Treatment of Cerebral Edema

Alejandro A. Rabinstein, MD

Background: Cerebral edema is a potentially devastating complication of various acute neurologic disorders. Its successful treatment may save lives and preserve neurologic function.

Review Summary: Different pathophysiological mechanisms are responsible for the formation of cytotoxic and vasogenic edema. Yet, these 2 types of edema often coexist and their treatment tends to overlap, with the exception of corticosteroids, which should be only used to ameliorate vasogenic edema. Currently available to control brain swelling include osmotic agents (with emphasis on mannitol and hypertonic saline solutions), corticosteroids, hyperventilation, sedation (propofol, barbiturates), neuromuscular paralysis, hypothermia, and surgical interventions. This article discusses the indications, advantages, and limitations of each treatment modality following an evidence-based approach.

Conclusions: The therapy for brain edema remains largely empirical. More research aimed at enhancing our understanding of the pathophysiology of cerebral edema is needed to identify new and more effective forms of treatment.

Key Words: cerebral edema, treatment, mannitol, hypertonic saline, intracranial pressure

(*The Neurologist* 2006;12: 59–73)

Cerebral edema may be comprehensively defined as a pathologic increase in the amount of total brain water content leading to an increase in brain volume.[1] This deceivingly simple definition fails to reflect the complex pathophysiological underpinnings of the various forms of cerebral edema that may occur in association with severe neurologic diseases. Nonetheless, it retains practical value, given the crude rationales on which we base the application of the alternatives available at present for the treatment of brain edema.

Edema in the brain may be topographically classified into focal or global. Focal edema generates a pressure gradient with adjacent regions and may result in tissue shift and herniation. Examples of focal edema can be found around tumors, hematomas, and infarctions. Global edema diffusely affects the whole brain and, when critical, it may cause intracranial hypertension, compromise perfusion, and lead to generalized ischemia. Cardiopulmonary arrest, severe traumatic injury, and fulminant liver failure are common causes of global cerebral edema.

A different classification based on the pathophysiologic mechanisms responsible for the production of the edema classifies it into 3 types: cytotoxic, vasogenic, and interstitial. In cytotoxic edema, the increased water content is localized intracellularly and is due to the failure of ionic pumps that normally maintain cellular homeostasis. Ischemia and profound metabolic derangements are the most common causes. Instead, in vasogenic edema the main problem is centered in a disruption of the blood-brain barrier, leading to increased permeability and escape of fluid from the intravascular to the extravascular, extracellular space. It accompanies tumors, inflammatory lesions, and traumatic tissue damage. Interstitial edema results from increased transependymal flow from the intraventricular compartment to the brain parenchyma; it typically occurs in the setting of obstructive hydrocephalus.

Cytotoxic edema preferentially affects gray matter and vasogenic edema tends to predominate in the white matter. This difference in distribution and the different characteristics of the 2 types on diffusion-weighted imaging (Fig. 1) permit their radiologic distinction. However, the clinical manifestations of brain edema tend to be similar regardless of whether the edema is cytotoxic or vasogenic. In fact, both types frequently coexist. For example, early after an ischemic brain infarction cytotoxic edema predominates, but later vasogenic edema becomes the major cause of mass effect as the blood-brain barrier loses continuity and local inflammation develops.

This review will be focused on the discussion of the therapeutic alternatives we can use to treat cerebral edema. However, I will first refer briefly to the ways in which we diagnose and monitor the progression and consequences of brain swelling.

Classification based on the pathophysiologic mechanisms responsible for the production of the edema classifies it into 3 types: cytotoxic, vasogenic, and interstitial.

From the Department of Neurology, University of Miami School of Medicine, Miami, Florida.
Reprints: Alejandro A. Rabinstein, MD, 1150 MW 14th Street, Suite 304, Miami, FL 33101. E-mail: arabinstein@med.miami.edu.

ISSN: 1074-7931/06/1202-0059
DOI: 10.1097/01.nrl.0000186810.62736.f0

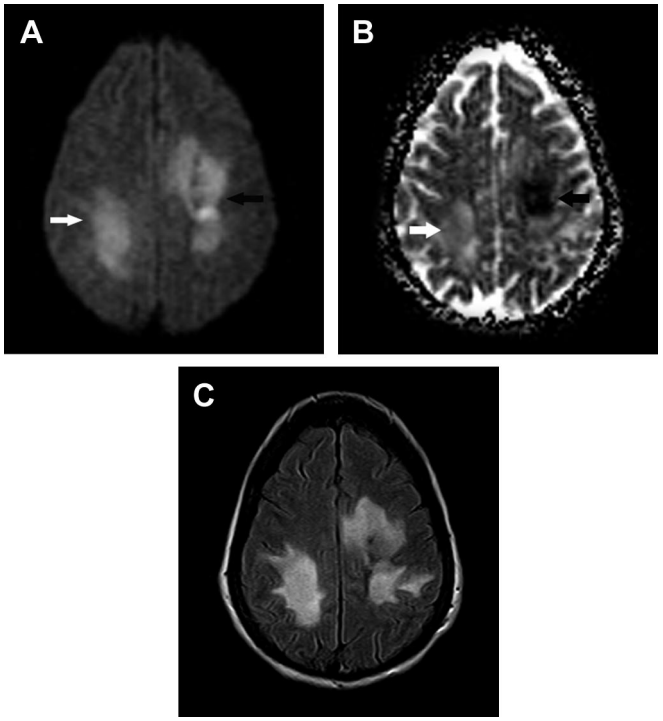

FIGURE 1. MRI scan showing a combination of cytotoxic and vasogenic edema. A, Diffusion-weighted sequence shows cytotoxic and vasogenic edema as bright signal; the bright signal corresponding to the area of vasogenic edema (white arrow) is due to "shine-through" effect from the T2 sequence. B, Apparent diffusion coefficient map clearly differentiates cytotoxic and vasogenic edema. Cytotoxic edema is associated with restriction in the movement of water molecules across the cellular membrane and thus with a low diffusion coefficient, which is seen as a dark signal (black arrow). Instead, vasogenic edema is associated with increased freedom of movement of water molecules, resulting in a high diffusion coefficient, which is seen as a bright signal (white arrow). C, Note that FLAIR sequence fails to distinguish between the 2 types of edema.

