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Brain Resuscitation in the Drowning Victim

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This manuscript is dedicated to the memory of Peter Safar, M.D. Peter Safar combined genius, incredible purpose, elegance, and humanism to move the collective fields of acute medicine to a new level. His work in resuscitation medicine, critical care, anesthesiology, emergency medicine, and disaster medicine saved countless lives. As a mentor he taught us a great deal. Peter left us with an important message—in both clinical care and research: namely, to always ask, “what is your intervention or research doing for the patient?” Whether physician or scientist, it is a critical message never to forget.

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Abstract

Drowning is a leading cause of accidental death. Survivors may sustain severe neurologic morbidity. There is negligible research specific to brain injury in drowning making current clinical management non-specific to this disorder. This review represents an evidence-based consensus effort to provide recommendations for management and investigation of the drowning victim. Epidemiology, brain-oriented prehospital and intensive care, therapeutic hypothermia, neuroimaging/monitoring, biomarkers, and neuroresuscitative pharmacology are addressed. When cardiac arrest is present, chest compressions with rescue breathing are recommended due to the asphyxial insult. In the comatose patient with restoration of spontaneous circulation, hypoxemia and hyperoxemia should be avoided, hyperthermia treated, and induced hypothermia (32–34 °C) considered. Arterial hypotension/hypertension should be recognized and treated. Prevent hypoglycemia and treat hyperglycemia. Treat clinical seizures and consider treating non-convulsive status epilepticus. Serial neurologic examinations should be provided. Brain imaging and serial biomarker measurement may aid prognostication. Continuous electroencephalography and N20 somatosensory evoked potential monitoring may be considered. Serial biomarker measurement (e.g., neuron specific enolase) may aid prognostication. There is insufficient evidence to recommend use of any specific brain-oriented neuroresuscitative pharmacologic therapy other than that required to restore and maintain normal physiology. Following initial stabilization, victims should be transferred to centers with expertise in age-specific post-resuscitation neurocritical care. Care should be documented, reviewed, and quality improvement assessment performed. Preclinical research should focus on models of asphyxial cardiac arrest. Clinical research should focus on improved cardiopulmonary resuscitation, re-oxygenation/reperfusion strategies, therapeutic hypothermia, neuroprotection, neurorehabilitation, and consideration of drowning in advances made in treatment of other central nervous system disorders.

Keywords

Drowning; Brain; Asphyxia; Cardiac arrest

Introduction

The greatest permanent harm in drowning accidents is to the brain, which has negligible metabolic substrate reserves to subsist upon in the absence of continuous delivery of oxygenated blood. Functional failure begins within seconds after abrupt disruption of circulation at normal body temperature [1]. The brain is sensitive to the timing, duration, and intensity of hypoxia. Irreversible injury develops in the hippocampus, basal ganglia, and

cerebral cortex within 4–10 min [2]. Resuscitation at this stage may manifest in memory, movement, and coordination disorders. Only a few additional minutes of hypoxia may result in persistent coma.

Two factors distinguish drowning from cardiogenic cardiac arrest (CA). First, submersion fluids may be cooler than normal brain temperature. Thus, if the drowning process is slow, the body and the brain will cool prior to the arrest. Hypothermia can decelerate neural tissue demise. Second, unlike cardiogenic CA, where there is near-immediate cessation of cerebral blood flow (CBF), submersion results in hypoxic deterioration to asphyxial CA (ACA). Flow continues for some interval, but oxygen delivery is insufficient contributing to injury. Thus, submersion duration may not reliably predict neurologic outcome.

Complicating these matters is delayed neuronal death [3]. Complex cellular responses to hypoxia and re-oxygenation/reperfusion are activated leading to pro-survival and death signals within brain cells. Consequently, immediate neurologic function after drowning rescue does not necessarily predict final outcome. In practical terms, first responders cannot reliably predict outcome at the site of rescue.

The unique sensitivity of brain to hypoxia and the lack of ability to predict outcome at point of rescue creates a challenge, particularly in patients who fail to sustain or recover consciousness. Little can change damage caused by the primary hypoxic event. The best hope is to prevent secondary injury that might exacerbate the initial injury. There is negligible research specific to mechanisms of post-resuscitative brain injury following drowning. The most important defense is to prevent the accident, but drowning still occurs. With modern cardiopulmonary resuscitation (CPR), restoration of spontaneous circulation (ROSC) may be achieved but brain recovery cannot be ensured. The best approach to managing a cerebral insult in survivors of drowning accidents remains undefined. There are no randomized double-blind prospective studies to provide definitive recommendations. Care is largely based on extrapolated knowledge and opinion. This review constitutes an evidence-based consensus effort to provide recommendations for brain-oriented care of drowning victims.

Epidemiology

A new definition of drowning has been established through a consensus procedure: Drowning is the process of experiencing respiratory impairment from submersion/immersion in liquid [4]. The recommended classification scheme is death, morbidity, and no morbidity [4]. With this definition the intention is to put an end to the variety and inconsistency of definitions, particularly the terms dry drowning and near-drowning [5, 6].

The World Health Organization estimates that 388,000 persons die from drowning worldwide annually [7]. In most countries, fatal drowning is among the top three causes of death in children ages 5–14 years, is the most important cause of injury-related death in children younger than four, and drowning accounts for 7 % of all injury-related deaths among all ages globally. The male:female ratio is approximately 4:1 in all ages globally. There are large incidence variations among regions of the world. Low- and middle-income countries account for 97 % of all drownings, of which 49 % occur in China and India alone [7-11].

Data on non-fatal drownings are difficult to obtain. The circumstances of these events can be complex, making it difficult to extract data from hospitals and other sources. Data are often not standardized if reported. A recent Danish study shows a ratio between mortality, morbidity, and no morbidity of 1:0.5:134 [12]. The relationship among these figures would seem highly dependent on the cause of drowning and the victim's age [13-15]. One to 3 %

of all drowning victims admitted to a hospital suffer severe neurological injuries [16]. National death statistics related to drowning contain inaccuracies, often due to poor or deficient coding infrastructure. The latter is often true in low- and middle-income countries, the very countries that experience the highest drowning fatalities. Coding using the tenth revision of the International Classification of Diseases (ICD-10) is strongly recommended [17, 18].

Prehospital Management

Drowning survival depends on a management chain, starting outside the hospital and continuing in-hospital during the post-resuscitation phase. Prehospital care personnel provide opportunity to perform rapid rescue from submersion. Re-establishing ventilation before CA nearly assures no long-term neurological sequelae [19, 20]. If CA occurs, CPR provides the best chance of neurological recovery. Controversy exists over the optimal CPR method. Bystander chest compressions alone may be better than rescue breathing combined with chest compressions (standard CPR) for resuscitating patients with sudden CA [21]. Drowning victims were excluded in this analysis. Drowning victims asphyxiate which leads to CA, so maximizing oxygenation in addition to perfusion during CPR may improve outcome [22, 23]. Two prospective, population-based cohort studies support performing standard CPR for drowning. Rescue breathing and chest compressions [24, 25] and bystanders [26] may play an important role. Thus, it is recommended that drowning victims with no signs of life be provided chest compressions with rescue breathing rather than compression CPR alone.

The best method for ventilating and oxygenating drowning victims has not been established. Supplemental oxygen should be provided to all drowning victims with evidence of hypoxemia or respiratory distress. Continuous or bi-level positive airway pressure may be advantageous if hypoxia is present and spontaneous ventilatory efforts are suboptimal in the conscious patient [27, 28]. Assisted ventilation with a bag-valve-mask should be performed in unconscious patients or those that cannot maintain their airway. Tracheal intubation requires equipment and skill. The decision to intubate at the scene may depend on the expertise of rescuers and first responders. Supraglottic airway devices have been found to not be effective in drowning [29]. Hypoxemia and hyperoxemia should be avoided. Optimal prehospital monitoring includes capnometry if intubation is performed [30] and pulse oximetry [31]. Pulse oximetry may be difficult with hypothermia. Arterial blood gases at hospital admission will best guide ventilatory support.

Arterial hypotension may negatively impact neurological outcome after acute brain injury [32]. Early detection may minimize brain damage. Blood pressure should be assessed at the scene and hypotension should be recognized and treated.

Temperature management is a critical determinant of neurological outcome. Body temperature should be measured as soon as possible after the initial resuscitation. The practice of aggressively warming all drowning victims should be abandoned. Case reports of remarkable neurological recoveries after prolonged CA in ice water drowning suggest a role for therapeutic hypothermia [33-35]. Patients considered candidates for therapeutic hypothermia may benefit from cooling as soon as possible and protocols exist for initiation of cooling by prehospital personnel [36, 37].

Many hospitals have limited experience with brain-directed patient care after ROSC. Prehospital providers may consider direct transport of these patients to facilities with expertise in neurocritical care [38]. Otherwise, transfer of drowning victims who are stabilized at the initial facility to a facility with neuroresuscitation expertise is recommended.

Most drownings occur in low- and middle-income countries. In the absence of advanced resources, key management practices may still be employed including effective CPR, assurance that drowning-induced hypothermia does not explain failure to recover consciousness, avoidance of hyperthermia, and titration of oxygen delivery to prevent hypoxemia and hyperoxemia.

Brain-Oriented Intensive Care Management

Treatment in the intensive care unit (ICU) should be directed toward stabilization of vital functions and prevention of secondary brain injury. This section describes important aspects of ICU treatment for drowning, with emphasis on the brain.

