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Medical management of cerebral edema

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✓Cerebral edema is frequently encountered in clinical practice in critically ill patients with acute brain injury from diverse origins and is a major cause of increased morbidity and death in this subset of patients. The consequences of cerebral edema can be lethal and include cerebral ischemia from compromised regional or global cerebral blood flow (CBF) and intracranial compartmental shifts due to intracranial pressure gradients that result in compression of vital brain structures. The overall goal of medical management of cerebral edema is to maintain regional and global CBF to meet the metabolic requirements of the brain and prevent secondary neuronal injury from cerebral ischemia. Medical management of cerebral edema involves using a systematic and algorithmic approach, from general measures (optimal head and neck positioning for facilitating intracranial venous outflow, avoidance of dehydration and systemic hypotension, and maintenance of normothermia) to specific therapeutic interventions (controlled hyperventilation, administration of corticosteroids and diuretics, osmotherapy, and pharmacological cerebral metabolic suppression). This article reviews and highlights the medical management of cerebral edema based on pathophysiological principles in acute brain injury.

Key Words • cerebral blood flow • cerebral edema • controlled hyperventilation • intracranial pressure • osmotherapy

Cerebral edema, simply defined as an increase in brain water content (above the normal brain water content of approximately 80%) and invariably a response to a primary brain insult, is commonly observed in a variety of brain injury paradigms, including TBI, SAH, ischemic stroke and ICH, primary and metastatic neoplasms, inflammatory diseases (meningitis, ventriculitis, cerebral abscess, and encephalitis), and severe toxic–metabolic derangements (hyponatremia and fulminant hepatic encephalopathy). In the clinical setting, cerebral edema is a frequent cause of morbidity and death in patients with neural injuries.

Cerebral edema has traditionally been classified into three major subtypes: cytotoxic, vasogenic, and interstitial (hydrocephalic)[7,11,12,36,71] (see the Underlying Mechanisms of Edema Formation section for more details). This classification is highly simplistic, given that it pertains to complex pathophysiological and molecular mechanisms, but is valuable as a simple therapeutic guide for treatment of cerebral edema. Most brain insults involve a combination of these fundamental subtypes of edema, although one can predominate depending on the type and duration of injury. Cytotoxic edema results from swelling of the cellular elements (neurons, glia, and endothelial cells) because of substrate and energy failure, and affects both gray and white matter. This edema subtype is conventionally thought to be resistant to any known medical treatment. Vasogenic edema that results from breakdown of the BBB due to increased vascular permeability, as commonly encountered in TBI, neoplasms, and inflammatory conditions, predominantly affects white matter. This edema subtype is responsive to both steroid administration (notably edema associated with neoplasms) and osmotherapy. Other causes of vasogenic edema include tissue hypoxia and water intoxication that may be responsive to osmotherapy but resistant to steroid administration.[7,11,12,35,71] Interstitial edema, a consequence of impaired absorption of CSF, leads to increases in transependymal CSF flow, resulting in acute hydrocephalus. This edema subtype is also not responsive to steroid administration, and its response to osmotherapy is debatable.[12]

Most cases of brain injury that result in elevated ICP begin as focal cerebral edema. Consistent with the Monroe–Kellie doctrine as it applies to intracranial vault physiology, the consequences of focal (with or without ICP elevation) or global cerebral edema can be lethal and include cerebral ischemia from compromised regional or global CBF and intracranial compartmental shifts due to ICP gradients, resulting in compression of vital brain

Abbreviations used in this paper: BBB = blood-brain barrier; CBF = cerebral blood flow; CBV = cerebral blood volume; CPP = cerebral perfusion pressure; CSF = cerebrospinal fluid; CT = computed tomography; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; ICP = intracranial pressure; ICU = intensive care unit; PEEP = positive end-expiratory pressure; rCBF = regional CBF; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury; THAM = tris(hydroxymethyl)-aminomethane.

TABLE 1

*Summary of the clinical subtypes of herniation syndromes**

Herniation Syndrome	Clinical Manifestations
subfalcian or cingulate	usually diagnosed using neuroimaging; cingulate gyrus herniates under the falx cerebrii (usually anteriorly); may cause compression of ipsilateral anterior cerebral artery, resulting in contralateral lower extremity paresis
central tentorial	downward displacement of one or both cerebral hemispheres, resulting in compression of diencephalon and midbrain through tentorial notch; typically due to centrally located masses; impaired consciousness and eye movements; elevated ICP; bilateral flexor or extensor posturing
lateral transtentorial (uncal)	most commonly observed clinically; usually due to laterally located (hemispheric) masses (tumors and hematomas); herniation of the mesial temporal lobe, uncus, and hippocampal gyrus through the tentorial incisura; compression of oculomotor nerve, midbrain, and posterior cerebral artery; depressed level of consciousness; ipsilateral papillary dilation and contralateral hemiparesis; decerebrate posturing; central neurogenic hyperventilation; elevated ICP
tonsillar	herniation of cerebellar tonsils through foramen magnum, leading to medullary compression; most frequently due to masses in the posterior fossa; precipitous changes in blood pressure and heart rate, small pupils, ataxic breathing, disturbance of conjugate gaze and quadriparesis
external	due to penetrating injuries to the skull, such as a gunshot wound, or skull fractures; loss of CSF and brain tissue; ICP may not be elevated due to dural opening

* Adapted from Harukuni et al.

structures ("herniation" syndromes; Table 1). Prompt recognition of these clinical syndromes and institution of targeted therapies constitutes the basis of cerebral resuscitation. It is imperative to emphasize the importance of a patient displaying cerebral herniation syndrome without increments in global ICP; in these cases, elevations in ICP may or may not accompany cerebral edema, particularly when the edema is focal in distribution.