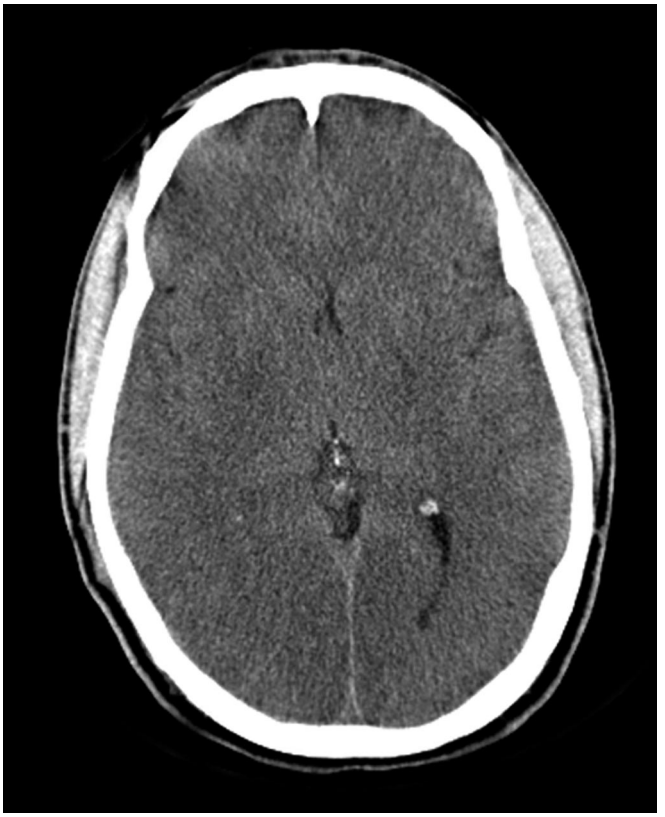

FIGURE 2. CT scan showing global brain edema. Note the effacement of the gray-white matter junction, loss of differentiation of the lenticular nucleus, and decreased visualization of the sulci, insular ribbon, and lateral ventricles.

Diagnosis and Monitoring

It is often not simple to distinguish the contribution of brain edema to the condition of a patient solely on the basis of the clinical examination. Worsening focal deficits may be seen in patients with localized edema, but most commonly the development or progression of edema results in diminished level of consciousness due to raised intracranial pressure (ICP). Thus, the correct diagnosis of brain edema and the reliable determination of its extent depend on the use of imaging studies.

CT scan reveals edema as an abnormal hypodense signal. When diffuse, it provokes effacement of the gray-white matter junction, loss of differentiation of the lenticular nucleus, and decreased visualization of the sulci, insula, and cisterns (Fig. 2). While the presence of vasogenic edema can be inferred from the appearance of hypodensity following the course of white matter tracts, CT is not very helpful to distinguish vasogenic from cytotoxic edema. Meanwhile, MRI shows edema as hypointense signal in T1-weighted sequences and hyperintense signal in T2-weighted and FLAIR sequences (Fig. 3). Delineation of the spread of edema is much clearer with MRI. Furthermore, it is important to reemphasize the value of diffusion-weighted imaging in differentiating the type of edema based on its apparent diffusion coefficient (low in cytotoxic swelling and high in vasogenic edema) (Fig. 1).

Herniation and intracranial hypertension are the most feared consequences of massive cerebral edema. A detailed description of the features of the various forms of brain herniation is beyond the scope of this review and can be found in a recent monograph.[2] ICP should be monitored in patients with severe traumatic brain injury with Glasgow Coma Scale (GCS) sum score <9 and abnormal CT scan or normal CT scan but 2 or more the following criteria: age >40, unilateral or bilateral motor posturing, systolic blood pressure <90 mm Hg.[3] It is difficult to extrapolate the value of these guidelines to patients with diagnoses other than trauma due to lack of specific data on ICP monitoring in those other conditions. Some experts advocate monitoring ICP in comatose patients with a large intracranial mass lesion (hematoma, abscess, large infarctions, etc) causing radiologically documented tissue shift. Patients with subarachnoid hemorrhage, intracerebral hemorrhage, or cerebellar ischemic or hemorrhagic strokes producing acute hydrocephalus have their ICP typically monitored once a ventriculostomy catheter has been placed primarily for drainage purposes.

It is important to reemphasize the value of diffusion-weighted imaging in differentiating the type of edema based on its apparent diffusion coefficient (low in cytotoxic swelling and high in vasogenic edema).