Ventilation and Oxygenation

Submersion in water results in breath holding usually followed by laryngospasm resulting in hypercapnia and hypoxemia. With increasing hypoxemia, laryngospasm abates, increasing risk of water and gastric contents aspiration [22, 39]. Water aspiration may rapidly result in acute lung injury or acute respiratory distress syndrome (ARDS). If so, ventilation/perfusion matching is altered and lung compliance will be low with varying degrees of hypoxemia and hypercapnia.

The incidence of pneumonia associated with submersion is unknown, but findings from case-series suggest rates between 30 and 50 % [40]. The risk is determined by the aspirate (gastric contents/water contamination). Aerobic Gram-negative and Gram-positive bacteria, anaerobes and fungi are common pathogens. *Pseudallescheria boydii* infections are most frequently reported, which may involve the respiratory tract and other organs, with high mortality rates [41]. The diagnosis of drowning-associated pneumonia may be difficult. Airway cultures may not differentiate between colonization and infection. In patients with fever or systemic signs of infection, antibiotic therapy is advised. One report suggests use of antibiotics found effective in bacteria similar to those found in the body of water where immersion occurred [42]. Routine steroid use should be avoided. Animal and human trials have not identified any clinical benefit.

Lung injury is, in part, the result of washout of surfactant in the lung. There are case reports documenting successful use of exogenous surfactant to treat lung injury associated with pediatric drowning [43-45]. Exogenous surfactant does not reduce mortality or improve pulmonary gas exchange in adult ICU patients [46, 47]. There is one case report of surfactant efficacy in adult drowning [48]. Although unproven, surfactant may be considered as a rescue treatment based on the specific pathophysiology.

No randomized studies have investigated ventilator strategies after drowning. Several animal and case studies support use of positive end-expiratory pressure (PEEP). Based on the underlying pathophysiology, it is reasonable to follow the protective ventilator strategy for ARDS patients. Tidal volumes < 6 mL/kg and sufficient PEEP to avoid extensive lung collapse at end-inspiration are recommended [49], while maintaining plateau pressures as low as possible. Positive pressure ventilation has potential adverse effects on cerebral perfusion. High PEEP levels may decrease cerebral venous outflow, cardiac output, and mean arterial pressure resulting in decreased cerebral perfusion pressure (CPP). In patients with acute brain injury and impaired cerebral autoregulation, PEEP did not change ICP, cerebral perfusion, or oxygenation if adequate blood pressure was maintained [50-52]. PEEP should not increase ICP if ICP exceeds right atrial pressure [53]. The cerebral hemodynamic effects of PEEP may also be related to effects of PEEP on respiratory mechanics [54]. When PEEP is sufficient to induce alveolar hyperinflation, PaCO₂ is increased with concomitant

ICP increases. When PEEP is limited to cause only alveolar recruitment, no ICP or cerebral perfusion effects occur.

Both hypoxemia and hyperoxemia have been associated with a poor outcome after CA [55, 56], although adverse effects of hyperoxia remain controversial [57, 58]. Current recommendations are titration of inspired oxygen so as to maintain hemoglobin oxygen saturation within 94–98 % once ROSC has occurred and measurement is feasible [59, 60].

Changes in PaCO₂ affect CBF. CO₂ reactivity is generally preserved in comatose patients treated with therapeutic hypothermia after CA [56]. Arterial hypocapnia decreases bicarbonate resulting in cerebrospinal fluid (CSF) alkalosis, which decreases CBF, cerebral oxygen delivery, and, to a lesser extent, cerebral blood volume. Hypercapnia increases cerebral blood volume thus inducing or aggravating intracranial hypertension. Permissive hypercapnia used as a protective ventilation strategy should not be applied in comatose patients without ICP monitoring. Extracorporeal CO₂ removal may be considered in patients with severe ARDS to prevent secondary brain injury. Mechanical ventilation in the prone position may improve arterial and cerebral tissue oxygenation with little adverse effect on ICP [61].

Hemodynamic Support

Hemodynamic failure is rare in resuscitated drowning patients. Most do not aspirate enough fluid to cause clinically relevant changes in blood volume. Drowning in fresh water results in a small and transient increase in blood volume [62, 63]. Aspiration of large quantities of seawater may induce hypovolemia.

There are no studies on the optimal hemodynamic targets in drowning. Since ICP may be elevated [64] and cerebral autoregulation impaired, hemodynamic management is important to ensure cerebral perfusion. Blood pressure should be continuously monitored with an arterial catheter. It is reasonable to target a pressure that is high enough to ensure adequate cerebral perfusion, taking into account for the patient's normal blood pressure and signs of elevated ICP. If hypovolemia is diagnosed, fluid resuscitation should be initiated rapidly, but monitored. Fluid overload may be adverse. Conservative strategy of fluid management is associated with improved lung function and a shorter duration of mechanical ventilation and ICU stay in patients with acute lung injury [65], although this has not been examined in drowning. Use of inotropes or vasopressors may be necessary. Advanced hemodynamic monitoring may facilitate goal-directed resuscitation.

Seizures

Seizures following hypoxic brain injury are common. Evaluation for seizures allows the potential for treatment and to inform prognosis. Clinical detection of seizures is difficult in the ICU as these patients are frequently sedated and subjected to neuromuscular blockade, thus masking clinical signs. Non-convulsive seizures are common, even in patients who are not paralyzed. Continuous electroencephalographic (EEG) monitoring in critically ill patients revealed a 13 % incidence of seizures; 92 % of those seizures were exclusively non-convulsive [66]. In an unselected population of critically ill children, continuous EEG monitoring detected seizures in 44 % of subjects and 75 % of these patients had purely non-convulsive status epilepticus [67]. Following CA, seizures occur in 47 % of children of which 2/3 had status epilepticus [68]. Myoclonic or EEG status epilepticus has been associated with poor outcome from CA and drowning [69-72]. A small subset of patients with status epilepticus undergoing therapeutic hypothermia may have a good outcome [68, 73-75].

A trial of anti-epileptic drugs is warranted in all patients with clinical seizures. In patients with non-convulsive seizures or non-convulsive status epilepticus, anti-convulsive treatment should be considered, although it is unclear whether treatment impacts outcome. Prophylactic anti-convulsant medications are unproven.

Electrolytes

Serum electrolyte changes after drowning are dependent on the type and amount of fluid aspirated. Clinically relevant electrolyte changes are rare because of the small amount of water that is typically ingested. Even after drowning in the Dead Sea (NaCl concentration in the surface water > 275 g/L) derangements in serum sodium occurred only in a minority of patients [76]. Care must be taken to avoid a hyposmolar state in patients with a hypoxic encephalopathy, which could promote cerebral edema further aggravate secondary brain damage. Definitive studies of sodium or osmolar management after drowning are lacking.

Glucose Management

Severe illness induces dysglycemia, with potential detrimental effects. Mild hypothermia has an additional effect on glucose homeostasis by decreasing sensitivity to insulin and the amounts of insulin secreted by the pancreas. Both hyperglycemia and hypoglycemia are independent risk factors for increased morbidity and mortality in ICU patients. The injured brain is particularly susceptible to changes in glucose concentrations. Strict glucose control has not proven beneficial in neurocritical care patients and has an unacceptable risk of hypoglycemia when not continuously monitored [77, 78]. The threshold for hypoglycemic injury is likely to be higher in the injured versus normal brain. Even mild hypoglycemia can induce neuroglycopenia. In TBI patients, arterial glucose levels < 108 mg/dL resulted in decreased brain glucose concentrations and increased cerebral glucose uptake [79]. Microdialyzed markers of brain metabolic distress were increased at brain glucose concentrations < 18 mg/dL, reaching the lowest levels at arterial blood and brain glucose levels between 108 and 162 mg/dL. Glucose control in patients after drowning should be focused on avoiding hypoglycemia, hyperglycemia, and wide or rapid fluctuations in glycemic state. There is no target level of blood glucose that has been demonstrated to improve outcome.

Temperature Management

Therapeutic hypothermia has been intensively investigated, the mechanisms of which have been detailed elsewhere [80]. This section will focus on efficacy of induced hypothermia as it may pertain to drowning. A detailed description of how to cool comatose patients for therapeutic hypothermia has been published [81].

Drowning

The use of hypothermia originated for management of the comatose [82] and adult CA patient [83]. In the latter, it was specifically stated that hypothermia should be initiated within 30 min of ROSC. Use of hypothermia in drowning built upon that work, reports of remarkable recovery from cold-water drowning, and an optimistic report on HYPER therapy (diuretics, hyperventilation, deep (30 °C) and sustained hypothermia, barbiturates, and glucocorticoids) [84]. However, therapeutic hypothermia fell out of favor after two small retrospective studies suggested that deep and sustained hypothermia applied in an aggressive resuscitation regimen to patients with absent vital signs on admission increased survival of patients in a persistent vegetative state only [85, 86]. Hypothermia was abandoned until laboratory studies identified the need for only moderate hypothermia to mitigate neuronal injury. Two randomized clinical trials in CA showed improved neurologically intact survival

with use of moderate hypothermia [87, 88] allowing reconsideration of efficacy in asphyxial injury.

