-hour survival.

[h2]Vasopressors During Cardiac Arrest

For many decades, the injection of epinephrine for cardiac arrest has been considered a standard of care during ALS. Given the limitations of observational studies and, therefore, uncertainty about the benefit or harm with regard to long-term survival, the 2015 Consensus on Science suggested that epinephrine continue to be administered to patients in cardiac arrest by using existing dosing and timing strategies.[36,37]

It is important to note that there have been no placebo-controlled prospective trials with adequate power to assess the effect of epinephrine on long-term outcome after cardiac arrest. An underpowered RCT of epinephrine vs placebo for OHCA documented a higher rate of ROSC without improving survival to discharge or neurologic outcome,[43] but in a meta-analysis of large observational studies, epinephrine has been associated with no change in survival to discharge and worse long-term neurologic outcomes even though ROSC rates were higher.[44] In a propensity-matched analysis of the Get With The Guidelines-Resuscitation registry published since the 2015 Consensus on Science, the administration of epinephrine within the first 2 minutes after the first defibrillation to patients with IHCA and an initially shockable rhythm was associated with decreased odds of survival (odds ratio, 0.70; 95% confidence interval, 0.59–0.82; $P<0.001$).[45] In contrast, a recent retrospective review of multiple databases suggested that decreased time to vasopressor administration was associated with favorable neurologic outcome.[46]

In addition to the ongoing question of epinephrine's benefit, specific knowledge gaps include the dose and timing of epinephrine administration during cardiac arrest. An ongoing randomized study of epinephrine (adrenaline) vs placebo for OHCA in the United Kingdom (Pre-hospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug administration In Cardiac arrest [PARAMEDIC-2]: The Adrenaline Trial, ISRCTN73485024)[47] will further our understanding of the role of epinephrine in outcome from cardiac arrest. Until high-quality, well-powered trials are completed comparing epinephrine with placebo, studies of dose response and timing of epinephrine are of lower priority except as a third arm embedded in an epinephrine-vs-placebo trial.

[h2]Physiologic Targets During Post–Cardiac Arrest Care

Approximately 60% of adult patients admitted to an intensive care unit (ICU) after either OHCA or IHCA die before hospital discharge.[48-50] Reducing post–cardiac arrest hospital mortality to 50% would save 1 additional life for every 10 patients admitted to an ICU after resuscitation from cardiac arrest. Improving the neurologic outcome of those who survive is also a key metric of success.

When considering the 2015 Consensus on Science recommendations related to physiologic targets during post–cardiac arrest care,[36,37] there are multiple knowledge gaps related to what deviations from normal or baseline physiologic values are harmful or, perhaps, protective in post–cardiac arrest patients, and what is the timing, magnitude, and duration of these deviations that impact outcome. Specific parameters that have been most widely studied include mean arterial pressure, partial pressure of oxygen and carbon dioxide in arterial blood (Pa_{O_2} and Pa_{CO_2}), central venous oxygen saturation (Scv_{O_2}), temperature, and serum glucose. With the exception of temperature, values significantly below and above the normal range have been associated with worse outcomes in retrospective observational studies, but prospective clinical trials comparing specific target ranges have been underpowered or are yet to be completed. In contrast, the currently recommended target temperature range of 32°C to 36°C for comatose adult cardiac arrest survivors is based on prospective randomized clinical trials demonstrating improved outcomes compared with no temperature control.[51,52] However, a follow-up trial detected no difference in outcomes with a target temperature of 33°C vs 36°C, although the time to reach target temperature was not reported.[53] A recent ILCOR advisory statement incorporated these findings as an update to the systematic review performed for the 2015 CoSTR recommendations.[54]

There is ongoing interest to determine if targeted temperature management (TTM) provides equivalent outcomes to a strategy of "controlled normothermia" with strict avoidance of fever. The TTM2 study (NCT02908308), a follow-up to the TTM study comparing 33°C to 36°C targets,[53] will be an international, multicenter, parallel-group, noncommercial, randomized, superiority trial in which a target temperature of 33°C will be compared with standard care with early treatment of fever (37.8°C or greater) for adults who remain unconscious after cardiac arrest.[55] Likewise, the optimal target temperature for postarrest management is being evaluated by the Finding the Optimal Cooling tempeRature After Out-of-HoSpiTal Cardiac Arrest (FROST) study, comparing target temperatures of 32°C, 33°C, and 34°C after ROSC for adults with OHCA and initial shockable rhythm.[56]

