Circulation

AHA SCIENTIFIC STATEMENT

Pediatric Post–Cardiac Arrest Care

A Scientific Statement From the American Heart Association

ABSTRACT: Successful resuscitation from cardiac arrest results in a post–cardiac arrest syndrome, which can evolve in the days to weeks after return of sustained circulation. The components of post–cardiac arrest syndrome are brain injury, myocardial dysfunction, systemic ischemia/reperfusion response, and persistent precipitating pathophysiology. Pediatric post–cardiac arrest care focuses on anticipating, identifying, and treating this complex physiology to improve survival and neurological outcomes. This scientific statement on post–cardiac arrest care is the result of a consensus process that included pediatric and adult emergency medicine, critical care, cardiac critical care, cardiology, neurology, and nursing specialists who analyzed the past 20 years of pediatric cardiac arrest, adult cardiac arrest, and pediatric critical illness peer-reviewed published literature. The statement summarizes the epidemiology, pathophysiology, management, and prognostication after return of sustained circulation after cardiac arrest, and it provides consensus on the current evidence supporting elements of pediatric post–cardiac arrest care.

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The authors of this statement were selected to ensure expertise relevant to post–cardiac arrest care (PCAC). The authors included adult and pediatric care providers with expertise in emergency medicine, critical care, cardiac critical care, neurology, cardiology, and nursing. Writing group members were invited to contribute, and they completed conflict of interest disclosures of any relationships with industry. These conflict of interest statements were reviewed and approved by American Heart Association (AHA) Emergency Cardiovascular Care National Center staff and then reviewed and approved by the AHA Manuscript Oversight Committee before writing began. Each topic was assigned to teams of 2 people: a primary author with a secondary author to review. Telephone conference calls, led by the writing group chair, were scheduled to discuss writing assignments and, later, to reach consensus on the text and on each treatment recommendation.

PubMed, the Cochrane Library, and ClinicalTrials.gov were searched from 1997 to 2017 for peer-reviewed publications related to pediatric care after cardiac arrest. All writing group members agreed on the structured approach to data presentation. The writing group agreed that if there were limited or no available pediatric post–cardiac arrest data, the group would summarize data from studies of adult cardiac arrest and, if available, data derived from critically ill or injured children. Editorials, letters, and case reports were excluded. Large prospective trials and ran-

Key Words: AHA Scientific Statements ■ cardiopulmonary arrest ■ cardiopulmonary resuscitation ■ child ■ outcomes ■ post-cardiac arrest care ■ targeted temperature management

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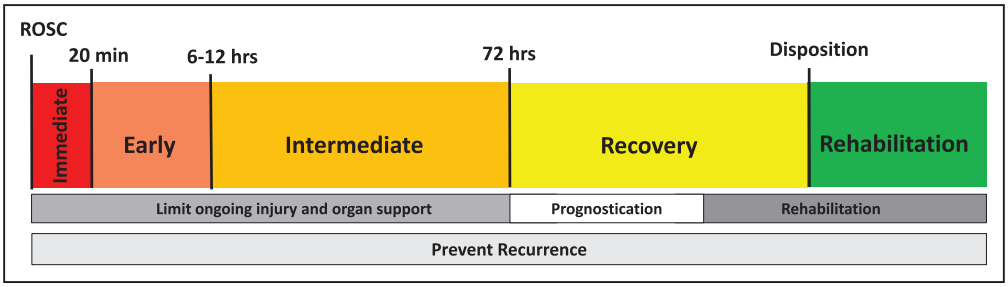

Figure 1. Phases of post–cardiac arrest syndrome.
ROSC indicates return of sustained circulation. Adapted from Neumar et al.[4] Copyright © 2008, American Heart Association, Inc.

domized controlled trials were highlighted, and case series and low-quality evidence were summarized.

The draft sections were edited by the chair and 2 senior writing group members (A.d.C. and M.F.H.). A draft was then circulated to the authors for review. The authors held final conference calls to achieve consensus on the evidence summaries and on all consensus statements before submission for approval of the AHA Manuscript Oversight Committee, peer review, and approval for publication.

DEFINITIONS

Return of Spontaneous/Sustained Circulation and Extracorporeal Circulation

In the past, the AHA guidelines and the guidelines update for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care training materials used the abbreviation ROSC for return of spontaneous circulation, defined as return of a perfusing heart rhythm accompanied by the presence of a palpable central pulse. In this publication, the abbreviation ROSC refers to return of sustained circulation, which can include circulation that results either from a perfusing spontaneous heart rhythm or from establishment of extracorporeal circulation with extracorporeal membrane oxygenation (ECMO). ECMO instituted during active CPR is abbreviated as ECPR.

Targeted Temperature Management

Over the past decade, there has been a shift in the nomenclature used to describe post–cardiac arrest temperature management. In the early studies, therapeutic hypothermia (32°C–34°C) was compared with standard (uncontrolled) temperature therapy that did not include fever prevention.[1] More recent follow-up studies compared therapeutic hypothermia with controlled normothermia (36°C–37.5°C), with fever actively prevented.[2,3] Currently, targeted temperature management (TTM) is the term used to refer to specified targeted temperature control to either hypothermia (32C°–34°C) or normothermia (36°C–37.5°C). In this document, we use either the terminology contained in the cited studies or TTM for both hypothermia or normothermia, with the targeted temperature(s) listed.

Phases and Time Periods

PCAC differs on the basis of both the phase of the post–cardiac arrest syndrome (PCAS) and the setting in which the care is delivered after ROSC. Consecutive phases of PCAS and intervals of care are illustrated in Figure 1.[4] Time intervals after the initial 20 minutes after ROSC may vary from patient to patient, depending on the severity of the PCAS, the trajectory of recovery, or the pace of deterioration. During all phases, the aim of care focuses on limiting ongoing injury and preventing the recurrence of cardiac arrest.

- The immediate phase: the first 0 to 20 minutes after ROSC
- The early phase: the period after ROSC from 20 minutes up to 6 to 12 hours
- The intermediate phase: 12 to 72 hours
- The recovery phase: approximately 72 hours to day 7. Starts at different times for different patients; the timing may be influenced by factors such as cardiovascular function or use of TTM
- The rehabilitation phase: traditionally began with the application of care after discharge from the acute care hospital, but rehabilitation services are now often initiated during the intermediate phase or the recovery phase

BACKGROUND

This scientific statement describes the available peer-reviewed published evidence on the care of children resuscitated from cardiac arrest, including pediatric PCAC and prognostication, and provides a list of knowledge gaps. The purpose of this statement is to provide clinicians with recommendations to optimize pediatric PCAC, highlighting the knowledge gaps that should be addressed by researchers to improve future care and outcomes.

In 2008, PCAS was defined for the international resuscitation community in an International Liaison Committee on Resuscitation scientific statement.[4] This statement addressed chiefly adult PCAC, highlighting the pathophysiology and the need for continued multisystem support after ROSC.[4] The statement described what are now accepted as 4 key components of PCAS: post–cardiac arrest brain injury, post–cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion response, and persistent precipitating pathophysiology.

Before 2008, the AHA pediatric advanced life support (PALS) guidelines focused chiefly on prevention of cardiac arrest, immediate recognition of cardiac arrest, and provision of early CPR because outcomes of pediatric cardiac arrest were poor.[5,6] In the 2008 International Liaison Committee on Resuscitation scientific statement, pediatric PCAC was addressed only as a special circumstance.[4] This section cited the very limited pediatric evidence available, including published studies in asphyxiated newborns demonstrating a positive effect of therapeutic hypothermia compared with no temperature control,[7,8] as well as a pediatric case series documenting an association between post–cardiac arrest fever and poor outcome.[9] The pediatric section of the International Liaison Committee on Resuscitation scientific statement suggested that focused care after ROSC may improve survival to discharge, and it highlighted the large gaps in evidence specific to the PCAC of children.

The past decade has led to focused efforts by resuscitation experts to address specific pediatric post–cardiac arrest knowledge gaps. The International Liaison Committee on Resuscitation International Consensus on CPR and Emergency Cardiovascular Care Science With Treatment Recommendations statements have systematically and rigorously identified the evidence, and AHA guideline statements are based on the evidence. Although much research is still needed, this document provides an overview based on a literature review and consensus expert opinion to guide the clinician in the understanding and management of the child after cardiac arrest. Data extrapolated from adult studies support a thoughtful, systems-based, and proactive bundled approach to PCAC, with the continued goal of improving long-term survival with favorable neurological outcomes.[10]

EPIDEMIOLOGY OF PEDIATRIC PCAS

The timing and severity of the phases of PCAS may differ between patients with out-of-hospital cardiac arrest (OHCA) and those with in-hospital cardiac arrest (IHCA) because witnessed status, preexisting conditions, cause of arrest, and timing and quality of bystander actions, such as immediate administration of high-quality CPR, may differ between OHCA and IHCA. Therefore, we describe the epidemiology of OHCA and IHCA separately.

The OHCA literature describes outcomes based on the denominator of all cardiac arrest events that occur in the prehospital setting such as data from the ROC (Resuscitation Outcomes Consortium),[11–13] regional registries such as CARES (Cardiac Arrest Registry to Enhance Survival)[14,15] or All-Japan Utstein Registry,[16] or 2 cohort studies of children with cardiac arrest who survived to hospital admission.[17,18] It is important to note the patient denominator in comparisons of reported survival rates. These differences are also relevant because the timing of initiation of PCAC may vary on the basis of where ROSC is achieved.

It is estimated that >5000 children experience OHCA annually in the United States,[11,19] with an estimated incidence of nontraumatic OHCA of 8.04 per 100 000 person-years.[11] With current ROSC rates of ≈36%,[13] we estimate that >1800 infants and children are at risk annually for PCAS after OHCA. Reported survival to hospital discharge after OHCA from the US CARES multistate registry and the North American ROC Epistry have not significantly increased over the past 10 years, with an overall survival in the ROC Epistry of 6.4% reported in 2005 to 2007[11] and 6.7% to 10.2% reported in 2007 to 2012[13] and survival averaging 8.2% in the CARES registry from 2005 to 2013.[14] Favorable neurological outcome has been reported in as many as 77% of pediatric OHCA survivors.[14] In a recent study of TTM in comatose children who survived OHCA to be admitted to a pediatric intensive care unit (ICU), 38% survived to hospital discharge.[18]

It is more challenging to determine outcomes after IHCA because published reports often used denominators that included only patients who received CPR. According to information from the AHA Get With The Guidelines–Resuscitation IHCA registry[20] and the Kids' Inpatient Database,[21] an estimated 6000 infants and children develop IHCA annually. Risk-adjusted rates of ROSC increased from 42.9% in 2000 to 81.2% in 2009, and risk-adjusted rates of survival to discharge improved from 14.3% in 2000 to 43.4% in 2009 without an increase in unfavorable neurological outcome.[22] Notably, with an emphasis on detection and treatment of prearrest conditions since 2003 to 2004, significantly more IHCA appropriately occurs in ICUs compared with general wards.[20] In a more recent series from Get With The Guidelines–Resuscitation of patients enrolled between 2011 and 2013, non–risk-adjusted ICU ROSC occurred in 78%, with 45% surviving to discharge; 89% of survivors had a favorable neurological outcome.[23] On the basis of these data, we estimate that ≈4800 infants and children are at risk for the development of PCAS annually after IHCA.

Although ROSC and survival rates after pediatric cardiac arrest have improved, >6500 children per year in

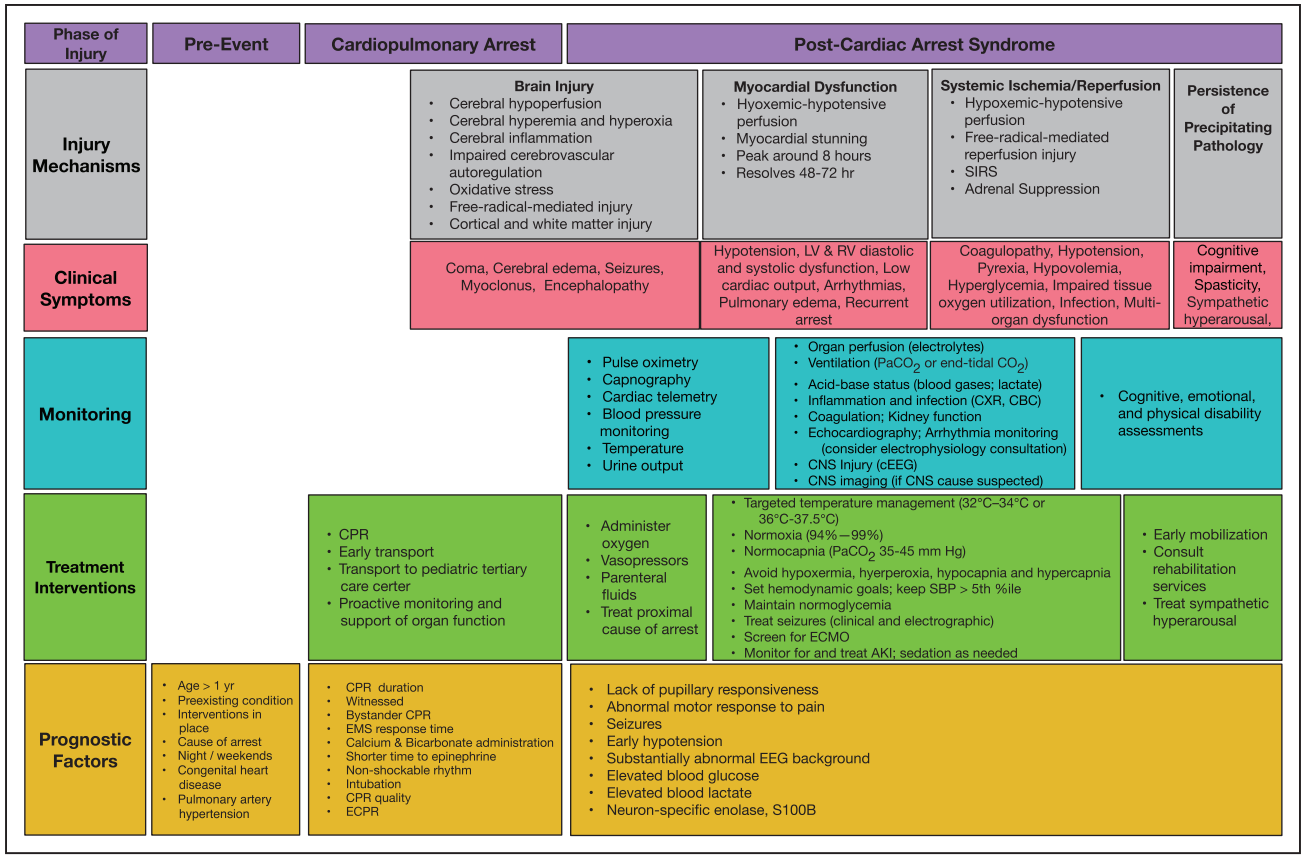

Figure 2. Phases of cardiac arrest with associated mechanisms, clinical symptoms, monitoring, treatment interventions, and prognostics factors. AKI indicates acute kidney injury; CBC, complete blood count; CNS, central nervous system; CPR, cardiopulmonary resuscitation; CXR, chest x-ray; cEEG, continuous electroencephalogram; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; EEG, electroencephalogram; EMS, emergency medical service; LV, left ventricular; RV, right ventricular; SBP, systolic blood pressure; and SIRS, systemic inflammatory response syndrome.

the United States have PCAS.[11,13,19–21] The goal of PCAC is to increase not only survival to hospital discharge but also survival with favorable neurological outcome.