Diagnosing and Monitoring Cerebral Edema

Determining a definitive contribution of cerebral edema to the neurological status of a patient can be challenging. Serial and close bedside monitoring with a focus on the level of consciousness and new or worsening focal neurological deficits is imperative and frequently requires admission of the patient to the ICU. Serial neuroimaging (CT scans and magnetic resonance imaging) can be particularly useful in confirming intracranial compartmental and midline shifts, herniation syndromes, ischemic brain injury, and exacerbation of cerebral edema (sulcal effacement and obliteration of basal cisterns), and can provide valuable insights into the type of edema present (focal or global, involvement of gray or white matter).[70] Monitoring of ICP is helpful in patients in whom neurological status is difficult to ascertain serially, particularly in the setting of pharmacological sedation and neuromuscular paralysis. The Brain Trauma Foundation guidelines recommend ICP monitoring in patients with TBI, a GCS score of less than 9, and abnormal CT scans, or in patients with a GCS score less than 9 and normal CT scans in the presence of two or more of the following: age greater than 40 years, unilateral or bilateral motor posturing, or systolic blood pressure greater than 90 mmHg.[12] No such guidelines exist for ICP monitoring in other brain injury paradigms (ischemic stroke, ICH, cerebral neoplasm), and decisions made for ICP monitoring in this setting are frequently based on the clinical neurological status of the patient and data from neuroimaging studies. The reader is referred to the Imaging and Monitoring section for details of ICP monitoring techniques.

Medical management of cerebral edema (with or without ICP elevation) involves a graded algorithmic approach, from general measures (optimal head and neck positioning for facilitation of intracranial venous outflow, avoidance of dehydration and systemic hypotension, and maintenance of normothermia) to specific therapeutic interventions (controlled hyperventilation, administration of corticosteroids or diuretics, osmotherapy, and pharmacological cerebral metabolic suppression).

General Measures for Managing Cerebral Edema

Several general measures that are supported by principles of altered cerebral physiology and clinical data from patients with brain injury should be applied to patients with cerebral edema; these measures are focused on limiting cerebral edema that may or may not be accompanied by ICP elevations. The primary goal of these measures is to optimize cerebral perfusion, oxygenation, and venous drainage; minimize cerebral metabolic demands; and avoid interventions that may disturb the ionic or osmolar gradient between the brain and the vascular compartment.

Optimizing Head and Neck Positions

Finding the optimal neutral head position in patients with cerebral edema is essential for avoiding jugular compression and impedance of venous outflow from the cranium, and for decreasing CSF hydrostatic pressure. In normal uninjured patients,[45] as well as in patients with brain injury,[22] head elevation decreases ICP.[58,75,77] These observations have led most clinicians to incorporate a 30° elevation of the head in patients with poor intracranial compliance. Head position elevation may be a significant concern in patients with ischemic stroke, however, because it may compromise perfusion to ischemic tissue at risk.[74] It is also imperative to avoid the use of restricting devices and garments around the neck (such as devices used to secure endotracheal tubes), as these may lead to impaired cerebral venous outflow via compression of the internal jugular veins.

Ventilation and Oxygenation

Hypoxia and hypercapnia are potent cerebral vasodila-

tors and should be avoided in patients with cerebral edema.[20,71,85] It is recommended that any patients with GCS scores less than or equal to 8 and those with poor upper airway reflexes be intubated preemptively for airway protection.[7,20] This strategy is also applicable to patients with concomitant pulmonary disease, such as aspiration pneumonitis, pulmonary contusion, and acute respiratory distress syndrome. Levels of $PaCO_2$ should be maintained that support adequate rCBF or CPP to the injured brain, and a value of approximately 35 mmHg is a generally accepted target in the absence of ICP elevations or clinical herniation syndromes. Avoidance of hypoxemia and maintenance of PaO_2 at approximately 100 mmHg are recommended.[20,71,86] One major concern is the deleterious role of positive-pressure ventilation (which may be required to maintain adequate oxygenation) on cerebral edema that results from elevations in central venous pressures and impedance of cerebral venous drainage. Delivery of PEEP greater than 10 cm H_2O in patients with severe TBI has resulted in elevated ICP.[4] In patients with SAH, slight increases in ICP have been documented with PEEP greater than 5 cm H_2O without clinical deterioration.[48] Therefore, careful monitoring of clinical neurological status, ICP, and CPP (mean arterial pressure – ICP) is recommended in mechanically ventilated patients with cerebral edema with or without elevations in ICP. Blunting of upper airway reflexes (coughing) with endobronchial lidocaine before suctioning, sedation, or, rarely, pharmacological paralysis may be necessary for avoiding increases in ICP.[24,44]

Intravascular Volume and Cerebral Perfusion

Maintenance of CPP using adequate fluid management in combination with vasopressors is vital in patients with brain injury, irrespective of origin. Systemic dehydration and the use of hypotonic fluids should be avoided at all cost. Euvolemia or mild hypervolemia with the use of isotonic fluids (0.9% saline) should always be maintained through rigorous attention to daily fluid balance, body weight, and serum electrolyte monitoring. The recommended goal of a CPP level greater than 60 mmHg should be adhered to in patients with TBI,[9] and, simultaneously, sharp rises in systemic blood pressure should be avoided. The maximum blood pressure tolerated in different clinical situations of brain injury is variable and controversial, particularly in a patient with early large ICH.[65] Judicious use of antihypertensives (labetalol, enalaprilat, or nicardipine) is recommended for treating systemic hypertension. Potent vasodilators (nitroglycerine, nitroprusside) are to be avoided, as they may exacerbate cerebral edema via accentuated cerebral hyperemia and CBV due to their direct vasodilating effects on cerebral vasculature.[20,99]