It is challenging to design a prospective clinical trial examining a goal-directed strategy that optimizes only 1 physiologic parameter. One study currently under way in Belgium is the Neuroprotective Goal Directed Hemodynamic Optimization in Post-cardiac Arrest Patients (NEUROPROTECT) trial (NCT02541591).[57] NEUROPROTECT is an adult prospective randomized study comparing a hemodynamic optimization strategy that includes mean arterial pressure 85 to 100 mm Hg and Scv_{O_2} of 65% to 75% to a control group with a mean arterial pressure goal of greater than 65 mm Hg and no Scv_{O_2} goal.

Many experts believe the most successful approach will be a personalized precision strategy that individually optimizes each patient's key physiologic parameters based on prearrest status, severity of injury, response to injury, and response to therapeutic interventions. However, which physiologic parameters are the most significant, as well as the time frame within which optimization is beneficial, remain to be determined. Moreover, more sophisticated monitoring modalities may be required, such as comparison between cerebral oxygen delivery and demand in real time at the bedside. The other significant challenge to this line of investigation is delays in physiologic optimization during early (pre-ICU) post–cardiac arrest care when monitoring capabilities are limited. However, if successful, the impact of optimizing immediate post–cardiac arrest physiology could be significant.

[h2]Emergency Angiography in Comatose Patients After ROSC

There have been numerous observational studies showing the consistent benefit of emergency angiography and primary percutaneous coronary intervention in comatose patients with ST-segment elevation myocardial infarction who have achieved ROSC, and a meta-analysis supporting use for patients with a mixed etiology of OHCA.[58] The most recent systematic review completed as part of the 2015 Consensus on Science also confirmed the benefit found in post-ROSC non‒ST-segment elevation patients, but the studies were not consistent or explicit in the criteria for patient selection.[59,60] The evidence for those patients with non‒ST-segment elevation on postarrest electrocardiogram (ECG) is more limited, and the decision to undertake emergent catheterization was infrequently documented, but it was commonly made at the discretion of the treating team. A number of factors could have influenced the decision, including age, duration of CPR, hemodynamic instability, presenting cardiac rhythm, neurologic status upon hospital arrival, and perceived likelihood of cardiac etiology.

Specific knowledge gaps include determination of which subgroups of patients with non‒ST-segment elevation are the most likely to benefit and which patients may not benefit at all. While there are no published randomized studies on emergency angiography and primary percutaneous coronary intervention after ROSC, multiple prospective trials are in progress. The Coronary Angiography After Cardiac Arrest (COACT) study currently in progress in the Netherlands is a prospective randomized study of immediate vs delayed coronary angiography for post-ROSC patients with non‒ST-segment elevation, with a primary outcome of 90-day survival.[61] The Pilot Randomized Clinical Trial of Early Coronary Angiography Versus No Early Coronary Angiography for Post-Cardiac Arrest Patients Without ECG ST Segment Elevation (PEARL) trial is a US multicenter study that will assess the safety and efficacy of early (less than 120 minutes) angiography in adults with suspected cardiac etiology of cardiac arrest and without ST-segment elevation on ECG after ROSC.[62] In Germany, the Immediate Unselected Coronary Angiography Versus Delayed Triage in Survivors of Out-of-hospital Cardiac Arrest Without ST-segment Elevation (TOMAHAWK) study will also address the timing of angiography, with a primary outcome of 30-day survival.[63] The Scandinavian Direct or Subacute Coronary Angiography for Out-of-Hospital Cardiac Arrest (DISCO) trial will compare the safety and efficacy of these 2 approaches.[64] The study called A Randomised tRial of Expedited transfer to a cardiac arrest center for non-ST elevation ventricular fibrillation out-of-hospital cardiac arrest (ARREST) will explore the effectiveness of transfer to a cardiac arrest center and immediate PCI in patients without ST-segment elevation on postarrest ECG.[65] The National Institutes of Health–funded ACCESS trial will compare early cardiac catheterization and treatment for patients with ventricular fibrillation/ventricular tachycardia OHCA with cardiac catheterization lab activation only after ICU admission and consideration by the cardiology and treatment teams.[66] These studies will help to determine if emergency angiography should be performed in all comatose patients after ROSC or whether there should be clearer criteria for selection.