Asphyxia

All but one study (children [89]) analyzed newborns (Fig. 1). There were two systematic reviews [90, 91], and five randomized clinical trials (RCT) [92-96] showing increased chance of outcome without disabilities with mild hypothermia therapy. The relative risk (RR) for reduction of death or major neurodevelopmental disability varied between 1.35 and 2.43. The first systematic review included 8 RCTs and showed therapeutic hypothermia to be beneficial to term newborns with hypoxic ischemic encephalopathy (HIE) [90]. The second included 6 RCTs and associated therapeutic hypothermia with a highly reproducible reduction in the risk of the combined outcome of mortality or moderate-to-severe neurodevelopmental disability [91]. In 4 RCTs [97-100] and in 1 non-randomized comparative trial [89], no difference was found between hypothermia and normothermia groups. In a feasibility RCT performed in a low-resource setting, survival was decreased with hypothermia therapy [101]. Follow-up work is underway [102].

Cardiac Arrest

Two randomized trials demonstrated improved neurological outcome at hospital discharge or at 6 months after hospital discharge in comatose patients after out-of-hospital ventricular fibrillation (VF) CA [87, 88]. A target temperature of 32–34 °C was maintained for 12–24 h. One small randomized trial of comatose patients after CA with non-shockable rhythms showed a higher rate of neurologic intact survival in patients treated with a cooling cap [103].

A systematic review demonstrated improved neurologic survival from therapeutic hypothermia with a RR of 1.55 (95 % CI 1.22–1.96) compared with standard post-resuscitation care [104]. Fourteen studies of comatose survivors of CA using historical controls found therapeutic hypothermia to improve neurological outcome [105]. This is in contrast to a more recent meta-analysis [106], which reported a low-quality evidence in existing studies due to not aggressively treating hyperthermia in patients randomized to control groups.

Summary

There are no high-level evidence studies of therapeutic hypothermia in drowning. Treatment recommendations are made by extrapolation from studies of asphyxia and CA. First, prevent hyperthermia in comatose victims. If hyperthermia occurs, treat it promptly. Second, consider maintaining a target core temperature of 32–34 °C for 12–72 h. Cooling should be started as soon as possible, and re-warming should be slow, at a rate no faster than 0.5 °C/h.

Pediatric Considerations

For every pediatric drowning death, at least two non-fatal drowning hospitalizations are reported [107]. Pediatric hospitalizations in the USA have decreased over the past 16 years, from 4.7 to 2.4 per 100,000 population [108]. Roughly 80 % of children with a history of drowning are admitted to hospital for at least 1 day, and as many as 20 % of survivors suffer severe and sustained disability [109-111]. Factors that influence outcome include the preexisting medical condition, initial electrocardiographic rhythm, duration of no-flow time, and the quality of the life-supporting therapies provided during and following resuscitation. Higher survival rates in children may be due to healthier baseline health status, improved CBF during CPR because of increased chest compliance, and reserve and tolerance of the young brain to hypoxia/ischemia.

Considerations for pediatric drowning resuscitation involve age-dependent developmental physiology, anatomy, pharmacology, and psychology. The most commonly discussed physiologic consideration is persistence of the *diving reflex* [112] that occurs with rapid immersion in almost 100 % of babies to the age of 6 months, and persists in 10–15 % of older children and adolescents. This response, which starts immediately upon submersion prevents aspiration of water, re-distributes oxygen to heart and brain, slows cardiac oxygen use, and initiates a hypometabolic state. An intact diving reflex may be associated with improved outcomes in young children, and is accentuated when the “dive” is into ice-cold water [112].

A child’s relatively large head-to-body ratio allows for rapid surface cooling of the brain. Young infants may have an open fontanelle, decreasing risk for increased ICP. Lungs are relatively small, with increased airway resistance and relatively easily depleted surfactant stores. The functional residual capacity is small, with a closing lung capacity that is near functional residual capacity increasing risk of atelectasis without PEEP. Their flat diaphragms provide little anatomic advantage, and lower esophageal sphincter tone compared to adults leads to stomach distension with air and fluid. They generally have healthy hearts and thus tolerate high heart rates and catecholamine infusions. Rapid vascular access, monitoring, and rescue equipment sizing can be challenging.

Children have developmental changes specific to enzyme activity, integrity of the blood–brain barrier, high cerebral oxygen and glucose consumption, and unique patterns of biomarker and inflammatory mediator responses [113, 114] to hypoxic–ischemic brain injury. They have unique patterns of energy utilization, brain dependence on glucose and ketones, and glucose transport [115, 116]. Pharmacokinetics and pharmacodynamics change as volume of distribution (water content) and compartments change, and metabolic enzymes mature. Neuronal plasticity changes over time [117].

Although there are unique features to childhood drowning, there is not yet a unique goal-directed approach that consistently differs from adult brain-oriented ICU principles.

Neuromonitoring

In a survey of 72 patients admitted to the hospital for drowning, 21 % had severe anoxic encephalopathy [118]. Neurologic monitoring following resuscitation from drowning is important for prognosis, titration of therapies, and stratification of patients eligible for interventional trials. In this section, specific focus will be on the use of non-invasive monitoring techniques including neurologic examination, EEG, neuroimaging, somatosensory evoked potentials (SSEP), and invasive ICP monitoring. Induced hypothermia may impact the timing and prognostic reliability of these techniques.

Neurologic Examination

Standard neurologic examination is the most pragmatic tool. Many patients who are awake and interactive on emergency department arrival will survive grossly intact. It is not as clear which patients who have altered mental status or coma will do poorly [119, 120].

Large and unreactive pupils are a hallmark of HIE. It is unclear when the absence of pupillary responsiveness to light predicts poor outcome. Small retrospective drowning studies have shown absence of pupillary response in the emergency department or ICU to be associated with poor neurologic outcome [119–123]. While pupillary response may return within hours of resuscitation [118], an absent pupillary response at 24 h is associated with poor neurologic outcome [70, 124, 125]. This marker may be influenced by therapeutic hypothermia [126].

While drowning victims who are awake on ICU admission do well, patients who are non-responsive within 24 h of resuscitation do not have a uniformly poor outcome [119, 120, 125]. A composite GCS score ≤ 5 on ICU admission after drowning is associated with poor outcome, however, it is only 75 % specific to detect patients with a poor outcome. Some patients with a GCS ≤ 5 on ICU admission may have intact neurologic survival [122, 123].

Admission neurologic examination, alone, is not predictive of outcome. Neurologic examinations should be serially repeated including level of consciousness, pupillary reactivity, brain stem reflexes, and motor function. Drowning victims have recovered motor function as late as 48 h after resuscitation [127, 128]. CA data supports these findings [70, 71, 124, 129, 130]. Following drowning, prediction of poor outcome cannot reliably occur based on absence of pupillary reactivity until 24 h after resuscitation and absence of motor score until 72 h after resuscitation.

Electroencephalography

Continuous EEG can be used for prognostication of brain injury severity, diagnosis, and titration of treatment for seizure activity, or stratification of patients for clinical studies. Trained neurologists usually perform EEG interpretation. In certain settings, real-time quantitative tools can be interpreted by ICU providers [131]. EEG has been used to prognosticate severity of injury following hypoxic ischemic insults and CA. There are little data specific to drowning. Non-standardized terminology makes it challenging to generalize findings. In small retrospective studies of drowned children, EEG progression to burst suppression was associated with poor outcome. The presence of normal sleep wake differentiation was associated with good outcome [69, 132]. Burst suppression, isoelectric patterns, profound background attenuation, and loss of reactivity to stimulation are associated with poor outcomes following CA and hypoxic ischemic injury (Fig. 2) [71, 125, 133-135]. Continuous EEG background with reactivity is re-assuring [71, 135].

Multiple CA studies evaluated the prognostic value of EEG background patterns during therapeutic hypothermia. Hypothermia can impact EEG background activity. The most profound effects are seen at temperatures below the target range of 32–34 °C. A study of 19 pediatric CA patients showed burst suppression or excessive EEG discontinuity to be predictive of seizures [68]. In a larger pediatric study, the presence of continuity without reactivity, discontinuity, burst suppression, or isoelectric background was associated with poor outcome during both hypothermic and normothermic phases of induced hypothermia [136]. Similar to normothermia, lack of EEG reactivity, burst suppression, and isoelectric patterns are associated with poor outcome in adult CA [74, 75, 126, 137]. Patients who demonstrate EEG reactivity with stimulation are likely to have a good outcome [137].

Neuroimaging

Early neuroimaging after drowning allows detection of injury requiring neurosurgical intervention and may aid in prognosticating the severity of brain injury.

Computerized Axial Tomography—A CT may be useful to detect head and neck trauma. An initially normal CT in a comatose patient should not be re-assuring [138, 139]. Comatose pediatric drowning victims who have an initial abnormal head CT or a normal CT with a subsequent abnormal CT have poor outcome [139]. Retrospective studies concluded that if there was no clinical evidence of trauma, CT is not necessary [138, 139]. Despite this, intracranial hemorrhage may be present following CA [140]. Early post-ROSC CT imaging may show loss of gray white matter differentiation and cerebral edema, which are associated with poor CA outcome [141, 142]; sulcal effacement is less reliable [143, 144]. The presence of a reversal sign (a bright cerebellum and dark cortex) is associated with poor

outcome [145]. Early loss of gray white matter differentiation may not be improved by hypothermia [146, 147].