Seizure Prophylaxis

Anticonvulsants (predominantly phenytoin) are widely used empirically in clinical practice in patients with acute brain injury of diverse origins, including TBI,[97] SAH,[105] and ICH,[10] although data supporting their use are lacking. Early seizures in TBI can be effectively reduced by prophylactic administration of phenytoin for 1 or 2 weeks without a significant increase in drug-related side effects.[34] The use of prophylactic anticonvulsants in ICH can be justified, as subclinical seizure activity may cause progression of shift and worsen outcome in critically ill patients with ICH.[106] Yet the benefits of prophylactic use of anticonvulsants in most causes leading to brain edema remain unproven, and caution is advised in their use in ICH and other clinical subgroups (such as in brain tumors).[32]

Management of Fever and Hyperglycemia

Numerous experimental and clinical[20,33,62] studies have demonstrated the deleterious effects of fever on outcome following brain injury, which theoretically result from increases in oxygen demand, although its specific effects on cerebral edema have not been elucidated. Therefore, normothermia is strongly recommended in patients with cerebral edema, irrespective of underlying origin. Acetaminophen (325–650 mg orally, or rectally every 4–6 hours) is the most common agent used, and is recommended to avoid elevations in body temperature.[20] Other surface cooling devices have demonstrated some efficacy (see section on hypothermia).

Evidence from clinical studies in patients with ischemic stroke,[33,62] SAH,[1,59] and TBI[78] suggests a strong correlation between hyperglycemia and worse clinical outcomes. Hyperglycemia can also exacerbate brain injury and cerebral edema.[11,31] Significantly improved outcome has been reported in general ICU patients (including 20% of patients with TBI and all patients undergoing craniotomies for all other indications) with good glycemic control,[104] although larger studies focused on specific brain injury paradigms are forthcoming. Nevertheless, current evidence suggests that rigorous glycemic control may be beneficial in all patients with brain injury.

Nutritional Support

Prompt institution and maintenance of nutritional support is imperative in all patients with acute brain injury. Unless contraindicated, the enteral route of nutrition is preferred. Special attention should be given to the osmotic content of formulations, to avoid free water intake that may result in a hypoosmolar state and worsen cerebral edema.[7,20,74]

Specific Measures for Managing Cerebral Edema

Controlled Hyperventilation

Based on principles of altered cerebral pathophysiology associated with brain injury, controlled hyperventilation remains the most efficacious therapeutic intervention for cerebral edema, particularly when the edema is associated with elevations in ICP. A decrease in $PaCO_2$ by 10 mmHg produces proportional decreases in rCBF (and decreases in CBV in the intracranial vault), resulting in rapid and prompt ICP reduction.[20,74] The vasoconstrictive effect of respiratory alkalosis on cerebral arterioles has been shown to last for 10 to 20 hours, beyond which vascular dilation may result in exacerbation of cerebral edema and rebound elevations in ICP.[55] Prolonged hyperventilation has been shown to result in worse outcomes in patients with TBI,[54] although its effect in other brain injury paradigms is unclear. Overaggressive hyperventilation may actually result in cerebral ischemia.[95] Therefore, the common clinical practice is to lower and maintain $PaCO_2$ by 10 mmHg to a

target level of approximately 30–35 mmHg[24,44,74] for 4 to 6 hours, although identifying the correct strategy for achieving this goal is unclear in terms of adjusting tidal volumes and respiratory rate. It should be noted that controlled hyperventilation is to be used as a rescue or resuscitative measure for a short duration until more definitive therapies are instituted and maintained that are tailored toward the particular patient (osmotherapy, surgical decompression, and others). Caution is advised when reversing hyperventilation judiciously over 6 to 24 hours,[20,24,44,74] to avoid cerebral hyperemia and rebound elevations in ICP secondary to effects of reequilibration.

Osmotherapy Use

Historical Perspective. The earliest description in the literature of the use of osmotic agents dates back to 1919.[110] While studying the transport of salt solutions into the neuraxis, Weed and McKibben observed that intravenous administration of a concentrated salt solution resulted in an inability to withdraw CSF from the lumbar cistern due to a collapse of the thecal sac. This serendipitous observation was followed by an elegant set of experiments in an animal model in which they demonstrated (under direct visualization via a craniotomy) egress of the brain away from the cranial vault with intravenous infusion of hypertonic saline solutions and herniation of brain tissue with administration of hypotonic fluids. This set of observations has formed the basis for osmotherapy. Concentrated urea was the first agent to be used clinically as an osmotic agent.[7,8,25,35,60] Its use was short-lived and is of historic interest only because of several untoward side effects (nausea, vomiting, diarrhea, and coagulopathy).[20,60] The interest in elevating plasma oncotic pressure as a strategy to ameliorate cerebral edema with the use of concentrated human plasma proteins, which appeared briefly in 1940, was short-lived due to several concerns, including cost, short half-life, cardiopulmonary effects, and allergic reactions.[60] Glycerol was possibly the second osmotic agent to be used clinically and is, interestingly, still used by some physicians in continental Europe because of tradition.[60] Mannitol, an alcohol derivative of simple sugar mannose, was introduced in 1960 and has since remained the major osmotic agent of choice in clinical practice.[7,8,35,60] Its long duration of action (4–6 hours) and relative stability in solution have enhanced its use over the years. The extraosmotic properties of mannitol have been studied extensively and may provide additional beneficial effects in brain injury, including decreases in blood viscosity, resulting in increases in rCBF and CPP, and a resultant cerebral vasoconstriction leading to decreased CBV,[76,81] free radical scavenging,[2] and inhibition of apoptosis.[42]

Renewed interest in hypertonic saline solutions reappeared in the 1980s, when they were used in small-volume resuscitation in patients experiencing hemorrhagic shock.[7,8,35,66,79,114] These studies demonstrated that prehospital restoration of intravascular volume improved morbidity and mortality rates and physiological parameters (such as systemic blood pressure, cardiac index, and tissue perfusion) in this subset of patients.[66,79,114] In subsequent studies, cerebral effects of these solutions were investigated in well-controlled experimental studies in animal models of acute brain injury. Like mannitol, hypertonic saline also possesses unique extraosmotic properties, including modulation of CSF production and resorption and accentuation of tissue oxygen delivery.[7,8,35,60] In addition, ongoing experimental studies suggest that hypertonic saline may modulate inflammatory and neurohumoral responses (arginine-vasopressin and atrial natriuretic peptide)[13] following brain injury that may act together to ameliorate cerebral edema. These studies continue to provide evidence for the potential use of these solutions in the clinical domains.