[h2]Neuroprognostication in Comatose Survivors of Cardiac Arrest

Determining the prognosis for recovery for patients after cardiac arrest is important for planning and coordinating postresuscitation care. In some settings, life-sustaining treatments are limited when the treating team believes favorable functional recovery is not possible[67]; the use of postarrest hypothermia added another layer of complexity.[68,69] The 2015 Consensus on Science identified multiple methods of patient assessment for estimating prognosis: clinical examination, neurophysiologic studies, blood biomarkers, and imaging studies.[36,37] There were specific knowledge gaps regarding prognostic tests as well as global concerns related to the design of prognosis studies. First, understanding how sedative drugs and neuromuscular blocking drugs alter prognostic testing requires prospective studies on drug pharmacokinetics in post–cardiac arrest patients, especially those treated with temperatures below normal.[70] Next, studies are needed to investigate the reproducibility of clinical signs and inter-rater reliability of tests and examinations used to predict outcome in comatose postarrest patients.[71] Finally, blood tests have used a variety of laboratory standards and techniques, making comparisons between studies difficult. Studies to standardize handling and assays are needed.[72]

Future studies of prognostic testing should eliminate some of the design limitations of prior studies. In most prognostication studies, treating teams were not blinded to the results of tests, and the results were used as a criterion for limitation or suspension of life-sustaining treatment. This lack of blinding may bias results toward overestimating the accuracy of tests for predicting poor outcomes or death ("self-fulfilling prophecy"). Many studies of computed tomography (CT) and magnetic resonance imaging (MRI) included very selected populations who were referred for imaging. Prospective studies in unselected patient cohorts resuscitated from cardiac arrest are needed to determine the actual prognostic accuracy of imaging studies. Most studies examined the performance of a single variable for predicting prognosis, but clinical practice uses multiple modalities to assess an individual patient.[73] More studies are needed on the accuracy and predictive value of prognostic tests when used in combination.[74] Similarly, studies to determine the incremental value of a given test, when other data about the patient are already known, would help clinicians design the most efficient evaluation rather than performing every test on every patient.[75] Many tests provide complex results, and the criterion for an “abnormal” or “poor” result varies widely between studies. For example, definitions of reactive and nonreactive electroencephalogram (EEG)-based predictors are inconsistent among prognostication studies. Standardized reporting of EEG, MRI, and CT scan data would improve the ability to compare cohorts.[76,77]

[h1]Pediatric Life Support

The global incidence of pediatric cardiac arrest is unknown; however, the premature death of a child leads to a greater proportion of life-years lost compared with an adult. The World Health Organization’s Global Health Observatory data estimated that 5.9 million children under the age of 5 died in calendar year 2015.[78] While primary heart disease is an uncommon cause of death in children, cardiac arrest represents the final common pathway for mortality from infection, trauma, and congenital anomalies.

Data from the ROC Epistry and the CARES registry estimate that 7000 children (aged 1–18 years) experience EMS-assessed nontraumatic OHCA per year in North America.[10] Of the 78% who are treated by EMS, the survival to hospital discharge is 13.2% (ROC) to 11.4% (CARES).[79] This translates to approximately 6000 pediatric lives lost per year, with a high rate of neurologic morbidity in survivors. Within North America, the outcomes from pediatric cardiac arrest are variable by region, with survival to hospital discharge ranging from 2.6% to 14.7%.[80] The incidence of pediatric IHCA has been estimated to be approximately 1 per 1000 hospital discharges, based on reports from administrative databases.[81] Survival to discharge for pediatric

IHCA has been increasing, with recent estimated rates of 43% to 45%.[81,82] According to the Centers for Disease Control's 2014 estimate of approximately 3 million overnight hospitalizations for patients under age 17, pediatric IHCA accounts for another 1300 deaths per year in the United States.[83]

[h2]Optimal Sequence of Interventions for Pediatric BLS (C-A-B vs A-B-C)

Prompt initiation of high-quality CPR is associated with increased rates of survival in both pediatric and adult patients.[19,79] The 2015 Consensus on Science[84,85] noted that time to first chest compression is decreased by the use of C-A-B vs A-B-C, based on manikin and simulation-based studies.[86-88] Specific knowledge gaps include whether suspected cardiac arrest etiology should influence the resuscitation sequence, but there are no published human studies comparing the outcomes of children in cardiac arrest who are treated with C-A-B vs A-B-C. Because of the lack of high-quality evidence, the CoSTR did not provide a treatment recommendation[84,85]; accordingly, the current pediatric BLS guidelines differ among ILCOR's resuscitation councils. For instance, the European Resuscitation Council recommends the use of the A-B-C approach for children,[89] while the AHA supports the use of the C-A-B approach for both children and adults.[90,91] This "natural experiment" provides an opportunity to collect observational data, although controlling for other resuscitation and postresuscitation factors, as well as differences in healthcare systems, would prove challenging.