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS OF PCAS

The term *postresuscitation disease* was first proposed by Negovsky and Gurvitch[24] in 1995 to refer to central nervous system and systemic pathological processes resulting from hypoxia-ischemia and occurring during recovery. This disease includes the cellular and pathophysiological inflammatory response that was well described by Neumar et al[4] in 2008.

The phases of PCAS are depicted in Figure 1. The key components of this syndrome are post–cardiac arrest brain injury, post–cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion response, and persistent precipitating pathophysiology; PCAS management requires multisystem support during each of the phases (Figure 2). The following sections present an overview of the pathophysiology of each phase based on data from clinical and preclinical models and the anticipated clinical manifestations in children.

Post–Cardiac Arrest Brain Injury

Post–cardiac arrest brain injury remains a leading cause of morbidity and mortality in adults and children because the brain has limited tolerance of ischemia, hyperemia, or edema. The first 3 phases of PCAS involve hypoxemic-hypotensive perfusion with energy deprivation. With ROSC, there is a burst of reactive oxygen species, and oxidative stress may ensue in tissue that is depleted of antioxidants.[25] As a result, reperfusion is associated with excitotoxicity, calcium accumulation, and free radical–mediated cell injury or death.[26] Both neuronal cellular necrosis and apoptosis result from this cascading injury and can continue in the days to weeks after ROSC. A variety of post–cardiac arrest clinical conditions, including hyperoxia, hypoxemia, and hypotension, can exacerbate the neuronal injury.

Preclinical studies of hypoxic-ischemic injury suggest that supranormal systemic arterial oxygen concentrations during reperfusion after cardiac arrest may exacerbate free radical–mediated neurological injury and protein disruption and may worsen neurological outcome, although the relevance of these animal models to humans is uncertain.[27] In preclinical studies, hyperoxic reperfusion led to an increase in delayed neuronal

cell death[28–30] and decreased the activity of hippocampal pyruvate dehydrogenase.[31] Therefore, hyperoxia after ROSC could further exacerbate neuronal injury.[25,32]

Clinical pediatric data are equivocal, with 3 small observational studies of pediatric IHCA and OHCA demonstrating no association between hyperoxia and outcomes,[33–35] whereas a large multicenter study found that the presence of normoxemia after ROSC (defined as a Pao_2 >60 and <300 mm Hg) compared with hyperoxia (Pao_2 >300 mm Hg) was associated with higher rates of survival to discharge.[36]

Arterial carbon dioxide tension influences cerebral perfusion in both children and adults.[37] Preclinical studies suggest that hyperventilation decreases coronary perfusion and survival after cardiac arrest.[38] Hyperventilation causes cerebral vasoconstriction and can decrease cerebral blood flow (CBF),[39] thereby potentially exacerbating cerebral ischemia. Hypercapnia causes cerebral vasodilation and increases CBF.[39] Cerebrovascular reactivity to carbon dioxide may be preserved in some patients after cardiac arrest.[40]

Clinical studies of post–cardiac arrest ventilation in children are limited. One small study of pediatric post–cardiac arrest hypoventilation demonstrated no association with outcome,[33] whereas another showed that hypercapnia ($Paco_2$ >50 mm Hg) and hypocapnia ($Paco_2$ <30 mm Hg) were independently associated with death.[35] Adult data demonstrate that there is no high-quality evidence supporting the association of hypercapnia or hypocapnia with worse survival and neurological outcomes.[41]

Clinical manifestations of brain injury after arrest include coma, cerebral edema, seizures, myoclonus, sympathetic hyperarousal, and long-term neurobehavioral and function deficits.

Post–Cardiac Arrest Myocardial Dysfunction

Post–cardiac arrest myocardial dysfunction in the clinical setting, including reports of myocardial stunning, was first described in the literature in the 1990s. Global myocardial dysfunction occurs even in the absence of a cardiac cause of the arrest, and the severity of the myocardial dysfunction may be related to the duration of no-flow time during cardiac arrest.[42] Myocardial dysfunction has been associated with early mortality despite successful initial resuscitation in children[42,43] and adults.[44–47]

The onset of post–cardiac arrest myocardial dysfunction begins within hours of the arrest, peaks at ≈8 hours, begins to improve at 24 hours, and typically resolves within 48 to 72 hours.[44] The pathophysiology contributing to this frequently reversible deterioration of cardiac function after cardiac arrest is not fully understood but is associated with cardiovascular ischemia/reperfusion injury, cytokine-mediated cardiovascular dysfunction, and induced myocardial injury secondary to catecholamines or electric shocks.[44,48–51] Children may initially demonstrate a hyperdynamic state and then develop cardiac dysfunction over time.[52] Because myocardial dysfunction is likely to develop in approximately two-thirds of patients after ROSC[51] and subsequently improve, it is thought to be a modifiable risk factor.

Pediatric post–cardiac arrest studies evaluating myocardial dysfunction are limited. In small retrospective studies of pediatric OHCA, elevations in troponin I and decreased ventricular shortening fraction and ejection fraction are associated with increased mortality.[43] In a retrospective study of 58 children within 24 hours of admission after ROSC from OHCA, transthoracic echocardiograms demonstrated decreased left ventricular systolic function in 41%, which was associated with increased mortality.[42] Left ventricular diastolic dysfunction was present in 64% of patients. Low systolic or diastolic arterial pressure and low central venous pressure at the time of the transthoracic echocardiogram were not associated with left ventricular systolic dysfunction, thus raising questions about whether qualitative echocardiographic assessment of left ventricular systolic function is an accurate measure of myocardial dysfunction and whether vital signs are reliable methods of screening for post–cardiac arrest myocardial dysfunction.

Although initial studies of post–cardiac arrest myocardial dysfunction focused on left ventricular systolic function, left ventricular diastolic dysfunction and right ventricular (RV) dysfunction after adult cardiac arrest have also been noted.[46,47,53] Cardiac arrhythmias are common during PCAC and may be exacerbated by catecholamine administration, which is required to maintain adequate cardiac output.[17]

Clinical manifestations of myocardial dysfunction include hypotension, left ventricular and RV systolic or diastolic dysfunction resulting in reduced cardiac output, arrhythmias, and pulmonary edema, which can result in recurrent cardiac arrest.

Systemic Ischemia/Reperfusion

The combination of systemic ischemia/reperfusion produces a state similar to the sepsis syndrome, with elevated cytokines, the presence of endotoxin in plasma, activation of coagulation pathways, and inhibition of anticoagulant pathways.[44,54]

Transient critical illness hyperglycemia occurs after cardiac arrest from a relative insulin-resistant state that is associated with high levels of endogenous catecholamines and cortisol secretion, with resulting gluconeogenesis and glycogenolysis. In children, the serum glucose is typically elevated in the first 12 to 18 hours after the insult and then falls to normal. This can be exacerbated

by therapeutic hypothermia. Although critical illness hyperglycemia has been linked to poor survival in critically ill children,[55,56] it is not clear if the hyperglycemia is the cause or the marker of poor outcomes.[57]

Clinical manifestations of systemic ischemia/reperfusion include capillary leak with intravascular hypovolemia, vasoplegia, coagulopathy, hyperglycemia, adrenal insufficiency, and impaired oxygen utilization and delivery, contributing to multisystem organ dysfunction.

Persistent Precipitating Pathophysiology

Management of the child after cardiac arrest includes diagnosis and treatment of the precipitating cause of cardiac arrest. Failure to identify and correct the original cause of cardiac arrest leaves the patient at risk for secondary injury and even recurrence of cardiac arrest. Examples of disease states with symptomatology that can complicate management after cardiac arrest include fever and continued shock in the septic patient, persistent hypercarbia or hypoxemia in the child with acute respiratory failure, electrolyte imbalance (eg, hyperkalemia), and, in traumatic cardiac arrest, uncorrected hypovolemic or obstructive shock.

THERAPEUTIC STRATEGIES

PCAC must begin promptly after ROSC, with a focus on supporting initial end-organ function, anticipating and treating PCAS, and addressing the underlying cause of arrest. A systematic approach is needed not only for the immediate management of the unstable patient but also to prevent decompensation in the initially stable patient. These interventions should be provided as soon as possible, and many can be implemented regardless of arrest location. Care immediately after ROSC should incorporate therapeutic strategies for support of systemic perfusion and organ function. A coordinated and integrated response from care providers in the prehospital, emergency department, and ICU settings may improve outcomes for initial survivors.

General Monitoring

In the post–cardiac arrest period, it is important for the healthcare team to anticipate and assess for evolving systemic and organ dysfunction and to proactively support organ function. This requires ongoing monitoring to guide intensive care therapies (Table 1).

PCAC begins with establishment of monitoring as soon as possible after ROSC, with simultaneous investigation and treatment of underlying disease and the proximal cause of arrest and management of critical abnormalities. Monitoring in the field continues through transport and includes ECG, pulse oximetry, capnography, noninvasive blood pressure measurement, and point-of-care glucose testing.

Table 1. PCAS: Monitoring

General monitoring
Oxygen saturation, continuously by pulse oximetry
Capnography (quantitative)
Arterial blood pressure (intra-arterial when possible or noninvasive)
Blood glucose (point of care)
Cardiac telemetry, continuous
ECG
Temperature, continuous core (esophageal, bladder, or rectal)
Urine output
Blood gas, arterial (pH, P_{AO_2}, P_{ACO_2})
Serum lactate, arterial
Blood glucose, electrolytes, creatinine, complete blood count, coagulation profile
Venous oxygen saturation
Central venous pressure
Chest radiograph
Additional hemodynamic monitoring
Echocardiography
Neurological monitoring
Neurological clinical examination, serial
EEG, continuous
Imaging: brain CT or brain MRI

CT indicates computerized tomography; EEG, electroencephalography; MRI, magnetic resonance imaging; and PCAS, post–cardiac arrest syndrome.

General Intensive Care Monitoring

General intensive care monitoring includes continuous cardiac telemetry, pulse oximetry, continuous capnography, continuous temperature monitoring, and measurement of blood pressure and urine output. Monitoring includes laboratory analysis of venous or arterial blood gases, serum electrolytes, and glucose and calcium concentration. Arterial lactate and central venous oxygen saturation assist in evaluation of the adequacy of tissue oxygen delivery. A chest x-ray aids evaluation of endotracheal tube position, heart size, and pulmonary status.[52] Additional monitoring includes evaluation of renal function, measurement of hemoglobin concentration, monitoring of coagulation function, and assessment for signs of inflammation and infection.

Hemodynamic Monitoring

Approximately 95% of pediatric IHCA occurs in an ICU,[20] and almost 50% of these patients will have arterial catheters in place before the cardiac arrest. If possible, an arterial catheter should be placed for continuous intra-arterial pressure monitoring to facilitate the identification and treatment of hypotension.[58] In addition,

central venous catheters may be useful to monitor central venous oxygen saturation and to provide a route for the administration of fluids and medications. Pulmonary artery catheters are now rarely used in pediatrics.

Although there is insufficient evidence to suggest the optimal timing or frequency of post–cardiac arrest echocardiography, it is a beneficial, noninvasive tool for identifying myocardial dysfunction and congenital and acquired cardiac abnormalities.[42] A 12-lead ECG may be helpful in establishing the cause of arrest.[52]

Neurological Monitoring

Brain monitoring is useful in comatose post–cardiac arrest patients to guide therapy aimed at preventing secondary neurological injury. Serial neurological examinations may help identify evolving hypoxic-ischemic brain injury. Given the high incidence of electrographic seizures after ROSC,[59] monitoring with an electroencephalogram (EEG) is increasing in pediatric PCAC.[60] Neuroimaging can be helpful to identify a cerebral cause of cardiac arrest and the presence of severe brain injury.[61,62]

Adult clinical trials are underway to evaluate the usefulness of monitoring cerebral oxygenation and CBF.[63] One small pediatric study (36 patients)[64] evaluated the role of cerebral autoregulation in guiding hemodynamic management and oxygen delivery and assisting in neuroprognostication in comatose children after cardiac arrest, but more studies are needed.[65]

Early Hemodynamic Optimization

Blood Pressure

Hemodynamic instability after ROSC is common in both children[66,67] and adults.[68,69] However, it is not fully understood whether hypotension after cardiac arrest is a harbinger of an inevitably poor outcome or whether it may be a modifiable risk factor that requires early intervention.

Early hypotension after pediatric cardiac arrest is associated with lower survival to hospital discharge.[66,67] An observational study of pediatric IHCA found that a systolic blood pressure less than the fifth percentile for age and sex within the first 6 hours after ROSC developed in 56% of 383 children and was independently associated with increased in-hospital mortality and unfavorable neurological outcome.[66] Furthermore, another study found that among 80 children who achieved ROSC after OHCA, a normal heart rate and normotension in the first hour were independently associated with survival to hospital discharge.[70] Most recently, a post hoc analysis of the THAPCA trial (Therapeutic Hypothermia After Pediatric Cardiac Arrest) of OHCA (THAPCA-OH) demonstrated that early hypotension occurred in 26.7% of patients and was associated with lower survival to discharge.[67] Despite these data, in a retrospective cohort of children <18 years of age, only 41% of patients with early post-ROSC hypotension received vasopressor therapy in the first 6 hours after ROSC.[66]

When post–cardiac arrest hypotension is present, it is not clear whether increasing the blood pressure through administration of fluids and inotropes/vasopressors can mitigate harm. Observational studies in children[71] and adults[53,72–74] have documented worse outcomes in patients requiring vasoactive agents in the post–cardiac arrest period.

To date, no pediatric or adult interventional studies have evaluated the survival effect of manipulating blood pressure after ROSC. Several adult post–cardiac arrest protocolized interventional trials that included blood pressure targets demonstrated improved outcomes during the protocol-directed period.[1,75,76] However, it is not possible to determine a causal or reversible relationship between hypotension and outcomes after ROSC.

Circulatory Support

Currently, there is no high-quality evidence to support any single specific strategy for post–cardiac arrest hemodynamic optimization in children. Treatment of post–cardiac arrest hypotension and myocardial dysfunction may be assisted by monitoring and evaluating arterial lactate and central venous oxygen saturation.[52] Parenteral fluids, inotropes, and vasoactive drugs are to be used as needed to maintain a systolic blood pressure greater than the fifth percentile for age.[58,77] Figure 3 provides more information.[78]

There are no published data to identify the optimal relative dose/volume of parenteral fluids versus inotropes/vasopressors; the preferred vasoactive agent or combination of agents; the optimal perfusion end points; the optimal time period to achieve targeted perfusion; or whether harm may result from fluid or inotrope/vasopressor administration, especially in subgroups such as cardiac and trauma patients. Previous guidelines have recommended vasopressor and inotropes with dosing ranges to treat hypotension and support cardiac output (Table 2). Appropriate vasoactive drug therapies should be tailored to each patient and adjusted as needed.[52] The severity of each patient's PCAS, combined with that patient's unique prearrest and intra-arrest characteristics, requires an individualized approach for each patient aimed at optimizing perfusion without creating excessive myocardial work.