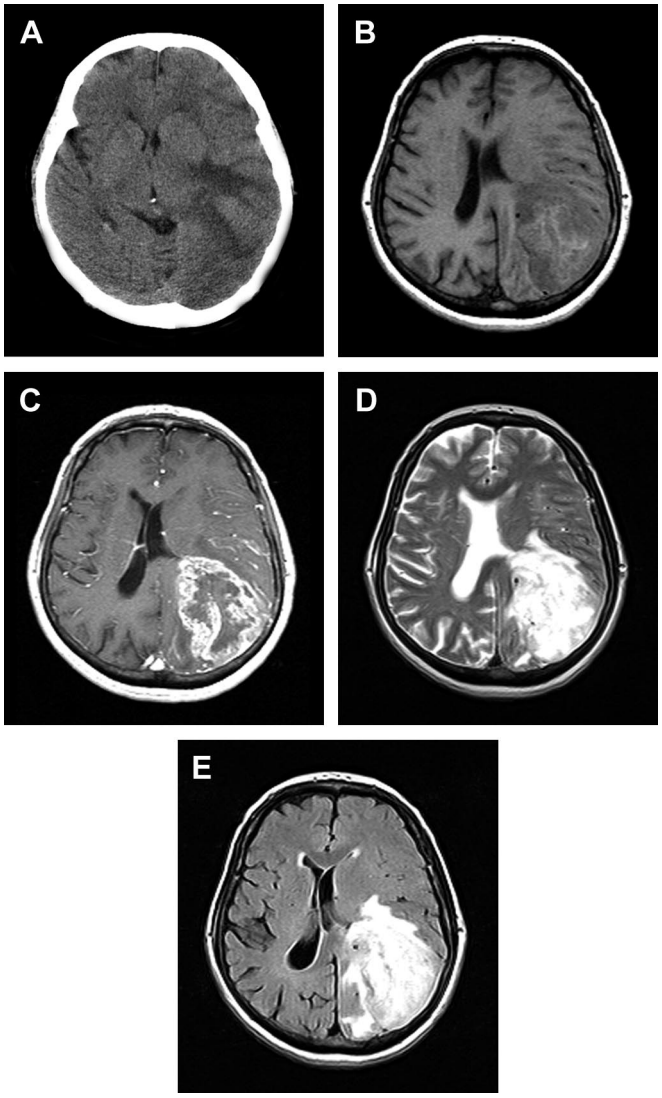

FIGURE 3. Imaging characteristics of brain edema (in this case caused by a tumor). CT scan (A) discloses edema spreading along white matter tracts. MRI T1-weighted sequence (B) shows an appearance similar to that of CT scan. T1-weighted sequence with gadolinium (C) highlights the contrast enhancement of the active tumor causing the edema. T2-weighted (D) and FLAIR (E) sequences better delineate edema in the form of bright signal.

Treatment: General Measures

The general medical and nursing measures to be enunciated in this section are applicable essentially to all patients at risk for or with established cerebral edema. The principles guiding these measures are quite simple: optimize perfusion, oxygenation, and venous drainage; minimize brain metabolic demands; and avoid interventions that may exacerbate the ionic or osmolar gradient.

Head position should be neutral, and any form of compression of the jugular veins should be avoided.

Head and Neck Positioning

Head position should be neutral, and any form of compression of the jugular veins should be avoided. Adhesive tapes used to secure the endotracheal tube in place should not be tightly attached to the sides of the neck. Subclavian venous access should be preferred over jugular sites. If it is necessary to turn the head during a procedure, this must be done with caution and for the shortest time possible.

The practice of head elevation to reduce brain edema is widespread but only supported by inconsistent data. ICP tends to be lower when the head of the bed is raised to 30 degrees compared with the horizontal position.[4–9] However, the effect of head elevation on cerebral perfusion pressure is less predictable. In various studies, cerebral perfusion pressure was found to be slightly increased,[7,8] unaltered,[4,7,9,10] or reduced[6,11] after head elevation. Summarizing available studies, it is reasonable to conclude that head elevation at 30 degrees appears safe and effective in reducing ICP as long as the patient does not have a borderline cerebral perfusion pressure. In patients with large ischemic strokes in whom there is still possibility of salvaging tissue in ischemic penumbra, it may be preferable to keep the head of the bed flat except at times of acute ICP crisis.[11] The advice to determine the optimal head position on an individual basis remains wise and should ideally be followed in each case.[5]

The advice to determine the optimal head position on an individual basis remains wise and should ideally be followed in each case.

Analgesia, Sedation and Paralysis

Pain, anxiety, and agitation increase brain metabolic demands, cerebral blood flow, and at times also ICP. Therefore, a rational regimen of analgesia and sedation is appropriate in most patients with cerebral edema who present these symptoms. Patients who are thrashing in bed, "fighting" the

ventilator, or "bucking" the endotracheal tube should be sedated to the point of motionless sleep. However, along with sedation, it is important to identify and effectively treat potential underlying causes of agitation, such as pain, bladder distension, bronchial secretions, or inappropriate ventilation. When sedation is instituted, it must be closely monitored and administered in frequent scheduled doses or through a continuous infusion to prevent undesired awakenings. If deemed safe, periodic planned awakenings may be scheduled at predefined intervals to allow neurologic examination and assessment of spontaneous breathing capacity.

Opiates, benzodiazepines, and propofol are the most commonly used agents to achieve sedation in neurologic intensive care units. A number of caveats must be kept in mind when prescribing these agents. Codeine is frequently used in awake patients to minimize sedation, but its analgesic potency may be insufficient in some situations. Fentanyl and sulfentanyl must be used with caution because they have been associated with increases in ICP in patients with severe brain trauma,[12] although this may be avoidable with careful dose titration.[13] On the positive side, morphine sulfate is extremely effective in controlling symptoms of excessive autonomic arousal ("autonomic storms").[14]

Benzodiazepines are less expensive than propofol (especially lorazepam) and have the advantage of inducing amnesia, as well as sedation. However, lorazepam has a more prolonged duration of action and midazolam has very short action when a few doses are administered intermittently, but sedative effects persist much longer as long-acting metabolites begin to accumulate. Propofol is a very useful agent because it provides effective sedation that can be easily controlled and quickly reversed. Duration of action becomes longer as fat deposits get saturated with continuous use, but rapid reversibility may be maintained if the infusion rate is titrated down accordingly. The value of propofol in head-injured patients is well validated.[15] It is pertinent to remember that benzodiazepines and propofol have anticonvulsive properties and lower cerebral metabolic rate. Barbiturates have similar characteristics, but their long duration of action makes them less desirable.

Pharmacologic neuromuscular paralysis should be reserved for refractory cases of intracranial hypertension if they are to be administered at all. Routine use of neuromuscular blocking agents in head trauma patients offers no advantage in ICP control.[16] Administration should be monitored using the train-of-4 responses to supramaximal electrical impulses to avoid prolonged weakness from accumulation of the drug.[17] However, these agents also increase the risk of developing critical illness polyneuropathy,[18] a less predictable and preventable complication.

Patients who are thrashing in bed, "fighting" the ventilator, or "bucking" the endotracheal tube should be sedated to the point of motionless sleep.