Therapeutic Basis and Goal of Osmotherapy. Put simply, the fundamental goal of osmotherapy is to create an osmotic gradient to cause egress of water from the brain extracellular (and possibly intracellular) compartment into the vasculature, thereby decreasing intracranial volume (normal brain volume 80%, normal blood volume 10%, and normal CSF volume 10%) and improving intracranial elastance and compliance.[7,8,35,60,74,79,114] In healthy individuals, serum osmolality (285–295 mOsm/L) is relatively constant, and the serum Na^+ concentration is an estimate of body water osmolality.[7,8,35,60] Under ideal circumstances, serum osmolality is dependent on the major cations (Na^+ and K^+), plasma glucose, and blood urea nitrogen. Because urea is freely diffusible across cell membranes, serum Na^+ and plasma glucose are the major molecules involved in altering serum osmolality.[7,8,35,60]

The goal of using osmotherapy for cerebral edema associated with brain injury is to maintain a euvolemic or a slightly hypervolemic state.[7,8,35,60,67] As a fundamental principle, a hypoosmolar state should always be avoided in any patient who has an acute brain injury.[7,8,35,60,74] A serum osmolality in the range of 300 to 320 mOsm/L has traditionally been recommended for patients with acute brain injury who demonstrate poor intracranial compliance;[7,8,35,60,74] however, values greater than 320 mOsm/L can be attained with caution, without apparent untoward side effects.[18]

An ideal osmotic agent is one that produces a favorable osmotic gradient, is inert and nontoxic, is excluded from an intact BBB, and has minimal systemic side effects.[7,8,35,60,79,114] The ability of the intact BBB to exclude a given compound has been quantified (reflection coefficient σ) by biophysicists.[7,35,42,60,67,114] Very simplistically, compounds with σ approaching 1 (completely impermeable) are considered to be better osmotic agents because they are completely excluded by an intact BBB, and conversely less likely to exhibit "rebound" cerebral edema during withdrawal of osmotherapy.[7,35,42,49,60,67,114] With mannitol ($\sigma = 0.9$) use, the potential for rebound cerebral edema exists as a result of a reversal of the osmotic gradient between the brain and the intravascular compartment in areas in which the BBB is disrupted.[60] This observation is consistent with the data showing that mannitol appears in the CSF with levels of approximately 12% of the corresponding plasma concentration 8 hours following its intravenous bolus administration,[46] and rebound increases in ICP have been well documented with its use. Similarly, glycerol ($\sigma = 0.48$) and urea ($\sigma = 0.59$) are less than ideal agents for osmotherapy because their osmotic effects are transient and they are only partly excluded by the intact BBB; therefore, equilibration between the brain and in-

travascular compartment can occur rapidly.[60,114] Because sodium chloride has a reflection coefficient of 1.0, it has been proposed to be a potentially more effective osmotic agent.[60,114]

Based on these theoretical concepts and observations, a number of experimental studies have demonstrated the efficacy of osmotherapy in the treatment of cerebral edema. A comprehensive discussion of these studies is beyond the scope of this article. Based on these experimental studies, however, several prospective clinical studies, particularly in the TBI paradigm, have demonstrated the beneficial effects of mannitol use for the treatment of elevated ICP. It should be noted that although many of these trials focused on ICP effects and changes in physiological variables in the acute phase, the literature contains few reports regarding their effects on long-term outcomes.

Mannitol and Hypertonic Saline. In an uncontrolled case series, treatment with an intravenous bolus of mannitol attenuated ICP to 34% of pretreatment values in patients with poor intracranial compliance.[51] In a prospective series of patients with elevated ICP and diverse intracranial diseases, bolus mannitol decreased ICP, with a mean reduction of 52% of pretreatment values.[39] In an uncontrolled series of patients with TBI, 0.25 g/kg of an intravenous bolus of mannitol was sufficient to attenuate elevated ICP.[47] In studies of patients with severe TBI treated with mannitol, ICP was significantly reduced, with improvement in rCBF and CPP.[50,53] Although the immediate response to mannitol was beneficial (ICP reduction) in a prospective, randomized trial in 80 patients with TBI,[94] long-term functional outcome was not affected in this subset of patients. A recent metaanalysis of all studies in the literature to date suggests that high-dose mannitol treatment may be preferable to conventional doses for acute TBI.[108]