[h2]Goal-Directed Physiologic Targets During CPR

CPR quality monitoring is recommended during adult and pediatric CPR.[92] Real-time visual feedback improves compliance with recommended chest compression depth,[93] which is associated with improved outcome from pediatric cardiac arrest.[94] $ETCO_2$ and arterial blood pressure are 2 physiologic parameters that can be used to guide chest compression performance, with pediatric animal studies showing that systemic perfusion pressure or diastolic blood pressure perform better than $ETCO_2$ to discriminate survivors from nonsurvivors.[34,35] In particular, using hemodynamic-directed CPR improves short-term survival from cardiac arrest in a pediatric animal model.[35] The 2015 Consensus on Science was unable to recommend targets for $ETCO_2$ or diastolic blood pressure because of lack of evidence.[84,85] Specific knowledge gaps include numeric physiologic parameters for $ETCO_2$ and diastolic blood pressure associated with high-quality pediatric CPR, as well as with improved outcomes.

[h2]Vasopressors During Cardiac Arrest

The efficacy of vasopressor administration during adult OHCA has been questioned due to high-quality randomized trials and meta-analyses.[95,96] There are no human studies comparing epinephrine or combination of vasopressors with controls for pediatric OHCA, although a small case series suggested that the use of epinephrine could be harmful in sudden, witnessed arrest.[97] The 2015 Consensus on Science recommended standard doses of epinephrine for pediatric cardiac arrest and noted a paucity of supporting evidence.[84,85]

For pediatric IHCA, the use of high-dose epinephrine has been shown to be harmful compared with standard-dose epinephrine,[98] but there are no placebo-controlled studies. A recent retrospective registry study of time to epinephrine in pediatric IHCA for patients with nonshockable rhythms showed that delay to epinephrine administration was associated with reduced ROSC, survival to discharge, and favorable neurologic outcome.[99] Use of vasopressin as a rescue therapy for pediatric ICU patients who are refractory to epinephrine has been reported.[100] Specific knowledge gaps include the question of harm vs benefit of vasopressors for pediatric cardiac arrest. In addition, for selected circumstances (eg, pulmonary hypertension, myocarditis), the role of vasopressors vs extracorporeal CPR rescue should be further investigated.

[h2]Defibrillation Energy Doses

The 2015 Consensus on Science recommended that the energy dose for defibrillation of pediatric ventricular fibrillation/pulseless ventricular tachycardia range from 2 to 4 J/kg, monophasic or biphasic, in the absence of strong evidence for any specific or subsequent doses.[84,85] The available evidence is largely observational and influenced by confounders such as the duration of the arrhythmia, mixed analysis of primary and secondary ventricular fibrillation, and different energy waveforms being used for defibrillation.[101,102] As with the sequence of actions for pediatric BLS, the resuscitation council–specific guidelines differ. The AHA guidelines currently recommend an initial dose of 2 J/kg, followed by a second shock of 4 J/kg if needed.[90] In contrast, the European Resuscitation Council guidelines recommend initial and subsequent doses of 4 J/kg.[89] Specific knowledge gaps include the risk/benefits of specific or titrated energy doses in both primary and secondary shockable rhythms.

[h2]TTM After IHCA

Two RCTs on the use of TTM after pediatric cardiac arrest have now been published, comparing therapeutic hypothermia to normothermia in OHCA and IHCA.[94,103] The Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) trials each included 2 cohorts: one group received 48 hours of therapeutic hypothermia at a target temperature of 33°C followed by 72 hours of normothermia, while the other group was managed with normothermia for 5 days at a target temperature of 36.8°C. The results of both trials showed no statistical difference in the prespecified primary outcome of survival with good functional status at 1 year. At the time of publication of the 2015 Consensus on Science, only the OHCA study results were available.[84,85]

Limitations of the out-of-hospital THAPCA trial included the fact that it was underpowered to detect clinically important differences in outcome. Time to initiation of therapy was 5.9 hours, and time to achieve target temperature was not reported. The in-hospital THAPCA study was terminated for futility before the predefined enrollment. Despite the rigorous trial design, differences of opinion persist about the implications of the results for clinical practice, indicating a need for additional studies.[95,96] Specific knowledge gaps include the optimal target temperature and the duration of TTM after ROSC.