Ventilation and Oxygenation

Hypoxia and hypercapnia are potent cerebral vasodilators; thus, they may lead to augmented cerebral blood volume and consequent elevation of intracranial hypertension, particularly in patients with abnormal capillary permeability. Intubation and mechanical ventilation are indicated if ventilation or oxygenation is insufficient in patients with brain edema. Special caution must be exercised during endotracheal intubation to avoid an additional rise in ICP due to worsening hypoxia and hypercapnia and reflex responses triggered by direct tracheal stimulation. Adequate preoxygenation and use of rapid-sequence protocols may minimize compromise of gas exchange. Intravenous lidocaine (1 mg/kg), etomidate (0.1–0.5 mg/kg), or thiopental (1–5 mg/kg) may be used to avert detrimental reflex responses.

Once the patient is intubated, ventilator settings should be adjusted to maintain normal PO_2 and PCO_2. The value of hyperventilation in the treatment of brain edema and intracranial hypertension is discussed in a later section. Concerns about detrimental effects of positive-end expiratory pressure (PEEP) on ICP are theoretically sound, but negative consequences are almost never seen in practice.[19,20] Thus, PEEP should be used as needed to improve hypoxia.

Intensive bronchial toileting is important to prevent complications from atelectasis and pneumonia. However, it should be performed cautiously to avert the occurrence of marked rises in ICP that may occur during suctioning. Administering a bolus of intravenous lidocaine prior to introducing the suctioning catheter is an effective preventive strategy. Brief periods of hyperventilation with 100% oxygen in anticipation of tracheal manipulation are also helpful in blocking ICP elevations.

Fluid balance should be maintained neutral (considering insensible losses) to sustain a state of euvolemia.

Fluid Management

Low serum osmolality must be avoided in all patients with brain swelling since it will exacerbate cytotoxic edema. This objective can be achieved by strictly limiting the intake of hypotonic fluids. In fact, there is clear evidence that free water should be avoided in patients with head injuries and brain edema.[21] In patients with pronounced, prolonged serum hyperosmolality, the disorder must be corrected slowly to prevent rebound cellular swelling. Fluid balance should be maintained neutral (considering insensible losses) to sustain a state of euvolemia. Negative fluid balance has been reported to be independently associated with adverse outcomes in patients with severe brain trauma.[22] Avoiding negative cumulative fluid balance is essential to limit the risk of renal failure in patients receiving mannitol.

Blood Pressure Management

The ideal blood pressure will depend on the underlying cause of the brain edema. In trauma and stroke patients, blood pressure should be supported to maintain adequate perfusion, avoiding sudden rises and very high levels of hypertension. Keeping cerebral perfusion pressure above 60–70 mm Hg is generally recommended after traumatic brain injury.[23] The value of blood pressure augmentation beyond those parameters using inotropic medications is under investigation.[24]

Blood pressure targets are controversial in cases of intracerebral hemorrhage, but it is probably safe to treat hypertension in the acute phase,[25] and this strategy may reduce the risk of early hematoma growth.[26] After the first 24–48 hours of hematoma onset, blood pressure should be treated to achieve near normotension since the risk of progression of edema persists for much longer.[27] In patients with ischemic stroke, rapid blood pressure reductions are detrimental in the acute phase (first 24–48 hours) since they can produce worsening of neurologic deficits from loss of perfusion in the penumbra.[28] However, in patients with large hemispheric strokes, such as malignant middle cerebral artery infarctions, this risk must be weighed against the hazards of hemorrhagic conversion and progression of edema that may be linked to severe hypertension. Normal blood pressure should also be the aim in patients with lesions associated predominantly with vasogenic edema, such as tumors and inflammatory or infectious masses.

Prevention of Seizures, Fever and Hyperglycemia

These various factors may be considered together because they all cause deleterious effects in the injured brain and should be prevented or aggressively treated when present. The benefit of prophylactic use of anticonvulsants remains unproven in patients with most conditions leading to brain edema. However, this preventive use is quite common in practice and may be defensible in patients with very limited intracranial compliance. Also, there is some evidence that subclinical epileptic activity may be associated with progression of midline shift and worse outcome at least in critically ill patients with intracerebral hemorrhage.[29] These preliminary data are concerning but require validation by further research. Conversely, widespread use of anticonvulsants is far from benign[30] and has been discouraged in patients with brain tumors.[31]

Fever and hyperglycemia worsen ischemic brain damage[32,33] and may markedly exacerbate cerebral edema.[34,35] Therefore, nursing orders must include frequent measurements of body temperature (including brain temperature if an intraparenchymal probe is available) and capillary glucose. Strict normothermia and normoglycemia (ie, blood glucose at least below 120 mg/dL) must be maintained at all times. Current evidence regarding the role of hypothermia for the treatment of brain edema is discussed later on this review.

Osmotic Therapy

Mannitol and hypertonic saline are the 2 osmotic agents most extensively studied and most frequently used in practice to ameliorate brain edema and intracranial hypertension. Both are effective regardless of the pathophysiology and distribution of edema.

Despite its widespread use for over 40 years, the precise mechanisms of action of mannitol remain incompletely defined. The 2 main mechanisms are osmotic and hemodynamic.

Mannitol

Despite its widespread use for over 40 years, the precise mechanisms of action of mannitol remain incompletely defined.[36] This is due at least in part to the multiple effects exerted by this agent that may contribute to its therapeutic benefit. The 2 main mechanisms are osmotic and hemodynamic.