Arrhythmias

The rhythm disturbances observed during the post–cardiac arrest period include premature atrial and ventricular contractions, supraventricular tachycardias, and ventricular tachycardias. Heart block is unusual but can be observed as a manifestation of myocarditis.[79,80] There is inadequate evidence in adults and no published stud-

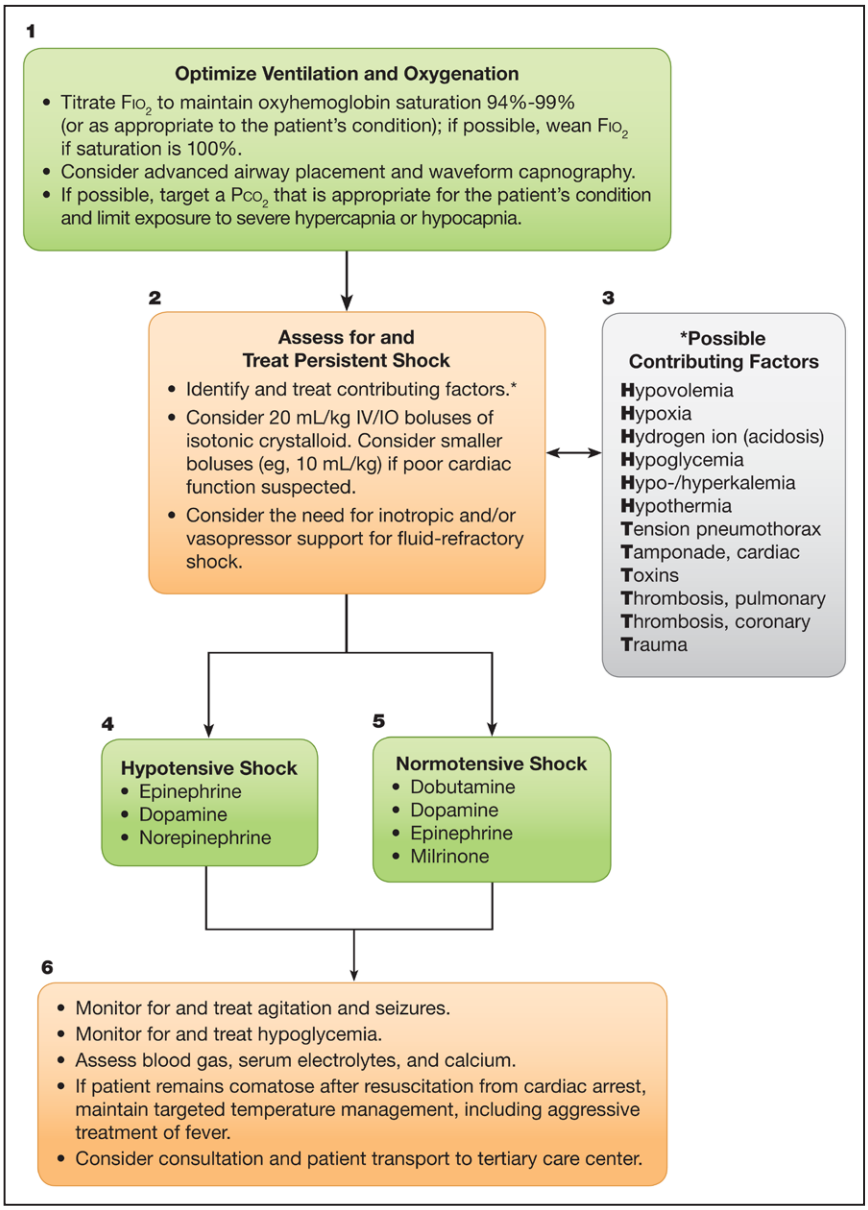

Figure 3. Management of shock after return of sustained circulation.
Reproduced from the *2015 Handbook of Emergency Cardiovascular Care for Healthcare Providers*.[78] Copyright © 2015, American Heart Association, Inc.

ies in children to support the routine administration of prophylactic antiarrhythmics after ROSC,[4,81] but rhythm disturbances during this period may warrant therapy. Treatment depends on the cause and hemodynamic consequences of the arrhythmias. Premature depolarizations, both atrial and ventricular, usually do not require therapy other than maintenance of adequate perfusion and normal fluid and electrolyte balance. Ventricular arrhythmias may signify more serious myocardial dysfunction.

For ongoing arrhythmias after ROSC, the selection of optimal drug therapy is highly dependent on underlying cardiac pathology and function, and pediatric cardiac electrophysiology consultation is often necessary. Many antiarrhythmic drugs are contraindicated in patients with long-QT syndrome[82] and Brugada syndrome.[83] In particular, any drug that prolongs the QT interval should generally be avoided in any patient suspected of having long-QT syndrome. Examples include amiodarone, procainamide, and sotalol.

Many of the vasoactive agents used to support myocardial function can increase myocardial irritability and risk of arrhythmias. Premature atrial or ventricular depolarizations are frequently observed and can be controlled by optimizing the dose of the vasoactive drugs.

Arrhythmias are frequently reported during TTM.[2,3,84,85] Bradycardia is particularly common with TTM but usually does not require treatment.

Extracorporeal Membrane Oxygenation

ECMO can be initiated during CPR or after ROSC when the patient has ongoing cardiovascular instability and is at high risk of repeat cardiac arrest. When ECMO is initiated during CPR (ie, ECPR), it is continued during the post–cardiac arrest period until the patient can be

Table 2. Vasoactive Infusions That May Be Used to Optimize Hemodynamics During PCAS

Medication	Dose Range	Type of Drug	Side Effects
Dobutamine	2–20 μg/kg per 1 min IV/IO	Inotrope; vasodilator	Tachyarrhythmias; peripheral vascular injury
Dopamine	2–20 μg/kg per 1 min IV/IO	Inotrope; chronotrope; renal and splanchnic vasodilator in low doses; vasopressor in high doses	Tachyarrhythmias; peripheral vascular injury
Epinephrine	0.1–1 μg/kg per 1 min IV/IO	Inotrope; chronotrope; vasodilator in low doses; vasopressor in high doses	Tachyarrhythmias; peripheral vascular injury
Milrinone	0.25–0.75 μg/kg per 1 min IV/IO	Inotrope; lusitrope; vasodilator	Hypotension
Norepinephrine	0.1–2 μg/kg per 1 min	Vasopressor	Peripheral vascular injury

IO indicates intraosseous; IV, intravenous; and PCAS, post–cardiac arrest syndrome.
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separated from mechanical support. The 2015 AHA guidelines update for CPR and emergency cardiovascular care and the "2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations" recommended that ECPR may be considered for children with known cardiac diagnoses who experience IHCA, although significant consideration should be given to the availability of skilled personnel and to the need for effective protocols and equipment.[58,86]

The clinical effectiveness of ECMO for cardiovascular support after ROSC has not been thoroughly investigated. In a study in a PICU population, the use of ECMO within 24 hours after ROSC was associated with reduced mortality.[87] Case series have documented the role of ECMO[88] and ventricular assist device support[89,90] in children with refractory cardiogenic shock or acute fulminant myocarditis.[88,91] During PCAC, mechanical circulatory support (ECMO) may be considered if significant cardiorespiratory instability persists despite appropriate volume expansion and administration of inotropes, vasopressors, and, if indicated, antiarrhythmics.

Oxygenation and Ventilation

Optimal oxygenation and ventilation of children after ROSC may be hampered by the pathology that precipitated the cardiac arrest and by the ensuing post–cardiac arrest pathophysiology. Further management challenges may be caused by aspiration and lung injury occurring during resuscitation efforts,[92] as well as by subsequent ventilator-associated lung injury.[93] In addition, providers must be mindful of the fact that therapeutic hypothermia used after ROSC alters the relationship between arterial oxygen saturation and arterial oxygen tension such that, for a given arterial oxygen saturation, the arterial oxygen tension (Pao_2) is lower than that observed when the temperature is normal. Hypothermia also decreases the metabolic rate; thus, carbon dioxide production will be lower at any given minute ventilation.[94,95] Consequently, the management of the intubated child after cardiac arrest poses unique challenges that require careful consideration.

Oxygenation

Oxygen therapy is a reflexive treatment in critically ill patients, including those who have ROSC after cardiac arrest. Although hypoxemia is widely accepted to be harmful, study conclusions have been inconsistent on the value of high arterial oxygen tension, or hyperoxia, after pediatric cardiac arrest.

Post–cardiac arrest blood gas abnormalities are common in children, particularly in the first hours after ROSC,[33,34] and the published evidence has failed to demonstrate a consistent effect of post–cardiac arrest hyperoxia or hypoxemia on outcome. In a retrospective study of 195 children, only 13% were both normoxemic and normocarbic (ie, normoventilated) in the first 6 hours after ROSC, and arterial hyperoxia was not associated with outcome.[33] In 1 retrospective (n=74)[34] and 1 prospective (n=223)[35] pediatric post–cardiac arrest study, neither hyperoxia (Pao_2 >300 mm Hg) nor hypoxemia (Pao_2 <60 mm Hg) in the first 24 hours after ROSC was associated with 6-month mortality. In contrast, a large multicenter retrospective study of 1875 children after cardiac arrest found increased mortality with both hyperoxia (Pao_2 ≥300 mm Hg; odds ratio, 1.25 [95% CI, 1.17–1.37]) and hypoxemia (Pao_2 <60 mm Hg; odds ratio, 1.92 [95% CI, 1.8–2.21]), with the highest survival among children with a Pao_2 of 60 to 300 mm Hg.[36] To address the impact of cumulative oxygen exposure over time, a 2015 study analyzed arterial blood gas samples at 3 time intervals during the first 24 hours after ROSC in 200 children treated with or without mild therapeutic hypothermia. Survivors had higher cumulative oxygen exposure than nonsurvivors, but this association was seen only in patients treated with mild therapeutic hypothermia.[96]

Existing studies evaluating the effects of hypoxemia and hyperoxia have been subject to clinician discretion as to timing of blood gas analysis, with many reports relying on the first gas analysis and others documenting maximum or minimum blood gas values in a 24-hour period.[34–36,97–102] One or 2 blood gas measurements, possibly hours after ROSC, may not reflect the impact of excessive oxygen administration in the minutes to early hours after ROSC.

After ROSC, it is reasonable to aim for normal Pa_{O_2} (or the value appropriate for the child's condition if the child has, for example, cyanotic heart disease) and to use the lowest possible fraction of inspired oxygen, weaning to maintain an oxygen saturation of 94% to 99% as a guideline.[52] Throughout PCAC, hypoxemia must be avoided whenever possible, particularly during oxygen titration.[58] The 2010 AHA PALS guidelines recommended prompt arterial blood gas analysis as soon as possible after ROSC and within 10 to 15 minutes of establishing initial mechanical ventilation to guide oxygen administration and titration and to support mechanical ventilation.

Ventilation

Post–cardiac arrest derangements in Pa_{CO_2} are common.[33,35,103,104] Alterations in Pa_{CO_2} could affect outcome by exacerbating the ischemic insult through hypocarbia-induced cerebral vasoconstriction[38,105] or through hypercarbia-induced cerebral vasodilation and edema.

Small retrospective pediatric post–cardiac arrest studies have demonstrated that hypocapnia and hypercapnia are common, particularly in the first hours after ROSC. In a prospective, multicenter, observational post–cardiac arrest study of 223 children 1 month to 18 years of age, both hypocapnia (Pa_{CO_2} <30 mm Hg) and hypercapnia (Pa_{CO_2} >50 mm Hg) were present and were independently associated with mortality.[35] However, in a later, smaller retrospective analysis of 195 children 24 hours to 18 years of age, neither oxygenation (ie, Pa_{O_2}) nor ventilation (ie, Pa_{CO_2}) status during the first 6 hours after ROSC was associated with outcome.[33]

Data extrapolated from pediatric critical care suggest that during PCAC, lung protective strategies, including low inspiratory volume and positive end-expiratory pressure, are warranted to minimize lung injury and hemodynamic compromise.[106,107]

On the basis of available evidence, after ROSC, it is reasonable to target normocapnia (ie, normal for the child, or Pa_{CO_2} 35–45 mm Hg) or a Pa_{CO_2} specific for the patient's condition, limiting exposure to severe hypercapnia and hypocapnia.[58] Early evaluation of Pa_{CO_2} is warranted because the initial prescribed minute ventilation may only have a weak correlation with subsequent Pa_{CO_2}.[108] In addition, although it may be helpful to determine the correlation of Pa_{CO_2} with end-tidal CO_2 (P_{ETCO_2}) to assist in noninvasive monitoring of ventilation,[52] clinicians should be cautious in using P_{ETCO_2} as a surrogate for Pa_{CO_2} because cardiac output and increased alveolar dead space will affect their correlation.[109]

Treatment of Persistent Precipitating Pathophysiology

In the immediate post-ROSC period, treatment of the cause of cardiac arrest may require specific targeted interventions (eg, hemodialysis for poisonings, surgery for hemorrhagic shock or intracranial mass lesions). Because these interventions bring an inherent risk of destabilizing the patient, providers must consider their risk-to-benefit ratio. It is essential for all members of the multidisciplinary healthcare team, including anesthetic and surgical team members and other consulting healthcare teams, to have a clear understanding of post–cardiac arrest management priorities.

Targeted Temperature Management

Post–cardiac arrest pyrexia (elevated core body temperature) is common, and persistent hyperthermia is associated with unfavorable neurological outcomes in children.[9,110]

Two recent multicenter multinational randomized controlled trials evaluated the impact of TTM to 32°C to 34°C versus TTM to 36°C to 37.5°C on 1-year survival, with favorable neurological outcome in children >2 days and <18 years of age. The THAPCA study included both an OHCA (THAPCA-OH) trial[3] and an IHCA (THAPCA-IH) trial.[2] For both trials, children comatose within 6 hours of ROSC were randomly assigned to TTM to 32°C to 34°C or TTM to 36°C to 37.5°C. Children randomized to the lower temperature range were cooled to 32°C to 34°C for 48 hours, rewarmed over 16 to 24 hours, and maintained at 36°C to 37.5°C until 120 hours after the initiation of TTM. Children receiving TTM to the higher temperature range were actively maintained at 36°C to 37.5°C for 120 hours (5 days).

In THAPCA-OH,[3] the percentage of survivors with favorable neurological outcomes at 1 year (defined as Vineland Adaptive Behavior Scales, second edition score ≥70) did not significantly differ between the TTM groups (TTM to 32°C–34°C: 20% versus TTM to 36°C–37.5°C: 12%; relative risk, 1.54 [95% CI, 0.86–2.76]; *P*=0.14). Hypokalemia and thrombocytopenia were more common in children treated with TTM to 32°C to 34°C, and renal replacement therapy (RRT) was more frequently used in the TTM to 36°C to 37.5°C group. There was no difference in the incidence of infection, bleeding, serious arrhythmias, or mortality at 28 days.

Enrollment in THAPCA-IH was stopped early because of futility.[2] No differences were observed in 1-year survival with favorable neurological outcome (36% for TTM to 32°C–34°C versus 39% for TTM to 36°C–37.5°C: risk reduction, 0.92 [95% CI, 0.67–.27]; *P*=0.63), change in neurological baseline to 1-year (*P*=0.70), or 1-year overall survival (49% for TTM to 32°C–34°C versus 46% for TTM to 36°C–37.5°C; relative risk, 1.07 [95% CI, 0.85–1.34]; *P*=0.56). Children treated with both TTM regimens had similar side effects.

Important differences exist between the subjects in THAPCA-OH and those in THAPCA-IH. Seventy-two percent of patients in THAPCA-OH had a respiratory

cause of arrest, whereas 65% of patients in THAPCA-IH had a cardiac cause of arrest. Notably, >50% of THAPCA-IH subjects were managed with ECMO. In addition, 37% of patients in THAPCA-IH versus 16% of patients in THAPCA-OH trials had a favorable neurological outcome at the 1-year follow-up.

Implementation of TTM

TTM to 32°C to 34°C can be divided into 3 phases: induction, maintenance, and rewarming.