[h3]Education, Implementation, and Teams

The Utstein "Formula for Survival" emphasizes that cardiac arrest outcome is influenced by more than just our collective scientific understanding.[104] The 3 multiplicands in the formula

"Science," "Education," and "Implementation" interact together to affect survival rates after cardiac arrest. It is recognized that considerable variability still exists in the survival of cardiac arrest victims in both the out-of-hospital and in-hospital settings, and there continues to be a critical need to improve educational quality and efficiency as well as address systems of care. Research into optimizing resuscitation training and addressing implementation-related issues will be essential to improve the outcomes of cardiac arrest victims.

[h2]Retraining Intervals for BLS and ALS

It is well documented that CPR skills can decay within weeks to months after traditional single-encounter courses and well before the usual retraining intervals of 1 to 2 years.[105,106] The evidence related to optimal retraining intervals for resuscitation education is limited in both quantity and quality. Educational psychology literature has suggested a pedagogic benefit to the "spacing effect" on learning: educational encounters spaced over time result in more efficient learning and improved learning retention.[107] Future research should ensure that the outcome measures used have established validity for their use because it is difficult to make generalizable conclusions without that evidence. Specific knowledge gaps include the effectiveness and efficiency of more frequent refreshers as well as the optimal amount of time to achieve specific educational objectives. Other key aspects of refresher training include feasibility, learner preference, self-efficacy,[108] and cost-effectiveness, especially the option of completing refresher training within the work flow of the clinical environment.

[h2]Leadership and Team Training

The 2015 Consensus on Science recommends team and leadership training as part of ALS training for healthcare providers despite low-quality evidence because of the potential benefit, lack of harm associated with the training, and high level of acceptability to learners and faculty.[105,106] The Education, Implementation, and Teams Task Force viewed these important considerations as more significant than the potential increased costs associated with team and leadership training. Specific knowledge gaps include the impact of team and leadership training on patient outcomes, long-term retention, and application of knowledge and skills in the clinical and simulated-learning environments. Furthermore, it would be useful to conduct a formal cost analysis of the additional training required for adequate teamwork and leadership skills and to assess the optimal methods to teach them.

[h2]Social Media Strategies

The 2015 Consensus on Science considered the potential impact of the use of social media/digital technologies as a mechanism for mobilizing citizen bystanders as cardiac arrest first responders.[105,106] A recent RCT conducted in Sweden showed improved bystander CPR rates by using a mobile phone positioning system for locating and recruiting CPR-trained lay responders, although survival was not increased, possibly due to lack of statistical power.[29] Because early bystander CPR has been shown to improve survival in OHCA, further research is required to better understand the role of social media in bystander recruitment ("crowdsourcing").[109] In addition, there is a need for further research into the potential for the audio, video, and motion-sensing capabilities of digital technologies to be exploited for real-time resuscitation events and education.[110]

As identified by the recent AHA Scientific Statement, digital strategies, such as the use of mobile devices, social media, and crowdsourcing, are important to achieving the 2020 impact goals; however, “there is a need for rigorous research…to ensure safety and effectiveness.”[30]

[h2]Impact of Cardiac Arrest Centers on Outcomes

There are no RCTs specifically testing the relationship between specialized cardiac arrest centers and patient outcomes. There is a growing body of evidence from observational studies showing a positive relationship between cardiac arrest case volume/hospital capabilities and survival outcomes.[111-113] Consistent with other emergent conditions such as trauma[114] and acute myocardial infarction,[115] the concept of cardiac arrest centers that deliver evidence-based postresuscitation care is intuitively appealing. However, as identified in the 2010[116] and 2015[105,106] CoSTR, there are multiple specific knowledge gaps: the particular treatments to be provided by a cardiac arrest center, the safe patient transport interval (time taken to travel from scene to hospital), the optimal mode of transport (eg, ground ambulance, helicopter), the role of secondary transport (transfer from a receiving hospital to a cardiac arrest center), and the cost-effectiveness of cardiac arrest centers. It is uncertain if sufficient clinical equipoise exists for an RCT to be conducted.