The osmotic effect is based on the fact that mannitol does not cross the cellular membrane or the intact blood-brain barrier. Hence, mannitol increases intravascular tonicity, thereby establishing a concentration gradient across the blood-brain barrier that forces movement of water from the edematous brain tissue to the intravascular space. This is followed by rapid renal excretion of mannitol and water. However, the timing and dose of mannitol required to exert a change in brain water content in animal models is not consistent with the changes in ICP that are seen in clinical practice. Effective changes in ICP clinically occur at much lower doses of mannitol than those used in animal experiments. It has also been experimentally documented that the decline in ICP precedes the fall in brain water content that occurs after a bolus of mannitol, arguing in favor of a mechanism other than dehydration being responsible for the early effects of the agent.[37] Still, mannitol does reduce brain water content as proven by experimental evidence,[38] intraoperative biopsies in trauma patients,[39] and radiologic studies with CT[40] and MRI.[41]

In models of ischemic infarction, the reduction in brain water content after mannitol infusion is greater in the normal than in the damaged hemisphere.[37] However, a human study using CT scan before and shortly after a bolus of mannitol showed no significant effect of the administration of the agent on horizontal or vertical midline shift.[42] Further analysis of the data from this study demonstrated that volume shrinkage occurred preferentially in the noninfarcted hemisphere during the first hour after mannitol administration.[43] The effect of mannitol on brain volume after 1 hour remains to be formally studied. Nonetheless, these studies argue that the preferential dehydrating effect of mannitol on the noninfarcted hemisphere is not clinically meaningful.[36]

The hemodynamic effects of mannitol are proposed to be mediated by a reduction in blood viscosity that would lead to increased cerebral blood flow and a subsequent reduction in cerebral blood volume due to passive vasoconstriction.[44,45] The rheologic changes are caused by dilution of blood and increased deformability of erythrocytes.[46] These changes can occur quite

rapidly and could account for the early drop in ICP observed prior to the fall in brain water content. However, this theory is not substantiated by other studies that actually found rises in cerebral blood volume after administration of mannitol.[47]

Other proposed mechanisms of action of mannitol include free radical scavenging,[48] inhibition of apoptosis,[49] and augmentation of cerebral perfusion pressure leading to autoregulatory vasoconstriction and consequent reduction in cerebral blood volume.[50] The latter mechanism is theoretically appealing but probably not clinically significant since it contends that mannitol causes systemic blood pressure elevation as a result of intravascular volume expansion, a finding that is rarely seen in practice. In addition, it depends on conservation of normal autoregulatory responses, which are actually often abolished in many conditions associated with brain edema.[36]

The incomplete understanding of the mechanisms underlying the effects of mannitol on ICP and the lack of systematic studies of mannitol treatment in humans explain the lack of agreement on what is the optimal way of administering the agent. A standardized dosing regimen (eg, 1 to 1.5 g/kg of 20% mannitol in a bolus followed by 0.25 to 0.5 g/kg every 4 to 6 hours) may be complicated by volume depletion. There is also concern about possible leakage of mannitol into damaged brain tissue potentially leading to "rebound" rises in ICP.[51,52] In fact, accumulation of mannitol in white matter has been reported after multiple doses, but not after a single dose, of the medication.[52] To avoid this, repeated boluses of mannitol administered only when required by elevations of ICP may be favored instead. Still, most experts allow mannitol to produce some dehydration to induce transient cellular shrinkage. Adequate volume repletion with isotonic or slightly hypertonic solutions is essential to keep the patient euvolemic.

Mannitol dosing is customarily monitored by checking serum osmolality prior to each dose. High serum osmolality increases the risk of renal failure (in the setting of coexistent volume depletion) but does not correlate well with serum mannitol levels. The osmolal gap (difference between calculated and measure serum osmolalities) correlates better with serum mannitol levels and a normal osmolal gap indicates sufficient clearance of previous doses of mannitol to allow safe administration of a new dose.[53] A serum osmolality of 320 mOsm/L is generally quoted as the maximal allowable serum osmolality when the patient is receiving mannitol. However, it is important to understand that this cutoff number is a limitation designed to prevent renal tubular damage based on very limited evidence. Crossing this threshold is not necessarily dangerous as long as the patient is not volume depleted.[36]

Perhaps the strongest indication for hypertonic saline at this stage is in patients with recalcitrant intracranial hypertension from various intracranial pathologies in whom other therapies have failed.

Hypertonic Saline

Hypertonic saline solutions have recently received considerable attention as an alternative to mannitol for the treatment of brain edema in various acute conditions. As is the case with mannitol, various and possibly interacting mechanisms may be responsible for the reduction in brain edema and ICP achieved with hypertonic saline.[54,55] They include osmotic dehydration of the brain, decreased blood viscosity,[56] increased regional brain perfusion from endothelial cell dehydration and possible pial artery vasodilatation,[21,57] enhanced cardiac output[56,58] and, to a lesser degree, mean arterial pressure,[56] attenuation of inflammatory responses at the microcirculatory level,[59] and reduction of extravascular lung volume, facilitating improvement in gas exchange and oxygenation.[60]

Animal models of focal brain injury have demonstrated significant decreases in cerebral water content and ICP with the use of hypertonic solutions.[61,62] In these studies, hypertonic saline has resembled mannitol in that water content is preferentially reduced in the noninjured hemisphere.[62,63] Experimental designs comparing hypertonic saline with mannitol have offered conflicting results (Table 1). Brain water content was reduced more effectively by hypertonic saline in studies of focal hemorrhage[64] and ischemia[60] but not in others models.[62,65,66] The duration of ICP reduction may be longer with hypertonic saline,[62,64,66] but this difference may be restricted to the first bolus and disappear with repeated doses.[62] Disappointingly, neither mannitol nor hypertonic saline has proven to improve oxygenation of the injured brain.[67,68]

Clinical data on hypertonic saline is promising but far from definitive. Initial enthusiasm for this treatment was fueled by experimental data and small clinical trials using hypertonic saline for volume resuscitation in hemorrhagic shock that showed an improvement in survival attributed to reduction in ICP.[69,70] However, in a larger recent trial, hypertonic saline was compared with conventional fluid management (lactate Ringer) for the prehospital resuscitation of patients with severe brain trauma and hypotension, and it failed to improve neurologic outcome.[71] Preferential benefit in patients with trauma or postoperative edema (against no detectable benefit on lateral displacement in patients with nontraumatic intracranial hemorrhage or infarction) was reported in one study,[72] but hypertonic saline has also been effective in reducing ICP in patients with severe subarachnoid hemorrhage.[73] Perhaps the strongest indication for hypertonic saline at this stage is in pediatric and adult patients with recalcitrant intracranial hypertension from various intracranial pathologies in whom other therapies have failed.[74–76]

Several small randomized trials comparing hypertonic saline with mannitol in head injury have shown better results with hypertonic saline (Table 1). However, no definite conclusions can be drawn at present because the studies involved a wide range of saline concentrations, and equiosmolar solutions were not consistently used. Further carefully designed studies comparing the 2 agents are needed before superiority of one of them can be firmly postulated.