Induction of hypothermia can be achieved with multiple modalities, including positioning servo-controlled cooling blankets under or above the patient; providing surface cooling with ice packets, a cold-water bath, or a fan; lowering the room temperature; and occasionally performing gastric lavage with iced saline. Target temperature should be achieved as quickly as possible to be effective, but the optimal interval to achieve target temperature is unknown. The use of continuous infusions is relatively safe to lower the temperature, whereas intravenous push administration of cold saline may increase the risk of profound bradycardia.[111] Endovascular cooling catheters are not used in pediatrics because they have a large diameter and may cause thrombosis; they may be considered for older children.[112] Patient core temperature should be continuously monitored.[58] Available techniques include rectal, esophageal, or bladder core temperature probes.

Induction of TTM to 32°C to 34°C is associated with changes in the patient's metabolic rate, serum electrolyte concentrations, and hemodynamics. Hypokalemia, hypophosphatemia, hypomagnesemia, and hypocalcemia develop during hypothermia and may precipitate arrhythmias.[3,4,112–114] Close monitoring of electrolyte concentrations and treatment of imbalances are required, especially during induction of hypothermia. Hypothermia also decreases insulin sensitivity, and patients are at risk for hyperglycemia.[115] Bradycardia and hypotension have been observed.[112,113,116] Although thrombocytopenia has been observed during hypothermia,[3,112] it has not been associated with an increase in bleeding or blood product requirements. Hypothermia can alter the immune system function, but no differences in rates of infections were noted in the recent THAPCA trials.[2,3,113]

The maintenance phase of TTM to 32°C to 34°C requires careful monitoring to avoid fluctuations in temperature. Topjian et al[112] reported only 78% compliance with recommended temperature range (ie, more than one-fifth of patients were not maintained at the recommended temperature) despite the use of a management protocol. Temperatures <32°C have been reported in ≈15% of patients in hypothermia studies[112,113] and have been associated with increased mortality.[113,116] The ideal duration of hypothermia is unknown.

Published studies have not identified an optimal method or rate of rewarming after TTM to 32°C to 34°C. In children, warming is generally accomplished at a rate no faster than 0.5°C every 2 hours to reduce the risk of cerebral hyperperfusion, vasogenic edema, and acute systemic hypotension that has been documented during rewarming of children treated with hypothermia after traumatic brain injury.[117] For children who are comatose after OHCA and IHCA, TTM to 32°C to 34°C for 24 to 48 hours is relatively safe.[2,3,116] It is unclear whether a shorter interval to achieve target temperature, a shorter or longer duration of targeted temperature control, or a different temperature target would provide benefit.

During PCAC, fever (≥38°C) should be aggressively treated.[58] Timely continuous core temperature monitoring and active methods to achieve TTM should be used for patients who are comatose after ROSC. To treat the child who remains comatose after OHCA, the 2015 AHA PALS guidelines update recommended that it is reasonable either to maintain continuous normothermia (TTM to 36°C–37.5°C) for 5 days or to maintain 2 days of continuous hypothermia (TTM to 32C°–34°C) followed by 3 days of continuous normothermia (TTM to 36°C–37.5°C).[2] Because increased mortality was associated with temperatures <32°C, if TTM to 32°C to 34°C is used, meticulous care must be provided to prevent temperatures <32°C.[2,113,118]

Sedation and Neuromuscular Blockade

Children with PCAS are likely to need treatment with sedatives or analgesics. Individual patients may have different drug requirements (in choice of both agents and dose) based on comorbidities, patient age, developmental status, the degree of neurological injury, and the interval since the cardiac arrest.[119] No high-quality evidence exists to guide decisions on sedation/analgesia for children with PCAS.

Data on the pharmacological approach to analgesia and sedation in adults are limited,[120] and pharmacological approaches vary considerably in actual practice. Combinations of opioids and benzodiazepines are commonly used in adults, although sedative-anesthetic agents such as propofol and dexmedetomidine are also options.[120] The use of these drugs must be balanced against the risk of complications (eg, infection and pneumonia, hypotension, and prolonged mechanical ventilation) that may arise from their use. In adult patients with PCAS, excessive medication effects resulting in persistent sedation confound neurological examination and prognostication.[121] There is insufficient evidence to determine how commonly this occurs in children or how long these agents should be withheld before a clinical examination is used for prognostication.

Sedation and analgesia are important to manage the shivering that commonly occurs in patients being treated with TTM.[122] Shivering can increase cerebral metabolic rate at a time when cerebral oxygen delivery may already be compromised by inadequate cardiac output; this can create secondary cerebral injury.[123] Shivering can also worsen fever or cause temperature instability, complicating TTM.[124] It is important to note that shivering can occur at different goal temperatures during TTM, including both therapeutic hypothermia (32°C–34°C) and therapeutic normothermia (36°C–37.5°C).[125]

Opioids, given by either bolus or infusion, are commonly used first-line agents to treat shivering. However, the aggressive use of sedatives/hypnotics or opioids may lead to hypotension. The limited published evidence on the effects and complications of sedation and analgesia protocols during hypothermia consists of small adult series.[126,127]

Neuromuscular blockade (NMB) can facilitate cooling of the patient with PCAS. No pediatric studies as yet have reported associations between NMB use for cooling and patient outcomes. Adult data on this are conflicting.[128,129] Adults who received bolus-dose NMB had faster time to achieve NMB,[129] required lower cumulative doses of midazolam and fentanyl, had a higher number of administered doses of rocuronium, but had earlier wakening and shorter ICU stays.[122]

The use of NMB masks response during the clinical neurological examination and can potentially lead to oversedation, undersedation, or masking of worsening neurological examination findings. In addition, NMB will mask seizures. Further research is needed to evaluate the role of cerebral physiological monitoring to guide sedation in the patient with PCAS.

If TTM is used, practitioners must be aware that the pharmacokinetics and pharmacodynamics of sedatives/hypnotics and neuromuscular blocking agents will be altered, resulting in prolonged time to both hepatic and renal clearance.[130] Reduced clearance of these drugs will delay practitioners' ability to clinically assess patients and to reliably prognosticate patient outcome.[131] Drug metabolism may be further complicated by the multiple organ dysfunction often associated with PCAS.[132] Train-of-four monitoring can help quantify the degree of NMB in patients with PCAS but has been shown to be less reliable when used in hypothermic patients.[133]

The 2010 AHA PALS guidelines[52] recommended controlling pain and discomfort with analgesics (eg, morphine, fentanyl) and sedatives (eg, lorazepam or midazolam). Neuromuscular blocking agents (eg, vecuronium or pancuronium) with analgesia or sedation (or both) may improve oxygenation and ventilation in case of patient-ventilator dyssynchrony or severely compromised pulmonary function. Providers are cautioned, however, that NMB agents can mask seizures and impede neurological examinations.[52]

Treatment of Seizures

Seizures occur in 10%[134] to 50%[135] of children who remain encephalopathic after achieving ROSC. The seizure burden is often substantial, with electrographic status epilepticus in approximately half of those children who experience seizures after ROSC.[135] Furthermore, about half of children with post-ROSC seizures experience exclusively nonconvulsive (subclinical, EEG only) seizures, which cannot be identified by clinical observation alone.[135] Although most studies used to predict seizure incidence include heterogeneous pediatric cohorts with subsets of patients with hypoxic-ischemic brain injury,[136–148] several single-center studies have described larger cohorts of children after cardiac arrest.[134,149] An early, small prospective study of consecutive children undergoing therapeutic hypothermia after cardiac arrest reported electrographic seizures in 47%; two-thirds had nonconvulsive status epilepticus, and one-third had only electrographic seizures without any clinical signs.[135] Seizures occurred more often in those subjects with more abnormal EEG background patterns (eg, excessive discontinuity, burst suppression, or highly attenuated featureless tracings).[135] Recent pediatric series demonstrated lower seizure rates, which may reflect the inclusion of less severely injured patients with increased use of EEG monitoring over time. Two recent retrospective studies of children during PCAC demonstrated electrographic seizures in 10%[149] to 16%,[134] and 71%[149] to 80%[134] of these constituted electrographic status epilepticus. Seizures could not be predicted from any clinical or resuscitation variables. Seizures were associated with unfavorable gross neurological outcomes at discharge but not with higher mortality.

In a 2013 survey of primarily large academic pediatric institutions in the United States and Canada, 68% of institutions performed continuous EEG monitoring to identify electrographic seizures in children after cardiac arrest.[60] A recent consensus statement from the American Clinical Neurophysiology Society Critical Care Continuous EEG Guidelines Committee recommends continuous EEG monitoring for adult and pediatric patients who remain encephalopathic after cardiac arrest to identify electrographic seizures.[150,151] The statement recommends initiating EEG monitoring as soon as feasible, continuing monitoring for 24 to 48 hours in most patients, but continuing until after 24 hours of normothermia in patients treated with hypothermia.[150,151]

Because seizures increase metabolic demand, can worsen metabolic dysfunction, and can increase intracranial pressure, they can contribute to secondary brain injury. For these reasons, many clinicians aim to treat seizures, although the approach is generally guided by the child's overall medical condition and other prognostic indicators. However, we found insufficient evidence to determine whether treatment of clinical or electro-

graphic seizures results in improved patient outcomes and what the optimal methods are to manage seizures after cardiac arrest.

Typical acute clinical or electrographic seizures are often initially treated with benzodiazepines, levetiracetam, or phenytoin. Myoclonic seizures may be refractory to treatment.[149] Providers must be alert for potential adverse effects of anticonvulsants such as cardiac arrhythmias, hypotension, and respiratory depression. In addition, sedation induced by antiseizure drugs may complicate the neurological examination.

Prospective studies are needed to determine the impact of seizures on patient outcomes and whether treatment of seizures in the post–cardiac arrest period improves patient outcomes.

Glucose Control

There is very limited published evidence on post–cardiac arrest glucose control. In a large multicenter retrospective cohort of children with IHCA in an 18-month period during 2003 and 2004 (n=353), peak glucose concentrations in the first 12 hours after cardiac arrest were not associated with mortality in a multivariable logistic regression model that included prearrest, intra-arrest, and post–cardiac arrest clinical and laboratory factors.[152] To date, no interventional clinical trials of glucose control have focused exclusively on children during PCAC.

Both hypoglycemia and hyperglycemia have been associated with unfavorable outcomes in critically ill children[153–155] and adults.[156–158] Randomized controlled trials using insulin infusions to maintain tight glycemic control in critically ill children[159–161] and adults[159,162] have had mixed results and have raised concerns about the long-term effects of episodes of hypoglycemia observed in patients randomized to tight glycemic control.[160,161,163] Most recently, a 35-center randomized controlled trial of lower-target glucose versus higher-target glucose control involving 713 infants and children (2 weeks–17 years of age) was stopped early because of a low likelihood of benefit and the possibility of harm associated with lower-target glucose control. This trial randomized critically ill children who had confirmed hyperglycemia (2 consecutive measurements of serum glucose ≥150 mg/dL or ≥8.3 mmol/L) to a lower-target glycemic control group (glucose concentration maintained 80–100 mg/dL or 4.4–6.1 mmol/L) or a higher-target group (glucose concentration maintained 150–180 mg/dL or 8.3–10.0 mmol/L). The serum glucose concentration was measured continuously, and a continuous insulin infusion was titrated to maintain the serum glucose within the target range. There were no differences in the primary outcome of ICU-free days between the 2 groups, but the lower-target glucose group had higher rates of health care–associated infections and of severe hypoglycemia, defined as a blood glucose level <40 mg/dL (2.2 mmol/L).[160]

During PCAC, clinicians should avoid and promptly treat hypoglycemia. Historically, the PALS course has defined hypoglycemia as a glucose concentration ≤45 mg/dL in the newly born and ≤60 mg/dL in the child. Severe hyperglycemia can also be problematic because it can lead to uncontrolled osmotic diuresis, which can exacerbate post–cardiac arrest volume depletion and hemodynamic instability. Therefore, it is important to monitor serum glucose concentration, to treat significant hyperglycemia, and to monitor urine volume.

There is currently insufficient published evidence to determine the optimal blood glucose concentration during PCAC that will maximize neurological outcome. In addition, there is insufficient published evidence to determine the ideal method of controlling serum glucose concentration, the ideal duration of any glucose control, and the ideal frequency of glucose monitoring needed to reduce the risk of hypoglycemia.

Identification and Treatment of Adrenal Dysfunction

We were not able to identify any published data on the methods of identification, the incidence, the outcome, or the effectiveness of treatment of adrenal insufficiency in pediatric patients after cardiac arrest. Relative adrenal insufficiency is common after adult cardiac arrest and is associated with low survival to hospital discharge.[164,165] In several small adult series, nonsurvivors (compared with survivors) had higher cortisol and adrenocorticotropic hormone levels and a less robust response to adrenocorticotropic hormone stimulation during the first 48 hours after ROSC.[164,166–168] In a randomized double-blind placebo-controlled adult trial, administration of stress-dose hydrocortisone for shock after ROSC did not improve post–cardiac arrest outcomes, including time to shock reversal, neurological outcome, and survival to hospital discharge.[169] Acknowledging the low quality of published evidence available, recent guidelines from the Society of Critical Care Medicine on adult critical illness–related corticosteroid insufficiency suggest the use of corticosteroids after adult cardiac arrest. This language is consistent with a weak or conditional recommendation.[170]

Approximately 30% of critically ill children have relative adrenal insufficiency, but this has not been evaluated in children resuscitated from cardiac arrest.[171] Although critically ill children who have relative adrenal insufficiency require more vasopressor support and fluid boluses to maintain blood pressure, a recent meta-analysis did not demonstrate a difference in outcomes between those who did and those who did not receive exogenous steroids.[172] Current guidelines for the management of pediatric and neonatal sepsis recommend that the provider

consider steroid administration if the patient is at risk for adrenal insufficiency with refractory shock.[147]

There is insufficient evidence to support the routine use of corticosteroids after cardiac arrest. Patients should be treated per recommendations for critically ill children.

Management of Renal Failure

Data describing the incidence and clinical course of pediatric post–cardiac arrest acute kidney injury (AKI) are limited. In a recent retrospective study of 296 children during PCAC, 37% had AKI, 11.5% had severe AKI by Acute Kidney Injury Network criteria, and 6.4% required RRT within 48 hours of ROSC.[173] Risk factors for severe AKI after cardiac arrest included abnormal baseline creatinine, lack of a chronic lung condition, in-hospital arrest location, higher number of doses of epinephrine during arrest, and worse post–cardiac arrest acidosis.[173] In the THAPCA-OH trial, 4.4% of patients required RRT in the 5 days after ROSC; RRT was needed more often in patients treated with TTM to 36°C to 37.5°C than in those treated with TTM to 32°C to 34°C.[3] In the THAPCA-IH study, 24% of patients required RRT, but there was no difference between TTM treatment groups.[2]

AKI in critically ill children is associated with increased mortality and morbidity. Children with severe AKI who were treated with RRT or vasoactive support had significantly increased mortality.[174] Notably, risk factors for early AKI include preadmission cardiac arrest and a serum pH <7.21, among other independent predictors identified within 72 hours of admission.[175]

Throughout PCAC, it is important to monitor kidney function, including urine output and creatinine, because patients are at risk for developing AKI, and RRT may be indicated. Nephrotoxic medications and medications excreted by the kidneys should be used with caution, and dose adjustment may be needed. Serum concentrations of nephrotoxic medications should be closely monitored.