[h2]Implementation of Resuscitation Guidelines

The 2015 Consensus on Science recommended the implementation of resuscitation guidelines by organizations that provide care for cardiac arrest patients despite the absence of any strong evidence.[105,106] This so-called discordant recommendation was made in recognition of the likely benefits relative to harm of a consistent "evidence-based" response by rescuers to a life-threatening event. Despite the international effort that underpins the development of resuscitation guidelines, it has been shown that the uptake of resuscitation guidelines into practice at the local level can be delayed for a variety of reasons.[117-120] Specific knowledge gaps include the most effective (and cost-effective) strategies for dissemination and implementation of resuscitation guidelines.

[h3]First Aid

First aid is defined as the helping behaviors and initial care provided for an acute illness or injury. The goals of first aid are to preserve life, alleviate suffering, prevent further illness or injury, and promote recovery. First aid can be initiated by anyone in any situation and is the overarching title for all resuscitation and associated life-preserving procedures.[121,122] First aid can therefore be considered to be the primary preventive precardiac arrest strategy to avert the need for resuscitation, as well as the post–cardiac arrest management that prevents further harm or rearrest. As with other domains, there is a serious lack of evidence-based science to support or refute the current first aid recommendations.

[h2]Recovery Position

The 2015 Consensus on Science suggested the use of a lateral side-lying recovery position for persons with medical conditions who are unresponsive but breathing normally.[121,122] Specific knowledge gaps include determination of the optimal recovery position for both adults and children. Most studies have used discomfort in healthy volunteers as the outcome measure; only a single study has looked at aspiration in relation to position,[123] and no studies have looked at mortality. Further complicating the topic are anecdotal reports of resuscitation being delayed while the victim is placed in the recovery position and mistaking agonal gasps for normal respiratory effort.[124]

Specific knowledge gaps include situations where use of a recovery position may be beneficial. For example, placing a patient with a generalized seizure into a lateral recumbent recovery position may be associated with a lower incidence of sudden death in epilepsy.[125] Another recent study showed a lower incidence of hospital admissions among children with loss of consciousness primarily due to seizures and vasovagal syncope who were placed in a recovery position.[126] The use of a recovery position for acute drug and alcohol ingestions also deserves future study.

[h2]Use of Oxygen for Conditions Other Than Chest Pain/Cardiac Arrest

The 2015 Consensus on Science focused on the use of oxygen for dyspnea and decompression injury.[121,122] A single large observational study evaluated oxygen use in suspected decompression sickness,[127] and smaller studies examined oxygen use in patients with advanced cancer and dyspnea combined with hypoxemia.[128-131] Specific knowledge gaps include the use of oxygen by first aid providers for conditions such as suspected carbon monoxide poisoning, inhalation injury, seizures, or most other illnesses and injuries.

[h2]Control of Bleeding

The ability to control severe, life-threatening bleeding is considered a primary first aid intervention and one that was the focus of a recent public health initiative in the United States ("Stop the Bleed" Campaign).[132] The 2015 Consensus on Science suggested the use of tourniquets for severe external limb bleeding that could not be controlled by direct pressure.[121,122] Research into the use of tourniquets comes primarily from the military setting in the form of case series or animal studies.[123-140] Civilian sector studies are limited and consist chiefly of small observational studies.[141,142]

There are no direct comparative studies looking at tourniquets vs hemostatic dressings for extremity wounds with massive bleeding or use of a second tourniquet when initial tourniquet application fails. There are no studies specifically comparing improvised tourniquets that might be used by a first aid provider for outcomes of control of bleeding. Research looking at hemostatic dressings is almost exclusively from animal studies. Further research comparing different methods of hemorrhage control are needed because it would be unethical to perform studies by using a control group that did not receive treatment. Specific knowledge gaps include the optimal educational techniques for first aid providers and lay public members in the proper application of tourniquets, both commercial and improvised.

[h2]Treatment of Mild Hypoglycemia

The 2015 Consensus on Science suggested that first aid providers administer glucose tablets or other forms of dietary sugars for symptomatic patients suspected of being hypoglycemic.[121,122] There are no studies looking at buccal or sublingual absorption of glucose gel or paste to determine a comparable dose equivalent to oral glucose tablet or liquid glucose administration. Studies that look at buccal or sublingual administration suggest that the dose was swallowed rather than absorbed through mucosa.[143] Preliminary studies show comparable improvement in moderate to severe hypoglycemia in children with malaria when treated with repeat doses of sublingual glucose as compared with intravenous glucose infusion.[144] Specific knowledge gaps include the safety and efficacy of glucagon use by first aid responders for hypoglycemia, despite the existence in many states in the United States of protocols allowing the use of injectable glucagon by trained first aid providers or family members.