TABLE 1. Summary of Experimental Studies and Clinical Trials Comparing Different Formulations of Hypertonic Saline (HS) With Mannitol 20% (M)

Study	Experimental Model (No. of Patients/Diagnosis)	HS Formulation	Mode of Infusion	Results
Zornow et al (63)	Focal cryogenic lesion in rabbits	3.2% NaCl	Bolus	Similar ICP reduction. Similar MAP response.
Freshman et al (163)	ICP elevation by epidural balloon inflation in sheep	7.5% NaCl	Bolus	Similar ICP reduction. Similar brain water content.
Berger et al (62)	Focal brain lesion and epidural balloon inflation in rabbits	7.2% NaCl/10% dextran-60*	Serial boluses	Similar ICP reduction (longer response with M after first dose but not later). HS increased BP. Water content in damaged hemisphere increased with HS vs unchanged with M.
Qureshi et al (64)	Model of ICH by autologous blood injection in dogs	Iso-osmolar 3% and 23.4% NaCl*	Bolus	ICP dropped faster with HS (both concentrations). ICP response after 2 h remained significant only with 3% NaCl. Water content in damaged white matter was lower with 3% NaCl.
Mirski et al (66)	Focal cryogenic lesion in rats	11 mOsm/kg NaCl*	Bolus	Greater and longer ICP reduction with HS. Similar brain water content.
Tuong et al (65)	Temporary MCA occlusion (2 h) in rats	7.5% NaCl/acetate	Continuous	HS attenuated maximal edema in both hemispheres less robustly than M.
Tuong et al (60)	Permanent MCA occlusion in rats	5% And 7.5% NaCl/acetate	Continuous	HS (both concentrations) reduced lung and brain water content more effectively than M.
Gemma et al (164)	(50/Elective neurosurgery)	7.5% NaCl	Bolus	No differences in CSF pressure
Schwarz et al (165)	(9/Ischemic infarction with raised ICP)	75 g/L NaCl plus 60 g/L hydroxyethyl starch (2570 mOsm/L)	Serial boluses	HS lowered ICP more effectively M increased CPP more effectively.
Vialet at el (166)	(20/TBI with coma and raised ICP)	7.5% NaCl	Serial boluses	HS had lower rate of failure to drop ICP.
Battison et al (167)	(9/TBI)	7.5% NaCl plus 6% dextran-70*	Two boluses of HS and M	HS produced greater and longer ICP reductions.

BP indicates blood pressure; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; HS, hypertonic saline; ICP, intracranial pressure; M, mannitol 20% solution; MAP, mean arterial pressure; MCA, middle cerebral artery; TBI, traumatic brain injury.

*Equiosmolar doses of mannitol 20% (osmolarity 1160 mOsm/L) and HS were used.

Concentrations of hypertonic saline ranging from 3% to 23.4% have been used in clinical studies. Combinations with dextran, hydroxyethyl starch, and acetate have been tested. Continuous infusion and intermittent boluses have been evaluated. However, comparisons of all these various options are not available, and therefore there is no clear information on what may be the ideal form of administration of hypertonic saline. Future work evaluating the use of hypertonic saline will require a study of dose escalation evaluating safety and efficacy profiles.

Although hypertonic saline has been saluted as a safer option than mannitol, a number of potential and documented adverse effects must be considered when infusing this solution. Rebound edema may occur, especially with continuous drips.[77] Congestive heart failure is a potential complication in patients with preexistent cardiac dysfunction who cannot handle the expansion of intravascular volume. Decreased platelet aggregation and prolongation of coagulation times have been reported,[78] but their clinical significance is questionable since bleeding complications have not been noted. Local phlebitis may be easily prevented using a large-bore access. Hyperchloremic metabolic acidosis is avoided by combining hypertonic saline with acetate. Complications from severe hypernatremia, although feared, are rarely encountered in practice. The risk of renal failure is most likely very low, and thus it may be reasonable to consider using hypertonic saline instead of mannitol in patients with renal insufficiency.

Steroids

Glucocorticoids are very effective in ameliorating the vasogenic edema that accompanies tumors, inflammatory conditions, and other disorders associated with increased permeability of the blood-brain barrier, including surgical manipulation.[79] However, steroids are not helpful to treat cytotoxic edema and are detrimental in patients with brain ischemia.

Defective endothelial tight junctions are primarily responsible for the formation of edema in brain tumors.[80] Molecular mechanisms involved in this abnormal permeability include underexpression of tight junction proteins (eg, occluding, claudin-1, claudin-5), up-regulation of the water channel aquaporin-4, and high levels of vascular endothelial growth factors.[80] Glucocorticoids are the main treatment of cerebral edema caused by primary or metastatic brain tumors.[81] The reduction in peritumoral edema with corticosteroids may occur because of decreased endothelial cell permeability,[82,83] increased clearance of fluid in the extracellular space,[84] or metabolic changes induced in the tumor tissue.[85]

Dexamethasone is the preferred agent due to its very low mineralocorticoid activity. The usual initial dose is 10 mg intravenously or by mouth, followed by 4 mg every 6 hours. This is equivalent to 20 times the normal physiologic production of cortisol. Responses are often prompt and remarkable, sometimes dramatic, but some tumors are less responsive.[86] Higher doses, up to 96 mg per day, may be used with chances of success in more refractory cases.[87] After several days of use, steroids should be tapered gradually to avoid potentially serious complications from recurrent edema and adrenal suppression.