Given the aforementioned theoretically greater benefits of hypertonic saline compared with mannitol, investigators describing results from several laboratory-based experimental studies have reported the antiedemic effects of hypertonic saline in a variety of brain injury paradigms and postulated the mechanistic bases for these observations. An exhaustive review of these studies is beyond the scope of this article, but a few are notable. The use of hypertonic saline solutions in animal models of hemorrhagic shock (without neuroinjury) resulted in lower ICP, decreased cerebral edema, increased rCBF, and improved oxygen delivery.[19,80] In a rat cryogenic brain injury model of contusive TBI, the administration of 23.4% hypertonic saline (8008 mOsm/L) produced both a greater and more sustained reduction in ICP ($>$ 8 hours of observation) than did equiosmolar doses of mannitol.[52] In an animal model of elevated ICP (using inflation of a balloon in the epidural space), boluses of 7.5% hypertonic saline reduced ICP and cerebral edema to the same extent as mannitol.[26] In a focal brain lesion (epidural balloon inflation model in rat), a mixture of 7.2% NaCl and 10% dextran-60 produced similar reductions in ICP, compared with equimolar doses of 20% mannitol. The water content in the damaged hemisphere increased with hypertonic saline, however, and was unchanged with mannitol in this study.[6] In an experimental ischemic stroke model, the benefits of hypertonic saline in stroke-associated cerebral edema have been studied and reported.[100–102] For example, in a rat model of transient (2-hour) cerebral ischemia, continuous intravenous infusion of 7.5% NaCl/acetate begun 6 hours after the ischemic insult demonstrated attenuation of water content in the ischemic and nonischemic hemispheres (serum Na^+ maintained at 145–155 mg/L), compared with a bolus of high-dose mannitol (2 gm/kg intravenously every 6 hours).[102] Treatment with continuous intravenous infusion of 5 and 7.5% hypertonic saline in a model of permanent focal ischemia attenuated brain and lung water to a greater extent than did mannitol.[100,101] In an experimental canine model of ICH, treatment with isoosmolar 3 and 23.4% hypertonic saline boluses attenuated ICP to a greater extent and was sustained for a longer duration than ICP treated with standard doses of mannitol.[69] In an experimental model of brain tumor, a continuous intravenous infusion of 7.5% hypertonic saline was more effective in attenuating brain water content than high-dose mannitol or furosemide.[103]

The use of hypertonic saline solution in the treatment of cerebral edema and elevated ICP in the clinical setting is largely based on an extension of laboratory-based research, a few prospective studies in humans, and anecdotal case reports. The first report to demonstrate the efficacy of hypertonic saline in patients with TBI[113] involved two patients with elevated ICP refractory to mannitol who were treated successfully with a single intravenous bolus of 30% saline, after which ICP decreased and systemic perfusion improved. Continuous intravenous infusion of 2.5 and 5.4% hypertonic saline enhanced CPP and improved somatosensory evoked potentials after brainstem trauma.[29] Likewise, in an uncontrolled, nonrandomized study,[111] reductions in ICP were noted with the use of 7.5% hypertonic saline treatment following TBI. In a double-blind crossover study, in which 3% hypertonic saline for TBI was used in a pediatric population, ICP was reduced by approximately 5 mmHg for 2 hours compared with ICP in patients who required equal volumes of isotonic saline.[23] In an uncontrolled, nonrandomized, retrospective clinical case series, the beneficial effects (clinical and radiographic evidence of improvement in midline shift) following treatment with 3% hypertonic saline were documented in patients with TBI and postoperative cerebral edema but not in patients with ICH or ischemic stroke.[68] In a prospective, randomized trial in 34 patients with TBI, both hypertonic saline and hypertonic lactated Ringer solution were effective therapies in controlling ICP.[88] In a prospective, randomized, controlled study in children with severe TBI, hypertonic saline therapy lowered ICP and augmented CPP with fewer complications than lactated Ringer solution, resulting in a shorter ICU stay.[90] In a retrospective case series, 30 ml of an intravenous bolus administration of 23.4% hypertonic saline reduced ICP and augmented CPP for up to 3 hours in patients with intractable elevations in ICP from diverse origins that were refractory to all conventional therapeutic modalities (hyperventilation, mannitol therapy, and barbiturates).[96] A retrospective review of 13 patients treated with a 23.4% intravenous bolus of hypertonic saline or mannitol documented a much longer duration of ICP lowering with hypertonic saline than with mannitol (96 hours compared with 59 minutes) without complications.[109]

Few studies have made direct comparisons between mannitol and hypertonic saline. In a prospective, randomized comparison of 2.5 ml/kg of either 20% mannitol (1400 mOsm/kg) or 7.5% hypertonic saline (2560 mOsm/kg) in patients undergoing elective supratentorial procedures,[30] ICP and intraoperative clinical assessment of brain swelling were similar in both treatment groups. In a prospective, randomized trial of hypertonic saline with hydroxyethyl starch (for more prolonged action), hypertonic saline was shown to be more effective than equiosmolar doses of mannitol in lowering elevated ICP and augmenting CPP in patients with ischemic stroke.[87] Likewise, intravenous bolus injection of 10% hypertonic saline was shown to be effective in lowering ICP in patients with ischemic stroke who failed to show such a response to conventional doses of mannitol.[86] More recently, in a small prospective study, isovolemic intravenous infusion of 7.5% hypertonic saline was more effective in the control of ICP following TBI, compared with mannitol treatment.[107] In a prospective, randomized, controlled, crossover trial in 20 patients with TBI, treatment with 7.5% saline and 6% dextran solution was more effective than equiosmolar doses of mannitol in controlling ICP.[5] In summary, the literature supports the use of hypertonic saline as a therapy to decrease ICP in patients following TBI and stroke and to optimize intravascular fluid status in patients with SAH-induced vasospasm.