Incidence of Infection

Infection is common after pediatric cardiac arrest. Most studies reporting the incidence of infection during PCAC enrolled children treated with therapeutic hypothermia with temperatures <36°C rather than those treated with TTM to 36°C to 37.5°C.

In a systematic review of therapeutic hypothermia after pediatric cardiac arrest (n=102), 27.5% of children treated with therapeutic hypothermia were diagnosed with post–cardiac arrest pneumonia, and 9.8% were diagnosed with post–cardiac arrest sepsis.[118]

In the THAPCA trials, infection within 7 days of randomization was reported as a safety outcome.[2,3] For IHCA, the incidence of culture-proven infection did not differ between patients treated with TTM to 32°C to 34°C (incidence, 27%) and those treated with TTM to 36°C to 37.5°C (incidence, 29%). The rate of infections per 100 days was 5.0 (95% CI, 3.7–6.5) in the TTM to 32°C to 34°C group and 4.9 (95% CI, 3.7–6.4) in the TTM to 36°C to 37.5°C group.[2] For OHCA, culture-proven infection did not differ on the basis of TTM temperature range, occurring in 46% of patients treated with TTM to 32° to 34°C and 39% of patients treated with TTM to 36°C to 37.5°. The rate of infections per 100 days was 11.1 (95% CI, 9.2–13.4) in the group treated with TTM to 32°C to 34°C and 9.9 (95% CI, 7.8–12.4) in the group treated with TTM to 36°C to 37.5°C.

In a single-center retrospective study of therapeutic hypothermia (33.5°C–34.8°C) versus standard of care after pediatric cardiac arrest, 8.8% of subjects had a positive culture on days 3 and 4 after the arrest, considered to represent hospital-acquired infection. However, there was no difference in the incidence of positive cultures between patients treated with hypothermia and those receiving standard care.[113]

Similar rates of post–cardiac arrest infection occurred in children who received ECPR.[176] Data from the ELSO registry (Extracorporeal Life Support Organization) between 1998 and 2008 documented a 10.8% infection rate during ECMO therapy, translating to 22.8 infections per 1000 ECMO days.[176]

Monitoring for signs of infection is important during PCAC. The decision to obtain cultures and to initiate empirical antimicrobial coverage should follow local PICU protocols.

Management of Inflammation and Coagulation Abnormalities

Inflammatory pathways are activated as part of PCAS, including disturbances of the coagulation cascade. The effects of blocking or modulation of these pathways have been studied in adults and in animal models; we identified no studies to date involving infants or children.

Recent adult randomized controlled trials have failed to demonstrate any positive effect of post–cardiac arrest intravenous hydrocortisone on time to shock reversal in patients with vasopressor-dependent shock,[169] post–cardiac arrest intravenous cyclosporine on multiple organ failure in OHCA with nonshockable rhythms,[177] post–cardiac arrest intravenous erythropoietin on improved neurological outcome in comatose survivors of OHCA,[178] or administration of the glucagon-like peptide-1 analog exenatide on serum levels of neuron-specific enolase (NSE; as a marker of neurological injury) in comatose patients during the first 72 hours after admission after OHCA.[179]

A recent multicenter randomized single-blind controlled trial in adults after IHCA compared 28-day survival after a standardized post–cardiac arrest bundle of care with or without a 14-day course of intravenous Shenfu, a traditional Chinese medicine with anti-inflammatory and antiapoptotic properties.[180] The trial (n=978) demonstrated a 12% absolute increase in 28-day survival (number needed to treat, 8) that persisted with multivariable analysis. Although the results of this single study are encouraging, validation of the results in larger studies in adults and children is required.

Extensive animal research into blocking or modifying inflammatory pathways has yielded promising results. However, to date, most attempts to translate this work to humans have been unsuccessful.

Because inflammation can alter the coagulation cascade, providers should monitor for signs of bleeding or coagulopathies; this is particularly important for patients receiving ECMO support. At this time, there is insufficient evidence to support specific treatments to modulate inflammatory pathways during PCAC.

Rehabilitation and Recovery After Cardiac Arrest

Children surviving cardiac arrest are at high risk for physical, cognitive, and emotional disabilities that can affect quality of life, family function, activities of daily living, school performance, and employment.[181–184] Longitudinal and comprehensive patient and family evaluations are not routinely performed after cardiac arrest, although there is mounting evidence that they are needed.

Although several patient, family, event, and hospital care characteristics associated with outcomes after pediatric OHCA are well understood,[13,18] there is little evidence on specific interventions during PCAC that will improve functional outcomes of children after cardiac arrest. Small observational studies of children after critical illness or injury suggest that children with anoxic injury have more severe disability and demonstrate less improvement compared with children with traumatic brain injury.[185,186]

There is insufficient evidence to support specific rehabilitation interventions or the optimal timing of initiation of such interventions. However, on the basis of the benefits of rehabilitation for patients with traumatic brain injury and stroke, it is reasonable for providers to consult rehabilitation experts within the first 72 hours after cardiac arrest to tailor a plan of rehabilitation interventions for survivors of cardiac arrest.

There is a critical need to determine the effectiveness of specific rehabilitation interventions for pediatric survivors of cardiac arrest, the best time to initiate rehabilitation therapy (ie, early in the ICU versus after discharge), and doses of specific interventions (eg, physical therapy, cognitive therapy). In addition, more information is required to identify the optimal timing of pediatric post–cardiac arrest longitudinal outcomes assessment and the optimal tools to use.

Table 3. PCAC Checklist

Oxygenation and ventilation	
Measure oxygenation and target normoxemia 94%–99% (or child's normal/appropriate oxygen saturation).	☐
Avoid hypoxemia.	☐
Measure $Paco_2$ and target a clinically appropriate value.	☐
Avoid hypocapnia.	☐
Hemodynamic monitoring	
Set specific hemodynamic goals during PCAC and review daily.	☐
Use cardiac telemetry.	☐
Monitor arterial blood pressure.	☐
Monitor serum lactate, urine output, and central venous oxygen saturation to help guide therapies.	☐
Use parenteral fluid bolus with or without inotropes or vasopressors to maintain a systolic blood pressure greater than the fifth percentile for age and sex.	☐
TTM	
Measure and monitor continuous core temperature.	☐
Prevent and promptly treat fever.	☐
Apply TTM (32°C–34°C) for 48 h and then maintain TTM (36°C–37.5°C) for 3 d after rewarming, or apply TTM (36°C–37.5°C) for 5 d if patient is unresponsive after ROSC.	☐
Prevent shivering.	☐
Monitor blood pressure and treat hypotension during rewarming.	☐
Prevent fever after rewarming.	☐
Neuromonitoring	
Treat clinical seizures.	☐
Ensure no routine use of pharmacological prophylaxis for seizures.	☐
Consider early brain imaging to diagnose treatable causes of cardiac arrest.	☐
Glucose control	
Measure blood glucose.	☐
Avoid hypoglycemia.	☐
Sedation	
Treat with sedatives and anxiolytics.	☐
Prognosis	
Always consider multiple modalities (clinical and other) over any single predictive factor.	☐
EEG in conjunction with other factors may be useful within the first 7 d of PCAS.	☐
Neuroimaging such as MRI during the first 7 d may be valuable.	☐
Remember that assessments may be modified by TTM or induced hypothermia.	☐

EEG indicates electroencephalogram; MRI, magnetic resonance imaging; PCAC, post–cardiac arrest care; PCAS, post–cardiac arrest syndrome; ROSC, return of sustained circulation; and TTM, targeted temperature management.

Summary

Collectively, these data suggest that, similar to sepsis, a bundle of PCAC targeting multiple physiological processes, including circulatory support and support of oxygenation and ventilation, may be more effective than any single intervention. PCAC may need to be individually tailored on the basis of the child's age, cause of cardiac arrest, comorbidities, and phase of PCAS.[187] A standardized approach such as a checklist (Table 3) can help the clinician confirm that important therapeutic options are addressed.

POST–CARDIAC ARREST PROGNOSTICATION

Observational studies of pediatric cardiac arrest have identified numerous prearrest, intra-arrest, and post–cardiac arrest factors that have been associated with favorable or unfavorable patient outcomes in univariate analysis. However, the list of factors associated with significant differences in outcomes becomes substantially shorter when these factors are further subjected to multivariable logistic regression analysis. Even those variables that are strongly associated with outcomes have limited prognostic ability for individual patients who are likely to have unmeasured confounders. Providers must consider multiple variables when attempting to prognosticate outcomes during and after cardiac arrest. Although there are factors associated with better or worse outcomes, no single factor studied predicts outcome with sufficient accuracy to recommend termination or continuation of CPR or to enable prognostication after ROSC.[58] Understanding these factors may help providers evaluate and treat children during PCAC and anticipate a child's severity of illness and potential for recovery.

Prearrest Factors Associated With Outcomes

Several prearrest conditions and therapies have been independently associated with worse survival to discharge and unfavorable neurological outcomes after pediatric cardiac arrest (Table 4).[12,13,21,87,152,188–196,199] Worse outcomes from OHCA are associated with decreased age[13,188] and some causes of arrest, including sudden infant death syndrome[194] and blunt trauma.[193] Factors associated with lower survival after IHCA include older age[21,189]; presence of preexisting conditions[21,87,190–192,194]; interventions such as tracheal intubation,[152,190] mechanical ventilation,[194] and use of vasopressors at the time of arrest[87,191,192]; and arrests occurring during nights and weekend shifts.[195]

Initial Arrest Rhythms Associated With Outcomes

For both OHCA[12,199,200] and IHCA,[190,201] initial arrest rhythms of bradycardia[190] and ventricular fibrillation/pulseless ventricular tachycardia were associated with higher survival. For IHCA[198] and OHCA,[188] pulseless electrical activity was also associated with higher survival than asystole.

Intra-Arrest Factors Associated With Outcomes

Multiple intra-arrest factors are associated with better patient outcomes after OHCA, including witnessed arrest,[13,188] bystander CPR,[200] and less frequent doses of epinephrine.[204] Better patient outcomes from IHCA were associated with shorter time to epinephrine administration,[198] use of ECPR,[190] AHA-compliant CPR compression depth,[206] and diastolic blood pressure >25 mm Hg in infants and >30 mm Hg in children.[205]

Table 4 provides additional details of factors independently associated with resuscitation outcomes in children.

Post–Cardiac Arrest Assessment and Factors Associated With Outcomes

Post–cardiac arrest assessment findings and factors associated with outcome and their role in neuroprognostication are described in the following sections.

Clinical Neurological Examination

Post–cardiac arrest prognostication using neurological examination in children must consider the child's developmental stage and can be complicated by the use of pharmacological agents (ie, sedatives, analgesics, and NMB agents) and by pathophysiological states such as hypotension and severe metabolic abnormalities. There is little high-quality evidence to support the use of isolated abnormal neurological examination findings for post–cardiac arrest prognostication in children. In a small prospective cohort of 57 consecutive children with hypoxic ischemic injury, including 44 who had cardiac arrest, 3 characteristics had a 100% positive predictive value of unfavorable outcome: a Glasgow Coma Scale score <5, the absence of spontaneous respiratory activity, and the absence of pupillary reflexes at 24 hours after ROSC.[209] A small pediatric study of outcomes after acute brain insult or injury included 36 children after cardiac arrest. The sensitivity and specificity for unfavorable outcome (ie, severe disability on Glasgow Outcome Scale or death at 5 years after injury) were 93% and 50% for absent motor response and 47% and 100% for absent pupillary response, respectively.[210]

Table 4. Summary of Key Prearrest and Intra-Arrest Factors That Are Independently Associated With Outcomes

Phase	Factor*	Outcome Type	Survival	Arrest Location
Prearrest	Younger age:			
	Fink et al[13]	Survival to hospital discharge	Decreased	OHCA
	Goto et al[188]	1-mo survival		
	Older age[21,189]	Survival to hospital discharge	Decreased	IHCA
	Preexisting condition: Genetic/metabolic[152] Acute renal failure[21,87,190] Sepsis[21,191] Hepatic insufficiency[21] Hematologic/oncological/immunological[152,191,192] Baseline neurological abnormality[21,192] Congenital heart disease[21]	Survival to hospital discharge	Decreased	IHCA
	Preexisting lung/airway disease[18]	Survival to hospital discharge	Increased	OHCA
	Postoperative patient[152] Post–cardiac surgery[193]	Survival to hospital discharge	Increased	IHCA
	Intervention in place: Endotracheal tube[152,190] Vasopressor infusion[87,191,192]	Survival to hospital discharge	Decreased	IHCA
	Cause of arrest:			
	SIDS[194]	1-y survival	Decreased	OHCA
	Trauma[193]	Survival to hospital discharge	Decreased	IHCA
	Drowning[12,18]	Survival to hospital discharge	Increased	OHCA
	Asthma[21]	Survival to hospital discharge	Increased	IHCA
	Day and time of arrest:			
	Nights[195]	Survival to hospital discharge	Decreased	IHCA
	Nights[196]	1-mo survival	Decreased	OHCA
	Weekends:			
	Meert et al[194]	1-y survival	Decreased	OHCA
	Kitamura et al[196]	1-mo survival		
	Public-access defibrillation[197]	1-mo survival	Increased	OHCA
	Shorter EMS response time[188]	1-mo survival	Increased	OHCA
Intra-arrest	Witnessed status:			
	Goto et al[188]	1-mo survival	Increased	OHCA
	Fink et al[13]	Survival to hospital discharge		
	Meert et al[194]	1-y survival		
	Andersen et al[198]	Survival to hospital discharge		IHCA
	Arrest rhythm VF/pVT:			
	Tijssen et al[12]	Survival to hospital discharge	Increased	OHCA
	Kitamura et al[199]	1-mo survival		
	Goto et al[200]			
	Initial VF/pVT vs initial non-VF/VT[190,201]: PEA vs asystole[198] Bradycardia[190]	Survival to hospital discharge	Increased	IHCA
	PEA vs asystole[188]	Survival to hospital discharge	Increased	OHCA
	Asystole[13] PEA[12]	Survival to hospital discharge	Decreased	OHCA
	Subsequent VF/pVT vs primary VF/pVT[191] Subsequent VF/pVT vs primary non-VF/pVT[191]	Survival to hospital discharge	Decreased	IHCA
	Subsequent VF/pVT vs sustained non-VF/pVT[188]	1-mo favorable neurological survival	Increased	OHCA

(*Continued*)

Table 4. Continued

Phase	Factor*	Outcome Type	Survival	Arrest Location
Intra-arrest (Continued)	Shorter time to shock for subsequent VF/VT[188]	1-mo favorable neurological survival	Increased	OHCA
	CPR with ventilation vs chest compression–only CPR:			
	Infants[202]	Survival to hospital discharge	Increased	OHCA
	>1 y of age[202,203]	1-mo favorable neurological survival or survival to hospital discharge	No difference	
	Bystander CPR[200]	1-mo survival	Increased	OHCA
	Dispatcher-assisted CPR[200]	1-mo survival	Increased	OHCA
	Less frequent epinephrine administration[204]	Survival to hospital discharge	Increased	IHCA
	Shorter time to epinephrine[198]	Survival to hospital discharge	Increased	IHCA
	Use of ECPR[190]	Survival to hospital discharge	Increased	IHCA
	Shorter EMS scene time[12]	Survival to hospital discharge	Increased	OHCA
	Diastolic blood pressure ≥25 mm Hg in infants, ≥30 mm Hg in children during CPR[205]	Survival to hospital discharge	Increased	IHCA
	AHA-compliant CPR depth (>1 y) ≥51 mm[206]	Survival to hospital discharge	Increased	IHCA
	Drugs administered during CPR: Calcium[87,152] Sodium bicarbonate[152,190] Epinephrine[190] Atropine[18] Epinephrine[18,188]	Survival to hospital discharge	Decreased	IHCA
	Longer duration of CPR			
	Goto[188]	1-mo survival	Decreased	OHCA
	López-Herce et al[207]	1-y survival		OHCA
	Meert et al[194]			
	Del Castillo et al[192]	Survival to hospital discharge		IHCA
	Matos et al[193]			
	Endotracheal intubation during CPR[208]	Survival to hospital discharge	Decreased	IHCA

AHA indicates American Heart Association; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal resuscitation (use of extracorporeal circulation during resuscitation); EMS, emergency medical services; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; SIDS, sudden infant death syndrome; VF/pVT, ventricular fibrillation/pulseless ventricular tachycardia; and VF/VT, ventricular fibrillation/ ventricular tachycardia.