Corticosteroids are also effective to alleviate brain edema related to brain radiation, radiosurgical treatments, and neurosurgical manipulation.[79,88,89] Steroids could also be protective against brain damage from radiation.[90] The effectiveness of steroids is much greater against the acute swelling following radiation treatment than against subacute edema or chronic radionecrosis.[89]

Glucocorticoids are also useful to treat brain edema in cases of bacterial meningitis. Edema in these patients develops as part of the inflammatory reaction triggered by the lysis of bacterial cell walls induced by antibiotics. Inflammation is mediated through the increased production of cytokines and chemokines by microglia, astrocytes, and macrophages. Interleukin-1 (IL-1) and tumor necrosis factor (TNF) increase vascular permeability both directly and indirectly by increasing leukocyte adherence to the endothelium. Apart from previously mentioned mechanisms, glucocorticoids exert a depressant effect on both the synthesis and translation of IL-1 and TNF mRNA. The timing of glucocorticoid use may be critical as the maximal reduction in the production of these inflammatory cytokines occurs only if therapy is started prior to the release of the bacterial cell wall components.

Glucocorticoid use decreases morbidity and mortality in animal models[91,92] of meningitis and has been shown to reduce the risk of hearing loss in pediatric patients with *Haemophilus influenzae* type b meningitis.[93] Although other clinical trials produced conflicting results,[94] a meta-analysis of clinical studies supported the use of dexamethasone in children with both *H influenzae* type b and *Streptococcus pneumoniae* meningitis.[94] Dexamethasone is currently recommended for children older than 2 months of age with bacterial meningitis. The suggested dose is 0.15 mg/kg given intravenously every 6 hours for the first 4 days of antibiotic treatment. The first dose should be administered before or concurrent with the start of antibiotic treatment.

The use of corticosteroids in adult patients with bacterial meningitis has been more controversial. Animal models have shown a decrease of antibiotic penetration into the CSF of animals pretreated with dexamethasone,[95,96] a concern that led to prematurely halting a trial testing dexamethasone in adults with severe meningitis.[97] Furthermore, until recently, trials of dexamethasone in adults with meningitis had produced conflicting results.[93,97,98]

The debate, however, appears to have been resolved by the results of a recent prospective, randomized, double-blinded trial of adjuvant treatment with dexamethasone versus placebo in adults with bacterial meningitis. In this study, dexamethasone started 15–20 minutes prior to the first dose of antibiotics and given for the first 4 days of treatment (10 mg every 6 hours) was associated with reduced mortality ($P = 0.04$) and improved functional outcome ($P = 0.03$). Treatment was most effective for the sickest patients, as evaluated by their admission GCS sum score and in patients with pneumococcal meningitis.[99] Based on the above study, adjunctive therapy with dexamethasone is warranted in most adults with suspected

meningitis.[100] However, there is lingering concern about the appropriateness of this approach in populations with a high incidence of penicillin-resistant pneumococcus or susceptible to infection by *Staphylococcus aureus* (eg, neurosurgical patients) since dexamethasone use could reduce the already limited permeability of the blood-brain barrier to vancomycin.[101]

In patients with severe head injury, the use of glucocorticoids is not recommended for improving outcome or reducing ICP.[102] Several prospective randomized trials have evaluated different regimens of glucocorticoids in this population and consistently found no evidence of therapeutic benefit.[103–106] Furthermore, the recently published CRASH trial found a trend towards increased 2-week mortality rates in head-injured patients treated with large doses of corticosteroids (methylprednisolone 2 g bolus initiated within 8 hours of the trauma and then infusion of 400 mg/h continued for 48 hours).[107] These negative results may be explained, at least in part, by the untoward metabolic (particularly hyperglycemia) and nutritional effects exerted by megadoses of glucocorticoids on critically ill patients.[108,109]

Several randomized clinical trials have consistently shown that corticosteroids have no value in the treatment of ischemic stroke.[110–113] Steroid use also failed to benefit patients with intracerebral hemorrhage.[114,115] However, more recent animal studies have indicated that steroids might decrease infarct volume and decrease cerebral edema in models of temporary (but not permanent) focal cerebral ischemia.[116,117] This raises the possibility that corticosteroids may prove useful in patients that receive intravenous or intraarterial thrombolysis. However, growing awareness of the immensely detrimental impact of hyperglycemia on the acutely injured brain is very likely going to deter initiatives to design new trials to reevaluate the administration of steroids in patients with ischemic infarction or intracerebral hemorrhage.[33,118,119] Particularly noteworthy is the observation that hyperglycemia has been associated with hyperacute decline, worse outcome, and increased risk of hemorrhagic transformation in stroke patients treated with thrombolysis.[33,120,121]

Hyperventilation must only be used in acute ischemic stroke as a temporizing measure because vasoconstriction might exacerbate cerebral ischemia.

Hyperventilation

Although not a treatment of brain edema per se, hyperventilation is very efficacious in reducing elevated ICP. It achieves this effect by producing cerebral vasoconstriction and hence diminishing cerebral blood volume. Small resistance vessels are very sensitive to the acidity of the cerebrospinal fluid. Since the blood-brain barrier is impermeable to bicarbonate and hydrogen ions but permeable to carbon dioxide, changes in cerebrospinal fluid hydrogen ion concentration can be fostered by changes in serum pCO_2. The reduction in CBF occurs immediately and lasts for up to 30 minutes. In the setting of intact autoregulation, each torr change in pCO_2 generates a 3% change in CBF. The response lessens as the level of pCO_2 decreases. Loss of vasomotor reactivity to CO_2 is a grave prognostic indicator after head injury.[122]

The use of chronic hyperventilation to control intracranial hypertension is generally avoided due to concerns that cerebral vasoconstriction may worsen cerebral ischemia. The choroid plexus buffers the augmented hydrogen ion concentration approximately 3–4 hour after any acute change, but ICP levels may return to prehyperventilation baseline long before this. The addition of weak bases or the buffer agent tromethamine (THAM) can sustain a reduction in ICP for longer periods of time. However, the only randomized trial evaluating chronic hyperventilation in head trauma found a significantly worse functional outcome at 6 months in hyperventilated patients with initial GCS motor score of 4–5.[123] Additionally, brief moderate hyperventilation has been shown to reduce brain tissue PO_2 below ischemic levels[124] and to increase extracellular concentrations of markers of anaerobic metabolism (pyruvate, lactate) and excitotoxicity (glutamate).[125] Although hyperventilation should not be totally abandoned in patients with intracranial hypertension from traumatic brain injury,[126] it should be used with caution.