Treatment Protocol for Osmotherapy. The conventional osmotic agent mannitol, when administered at a dose of 0.25 to 1.5 g/kg by intravenous bolus injection, usually lowers ICP, with maximal effects observed 20 to 40 minutes following its administration.[60] Repeated dosing of mannitol may be instituted every 6 hours and should be guided by serum osmolality to a recommended target value of approximately 320 mOsm/L; higher values result in renal tubular damage. This therapeutic goal is based on limited evidence, however, and higher values can be targeted provided that the patient is not volume depleted.[18]

A variety of formulations of hypertonic saline solutions (2, 3, 7.5, 10, and 23%) are used in clinical practice for the treatment of cerebral edema with or without elevations in ICP. Hypertonic saline solutions of 2, 3, or 7.5% contain equal amounts of sodium chloride and sodium acetate (50:50) to avoid hyperchloremic acidosis.[7,8,35,67,79,114] Potassium supplementation (20–40 meq/L) is added to the solution as needed. Continuous intravenous infusions are begun through a central venous catheter at a variable rate to achieve euvolemia or slight hypervolemia (1–2 ml/kg/hr). A 250-ml bolus of hypertonic saline can be administered cautiously in select patients if more aggressive and rapid resuscitation is warranted. Normovolemic fluid status is maintained, guided by central venous pressure or pulmonary artery wedge pressure (if available). The goal in using hypertonic saline is to increase serum sodium concentration to a range of 145 to 155 mEq/L (serum osmolality approximately 300–320 mOsm/L), but higher levels can be targeted cautiously. This level of serum sodium is maintained for 48 to 72 hours until patients demonstrate clinical improvement or there is a lack of response despite achieving the serum sodium target. During withdrawal of therapy, special caution is emphasized due to the possibility of rebound hyponatremia leading to exacerbation of cerebral edema. Serum sodium and potassium are monitored every 4 to 6 hours, during both institution and withdrawal of therapy,[7,8,35] and other serum electrolytes are monitored daily (particularly calcium and magnesium). Chest radiographs are obtained at least once every day to try and find evidence of pulmonary edema from congestive heart failure, especially in elderly patients with poor cardiovascular reserve. Intravenous bolus injections (30 ml) of 23.4% hypertonic saline have been used in cases of intracranial hypertension refractory to conventional ICP-lowering therapies; repeated injections of 30 ml boluses of 23.4% saline may be given if needed to lower ICP. Administration of this osmotic load, to lower ICP and maintain CPP, may allow extra time for other diagnostic or therapeutic interventions (such as decompressive surgery) in critically ill patients.[90,96]

Potential Complications of Osmotherapy. Safety concerns with mannitol include hypotension, hemolysis, hyperkalemia, renal insufficiency, and pulmonary edema.[7,8,35,60,67,79,114] Thus far, no Phase 1 trials have been conducted to investigate the safety of hypertonic saline solutions; however, clinical experience suggests that the side-effect profile of hypertonic saline is superior to mannitol, but some theoretical complications that are possible with hypertonic saline therapy are notable (Table 2). Myelinolysis, the most serious complication of hypertonic saline therapy, typically occurs when rapid corrections in serum sodium arise from a chronic hyponatremic state to a normonatremic or hypernatremic state. Experimental studies suggest that for myelin injury to occur, the degree of rapid change in serum sodium is much greater from a normonatremic to a hypernatremic state (change of approximately 40 mEq/L), but further study with neuroimaging techniques is required.[35]

Loop Diuretics

The use of loop diuretics (commonly furosemide) for the treatment of cerebral edema, particularly when used alone, remains controversial.[20] Combining furosemide with mannitol produces a profound diuresis; however, the efficacy and optimum duration of this treatment remain

TABLE 2

*Summary of theoretical potential complications of using hypertonic saline solutions**

CNS changes (encephalopathy, lethargy, seizures, coma)
central pontine myelinolysis
congestive heart failure, cardiac stun, pulmonary edema
electrolyte derangements (hypokalemia, hypomagnesemia, hypocalcemia)
cardiac arrhythmias
metabolic academia (hyperchloremic with use of chloride solutions)
potentiation of nontamponaded bleeding
subdural hematomas that result from shearing of bridging veins due to hyperosmolar contracture of brain
hemolysis with rapid infusions, resulting in sudden osmotic gradients in serum
phlebitis with infusion via peripheral route
coagulopathy (elevated prothrombin and partial thromboplastin time, platelet dysfunction)
rebound hyponatremia leading to cerebral edema with rapid withdrawal

* Modified from Bhardwaj and Ulatowski 1999 and Shell et al. CNS = central nervous system.

unknown.[20] If loop diuretics are used, rigorous attention to systemic hydration status is advised, as the risk of serious volume depletion is substantial[98] and cerebral perfusion may be compromised. A common strategy used to raise serum sodium rapidly is to administer an intravenous bolus of furosemide (10 to 20 mg) to enhance free water excretion and to replace it with a 250-ml intravenous bolus of 2 or 3% hypertonic saline. Acetazolamide, a carbonic anhydrase inhibitor that acts as a weak diuretic and modulates CSF production, does not have a role in cerebral edema that results from acute brain injuries; however, it is frequently used in outpatient practice, particularly for the treatment of cerebral edema associated with pseudotumor cerebrii.[20]

Corticosteroid Administration

The main indication for the use of steroids is for the treatment of vasogenic edema associated with brain tumors or accompanying brain irradiation and surgical manipulation.[71] Although the precise mechanisms of the beneficial effects of steroids in this paradigm are unknown, steroids decrease tight-junction permeability and, in turn, stabilize the disrupted BBB.[61,91] Glucocorticoids, especially dexamethasone, are the preferred steroidal agents, due to their low mineralocorticoid activity. The therapeutic role of steroids in TBI and stroke has been studied extensively. In TBI, steroids failed to control elevations in ICP or to show any benefit in outcome, and they may even be harmful.[17,72] In stroke, steroids have failed to show any substantial benefit[64] despite some success in animal models.[93] Given the deleterious side effects of steroid use (peptic ulcers, hyperglycemia, impairment of wound healing, psychosis, and immunosuppression), until further studies are published, caution is advised in the use of steroids for cerebral edema unless absolutely indicated. The role of steroids in the treatment of bacterial meningitis and postinfectious encephalitis is beyond the scope of this article.