Magnetic Resonance Imaging (MRI)—Diffusion weighted imaging (DWI) can detect injury within minutes after ischemia and improves the ability to predict poor outcome [148]. Cortical and deep brain DWI abnormalities are associated with poor outcomes as are lower apparent diffusion coefficients (Fig. 3) [149-151].

MRI grading systems have been proposed to prognosticate outcome. An 8-point system in children with hypoxic coma yielded a sensitivity of 96 % for an abnormal MRI observed within the first 3 days after injury to predict poor outcome. However, a normal early MRI was only 50 % specific (predictive) for good outcome. MRIs obtained 4–7 days following injury have a higher predictive value [152]. In drowning, children who had MRI evidence of basal ganglia injury, edema, and cortical abnormalities did poorly [153].

MR spectroscopy, which evaluates the metabolic profile of the brain, best predicts outcome 3–4 days after drowning and CA. When evaluated 1–2 days post-injury, several patients who remained vegetative or died had normal scans. MR spectroscopy sensitivity improved over time and had a lower false negative rate several days after injury [153, 154].

SSEP

SSEP measures an electrical signal in response to a sensory stimulus. N20 SSEP specifically evaluates the response in primary sensory cortical locations. Electrical noise can impact its accuracy. A skilled electrophysiologist must perform and interpret SSEP. Neurologic examination in patients with post-anoxic coma does not reliably predict N20 responses after CPR [155].

Following adult CA, bilateral N20 SSEP absence is sensitive for poor outcome between 24 and 72 h following resuscitation [70, 133]. Although several subjects will regain SSEP later, in one study all the subjects still had poor outcome. While N20 SSEP absence predicts poor outcome, N20 SSEP presence at 24 h does not always predict a good outcome. In pediatric CA, bilateral N20 SSEP absence at 24 h is also highly predictive of poor outcome [125, 156].

ICP

Intracranial hypertension is common after drowning and is strongly associated with a poor outcome [157-159]. Initial cerebral edema is most likely cytotoxic due to energy failure and transit of water into the intracellular compartment. This can contribute to intracranial hypertension and decreased CBF. While CBF improves during the first 24 h after ROSC, cerebral edema worsens as tissue deteriorates [157]. ICP monitoring is invasive with adherent risks. There has been no optimal anatomic site identified for monitoring ICP following drowning. Retrospective review showed that elevated ICP did not correlate with postmortem cerebral edema and that ICP monitoring did not impact drowning outcome [85]. No randomized trials are available for ICP monitoring and treatment in drowning. Pediatric case series have reported disappointing results with patients surviving in a vegetative neurologic state despite adequate ICP and CPP control [157-161]. One small prospective drowning study showed no benefit [162]. Currently, ICP monitoring is not routinely used following drowning. Re-evaluation of ICP-guided therapy in the context of current care is warranted. Modest elevation of the head reduces ICP. The lowest mean ICP is usually found with elevation of the head to 30 ° [163]. Elevation beyond 30 ° may adversely affect CPP.

Investigational Neuromonitoring

Continuous monitoring may allow the clinician to titrate therapies. Stratification of injury may also define which patients, based on severity of injury and individual characteristics, may benefit from select therapies. Microdialysis, brain tissue oxygenation monitors, near-infrared spectroscopy, and quantitative EEG transformations may be useful. Xenon CT and arterial spin-labeling MRI may allow intermittent evaluation of brain perfusion. Positron emission CT may allow intermittent evaluation of metabolic function.

Summary

Neurologic examination, EEG, neuroimaging, and SSEP can help prognosticate neurologic outcome after drowning (see Table 1). No single tool can reliably predict outcome prior to 24 h from resuscitation. The combination of these methods may enhance outcome prediction. Therapeutic hypothermia may necessitate re-calibrating the impact of the prognostic values of these tools and clinicians should be cautious in making predictions based on normothermic-derived investigations. Evaluation of established and novel neuromonitoring modalities in the drowning population is necessary.

Biomarkers

Biomarkers are quantifiable biological parameters, often proteins or parts thereof, which may be detected in a fluid compartment of the human body. This fluid compartment is often peripheral blood but can also be urine or CSF. The significance of biomarkers relates to drowning outcome and how they can aid in prognostication. There are few data and no good quality trials on use of biomarkers after drowning. Current understanding is predominantly based on extrapolation from data after CA. This seems relevant since the divider between a good and a poor outcome after drowning, other than submersion duration, often is whether or not the patient suffered CA [86, 164].

Biomarkers may be organ specific or more general, the latter reflecting a non-specific stress response. Drowning results in asphyxia and may lead to CA. Therefore, biomarkers of interest after drowning should be those mirroring an asphyxial insult to the brain, for example neuron-specific enolase (NSE) or S-100B, or an asphyxial insult to the heart (troponin I and T) [165]. Biomarkers of a non-specific stress response include blood glucose, lactate, cytokines, and products of oxidative stress (Table 2). Biomarkers are easy to sample and inexpensive to measure. Drawbacks include a multitude of methods in clinical use and lack of a standard, making it difficult to compare results between centers and to produce guidelines. Anticoagulant therapy or possible herniation may exclude use of CSF.

NSE is the best-studied biomarker and may be used as an adjunct in prognostication after CA [114, 166-168]. However, results from centers differ due to differences in methodology and lack of standard assay procedure [169, 170]. A low or moderately elevated NSE value ($< 33 \mu\text{g/L}$) in a patient remaining comatose should alert the clinician that a treatable condition might prevail [171]. A high NSE ($> 33 \mu\text{g/L}$) is often not only a sign of extensive injury but also may be caused by hemolysis, due to NSE in erythrocytes. Caution is warranted and biomarkers, like NSE, should never be the sole basis for a decision on level of care. Only one case report was identified where NSE-levels were presented in a drowning victim with CA [172]. This patient had a good outcome and peaked at $20.7 \mu\text{g/L}$, well below the $33 \mu\text{g/L}$ cut-off, which has been suggested in guidelines [71]. Other brain biomarkers that have been studied after CA without submersion include S-100B [166, 173, 174], GFAP [175], and tau [176].

Regarding biomarkers of a non-specific stress response, an association has been shown between high plasma glucose on admission and a poor drowning outcome [120, 123, 177].

Typically, admission plasma glucose values < 200 mg/dL were associated with better outcome. This is consistent with threshold values reported in other forms of acute brain injury. High blood lactate or low pH on admission may associate with a poor outcome after drowning, but the results are conflicting [13, 178]. Pro-calcitonin is another surrogate marker for CA outcome that has attracted interest [179, 180]. Its use after drowning has not been studied. Novel biomarkers to aid in prognostication after drowning may emerge. Such candidates include non-specific markers of oxidative stress and inflammation and novel, ultrasensitive markers of organ injury such as organ-specific micro-RNAs measured in peripheral blood [181].

A single sample of any biomarker may be false for various reasons. Repeated samples should always be secured, preferably as a timed series to capture trends that may add to their prognostic value [166, 168]. The issue of standardization of analytic procedures and normal values across laboratories must be solved before general recommendations regarding any biomarker can be given.

Summary

There are few data on use of biomarkers to aid in prognostication after drowning. Troponin I, plasma glucose, and possibly blood pH and lactate on admission are associated with outcome but the data is scarce and conflicting. The best-studied biomarker after CA is NSE and its use may be considered after drowning. Induced hypothermia for treatment of comatose survivors may affect the release profile of biomarkers and alter their predictive value. This is under active investigation in CA. Prospective high-quality studies to investigate the prognostic value of biomarkers after drowning are warranted.

Post-hypoxic Pharmacology

Systematic assessment of pharmacologic therapy for treatment of brain injury in drowning is non-existent. This is attributable to numerous factors. Drowning events are sporadic, the frequency of which vary with season, location, and age. Drowning reflects a heterogeneous presentation of anoxic brain insults. The duration of submersion, and thus asphyxia is often unknown. Drowning in cold water may be attributable to submersion alone or instead to hypothermia, which independently causes CA followed by submersion. There is little evidence distinguishing cerebral responses to fresh versus salt water drowning. Drowning may be complicated by TBI, spinal cord injury, drug use, or other factors. Finally, there are no pharmacologic agents with proven efficacy in HIE insults of any etiology that could be directly extended to drowning. These factors, combined, have made studies of pharmacologic efficacy in the drowning population implausible to date.

Given the potentially catastrophic outcome associated with a comatose state after ROSC in drowning, caregivers may consider application of clinically available putatively efficacious pharmacologic interventions, even if sufficient and rigorous evidence is not in hand to justify such therapy. Thus, data from other HIE insults have been considered to determine whether such efforts are appropriate.

Anesthetics

Barbiturates—Evidence that barbiturates substantially suppress cerebral metabolic rate offered hope that deprivation of energy substrate could be offset by decreased energy requirement. Although ATP synthesis was later shown to rapidly recover after restoration of CBF, efforts to use barbiturates for neuroresuscitative purposes continued.

The concept of using barbiturates for treatment of drowning was introduced as a component of HYPER therapy [182]. A retrospective investigation reported outcome advantages [183],

but further work was not supportive [85]. Multiple interventions were used simultaneously making it difficult to discern effects of most components of HYPER therapy. However, barbiturates have been specifically investigated. Outcome in pediatric drowning victims treated with HYPER therapy was no different with or without inclusion of the barbiturate component [184]. This parallels data from a prospective randomized trial of barbiturates in adult comatose survivors of CA, where thiopental failed to alter outcome [185, 186], and results of randomized trials of barbiturate loading in severe perinatal asphyxia [187, 188]. Rigorous study indicates no role for barbiturates in drowning.