*When a series of publications studying prognostic factors is derived from a single registry, the most recent publication from that registry is cited in this table.

In a small single-center study of pediatric IHCA and OHCA treated with therapeutic hypothermia, absent motor and pupillary responses during therapeutic hypothermia did not predict unfavorable outcome (Pediatric Cerebral Performance Category [PCPC] 4–6) at hospital discharge, but if these were absent at hour 24 after restoration of normothermia, they predicted unfavorable outcome at hospital discharge.[211] In 2 multicenter cohort studies of pediatric OHCA and IHCA, the presence of bilateral reactive pupils at 12 hours after resuscitation was independently associated with lower mortality at hospital discharge, although neurological outcomes were not assessed.[18,152]

For adults who are comatose after cardiac arrest, the 2015 AHA advanced cardiac life support guidelines update recommended that the earliest time to prognosticate unfavorable neurological outcome by using clinical examination in patients not treated with TTM is 72 hours after the arrest. The recommendations noted that the time until prognostication can be even longer if residual effects of sedation or NMB confound the clinical examination. For adult patients treated with TTM, the 2015 AHA advanced cardiac life support guidelines update noted that when a clinical examination is used in which sedation or paralysis could be a confounder, the timing for prognostication may be 72 hours after return to normothermia. The 2015 AHA advanced cardiac life support guidelines update noted that operationally this is typically 4.5 to 5 days after ROSC for patients treated with TTM.[212]

Given the absence of prospective data on the reliability and optimal timing of the clinical examination for neuroprognostication in children after cardiac arrest, adult studies were reviewed. Extrapolation from adult data and from the minimal pediatric data available suggests that caution should be used in the interpretation of the clinical neurological examination early after cardiac arrest. The reliability of the clinical neurological

examination in predicting neurological outcome improves with the use of serial examinations and with the passage of time after cardiac arrest. For children treated with hypothermia, the duration of normothermia (after rewarming) required to enable reliable interpretation of clinical findings has not been established.

Given the limitations of neurological examination in children after cardiac arrest, supporting neurophysiological tests (eg, EEG, evoked potentials [EPs], CBF and autoregulation,[64,213–215] neuroimaging,[61,216] and plasma biomarkers [ie, brain-specific proteins[217–220]]) are being actively studied in an effort to improve prognostication capabilities. These neurological tests are detailed in the following sections.

Neurophysiological Tests

Electroencephalography

EEG provides objective data on brain function and is often used to assess encephalopathy and to classify brain injury severity in children after cardiac arrest. EEG data can be acquired noninvasively at the bedside and may be assessed continually or at repeated intervals. Key EEG background features in children after cardiac arrest have substantial or better interrater agreement when interpreted by trained pediatric electroencephalographers.[137,221] However, technical expertise is required to obtain a high-quality EEG recording, and knowledge of the patient's clinical status is essential to ensure that EEG changes are not pharmacologically induced, related to substantial hypothermia, or caused by scalp edema or extra-axial fluid collections.[150] Furthermore, none of the EEG features have perfect predictive value for unfavorable outcomes, and none have been assessed with longer patient-centered neurobehavioral outcomes, so it is important to consider EEG findings within the overall clinical context.

Children with more severely abnormal EEG background patterns after cardiac arrest tend to have worse outcomes than patients with only mild or moderate background abnormalities. A single-center study assessed the EEG background in the initial 24 hours after cardiac arrest in 128 children who were not treated with therapeutic hypothermia.[134] The EEG background was categorized (from normal to worst) as normal, slow-disorganized, discontinuous or burst-suppression, or attenuated-featureless. After controlling for clinical covariates, for each incrementally worse background score, the odds of death were 3.6 and the odds of unfavorable neurological outcome at discharge were 4.4. In another single-center study of 73 children after cardiac arrest, including some who were treated with therapeutic hypothermia, continuous background EEG activity within 12 hours of ROSC was associated with favorable neurological outcome at hospital discharge.[149] In a third single-center study of 34 children after cardiac arrest, the presence of sleep spindles on the initial EEG at 24 hours, whether normal or abnormal morphologically, was associated with favorable outcome at 6 months. The sleep spindles were not present until a median of 12 hours after cardiac arrest, indicating that a long period of assessment, rather than a brief EEG, may be necessary to evaluate for sleep spindles.[222]

A study of 35 children managed with therapeutic hypothermia after cardiac arrest found that during hypothermia and normothermia phases, EEG tracings that were unreactive, were discontinuous or burst-suppressed, or lacked definite cerebral activity were associated with unfavorable gross neurological outcomes at discharge.[223] Similarly, a single-center study of 34 children after cardiac arrest who had EEGs obtained clinically at varying times after ROSC found that discontinuous and isoelectric EEG patterns had a 90% positive predictive value for unfavorable neurological outcome, whereas the negative predictive value of a continuous normal-voltage EEG for unfavorable neurological outcome was 91%.[224]

At the extremely low temperatures used in deep hypothermic circulatory arrest, the EEG may develop a discontinuous and then isoelectric pattern.[225–227] Although these severe EEG abnormalities were not seen with therapeutic hypothermia to temperatures as low as 33°C, EEG patterns sometimes evolved during the course of therapeutic hypothermia[135,228] as the result of evolving brain injury, temperature modulation, or sedative medication adjustments. Recent studies have demonstrated that EEG patterns seen during therapeutic hypothermia (32°C–34°C) have the same prognostic significance as those seen during normothermia.[223]

Older and smaller studies have reported that burst-suppression,[229] excessive discontinuity,[209] severe attenuation,[230] lack of reactivity,[209,231] and generalized epileptiform discharges[209] are associated with unfavorable prognosis. Conversely, rapid EEG improvement,[232] reactivity,[233] and normal sleep patterns[233,234] are associated with favorable prognosis.

Although alpha coma is often considered in relation to anoxic encephalopathy and unfavorable prognosis, it is a nonspecific pattern that can occur with a wide variety of pathogeneses, and outcome is probably chiefly dependent on pathogenesis. Alpha coma that is reactive to stimulation may indicate a more favorable prognosis.[235]

Future studies are needed with standardized EEG assessment from consecutive cohorts of children to identify the EEG patterns or combinations of patterns that predict not only short-term gross neurological outcomes but also patient-centered long-term neurobehavioral outcomes.

The 2015 AHA PALS guidelines update recommended that EEGs performed within the first 7 days after pediatric cardiac arrest may be considered in prognosticating neurological outcome at the time of hospital discharge but should not be used as the sole criterion.[58]

Evoked Potentials

The use of EPs for neuroprognostication is appealing because they can be performed at the bedside, are not affected by sedation or hypothermia, and can be assessed at repeated time points. The most commonly used EP is the somatosensory EP (SSEP). The SSEP tests the integrity of the peripheral nerve (median nerve), spinal cord, brainstem, and cerebral cortex (N20 wave). However, to avoid falsely concluding that absent N20 waves are caused by severe brain injury, it is important to consider that lesions before the N20 wave may impair SSEP conduction and that extra-axial lesions may impair the ability to record the N20 wave. Although a bilateral absence of the N20 waveform in adult comatose survivors of cardiac arrest on day 3 generally predicts unfavorable outcomes,[236] little information is available in children after cardiac arrest. A study of 42 children with hypoxic-ischemic encephalopathy who were comatose at 24 hours after PICU admission with unclear prognosis found that the bilateral absence of the N20 wave had 100% positive predictive value for unfavorable outcome.[209] This finding is consistent with smaller, older case series.[237,238] Studies that included populations with more heterogeneous pathogeneses (not only children with hypoxic-ischemic encephalopathy) showed similar findings but with slightly lower sensitivities and specificities. These studies describe some children with absent N20 waves who had favorable outcomes, particularly when SSEPs were obtained during the initial 24 hours after cardiac arrest, indicating that SSEPs must be considered in the overall clinical context. In addition, studies have not evaluated SSEPs in children managed with therapeutic hypothermia. In adults, 2 meta-analyses found that the reliability of SSEPs was the same for patients treated with or without hypothermia, with false-positive rates similar to those reported by the American Academy of Neurology before the use of hypothermia.[236,239,240] The optimal timing to obtain SSEPs relative to therapeutic hypothermia is uncertain.

The roles of brainstem auditory EPs (BAEPs) and visual EPs are even less clear. Because BAEPs use an auditory stimulus to evaluate the brainstem, they may lack utility in predicting neurocognitive outcome, which is based largely on cortical function. Older small studies and case series assessing BAEPs in heterogeneous cohorts demonstrated that abnormal BAEPs are inconsistently associated with unfavorable outcomes, that normal BAEPs are not always associated with favorable outcomes, and that initially absent responses sometimes return.[238,241,242] Similarly, older small studies and case series assessing visual EPs in heterogeneous cohorts demonstrated that abnormal visual EPs are inconsistently associated with unfavorable outcomes and that normal visual EPs are not always associated with favorable outcomes.[243–245]

There is insufficient evidence to support the routine use of EPs for neuroprognostication after pediatric cardiac arrest.

Neuroimaging

Neuroimaging after cardiac arrest may be performed to elucidate the cause of an arrest and to better understand its potential impact on the child's functional outcome. Both brain computed tomography (CT) and magnetic resonance imaging (MRI) can serve as diagnostic or prognostic tools during PCAC to inform clinical decision-making.

Diagnostic Neuroimaging

Diagnostic neuroimaging is most often considered after ROSC for the child who has not returned to his or her neurological baseline, when the neurological examination is confounded by sedation or NMB, when the cause of the cardiac arrest is unclear, or when the child presents with focal neurological findings. Brain CT scans may be obtained rapidly, and in some ICUs, a portable bedside machine can be used for unstable patients. Brain imaging obtained early after ROSC (ie, <24 hours after ROSC) may assist in identifying potential contributing factors leading to cardiac arrest—such as hemorrhagic stroke,[246] trauma,[247] mass,[248] or hydrocephalus—and thus guide therapeutic interventions.[249] Neck or spine imaging can identify trauma-associated injury (eg, trauma or impact- or violence-related injury),[250] drowning,[251] and hangings.[252]

Neuroimaging for Prognostication

Computed Tomography. Noncontrast CT is not a sensitive test early (<12 hours after ROSC) after mild ischemia but can typically identify more severe cerebral edema.[250,253–255] A retrospective convenience sample of 78 children with OHCA who underwent noncontrast CT within 24 hours of ROSC[61] found that 40% had loss of gray-white matter differentiation, 27% had sulcal effacement, 18% had basilar cistern effacement, 13% showed a reversal sign, and no patients had a midline shift. These signs were more likely to be present in children who underwent longer CPR duration (≥20 minutes). In this study, a normal brain CT (36%) was associated with survival (sensitivity, 62%; specificity, 90%) and favorable neurological outcome. The presence of ≥1 brain CT abnormalities was associated with higher mortality and unfavorable neurological outcome.[61] Similarly, Rafaat et al[62] found that the presence of nontraumatic lesions on brain CT (28 of 156 children) within 24 hours of ROSC after drowning in pediatric patients with cardiac arrest was associated with a Glasgow Coma Scale score of 3 and death. After drowning-associated cardiac arrest, children who had an initially normal brain CT and subsequently (after >24 hours) had an abnormal brain CT had poor outcomes.[62]

The published evidence is inadequate to determine the most suitable timing to acquire CT and whether brain CT in the first 24 hours after cardiac arrest is useful for prognostication of favorable neurological outcome.

Magnetic Resonance Imaging. Brain MRI is being used after cardiac arrest to obtain additional data to incorporate into patient prognostication and to plan for future care needs. MRI has superior accuracy to the CT scan in assessing regional injury severity resulting from hypoxic ischemic injury. Conventional (T1, T2) and diffusion-weighted imaging (DWI) sequences are largely standard across medical centers and have been the imaging techniques most frequently reported. DWI sequences rely on the restriction of water molecule movement, resulting from cytotoxic or vasogenic edema.[256] The interval between the cardiac arrest and the MRI influences the interpretation because lesions have typical time trajectories for appearance and resolution after the insult.[257] Different sequences provide different information at specific time points after injury.

Two single-center studies characterizing MRI (1.5 T) after pediatric cardiac arrest demonstrate potential for its utility in post–cardiac arrest prognostication. In a report by Fink et al[216] (n=28 children), abnormalities detected in the basal ganglia on conventional imaging and in the brain lobes with DWI in the first 2 weeks after cardiac arrest were associated with unfavorable outcome. Similarly, in a series of 23 children, DWI lesions in the cerebral cortex and basal ganglia within the first week after cardiac arrest were associated with unfavorable outcome.[258] Because MRI has increased sensitivity compared with CT for detecting abnormalities caused by hypoxic-ischemic insults, the presence of lesions on MRI was associated with unfavorable outcomes, but some children with regional lesions had favorable outcomes. A study of 14 children admitted to a tertiary children's hospital after cardiac arrest examined the relationship between CBF and neurological outcome using a brain MRI that included arterial spin labeling performed within 2 weeks of cardiac arrest. In this study, CBF and the apparent diffusion coefficient were calculated globally and in 19 brain regions. The global apparent diffusion coefficient was significantly decreased in children with an unfavorable outcome. The combination of increased CBF and decreased apparent diffusion coefficient in the same brain regions was associated with worse outcome, implying a relationship between water diffusion restriction and CBF.[213]

Proton ([1]H) magnetic resonance spectroscopy is an MRI sequence that can quantify several cellular metabolites on a global or regional level.[259] Ashwal et al[260] found that increased brain lactate and decreased brain N-acetylaspartate concentrations were associated with worse outcome after pediatric brain injury, including cardiac arrest. Performance and interpretation of magnetic resonance spectroscopy results require special expertise and protocols. Available published evidence is insufficient to identify magnetic resonance spectroscopy characteristics on which to base prognostication, and no prospective data have been published to determine its utility in prognostication after pediatric cardiac arrest.

There are several potential logistical factors and risks to consider in determining the clinical utility of imaging techniques. CT involves exposure to radiation, although dose-reduction protocols are increasingly available. MRI frequently involves exposure to the risks of sedation. Both CT and MRI may involve risks of intrahospital transport. Safety protocols should be used to ensure that implants and other contraindications are considered.

Studies presented here are limited by their designs (ie, retrospective) and are subject to selection bias introduced by clinicians who ordered tests in patients who were clinically worrisome yet presumably safe for testing. The studies are also limited by the lack of blinding in imaging interpretation and outcomes assessment. More work is needed to optimize the use of the various MRI sequences for prognostication after cardiac arrest, to determine the ideal timing of MRI after ROSC, to validate small-study data in larger cohorts, and to determine whether there is utility in repeat testing.