Pharmacological Coma

Barbiturates. Barbiturates were introduced in the therapeutic armamentarium in the 1960s, and have gained acceptance for the treatment of cerebral edema associated with intractable elevations in ICP that are refractory to other therapeutic modalities. Barbiturates lower ICP, principally via a reduction in cerebral metabolic activity, resulting in a coupled reduction in rCBF and CBV.[74] Yet their use in clinical practice is not without controversy. In patients with TBI, barbiturates are effective in reducing ICP[21] but have failed to show evidence of improvement in clinical outcome.[84] Evidence is limited for the utility of barbiturate treatment in cerebral diseases that include space-occupying lesions (such as tumor and ICH) and ischemic stroke. When used in the acute setting, pentobarbital, a barbiturate with an intermediate physiological half-life (approximately 20 hours) is the preferred agent rather than phenobarbital, which has a much longer half-life (approximately 96 hours) or thiopental, which has a much shorter half-life (approximately 5 hours).[20,74] The recommended regimen entails a loading intravenous bolus dose of pentobarbital (3–10 mg/kg), followed by a continuous intravenous infusion (0.5–3.0 mg/Kg/hr, serum levels of 3 mg/dL), which is titrated to sustain reduction in ICP or achieve a "burst-suppression pattern" on continuous electroencephalographic monitoring.[24] It is recommended that a barbiturate coma be maintained for 48 to 72 hours, with gradual tapering by decreasing the hourly infusion by 50% each day.[44] Longer periods of induced coma may be necessary, however, to reverse the underlying disease causing cerebral edema and ICP elevation. Several adverse effects of barbiturates that limit their clinical use are to be noted, including sustained vasodepressor effect (lowering of systemic blood pressure and CPP), cardiodepression, immunosuppression leading to increased risk of infection, and systemic hypothermia.[63,83] Vasopressor support and ionotropic agent use are frequently required. Perhaps the most important limitation with barbiturate coma treatment is the inability to track subtle changes in a patient's clinical neurological status, which necessitates frequent serial neuroimaging.

Propofol. Because of the potential side effects of barbiturates and their long half-life, propofol emerged as an appealing alternative, especially due to its extremely short half-life.[71] In addition to propofol's efficacy in controlling ICP in patients with TBI, it also has antiseizure properties and decreases cerebral metabolic rate.[41] Although propofol use continues to become more popular due to these properties, hypotension can be the limiting factor to its use in the clinical setting. Other adverse effects of propofol use include hypertriglyceridemia and increased CO_2 production due to the lipid emulsification vehicle;[3] careful monitoring of serum triglycerides is recommended with its use. Cases of "propofol infusion syndrome" that can be fatal have been reported, particularly in children, when propofol is used over a long period of time at high doses.[15]

Analgesia, Sedation, and Paralysis. Pain and agitation can worsen cerebral edema and raise ICP significantly, and should always be controlled. Judicious intravenous doses of bolus morphine (2–5 mg) and fentanyl (25–100 μcg) or a continuous intravenous infusion of fentanyl (25–200 μcg/hour) can be used for analgesia. A neuromuscular blockade can be used as an adjunct to other measures when controlling refractory ICP.[40] Nondepolarizing agents should be used, because a depolarizing agent (such as succinylcholine) can cause elevations in ICP due to induction of muscle contraction.[56]

Therapeutic Hypothermia

Whereas robust data from experimental and a few clinical studies clearly support the fact that hyperthermia is deleterious to brain injury, achieving normothermia is a desirable goal in clinical practice. The beneficial effects of therapeutic hypothermia observed in the experimental setting have not translated into the clinical setting, however, and have not resulted in improved neurological outcomes. The therapeutic goal of instituting and maintaining hypothermia and its specific effects on brain edema are emerging. Two recent trials of therapeutic mild hypothermia (32°C) following out-of-hospital cardiac arrest, accomplished within 8 hours and maintained for 12 to 24 hours, improved mortality and functional outcomes.[37,38] The role of hypothermia in TBI is less clear. The hypothermia