Lidocaine—Lidocaine, in antiarrhythmic doses, has been reported to decrease cognitive deficits after cardiac surgery [189, 190]. The mechanisms are presumed to be inhibition of cellular ion fluxes and cerebral metabolic suppression [191]. No clinical trials have examined lidocaine neuroresuscitative efficacy in drowning, CA, or asphyxia.

Glutamate Antagonists and Calcium Channel Blockers

Extracellular glutamate is increased in ischemic/anoxic brain leading to toxic increases in intracellular calcium and sodium. Multiple glutamate receptor antagonists have been studied experimentally. None has achieved approval as neuroresuscitative agents. Magnesium and L-type calcium channel blockers are clinically available and have been proposed as having neuroprotective properties by inhibiting calcium entry into neurons, similar to selective glutamate antagonists.

Magnesium—No studies have been conducted in drowning. In perinatal asphyxia, five trials have been reported. EEG and outcome responses were studied in 30 neonates randomized to MgSO₄ or 0.9 % NaCl treatment [192]. No effect of magnesium was observed other than decreased blood pressure. This was followed by a trial in neonates randomized to MgSO₄ with dopamine or placebo [193]. MgSO₄ plus dopamine improved short-term outcome. Forty neonates were randomized to MgSO₄ or saline [194]. Short-term neurologic outcome was better with MgSO₄. Another trial studied 40 patients followed for 6 months after birth [195]. A pattern of MgSO₄ efficacy was present, but not consistent. None of these studies evaluated large populations and mechanisms of action were not addressed. Extension of birth asphyxia to drowning in children and adults is not supported by direct evidence.

There was only one trial of magnesium treatment in adult CA [196]. Three hundred patients were randomized to receive placebo, 2 g MgSO₄, or 2 g MgSO₄ plus 10 mg diazepam. No adverse events were observed, but there was no benefit from treatment. Magnesium worsened morbidity and increased mortality in a large TBI trial [197]. While the CA study was negative, it has been suggested that a combination of induced hypothermia and magnesium may be efficacious [198]. In summary, there is no evidence that magnesium improves drowning outcome. Although showing some benefit in birth asphyxia, magnesium has no benefit in CA and worsens TBI and thus cannot be recommended.

Calcium Channel Blockers—L-type calcium channel blockers are purported to impede Ca⁺⁺ entry into neurons rendering them more tolerant to ischemia. One drowning case report was retrieved. A 27-month-old child made a full recovery from a comatose state following drowning and CPR. Verapamil (1 mg) was given creating hemodynamic instability [199]. Hemodynamic instability was also observed in four full-term asphyxiated infants treated with nimodipine [200]. Two clinical trials have been conducted. Out-of-hospital VF CA patients were randomized to nimodipine or placebo with no change in 1-year survival [201]. Similar findings were reported for lidoflazine [202]. These studies ended efforts to further explore calcium channel blockers, which are not recommended in drowning.

Antioxidants

Oxidative stress is a known component of ischemic/asphyxia brain injury. Pharmacologic inhibition of free radical damage and signaling has been found therapeutic in preclinical experimental paradigms. Antioxidants have not been studied in drowning. One randomized trial found no benefit from ascorbic acid and ibuprofen in asphyxiated neonates [203]. There were no articles associated with CA. Allopurinol inhibits xanthine oxidase decreasing superoxide production [204]. Three trials were performed in perinatal HIE [205-207] and subjected to meta-analysis. Insufficient evidence was available to define efficacy [208]. A major allopurinol trial is now underway [209]. No work has been done on modern molecules offering known blood-brain barrier penetration or potent redox activity. To date, there is insufficient evidence that clinically available drugs having anti-oxidant activity will be of benefit in drowning.

Glucocorticoids

Glucocorticoids are hypothesized to stabilize cellular membranes exposed to oxidative stress. Searches retrieved only case reports for glucocorticoid use in drowning [210]. Glucocorticoids were typically given in the context of barbiturate coma and hyperventilation. Specific glucocorticoid efficacy could not be determined. There are no recent reports in drowning representing abandonment of this therapy. For CA, two large retrospective studies were identified with concurrent controls [211, 212]. No benefit from glucocorticoid use was observed. No evidence was found to support glucocorticoid use in drowning.

Erythropoietin

Erythropoietin is clinically available to stimulate erythropoiesis. Erythropoietin receptors are present in brain. Erythropoietin has growth factor, anti-apoptotic, antioxidant, and anti-inflammatory properties. Structural modifications of the parent molecule are being developed to preserve neuroprotective properties, without stimulating erythropoiesis. Erythropoietin has not been evaluated in drowning, but has been investigated as a post-ischemic/anoxic therapeutic [213]. CA patients were treated with erythropoietin during chest compression [214]. Neurologic outcome was not assessed. In another study [215], patients were treated with erythropoietin and hypothermia. Erythropoietin had no benefit, but thrombocytosis was increased.

Erythropoietin has been studied in neonatal HIE. Eighteen-month outcomes were assessed in neonates with asphyxia injury [216]. Erythropoietin did not have an effect on primary neurologic outcome end-points. Post hoc analysis of neonates with only moderate asphyxia found benefit, suggesting efficacy only with specific severities of injury. A case-control study on a small population of neonates with birth asphyxia found fewer neurologic and developmental abnormalities at 6 months with erythropoietin [217].

Optimism remains for a clinical role for erythropoietin in CA and birth asphyxia, but efficacy is unproven and adverse events are unmeasured. There are no data specific to drowning. There is insufficient evidence to recommend use of erythropoietin in drowning.

Summary

There have been no systematic pharmacologic studies in drowning outside study of HYPER therapy, which combined numerous interventions and no benefit was observed. Thus, no neuroresuscitative pharmacologic therapy can be recommended. Brain pathobiology following a severe and sustained reduction in critical substrate delivery is complex. Research efforts continue to reveal novel targets for pharmacologic intervention. As new pharmacologic opportunities emerge, investigation in drowning remains a priority.

Animal Experimentation

The principle etiology of the neurological insult in drowning is ACA. Rodent and large animal ACA models offer acute physiology and, in some cases, neuropathological and behavioral outcomes. Both adult and pediatric models are available. There are few drowning models [218]. ACA models show important pathophysiological differences from VF, supporting the need to use ACA models for drowning research. In contrast to other forms of acute brain injury, ACA represents one of the few experimental conditions where translation of a beneficial neuroresuscitative therapy from animals to human has been shown, namely conventional versus compression only CPR in ACA (unlike VF). This was originally shown in a piglet ACA model [219] and predicted results from large-scale CPR studies in children [24, 25]. Similarly, mild hypothermia was successfully translated from neonatal asphyxia sheep models to clinical use [220].

ACA Models that Include Drowning

Animal models have generally not incorporated drowning into an ACA paradigm and those that exist have not been used to study neuroprotection. One exception examined cold-water exposures in canine models and showed benefit of hypothermic protection [218]. The value of intra-arrest hypothermia in cold water was already supported by clinical literature [182, 221]. Given the lack of use of drowning models, the recommendations that can be gleaned from preclinical research are based on ACA studies alone.

Rat ACA Models

There are excellent models that produce ACA in anesthetized adult rats using neuromuscular blockade, which, after a brief interval results in a no-flow state, mimicking the human condition [222-229]. The model incorporates a clinically realistic resuscitation, post-arrest coma, long-term survival (after 6–8 min insults), and characteristic delayed neuronal death in selectively vulnerable regions. It can be used to test behavioral outcomes [222, 228] and molecular tools are available for study of rats. Limitations include a short CPR phase (usually < 1 min) and the inability to perform long-term ICU care. The model is excellent for screening therapies and is inexpensive. Several therapies have shown promise in this model, e.g., mild hypothermia, glucose and insulin, and neurotensin [223, 226-229]. There also are pediatric analogs [230-233], which use post-natal Day 17 rats. Promising results have been obtained with hypothermia and minocycline [231, 233]. Mouse ACA models have not been developed.

Pig ACA Models

Due to their size, pigs better mimic the CPR-related aspects of drowning resuscitation and ICU care is feasible [234-237]. However, neuropathological targets and long-term outcome are not well defined. Behavioral testing is also poorly developed limiting ability to link structure and function in contrast to rodents in which cognitive function can be readily assessed with mazes. There are few molecular tools for use in pigs, although this is improving. Expense is another concern. There are pediatric piglet models [219, 238-245]. More work has been done in pediatric than adult ACA models likely related to the importance of ACA in children. Once again, piglet CPR-related physiology mimics many aspects of the human condition. Use of piglet ACA models to optimize CPR has had excellent success for direct translation to the clinical condition [219, 238-245]. However, neuropathological targets are less defined than in rodent models and behavioral testing of piglets limited. Nevertheless, a number of aspects of cardiovascular and brain development are similar to humans [246]. Thus, there is opportunity for drowning studies in piglet ACA.