Brain CT is a useful diagnostic test early after ROSC to identify potentially treatable intracranial causes of cardiac arrest. There are insufficient data to support the early use of CT for neuroprognostication. Brain MRI using conventional imaging and DWI in the first 3 to 7 days after ROSC may be helpful to supplement the clinical assessment, including serial neurological examinations, EEG, and, in some cases, SSEPs. Together, these modalities can be used to prognosticate for the spectrum of neurological recovery.

Biomarkers

Biomarkers can be sampled from the blood early after cardiac arrest with the goal of prognosticating mortality and neurological outcome. Concentrations of brain-based biomarkers reflect the impact of hypoxia and ischemia on neurons, glia, and astrocytes. Their concentrations can be measured from the blood after transport across the blood-brain barrier. Other biomarkers measured in the serum such as lactate can reflect systemic injury.[261] Some brain biomarkers (eg, glial fibrillary acid protein, ubiquitin carboxy-terminal hydrolase L1) are more exclusive to the brain than others (eg, S100B, NSE). NSE is a glycolytic enzyme that is released from neuronal cytoplasm. In small studies of pediatric cardiac arrest, higher NSE concentrations 24 to 96 hours after cardiac arrest are associated with mortality or unfavorable neurological outcomes.[218,220,262] NSE concentra-

tions may remain elevated for weeks to months after severe brain injury.[263] S100B is a calcium-binding protein found in the astroglia and Schwann cells. Studies in children after cardiac arrest demonstrate inconsistent results. In a single-center study, higher concentrations at 48 and 72 hours after cardiac arrest were associated with unfavorable neurological outcome at 6 months,[218] and higher levels at 48, 72, and 96 hours after arrest were associated only with discharge mortality in another study.[220] NSE and S100B values may be influenced by therapeutic hypothermia, and their serum concentrations should be interpreted with caution.[264]

Glial fibrillary acid protein is a neurofilament found in astrocytes. In 1 pediatric study, early (ie, 10 hours after cardiac arrest) glial fibrillary acid protein concentrations did not predict outcome, whereas higher concentrations later (ie, 60 hours after cardiac arrest) were significantly associated with unfavorable neurological outcome.[217] Myelin basic protein is present in the myelin sheath surrounding axons. Elevated myelin basic protein concentrations may represent axonal injury and are associated with mortality and unfavorable neurological outcome after pediatric cardiac arrest.[218] Ubiquitin carboxy-terminal hydrolase L1 is a deubiquinating enzyme specific to neuronal cytoplasm. In a small (n=43) study of children after cardiac arrest, ubiquitin carboxy-terminal hydrolase L1 levels at 60 hours after cardiac arrest were higher in patients with unfavorable outcomes.[217]

Numerous other promising biomarkers of neurological injury, systemic inflammation, and genetic polymorphisms are currently under evaluation.[262] An ongoing trial is investigating concentrations of NSE, S100B, glial fibrillary acid protein, and ubiquitin carboxy-terminal hydrolase L1 in the first 72 hours after pediatric OHCA and their association with 1-year neurological outcomes.[265]

Lactate is produced during anaerobic metabolism, and the serum lactate concentration is followed up as an indirect indicator of end-organ perfusion abnormalities and response to treatment. After cardiac arrest, elevations in lactate concentration may reflect not only severe post–cardiac arrest systemic hypoperfusion but also severe cerebral hypoperfusion. In several pediatric cardiac arrest studies, higher serum lactate concentrations in the first 12 hours after cardiac arrest were associated with increased mortality, and higher concentrations within 12 hours of ROSC were modestly predictive of unfavorable outcome (area under the curve: for IHCA, 0.76; for OHCA, 0.75).[18,152,266]

Currently, there is insufficient evidence to support the use of serum biomarker concentrations alone to predict outcome after pediatric cardiac arrest. Although specific biomarkers have shown promise, they have yet to be validated in prospective pediatric studies after cardiac arrest.

Cerebral Oxygenation and CBF

CBF and cerebral autoregulation can be continuously evaluated noninvasively with transcranial Doppler and near-infrared spectroscopy. Transcranial Doppler measures blood flow velocities through the middle cerebral arteries and has been used to define abnormal CBF patterns/cerebral autoregulation. In a small (n=17) study of transcranial Doppler after pediatric asphyxial cardiac arrest, reversal or absence of diastolic cerebral arterial blood flow during the use of therapeutic hypothermia was associated with either a vegetative state or death.[267] Data from adult studies are equivocal, with no clear correlation between transcranial Doppler–measured ischemia or hyperemia and outcomes.[268,269]

Near-infrared spectroscopy can be used to evaluate cerebral autoregulation by determining the degree of correlation between an near-infrared spectroscopy–derived hemoglobin volume index and mean arterial pressure (MAP).[64] The range of MAP that maintains CBF within a zone in which autoregulation is preserved is considered the optimal MAP. One prospective study of 36 children after cardiac arrest evaluated cerebral autoregulation by using near-infrared spectroscopy and MAP; those who had greater deviation from optimal MAP during the first 48 hours after ROSC were more likely to die, to require a gastrostomy or tracheostomy, or to have a decrease in PCPC score.[64]

The pediatric studies of these neuromonitoring tools are limited by size, retrospective design, timing of the investigations, use of inconsistent definitions, and inability to adjust for potential confounding factors. Future investigations may identify how these tools can be used to prognosticate outcomes after cardiac arrest.

Impact of Hypothermia on Neuroprognostication

The effect of TTM on neuroprognostication is poorly characterized after pediatric arrest, but it is reasonable to assume that a cautious delay in assessment for neuroprognostication is warranted. Supporting this concept, in a recent study of pediatric post–cardiac arrest prognostication, neurologist agreement improved over time and was more accurate at days 5 to 7 after the arrest than at day 1 or days 2 to 4 after the arrest.[270]

A number of recent studies suggest that signs of neurological recovery in survivors of adult cardiac arrest may not appear for 3 to 4 days or longer after ROSC.[131,271,272] The delay in clinical arousal, combined with the poor predictive power of neuroimaging, neurophysiological investigations, and biomarkers, has created challenges for prognostication in adults after cardiac arrest.

The complexity of prognostication is made more difficult by the use of TTM as a post–cardiac arrest therapy. TTM may prolong clearance of sedative and

analgesic medications that are used during PCAC, leading to delays in clinical arousal (Sedation and Neuromuscular Blockade section). Furthermore, TTM may alter cerebral metabolism and neuronal activity such that the biological recovery may be delayed regardless of whether sedation is used.[273] These phenomena have led the 2015 AHA advanced cardiac life support guidelines update to suggest that the earliest time for prognostication by using clinical examination in adult patients treated with TTM may be 72 hours after return to normothermia compared with 72 hours after cardiac arrest for those not treated with TTM. These guidelines noted that operationally for adult patients treated with TTM, the timing for prognostication is typically 4.5 to 5 days after ROSC.[212] Indeed, in a clinical study of adult post–cardiac arrest recovery using TTM, many patients demonstrated volitional motor activity or eye opening only after 4 to 5 days after ROSC.[131] The effect of TTM on the predictive ability of brain CT or MRI has not been sufficiently studied in children during PCAC to provide guidance.

Prognostication Summary

No single variable has been found to be sufficiently accurate and reliable for prognostication in children after cardiac arrest. Practitioners should consider multiple factors when predicting outcomes in infants and children who achieve ROSC after cardiac arrest.[58]

SPECIAL CONSIDERATIONS

Congenital Heart Disease

Patients with congenital heart disease, especially those with left-sided heart obstructive lesions, atrial switch for transposition of the great arteries, pulmonary artery hypertension, single-ventricle physiology, and lesions that required a surgical ventriculotomy during repair, are at greater risk of cardiac arrest, particularly in the postoperative period.[274] Additional risk factors include prior arrhythmias, decreased ejection fraction, and unbalanced systemic and pulmonary circulations.[274] In the post–cardiac arrest period, it is important to identify the child's underlying cardiac pathology and physiology because pharmacological and mechanical ventilation management will often differ from that required by a child with a normal heart. This is especially true for the patient with single-ventricle physiology. For additional details, readers are referred to a comprehensive AHA scientific statement on CPR in infants and children with cardiac disease.[275]

This publication focuses on PCAC of children who have any of the following 3 conditions: single-ventricle physiology, pulmonary artery hypertension, or right-sided heart disease.

Single-Ventricle Physiology

Patients with single-ventricle physiology typically require a 3-stage repair to achieve a separation of the pulmonary and systemic circulations.[276]

Until the time of the stage 3 palliation, the balance between pulmonary and systemic blood flow is controlled by the size of the pulmonary shunt and by the relative resistances in the pulmonary and systemic vascular beds, which can be highly dynamic in a young child. In the post–cardiac arrest period, manipulation of the pulmonary and systemic vascular resistances will help to optimize systemic perfusion and oxygenation. Pulmonary overcirculation can result from low pulmonary vascular resistance or high systemic vascular resistance and will compromise systemic blood flow. In patients with pulmonary overcirculation, especially before stage 2 palliation, high inspired oxygen concentration can dilate the pulmonary vascular bed and decrease pulmonary vascular resistance, increasing pulmonary blood flow at the expense of systemic blood flow. This causes or contributes to low cardiac output syndrome. To increase systemic blood flow and perfusion and to reduce pulmonary overcirculation, it will be necessary to eliminate factors such as high inspired oxygen concentration that cause decreased pulmonary vascular resistance and to reduce systemic vascular resistance with phosphodiesterase inhibitors (milrinone) or α-adrenergic blockers (phenoxybenzamine, phentolamine). Thus, use of oxygen as needed and reduction of systemic vascular resistance will be the most useful therapies to increase systemic blood flow and oxygen delivery.[275]

After stage 2 palliative surgery (superior cavopulmonary anastomosis), when superior vena cava venous return flows directly into the pulmonary arteries, mild hypoventilation with hypercarbia will improve systemic perfusion. The mild hypercarbia produces cerebral vasodilation, increased CBF, and cerebral venous return. This increases superior vena cava to pulmonary artery blood flow and pulmonary venous return, with a resulting increase in systemic ventricular preload and systemic perfusion.

After completion of the third stage of correction (Fontan procedure), all systemic venous blood is diverted directly into the pulmonary circulation, so pulmonary blood flow and pulmonary venous return to the systemic ventricle are dependent on passive blood flow through the pulmonary vascular bed. This passive blood flow requires a pressure gradient across the pulmonary vascular bed. Hypoventilation (with resulting alveolar hypoxia) and acidosis must be avoided because they can result in increased pulmonary vascular resistance, decreased pulmonary blood flow, and decreased cardiac output and systemic perfusion. Positive pressure ventilation can increase intrathoracic pressure and impede pulmonary blood flow,[275] so mechanical ventilation

must be used judiciously, with weaning to spontaneous ventilation as soon as tolerated.

Pulmonary Artery Hypertension

Pulmonary artery hypertension is frequently present in infants and children with congenital heart disease, and it increases the risk of cardiac arrest. In addition, pulmonary hypertension is observed in up to 2% of postoperative patients.[277,278] Pulmonary hypertensive crises are accompanied by right-sided heart (ie, pulmonary ventricle) failure, systemic hypotension, and myocardial ischemia. These crises can be triggered by stimuli such as pain, anxiety, tracheal suctioning, hypoxia, and acidosis, as well as by withdrawal of pulmonary hypertension–specific therapy.[275] Once ROSC is obtained after cardiac arrest in the child with pulmonary hypertension, it is important to provide adequate oxygen administration; to minimize stimulation; to provide adequate analgesia, sedation, and possibly NMB; and to administer pulmonary vasodilators.[275] Alveolar hypoxia and acidosis should be aggressively treated to prevent pulmonary vasoconstriction. For multipronged initial therapy of pulmonary hypertensive crises in children, the AHA scientific statement suggests oxygen administration, induction of alkalosis through hyperventilation (for short periods of time only as needed) or alkali administration, and administration of inhaled or systemic pulmonary vasodilators. Inotropic/vasopressor therapy is suggested to avoid RV ischemia, which can result from systemic hypotension.[275,279]

Right-Sided Heart Obstruction and Dysfunction

Right-sided systolic and diastolic dysfunction occurs frequently in the postoperative period in patients who require reconstruction of the RV outflow tract with muscle resection or insertion of a conduit or a transannular patch. Risk of cardiac arrest increases with the age of the patient, severity of the outflow obstruction, volume overload, and presence of residual defects such as a ventricular septal defect or distal pulmonary artery obstruction.[275] After cardiac arrest, the goals of therapy should include careful avoidance of hyperinflation or hypoinflation of the lungs[280] and maintenance of atrioventricular synchrony.[281]

Pharmacological management is typically required to treat RV dysfunction with right-sided heart obstruction, but these medications, especially catecholamines, must be administered with caution. Coronary artery blood flow to the RV may be reduced when the RV is hypertrophied and RV end-diastolic pressure is elevated. As a result, the RV may become ischemic any time the myocardial oxygen demand increases such as with tachycardia and increased wall stress.[282] Systemic vasoconstrictors such as vasopressin and norepinephrine can support blood pressure and maintain coronary perfusion.[275]

The AHA scientific statement on CPR in infants and children with cardiac disease provides further information about special considerations for care of the child with cardiac disease.[275]

Arrhythmogenic Cardiac Arrest

In the previously healthy child who has a sudden cardiac arrest with an initial rhythm of ventricular fibrillation/pulseless ventricular tachycardia, an arrhythmic cardiac cause is most likely. This pathology can include genetic or congenital cardiac abnormalities such as hypertrophic or dilated cardiomyopathy, inherited channelopathy, long-QT syndrome, Brugada syndrome, RV cardiomyopathy or catecholaminergic polymorphous ventricular tachycardia, Wolff-Parkinson-White syndrome, or congenital heart disease. Acquired conditions that can cause arrhythmic cardiac arrest include myocarditis, commotio cordis, and drugs/toxins such as tricyclic antidepressants, anthracyclines, and drugs of abuse. For many patients with sudden arrhythmic causes of arrest, prompt bystander CPR and defibrillation result in high survival with good functional outcomes.[283]

In the immediate post–cardiac arrest period, the initial evaluation should include investigation for causes of primary (arrhythmic) cardiac arrest. Although no single test is diagnostic, echocardiography is useful to assess myocardial thickness and function, which are likely to be abnormal in children with cardiomyopathies and myocarditis. Electrocardiographic criteria may suggest the presence of a channelopathy, but additional testing and pediatric cardiac electrophysiological consultation is required. β-Blockers and implanted cardioverter-defibrillators are key therapies for the management of patients with long-QT syndrome, and antiarrhythmics that prolong the QT interval (ie, procainamide, sotalol, and amiodarone) should usually be avoided.[275]

Electrophysiological consultation will be essential to determine the appropriateness of pharmacological therapy or implantation of pacemakers/implantable cardioverter-defibrillators. If patients are found to have an inherited syndrome, screening of first-degree relatives has been shown to detect additional family members at risk.[284]

Cardiac Arrest Caused by Drowning

Drowning causes 25% to 31% of all pediatric OHCA,[18,194] and survival rates range from 9% to 46%.[18,194,285–289] Longer duration of submersion and longer duration of CPR are associated with worse survival and neurological outcomes.[287,290–296] The majority of children who receive >30 minutes of CPR and survive to 1 year do so with an unfavorable neurological outcome.[291,292]

Twenty-five percent of children in the THAPCA-OH trial had a drowning-associated cardiac arrest, with 46.4% surviving to 1 year and 24.6% having a favorable neurological outcome at 1 year.[194] Children with

cardiac arrest from drowning had better outcomes compared with children with other respiratory causes of arrest.[194] Children treated with TTM to 32°C to 34°C did not have better outcomes than those treated with TTM to 36°C to 37.5°C.[292]

ECMO has been used for rewarming and cardiopulmonary support in children with OHCA caused by cold-water drowning. In a review of the ELSO registry, of 198 children who received ECMO after a drowning event between 1986 and 2015, survival was 54%.[295] Of these, 15.7% were hypothermic at hospital admission, 35.4% had a cardiac arrest before extracorporeal life support (ECLS), and 28.8% underwent ECPR.[295] Survival rates specifically for children with drowning-associated OHCA were not reported, but the reported rate of survival for drowning victims of all ages with cardiac arrest before ECLS was 57%, and survival for those who underwent ECPR was 23.4%.[295]

Observational studies of ECLS in children with hypothermic OHCA resulting from drowning report mixed results. Although longer durations of CPR are associated with higher mortality rates, several case series included some victims who were successfully decannulated from ECLS and survived with favorable neurological outcome.[287,296–301]

There are insufficient published data to identify optimal management specific to children with drowning-associated cardiac arrest. Clinicians are encouraged to use the general PCAC identified in this statement.[251,302,303]

Multicenter prospective studies with long-term follow-up are needed to better define the role of ECLS, TTM, and other neuroprotective interventions in this patient population. ECLS for rewarming and circulatory support of cold-water drowning victims may affect survival. Unresolved issues for TTM in children with drowning-associated OHCA include the optimal rate of rewarming for children presenting with hypothermia, the optimal timing of initiation of TTM, the optimal target temperature, and the optimal total duration of TTM.[292]

Post–Cardiac Arrest Transport

The writing group identified no peer-reviewed published literature that specifically addresses the transport care of children or adults after cardiac arrest. The comments that follow are based on the published evidence addressing the care of critically ill children in the transport setting.