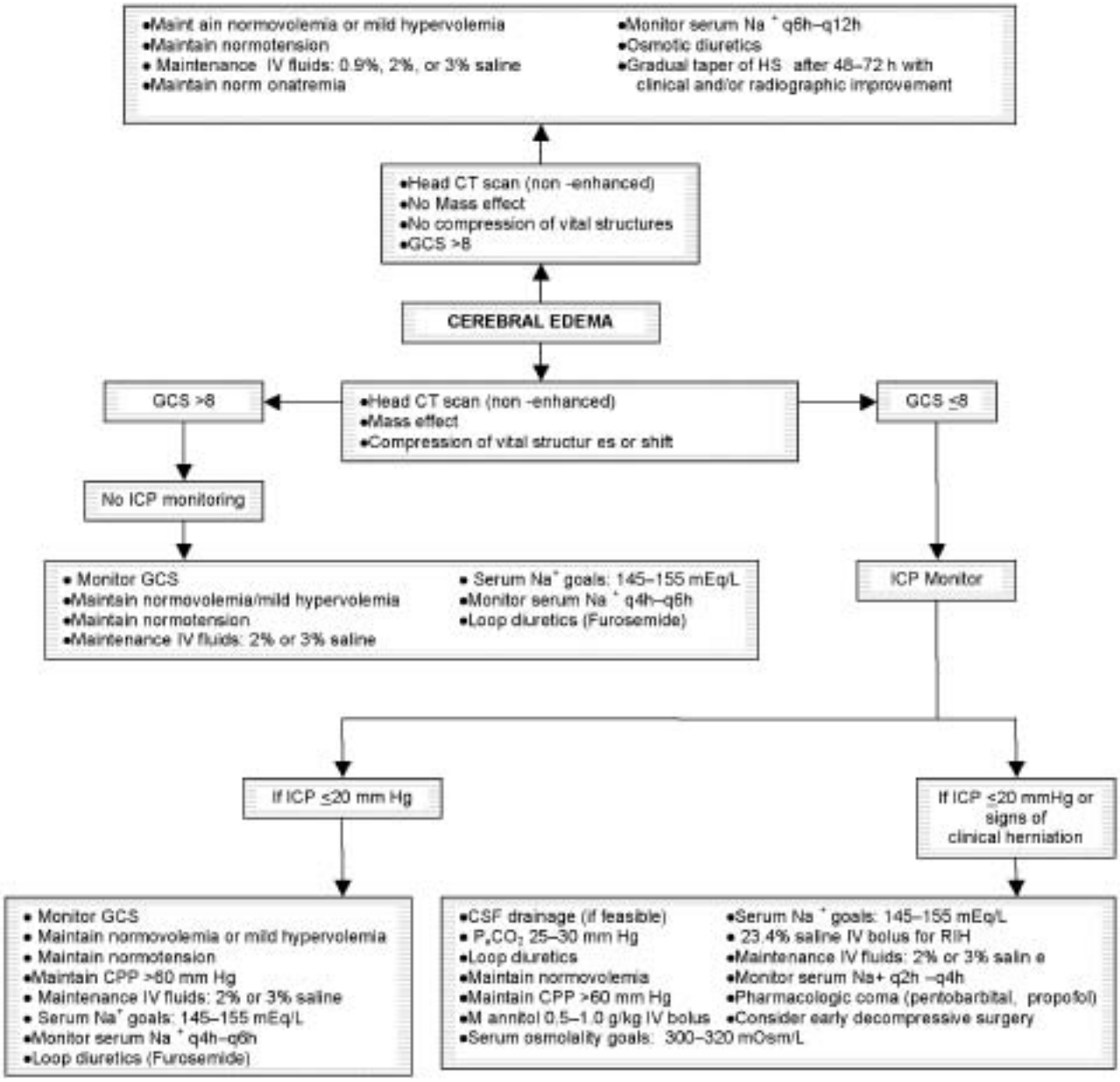

FIG. 1. Algorithm for the management of cerebral edema. GCS = GCS score; h = hours; HS = hypertonic saline; IV = intravenous; q = every; RIH = refractory intracranial hypertension. Modified from Bhardwaj and Ulatowski, 1999.

trial[14] of the National Brain Injury Study did not improve long-term outcome in patients with TBI, but it is plausible that a subset of patients with brain edema that results in ICP elevations may benefit from this intervention.[89] The present consensus is that adverse effects of therapeutic hypothermia outweigh the benefits in TBI.[28] A few small clinical series of patients with hypothermia in ischemic stroke are encouraging,[43,82] but definitive results from larger trials are awaited. From a practical standpoint, external cooling devices (such as air-circulating cooling blankets, iced gastric lavage, and surface ice packs) are the most commonly employed for hypothermia, although the efficacy of endovascular devices is currently being investigated.[16] At present, no consensus exists regarding the duration of hypothermia to use in patients with ischemic stroke, the method to be used (active versus passive), or the duration over which rewarming is to be employed.[20] The adverse side effects of induced hypothermia are substantial and require close monitoring; these include an increased incidence of systemic infection, coagulopathy, and electrolyte derangements.[20] Shivering, a common treatment accompaniment, can be controlled with pharmacological neuromuscular blockade or meperidine in combination with enteral buspirone.[20]

Other Adjunct Therapies

Other complementary therapies for cerebral edema that are prevalent in continental Europe but have not been in-

corporated into clinical practice in the US are worthy of mention. One such therapy is THAM, a buffer (pKa ~ 7.8) introduced in the 1960s, which has been shown to ameliorate secondary neuronal injury and cerebral edema in experimental animal models,[57] as well as in patients with TBI[27] (presumably by ameliorating tissue acidosis). A randomized, controlled clinical trial of THAM in TBI demonstrated its beneficial effects on lowering ICP; however, it did not demonstrate an improved neurological outcome.[112] Nevertheless, this agent holds potential as an adjunctive therapy for treatment of cerebral edema.

Further investigation is warranted of the use of hyperbaric oxygen for the treatment of cerebral edema, based on a clinical trial (100% oxygen at 1.5 atmospheres for 1 hour every 8 hours) that demonstrated enhanced survival in patients with TBI.[73] Although the mechanisms are poorly understood, indomethacin treatment has been shown to attenuate increases in ICP in TBI;[20,92] diminishing rCBF and fever prevention have been postulated as plausible mechanisms for this beneficial action.[92] Although numerous pharmacological neuroprotective agents have shown benefit in experimental models, their translation to the human brain injury paradigm has yet to provide clinical benefit. Nevertheless, the search for these neuroprotective agents continues.

Conclusions and Future Perspectives

Cerebral edema, irrespective of the underlying origin of brain injury, is a significant cause of morbidity and death. The treatment of cerebral edema involves an algorithmic approach (Fig. 1) based on principles of altered cerebral physiology in brain injury. Application of general principles and selective, timely, targeted therapies can help patients with devastating consequences of cerebral edema that may or may not be associated with elevations in ICP. A prospective clinical trial of mannitol compared with hypertonic saline will address the relative efficacy of these osmotic agents. Future experimental studies that investigate the optimal timing, duration of treatment, and serum osmolality in a variety of brain injury paradigms will aid in developing a therapeutic protocol for osmotherapy. Investigative studies of novel mechanisms, such as the role of aquaporins and neurohumoral responses, may aid in developing new pharmacological therapies and targets for the treatment of cerebral edema.

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