Canine ACA Models

Adult canines have been used to characterize ACA physiology, neuropathology, and functional outcome. Direct comparisons to other forms of CA, namely VF, have been made [218, 247-249]. For comparable no-flow durations, despite a shorter time to ROSC after ACA than VF, more severe brain injury is produced by ACA (Fig. 4). Neuronal death in selectively vulnerable regions was seen in both ACA and VF, but severe cortical microinfarcts were seen only after ACA. Histopathological damage scores were twice as high in ACA. Treatment targeting oxidative stress was effective in ACA while a calcium antagonist showed benefit in VF. Thus, therapeutic approaches may need to be different in ACA. ICU care has been applied to these models [218, 247-249]. Efficacy of intra-arrest deep hypothermia has been demonstrated in drowning-induced canine ACA [218]. As with pigs, cognitive outcome testing is limited and studies are expensive. Pediatric canine studies have targeted neonatal asphyxia rather than drowning [250, 251].

Summary

Excellent ACA models, across species and age, have been successfully used to translate therapies to humans. ACA differs importantly from VF with regard to neuropathological damage and possibly response to therapy. There is need for systematic evaluation of putative neuroresuscitative therapies specific to ACA if treatment is to be made available for drowning. There is also a need for better characterization of neuropathology and functional deficits in large animal models. Similarly, there is a need for ACA models that incorporate drowning since secondary insults could complicate neurological outcomes.

Future Research Questions

Key unanswered questions related to the development of optimal neuroresuscitation in drowning are presented below.

1. How should clinical targets for neuroprotection in drowning be identified? Clinical descriptive and outcome studies are needed [252, 253]. Guidelines for study of drowning have been recommended to standardize definitions, terminology, and data sets [6]. Advanced neuromonitoring, serum biomarkers, and brain imaging should be used to define key targets for neuroprotection, evaluate therapeutic efficacy, and predict outcome [136, 139, 153, 166, 174]. To define therapeutic targets, better use should be made of existing animal ACA models [224, 230, 249], and like clinical studies consider standardization of definitions, terminology, and recommended datasets.
2. What is the impact of conventional versus compression only CPR on neurological outcome in drowning? Data from adults, children, and laboratory piglet models have demonstrated a more favorable neurological outcome after ACA using conventional rather than compression only CPR [25, 254]. Although one would anticipate similar findings in drowning, data are needed. In addition, how other aspects of basic and advanced life support (e.g., management of arterial oxygen partial pressure, blood glucose, body temperature) influence neurological outcome in setting of drowning merits study.
3. Is post-resuscitation therapeutic hypothermia effective in drowning? Studies in adults have reported efficacy after VF CA. Efficacy for other rhythms is more controversial. ACA data are limited. Benefit has been shown in perinatal asphyxia. However, there are differences between ACA in children and adults and birth asphyxia, which often represents a series of intermittent insults over several hours. It is unclear whether therapeutic hypothermia should be employed before RCTs have been conducted in ACA. Can mechanisms of hypothermic neuroprotection be

better understood and efficacy improved [255-257]? Better definition of neuroprotective adjuncts to hypothermia is needed [228, 258]. If hypothermia is not used, should rigorous targeted normothermia be implemented [259]? For cold-water drowning, how should existing hypothermia and re-warming be managed [260]?

4. What is the best method to re-oxygenate the brain in drowning? VF studies indicate resuscitation with room air may be preferable to 100 % oxygen [261, 262]. ACA and drowning are different from VF with regard to respiratory physiology at the time of resuscitation. In ACA, the no-flow period is preceded by a period of anoxia. Pulmonary compromise may be present in drowning. AHA and ILCOR recommend titrated use of oxygen during VF resuscitation based on arterial saturation when pulse oximetry is available. This needs to be studied in drowning. There also may be developmental differences in antioxidant defenses. Might use of 100 % oxygen plus antioxidants be a better approach to oxygen administration?
5. How should reperfusion be optimized in drowning resuscitation? An opportunity for a breakthrough in resuscitation is use of extracorporeal support (E-CPR) for reperfusion, given that it can be used to optimize extra-cerebral physiology while also allowing immediate temperature control and administration of therapies that might not otherwise be tolerated [263-266]. Technical challenges to E-CPR are considerable. When is E-CPR indicated? Should “controlled reperfusion,” so as to limit reperfusion injury, be a research priority [267]? Some have suggested that reperfusion be totally re-thought. Should novel approaches, such as intermittent reperfusion (ischemic post-conditioning), be explored [268]?
6. What drugs might facilitate neurological recovery after ACA [233, 269]? Possibilities include laboratory and clinical investigation of drugs that are already approved for other uses that might be quickly brought to clinical trials, evaluation of novel therapies in laboratory ACA models, and investigation of the optimal rehabilitation of brain injury after drowning. Given neurogenesis and/or regenerative approaches to brain injury, optimizing the interaction between neuroprotection and neurorehabilitation deserves attention [269].
7. What novel resuscitation concepts should receive the highest priorities for exploration? Is it worthwhile to consider approaches that are “outside of the box”? Should novel non-pharmacological strategies such as the use of remote limb ischemia, so as to allow ischemic post-conditioning, be examined [270]? What novel pharmacological therapies under development for other forms of acute brain injury should be explored [271, 272]?
8. What is the best preclinical model for drowning research? Valid ACA models are available. Are there interactions between submersion, aspiration, and asphyxial arrest that are unique to neurologic outcome from drowning?

Consensus Recommendations for Clinical Management

Prevention is the best neuroprotective therapy for drowning. When drowning occurs, the initial strategy is optimized rescue and basic life support. For drowning victims who are comatose, the following brain-oriented resuscitation strategies are recommended for medical providers to improve neurological outcome. The injured brain is extremely vulnerable to secondary insults: it is the central tenant of neurocritical care to prevent secondary insults.

For patients with no signs of life after the rescue, provide immediate chest compressions with rescue breathing rather than compression only CPR. Support ventilation in patients with signs of life but inadequate spontaneous respiration. Hypoxemia and hyperoxemia

should be prevented. Optimal prehospital monitoring includes temperature, blood pressure, pulse oximetry, and capnography. Arterial hypotension should be anticipated, recognized, and treated. The victim should be transferred to a facility with expertise in post-resuscitation neurocritical care. Pediatric drowning victims should be managed in a center with expertise in pediatric post-CA care because of unique anatomic, physiologic, pharmacologic, prognostic, rehabilitation considerations. Care should be documented, reviewed, and a quality improvement assessment performed by providers and peers.

During ICU management, it is important for optimal brain resuscitation to ensure adequate oxygenation and ventilation, avoid hypoxemia and hyperoxemia, and maintain normocapnia. Blood pressure should be continuously monitored with an arterial catheter. Prevent arterial hypotension. Investigate the etiology of arterial hypertension. Optimize volume status and consider advanced hemodynamic monitoring in the setting of hemodynamic instability. Prevent development of a hypoosmotic state. Prevent hypoglycemia and treat hyperglycemia. Consider early enteral nutrition as tolerated. Treat clinical seizures and consider treating non-convulsive status epilepticus. Consider head midline and elevated 15 °–30 ° in hemodynamically stable patients. Titrate therapies to post-resuscitation goals.

Prevent hyperthermia in comatose drowning victims. Anticipate and aggressively treat hyperthermia promptly. Consider maintaining target temperature at 32–34 °C for 12–72 h. Cooling should be started as soon as possible, and re-warming should be slow, at a rate no faster than 0.5 °C/h. Provide an appropriate level of sedation and prevent shivering if cooling is used.

Provide serial neurological examinations and obtain brain imaging. Obtain frequent or continuous EEG monitoring in patients that remain comatose. Consider monitoring SSEP N20, EEG background pattern, and CT or MRI to aid in prognostication.

Consider the use of serum biomarkers (e.g., NSE) as an adjunct to aid in prognostication. Hypothermia may alter the predictive value of biomarkers.

There is insufficient evidence to support use of any specific brain-oriented neuroresuscitative pharmacological therapy, other than that used to maintain physiologic homeostasis (i.e., as needed to treat hypotension, hypertension, hypoglycemia, hyperglycemia, hypoxia, hyperoxia, shivering, and seizures), in drowning.

Evidence Basis for Consensus Recommendations

Experts in respective topics conducted focused literature reviews during a span of September 2011–February 2012 (search refreshed July 13, 2012). Databases searched included PubMed, Cochrane Library, and clinical trials.gov. Searches were limited to research on humans. Search terms incorporated key words associated with the topic (e.g., PEEP, hypoxia, hypothermia, etc.) combined with drown, drowning, near-drowning, asphyxia, HIE, or CA. To further refine the search, the terms brain or cerebral were included.

The search results were graded using the levels of evidence system reported by Sayre et al. [273] and modified as recommended for prognostic (P) applications, as appropriate.

LOE1: RCT or meta-analyses of RCTs.

LOE 2: Studies using concurrent controls without true randomization (e.g., “pseudo”-randomized).

LOE 3: Studies using retrospective controls.

LOE4: Studies without a control group (e.g., case series).

LOE 5: Studies not directly related to the specific patient population (e.g., different patient/population, animals models, mechanical models, etc.).

Expert Opinion

Each retrieved article was further graded with respect to whether the intervention was reported to provide beneficial, neutral, or harmful effects, or if effects were not specified [273]. Many of the studies rated as LOE 5, were judged as such because they were conducted in populations other than drowning. Often, such studies met the criteria for LOE 1 or LOE 2 in their respective populations. One goal of this search was to examine data directly derived from drowning and to demonstrate the general lack of information specific to this population. The reader is encouraged to carefully consider LOE 5 studies, as did members of the consensus committee in deriving recommendations, as such studies may provide the best evidence available to define treatment in drowning until information specific to drowning becomes available.