[h2]Cervical Spine Motion Restriction

While it is recognized that spinal immobilization has not been shown to prevent neurologic injury, there continue to be questions about the appropriate first aid response for patients at high risk for spinal injury. Few studies have evaluated the effectiveness of manual stabilization techniques such as head-squeeze or trap-squeeze.[145,146] Specific knowledge gaps include interventions that may be of benefit when providing first aid to a spine-injured/high-risk spinal injury patient, such as verbal prompts or manual stabilization, while awaiting arrival of advanced care providers.

[h1]Summary

The 2015 CoSTR used a rigorous process to evaluate the available evidence. Despite tremendous progress in the field of resuscitation medicine, multiple knowledge gaps remain. This Consensus Statement has outlined the major topic areas and attempted to prioritize the gaps in knowledge, based on potential impact on outcomes and feasibility to perform.

Acknowledgments

The writing group acknowledges the contribution of the ILCOR Task Force members who participated in the survey process, as well as the dedication and support of the AHA Emergency Cardiovascular Care staff.

Sources of Funding

The authors report no external funding for this manuscript.

Disclosures

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Figures

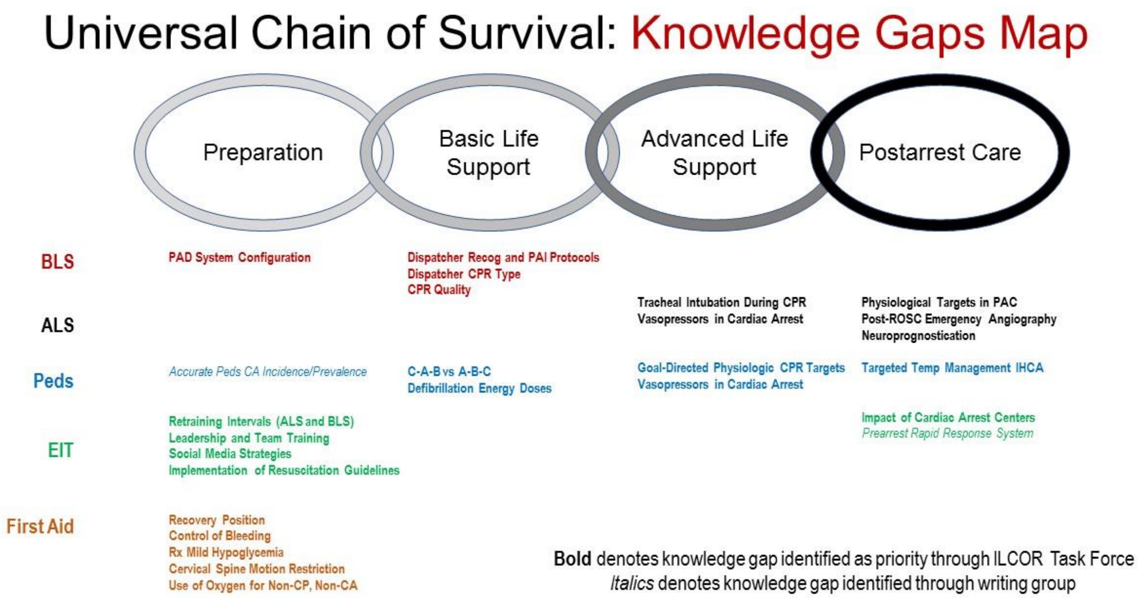

Figure. Universal Chain of Survival: knowledge gaps map.

A-B-C indicates airway, breathing, circulation; ALS, advanced life support; BLS, basic life support; CA, cardiac arrest; C-A-B, compressions, airway, breathing; CPR, cardiopulmonary resuscitation; EIT, Education, Implementation, and Teams; IHCA, in-hospital cardiac arrest; ILCOR, International Liaison Committee on Resuscitation; PAC, postarrest care; PAD, public access defibrillation; PAI, prearrival instructions; Peds, Pediatric; ROSC, return of spontaneous circulation.