Ideally, PCAC should be provided by a trained team from a pediatric tertiary care facility.[52] This often necessitates interfacility transfer at a time when PCAS, including inotrope-dependent ventricular systolic dysfunction, is evolving and when these patients are at particular risk of secondary injury.[42] Sicker patients (such as those with PCAS) are more prone to instability in the transport setting,[304] and longer-distance/time transports (such as interfacility transfer of patients to regional PICUs) are associated with a greater risk of patient destabilization.[305] Providers at the referring center should contact a transport team from the tertiary care facility as early as possible during the resuscitation attempt and coordinate transportation with the receiving unit.[52] Patient transfer is best coordinated by a transport team, with members who are trained and experienced in the care of critically ill and injured children, and supervised by a pediatric emergency medicine or pediatric critical care physician.[52] The use of these specialized teams (as opposed to adult-centric transport teams) has been associated with reduced intratransport morbidity[306] and reduced PICU morbidity and mortality.[304,305]

Practitioners should attempt to stabilize the post-ROSC patient before patient transfer rather than move the patient out of the referring center as quickly as possible ("scoop and run"). Appropriate respiratory, hemodynamic, neurological, and temperature monitoring is required during transport, as are establishing airway control, vascular access, and mechanical ventilation and providing hemodynamic support as necessary. It is important to monitor P_{ETCO_2} during interhospital or intrahospital transport of intubated patients.[52] Providers at the referring hospital should seek advice from experts at the tertiary receiving hospital because patients will be susceptible to cardiorespiratory instability as a result of PCAS, compounded by the drugs used to facilitate interventions.

During transport, patients should receive the same care with the same treatment targets as those used in the in-hospital setting. Close monitoring and timely intervention should prevent or promptly treat patient fever or inadvertent hypothermia, hypotension, hypoxemia, and hypocarbia or hypercarbia. Providers should anticipate changes in patient vital signs as a result of the transport environment itself (eg, effect of patient movement on blood pressure, effect of environmental temperature on the patient, effect of altitude on oxygenation). Such changes may be especially difficult to detect during transport because the quality of monitoring and type of equipment used are often less sophisticated than those available in the in-hospital setting.

LONG-TERM OUTCOMES

Cardiac arrest outcomes studies have historically focused on the short-term outcomes of ROSC, survival to hospital discharge, and gross neurological outcomes at discharge. In recent decades, improvements in discharge outcomes have led to a shift in focus from short-term discharge outcomes to long-term survival (>1 month after hospital), as well as neurobehavioral

Table 5. Summary of Available Tools for Follow-Up Assessment After Cardiac Arrest, Including Age Range, Duration, and Source of Data

Domain	Instrument Example	Age Range	Duration, min	Source
Overall health and function	PCPC/POPC[307]	0–21 y	5	Chart/interview
	GOS-E Peds[308]	1 mo–18 y	3	Chart/interview
	FSS	0–18 y	5	Chart/interview
Cognitive ability	Wechsler Intelligence Scales (WPPSI, WISC,[309,310] WAIS) MSEL[311]	4 y–adult	60–90	In person
		0–6 y	15–60	In person
Adaptive function	VABS[312]	0–adult	20–60	Interview/survey
	ABAS[313]	0–adult	15–20	Interview/survey
Development	BSID[314]	1–42 mo	30–90	In person
Emotional	CBCL	2–21 y	20	Interview/survey
	BASC	2–21 y	10–20	Interview/survey
Executive function	BRIEF	2 y–adult	10	Survey
Quality of life	CHQ[315]	5–18 y	5–15	Interview/survey
	ITQOL[316]	2 mo–5 y	2–60	Interview/survey
	PedsQL[317]	2–18 y	4	Interview/survey

ABAS indicates Adaptive Behavior Assessment System; BASC, Behavior Assessment System for Children; BRIEF, Behavior Rating Inventory of Executive Function; BSID, Bayley Scales of Infant and Toddler Development; CBCL, Child Behavior Checklist; CHQ, Child Health Questionnaire; FSS, Functional Status Scale; GOS-E Peds, Glasgow Outcome Scale–Extended Pediatric Revision; ITQOL, Infant Toddler Quality of Life Questionnaire; MSEL, Mullen Scales of Early Learning; PCPC, Pediatric Cerebral Performance Category; PedsQL, Pediatric Quality of Life Inventory; POPC, Pediatric Overall Performance Category; VABS, Vineland Adaptive Behavior Scales; WAIS, Wechsler Adult Intelligence Scale; WISC, Wechsler Intelligence Scale for Children (6–16 years of age); and WPPSI, Wechsler Preschool and Primary Scale of Intelligence (4–6.5 years of age).

and health-related quality of life (HRQOL) outcomes (Table 5).

Neurological outcomes at discharge have been based on the Utstein-recommended[318] PCPC, a global scale of neurological function.[307] This scale can be scored both in real time and from retrospective chart review but is limited by lack of applicability to the infant population. Recent cardiac arrest studies have used more granular metrics to describe long-term outcomes.[2,3,319]

Long-Term Survival and Neurological Outcomes

The writing group identified only a few small studies of long-term outcomes after pediatric cardiac arrest. In 2 small series of pediatric victims of OHCA who survived to hospital discharge, 91%[207] to 92%[320] survived 1 year, 86%[320] survived 5 years, and 77% survived 20 years.[320] Notably, 84% to 94% of patients who were discharged with a favorable outcome (PCPC 1 or 2) had a favorable neurological outcome at the 1-year follow-up,[207,321] whereas 40% to 54% of patients with an unfavorable outcome at discharge had died by follow-up.[207] In the THAPCA-OH trial of TTM for comatose children admitted after ROSC, half of discharged survivors had a change in neurological function at the 1-year follow-up, and one-third of subjects discharged with severe neurological function improved to normal to moderate function.[181]

In small studies of IHCA, 73% to 86% of those who survived to hospital discharge had long-term survival with favorable outcomes (PCPC 1 or 2),[322–324] with most having no change the first year.[324,325]

Neurobehavioral Outcomes

Recent prospective studies of neurobehavioral outcomes have focused on telephone and face-to-face follow-up; these methods obtain more granular information than chart reviews can obtain on neurobehavioral outcomes. Recent studies have used the Vineland Adaptive Behavior Scales.[2,3,326] Table 5 highlights tools that can be used to assess outcomes in children after cardiac arrest.

The largest pediatric study of 1-year neurobehavioral outcomes after OHCA was the THAPCA-OH trial of TTM for comatose children after ROSC. The results of this trial are not generalizable to all pediatric patients with OHCA because it followed up only a subset of all children with OHCA. One-third of enrolled subjects were alive at 1 year; one-third of these survivors had good functional status and average function,[3,182] and one-third had severely deficient function.[182] Ten percent had a change in function over the first year, with two-thirds (67%) improving and one-third (33%) worsening.[181]

Of children enrolled in the THAPCA-IH clinical trial, 47% were alive at 1 year. Thirty percent of these survivors had a <1-SD change from their prearrest Vineland Adaptive Behavior Scales score.[2]

Neuropsychological Testing

Until recently, reports of neuropsychological outcomes focusing on memory, language, and attention have

Table 6. Critical Knowledge Gaps Related to Pediatric PCAC and PCAS

Epidemiology
What is the contemporary epidemiology of pediatric PCAC?
How can we track the impact of PCAC on trends in outcomes?
Pathophysiology
What are the factors that influence the pathophysiology and evolution of PCAS in pediatrics with respect to cardiac and central nervous system function?
Are there age-dependent mechanisms?
How do these factors affect outcomes?
Does the cause of cardiac arrest affect the timing, mechanisms, and impact of PCAS?
Targets and therapies
What are the optimal targets and therapies that will affect outcomes? Are they age dependent? How do they change by phase of PCAS?
Ventilatory
Arterial oxygen tension
$Paco_2$
Hemodynamic
Arterial blood pressure (systolic, diastolic, mean)
Measurements of myocardial dysfunction and recovery
Cerebral
EEG background
Regional oxygen saturation
Intracranial pressure and cerebral perfusion pressure
Metabolic
Hemoglobin concentration
Serum lactate
Urine output
Central venous pressure
Are there novel indexes that could be used to target combinations of end points?
What is the role of TTM? Are there special populations for whom it is more advantageous?
What is the ideal vasoactive/pharmacological support needed to treat post–cardiac arrest myocardial function and hypotension?
What are the optimal timing and methods for initiating ECMO (ECMO or ECPR)?
What role does neuroimaging play in diagnostic approaches and prognostication?
Is there a role for antiarrhythmic prophylaxis in PCAS?
Are there iatrogenic factors that alter outcomes such as sedation and anesthetics?
Does implementing a bundle of care alter outcomes?
When is the best to time to initiate active physiotherapy, occupational therapy, music therapy, and comprehensive rehabilitation? What are the optimal interventions for children?
Special populations
How should PCAC be modified for special populations (eg, children with congenital heart disease, with trauma, after drowning)?
Healthcare systems
What is the best method (including team and timing) for transport to reduce morbidity and mortality?
Who are the key members of multidisciplinary teams to optimize PCAC?
Do pediatric cardiac arrest centers improve outcomes?
Does multidisciplinary, simulation-based education improve the implementation of PCAC?
Prognosis
What biomarkers, neurological assessments, and imaging techniques predict neurological injury and outcomes early and reliably?
Are there decision rules that can predict futility?
Outcome measures
What are the best measures to track long-term neurobehavioral and quality-of-life measures in both the child and the family?

ECMO indicates extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; EEG, electroencephalograph; PCAC, post–cardiac arrest care; PCAS, post–cardiac arrest syndrome; and TTM, targeted temperature management.

been limited to small studies that demonstrate substantial morbidity.[327] In the largest study to date of 52 pediatric survivors of cardiac arrest, their parents and teachers completed questionnaires 2 to 11 years after the child's ICU discharge (median, 5.6 years [range, 1.8–11.9 years]).[328] Survivors had worse IQ scores, verbal comprehension, perceptual organization index, and processing speed compared with a large representative sample of age-matched children from the general Dutch population.[319,328] After adjustment for IQ scores, survivors had worse visual memory, better recognition, and comparable attention and executive function. Although families reported that survivors had better executive functioning than the general population, teachers reported that they had worse organizational and planning skills. Many of these survivors also had attention and somatic problems[328] and required professional assistance for emotional/behavioral problems or special education.[329] Small studies of long-term follow-up (median, 8 years) demonstrated substantial neurological dysfunction (57% of patients) and lower IQs (<80 [range, 20–78]; population mean, 100; SD, 15) in survivors of drowning-associated cardiac arrest.[330,331]

HRQOL Outcomes

HRQOL and family burden are new and important areas of investigation because survivors of cardiac arrest can have significant dysfunction and dependence on caregivers. The parent-reported HRQOL of the cardiac arrest survivors cited worse role functioning, worse general health perception, and worse parental impact compared with healthy control subjects but higher family cohesion.[329–331] The patients reported no differences in HRQOL compared with representative samples of children who never had a cardiac arrest.[329]

Parents of children who survive cardiac arrest reported that they themselves had limitations in their

daily activities, but they also reported better physical, social, and emotional role functioning than an age-matched healthy population.[329] Pediatric survivors of OHCA, compared with survivors of IHCA, reported worse family cohesion and worse parental physical functioning.[329] Family burden in survivors from the THAPCA-OH trial was worse at 3 and 12 months after the cardiac arrest than before but improved over time.[183]

After cardiac arrest, long-term neurobehavioral and neuropsychiatric outcomes and HRQOL vary on the basis of a variety of cardiac arrest factors, and some patients improve over time. Future focus on assessment of these long-term outcomes and the long-term burden on survivors and families is important to be able to determine whether the long-term outcomes are improving as we strive to improve CPR quality and PCAC.

POTENTIAL FUTURE DIRECTIONS

The management of pediatric patients with ROSC after cardiac arrest is challenging and time sensitive, requiring the involvement of a wide range of expert providers from critical care to neurology, cardiology and rehabilitation medicine, nursing, social services, and respiratory therapy. Given this complexity, it has been proposed that PCAC should be concentrated at specific high-performing centers (ie, cardiac arrest centers or Level 1 post–cardiac arrest centers, as variously described in the literature), much like the trauma center model, to allow greater concentration of local experience and resources to improve outcomes.[332,333] Studies of adult OHCA suggest that transfer of post–cardiac arrest patients to such centers may improve survival.[334,335] Whether similar systems of care might improve survival and neurobehavioral outcomes after pediatric cardiac arrest remains unclear, although similar principles of time sensitivity and complexity of care apply to the pediatric post–cardiac arrest domain.

Another approach to improving care after cardiac arrest involves the need for more specialized education and training of experts in PCAC. After completion of a specific curriculum designed to improve the use of TTM and additional components of the post–cardiac arrest bundle of care, emergency and critical care nurses and physicians reported more consistent use of TTM and other components of the PCAC bundle.[336] More work is required to determine the most efficient and appropriate methods to scale such training experiences into the busy clinical environment.

CRITICAL KNOWLEDGE GAPS IN PEDIATRIC PCAC

- During the process of a literature review to address therapeutics and prognostication related to pediatric PCAC, numerous critical knowledge gaps were identified. We summarize these gaps in Table 6 with the goal of stimulating preclinical and clinical research.
- Several cardiac arrest databases and data sets are available and may be able to help address some of these critical gaps: For IHCA: AHA Get With The Guidelines–Resuscitation,[337] THAPCA-IH,[2] PC4 (Pediatric Cardiac Critical Care Consortium),[338] and ELSO[339]; and for OHCA, the ROC Epistry,[340] CARES,[341] THAPCA-OH,[3] and CanROC (Canadian Resuscitation Outcomes Consortium).[342]

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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