Prehospital Management

Prognostication

- 1 LOE 3 study in drowning [19].

Bystander CPR

- 1 LOE 4 study showing benefit in drowning [274].

Rescue Breathing During Bystander CPR

- 1 LOE 4 study showing benefit in drowning [20].
- 2 LOE 5 studies showing benefit in CA [24, 25].
- 1 LOE 5 study showing benefit from compression only bystander CPR [21].

BiPaP or CPAP

- 1 LOE 4 study showing benefit in drowning [27].
- 1 LOE 5 study showing benefit in ARDS [28].

Helicopter Transport

- 1 LOE 5 study showing benefit in CA [38].

Brain-Oriented Intensive Care Management

Positive End-Expiratory Pressure

- 4 LOE 4 studies showing benefit in drowning [275-278].

Hypoxia or Hyperoxia

- No studies in drowning.
- 3 LOE 5 studies in CA showing harm [55, 57, 262].

Arterial Hypotension

- No studies in drowning.

- 2 LOE 5 studies showing neutral effects [279, 280], and 5 showing harm [32, 281-284] in CA.

Anti-epileptics

- 2 LOE 4 studies in drowning showing benefit [285, 286].
- 10 LOE 5 studies showing benefit in CA [73, 126, 287-294].

Strict Glucose Control

- No studies in drowning.
- 1 LOE 5 study in CA showing neutral effects [295].

Therapeutic Hypothermia

- 2 LOE 3 studies showing neutral effects [85, 296], 1 LOE 4 report indicating benefit [297], 1 LOE 4 report indicating a neutral effect [298], and 7 LOE 4 studies for which the effect was not specified [184, 266, 299-303]. These studies were all in drowning.
- 25 LOE 5 studies showing benefit [87, 88, 90-96, 104, 226, 304-315], six LOE 5 studies showing neutral effect [89, 97-100, 103], 1 LOE 5 study showing harm [101], and 5 LOE 5 studies in which the effect was not indicated [147, 316-319]. These studies were in CA or birth asphyxia.

Neuromonitoring

- 1 LOE P2 study indicating benefit from neuromonitoring in drowning [154].
- 7 LOE P3 studies indicating benefit [120, 122, 123, 128, 132, 153, 320], 1 indicating neutral effects [121], and 1 indicating harm [85] in drowning.
- 5 LOE P4 studies indicating benefit [69, 118, 119, 144, 321] and one indicating a neutral effect [162] in drowning.
- 27 LOE P5 studies [70, 74, 75, 124, 125, 129-131, 136, 137, 139, 141, 142, 145-151, 322-328] and 1 expert opinion [71] indicating benefit, 4 LOE P5 indicating a neutral effects [68, 134, 143, 329], 1 LOE P5 indicating harm [152], and 1 LOE P5 not specified [140] in CA or HIE.

Biomarkers

- 1 LOE 3P study in drowning. The effect is not specified [120].
- 6 LOE 4P [13, 123, 165, 172, 177, 178] in drowning in which the effect was not specified, and 13 LOE 5P [168-171, 173-176, 179-181] studies and 1 expert opinion [71] in CA or HIE for which the effect was not specified.

Post-Hypoxic Pharmacology

Antioxidants (Allopurinol, Ascorbate, Edaravone, Alpha-Tocopherol)

- No studies have been conducted in drowning.
- 2 LOE 5 studies showing benefit [205, 207], and 3 showing a neutral effect in CA or HIE [203, 206, 208].

Barbiturates (Thiopental or Pentobarbital)

- 1 LOE 2 study showing neutral effects in drowning [184].

- 2 LOE 3 studies showing benefit [183, 330], and 1 showing a neutral effect [85] in drowning.
- 3 LOE 5 studies showing neutral effects in CA or HIE [184, 185, 187].

Calcium Channel Blockers (Nimodipine, Lidoflazine, Flunarizine)

- 1 LOE 4 study in drowning. The effect was not indicated [199].
- 2 LOE 5 studies showing benefit [185, 201], 1 showing harm [200] in CA or HIE.

Erythropoietin

- No studies in drowning.
- 1 LOE 5 study showing benefit [217], and 3 showing a neutral effect in CA or HIE [214-216].

Glucocorticoids (Dexamethasone or Methylprednisolone)

- 1 LOE 4 study showing benefit in drowning [210].
- 3 LOE 5 studies showing neutral effects in CA or HIE [211, 212, 331].

Lidocaine

- No studies in drowning, CA, or HIE.

Magnesium

- No studies in drowning.
- 3 LOE 5 studies showing benefit [193-195], 2 showing harm [192, 196], and 1 for which effects were not specified [332], all in CA or HIE.

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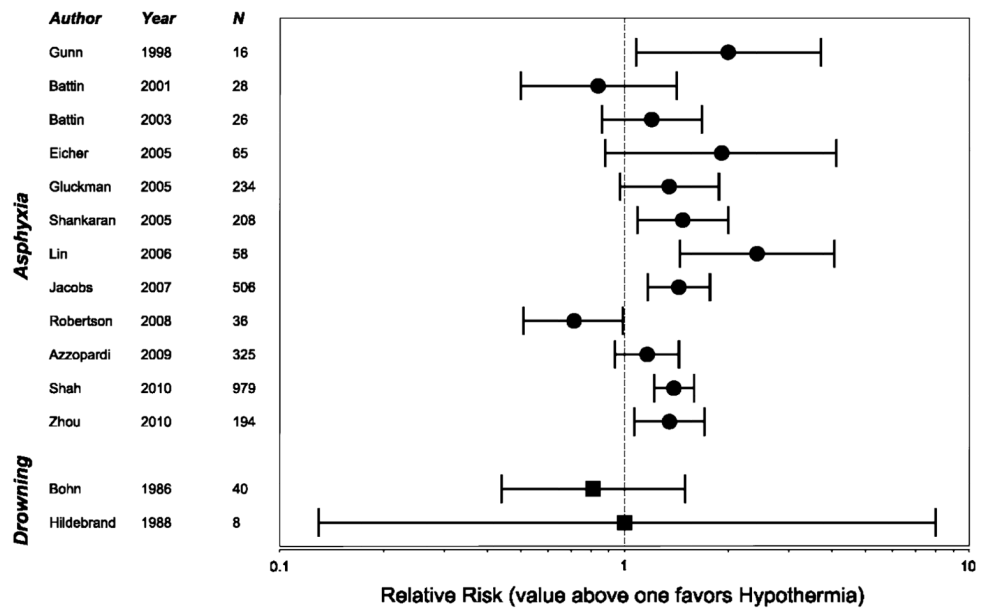


Fig. 1. Forrest plot of studies that used therapeutic hypothermia in the treatment of asphyxia and drowning. RR of good neurologic survival is presented. A value above 1 favors therapeutic hypothermia. Jacobs et al. [90] and Shah [91] were meta-analyses. *N*= total number of patients studied

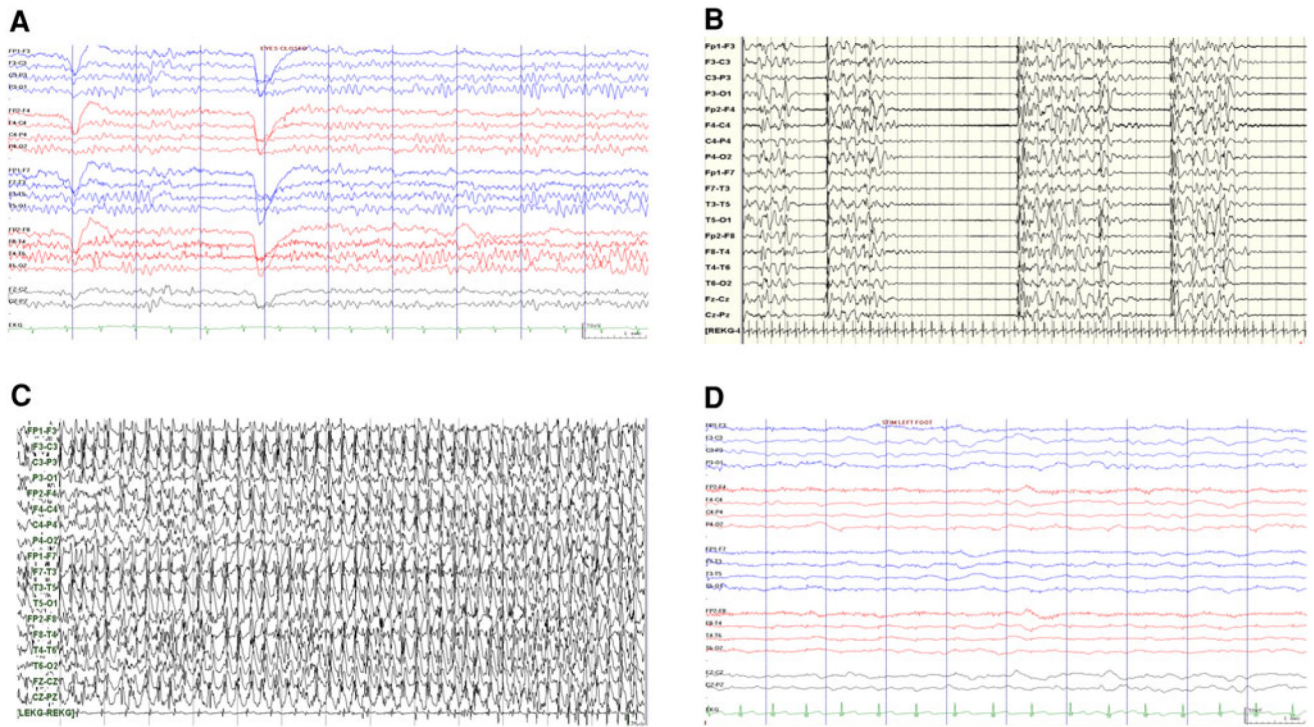


Fig. 2. EEG patterns that may be seen in patients following anoxic brain injury. **a** Normal, **b** burst suppression, **c** seizures in a patient with discontinuous background, and **d** comatose patient with low amplitude and non-reactive background

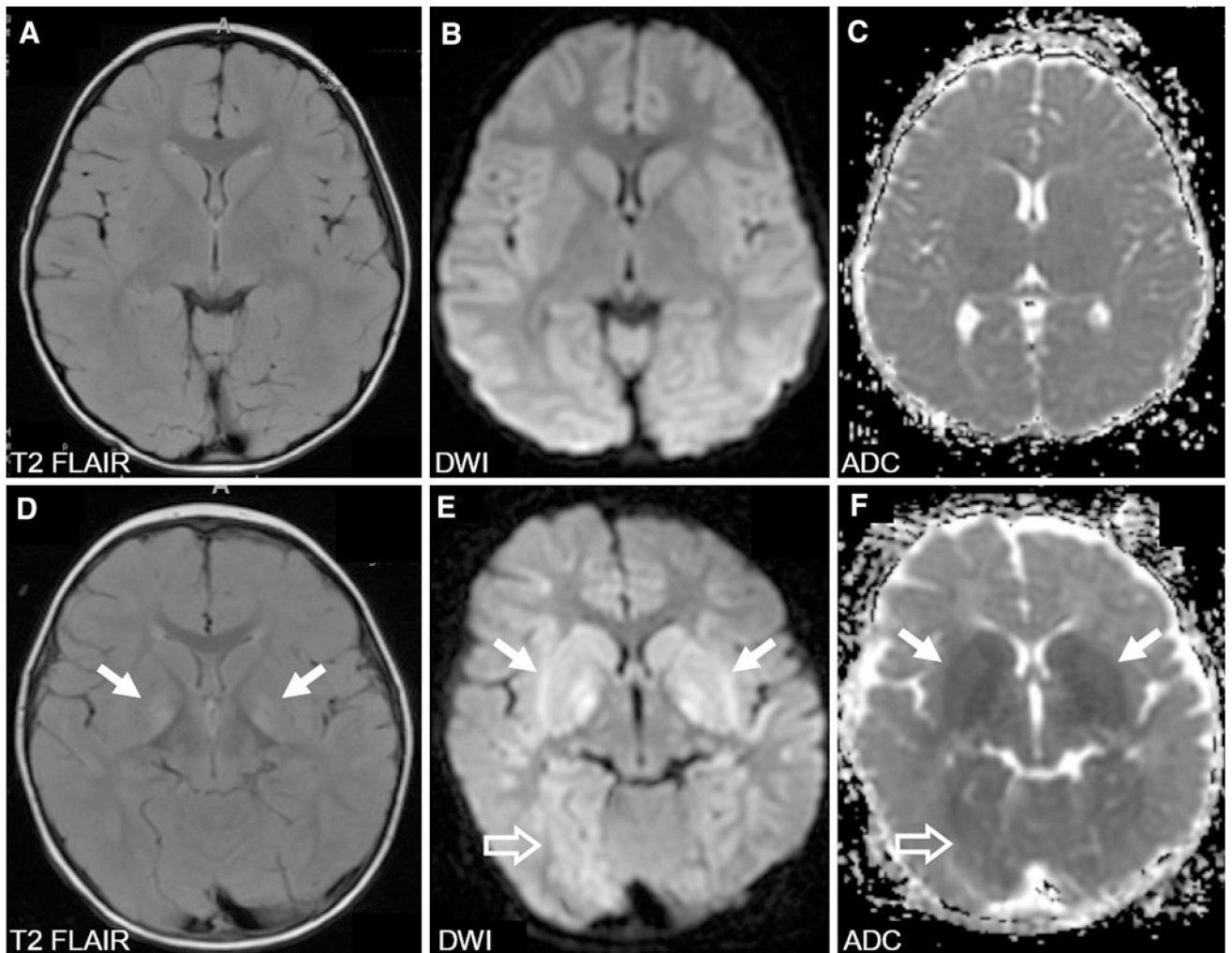


Fig. 3. Magnetic resonance imaging (MRI) of the brain in two children with divergent outcomes after drowning accidents. **a–c** A 4-year-old cold-water drowning victim who presented with a core temperature of 23 °C. MRI 4 days after the accident was normal as was the child’s neurological examination. **d–f** A 13-month-old bathtub-drowning victim who presented with a core temperature of 33 °C. MRI 4 days after the accident showed increased signal and restricted diffusion in the basal ganglia (*arrows*), particularly in the globus pallidus as well as the thalami. In addition, there are areas of restricted diffusion in the white matter bilaterally and to a lesser degree of the cortex most marked in the occipital and parietal regions (*open arrows*). This child remained in a minimally conscious state. *DWI* diffusion-weighted imaging, *ADC* apparent diffusion coefficient

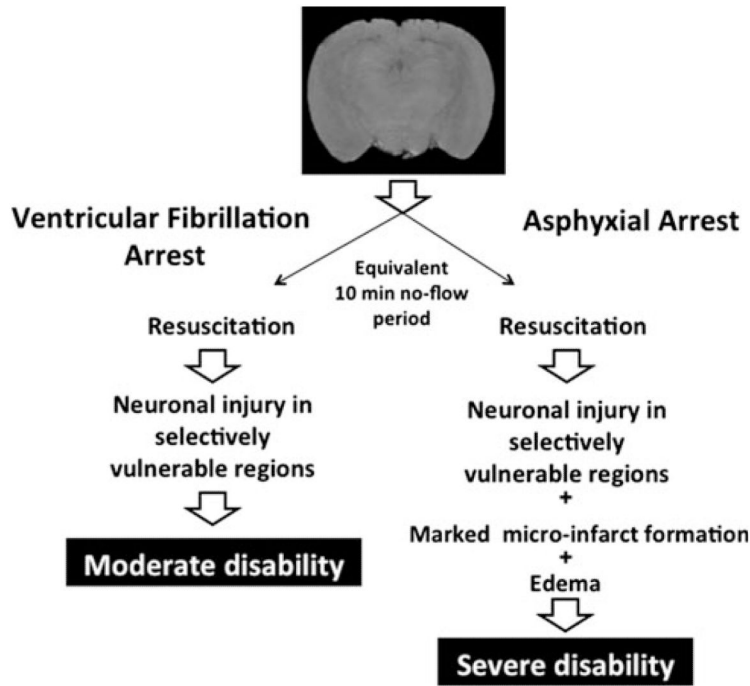


Fig. 4. Responses to asphyxial versus ventricular fibrillation cardiac arrest. Schematic based on the seminal work of Vaagenes et al. [249] using canine models of asphyxial versus ventricular fibrillation cardiac arrest. Despite identical (10 min) no flow durations in both models, a much more severe neuropathology was observed after asphyxial arrest. This was accompanied by poorer neurological outcome. Notably, the no flow period in asphyxial cardiac arrest was preceded in these studies by a period of ~ 7 min during which hypoxic perfusion of the brain occurred. The asphyxia scenario is highly germane to the pathobiology of drowning and thus suggests a very challenging and unique condition for the development of novel therapies

Table 1

Potential modalities for neuromonitoring in patients recovering from drowning

Modality	Invasive	Frequency	Expertise required
Neurologic examination	No	Intermittent	Minimal expertise
EEG	No	Intermittent or Continuous	Neurophysiology
CT	No	Intermittent	Imaging support
MRI	No	Intermittent	Imaging support
SSEP	No	Intermittent	Neurophysiology
ICP	Yes	Continuous	Neurosurgical/ advanced skill set

EEG electroencephalography, *CT* computerized tomography, *MRI*, magnetic resonance imaging, *SSEP* somatosensory evoked potentials, *ICP* intracranial pressure the development of novel therapies

Table 2

Evidence-based summary of biomarkers used in anoxic encephalopathy

	References	LOE
Brain biomarkers		
Neuron-specific enolase (NSE)	[114, 166-172]	4,5
S-100B	[166, 173, 174]	5
Glia fibrillary acidic protein (GFAP)	[175]	5
Tau	[176]	5
Cardiac biomarkers		
Cardiac troponin I	[165]	4
Cardiac troponin T	–	–
Micro-RNA	[181]	–
Non-specific biomarkers		
Plasma glucose	[120, 123, 177]	3,4
Lactate	[13, 178]	4
Pro-calcitonin	[179, 180]	5

All level of evidence (LOE) 3 (studies using retrospective controls) and LOE 4 (studies without a control group (e.g., case series)) investigations were performed on drowning victims. LOE 5 (studies not directly related to the specific patient/population) investigations were performed on cardiac arrest patients