Hyperventilation must only be used in acute ischemic stroke as a temporizing measure because vasoconstriction might exacerbate cerebral ischemia. Still, in selected cases, brief use of moderate hyperventilation may be justified as a bridge to safer and more definitive antiedema treatments (such as osmotherapy or hemicraniectomy). Similar concepts may be applied to the case of intracerebral hemorrhage.

Barbiturates

Barbiturates can effectively reduce ICP in patients with severe head injury.[127] They are generally reserved for cases refractory to other medical measures. Metabolic suppression is the desired effect and presumed mechanism of action. Barbiturate dosing is typically titrated to a target ICP, but there is little additional effect on ICP once a burst suppression pattern is present on bedside electroencephalography. Whether barbiturates improve outcome remains controversial. Benefit in survival was noted in 1 trial,[127] but no functional improvement was found in others.[128,129] Functional recovery after treatment with barbiturates, especially in terms of cognitive function, may be limited.[130] However, acceptable quality of life may be achieved, particularly by younger patients.[130] In patients with large ischemic infarctions, barbiturates only seem to offer limited and short-lasting benefits that may be counterbalanced by adverse effects, especially if hypotension occurs.[131]

Use of high-dose barbiturates is fraught with complications, including hypotension, hepatic dysfunction, and in-

creased risk of pneumonia and sepsis. Thus, there is interest in investigating alternative measures to promote controlled suppression of brain metabolism. Propofol infusion and induced hypothermia are the most attractive options.

Other Pharmacological Alternatives

Intravenous glycerol is sometimes used as an alternative osmotic agent for the treatment of brain edema. It readily reduces ICP for up to 60 minutes without pronounced or long-lasting effects on serum osmolarity.[132] It has been tested for the treatment of edema caused by large ischemic or hemorrhagic strokes.[133] In patients with extensive brain infarctions, MRI evidence demonstrated that glycerol reduces edema volume in the affected hemisphere without detectable effects on the healthy side or exacerbation of tissue shift.[134] Glycerol diffuses rapidly across the blood-brain barrier and accumulates in the brain shortly after its administration; this may lead to a brief rebound elevation in ICP.[132] The clinical significance of this phenomenon is not well defined, and, although probably not large, it may argue for exercising caution when using repeated boluses of this agent. Conversely, glycerol may offer advantages over other osmotic agents such as providing an alternative source of fuel to the ischemic tissue[135] and attenuating leukocyte adherence to the endothelium, thus improving blood cell and plasma flow.[136]

THAM may be used to buffer cerebrospinal fluid acidity. It has been shown to ameliorate the deleterious effects of prolonged hyperventilation and may be useful to control raised ICP in patients with traumatic brain injury.[137] Still, THAM has not been evaluated in recent studies and is rarely used in practice, at least in the United States. A relative disadvantage is that THAM must be administered through a central venous access because peripheral infusion carries the risk of soft-tissue necrosis.[138] The efficacy of THAM can be assessed by infusing 1 mmol/kg in 100 mL of 5% glucose over 45 minutes. If ICP falls by 10–15 mm Hg within 15 minutes, THAM should be continuously infused to reach a pH between 7.5 and 7.55.[139] Available information on THAM supports the appropriateness of renewed research to delineate its role in modern protocols of treatment of intracranial hypertension.

Furosemide is sometimes administered in combination with mannitol. This dual therapy has been tested with variable success.[140–142] Similar inconsistent results were achieved when furosemide alone was evaluated.[143,144] While furosemide may enhance the effect of mannitol, it may need to be administered in very large doses to reach this goal.[142] In such case, the risk of volume contraction may outweigh any potential benefit on ICP.

The role of acetazolamide, a carbonic anhydrase inhibitor that reduces production of cerebrospinal fluid, is restricted to patients with high-altitude illness and benign intracranial hypertension. Indomethacin decreases cerebral blood flow and consequently ICP in patients with severe traumatic brain injury, although at the expense of a drop in cerebral perfusion pressure. While this drop seems to be modest, more research is needed before indomethacin can be formally recommended for clinical use.[145]

Hypothermia

Induced hypothermia has generated enormous interest as a potential neuroprotective intervention in patients with acute brain insults. Sound experimental data provide a solid foundation to the clinical evaluation of hypothermia to treat acute brain ischemia and traumatic injury.[146–149] Furthermore, early application of hypothermia in patients with cardiac arrest was associated with significant improvements in neurologic outcome in 2 highly influential trials,[150–152] arguing that this intervention should become a standard part of resuscitation efforts.

The experience using hypothermia to treat acute stroke has been recently reviewed in detail.[153,154] While observational studies have established that normothermia and mild hypothermia are predictive of favorable outcome,[155,156] clinical studies on therapeutic moderate hypothermia have only included small numbers of patients and different modes of induction of hypothermia.[157,158] Although these studies offered encouraging preliminary results, the safety and efficacy of this treatment modality requires validation in larger, randomized trials.

Hypothermia (target bladder temperature 33°C reached within 8 hours of injury and maintained for 48 hours) failed to improve outcome in a large prospective, multicenter, randomized trial of patients with traumatic brain injury and a GCS sum score of 3–8.[159] Given the wealth of data from laboratory studies indicating that hypothermia may exert important neuroprotective effects in the acutely traumatized brain, more clinical research in this area is warranted. Focusing future studies on earlier institution of hypothermia, perhaps using endovascular rather than external methods of cooling, and applying it on patients with documented intracranial hypertension may be desirable.

Different cooling methods are currently available, including external (ice packs, iced gastric lavage, water or air circulating blankets, cooling vest) and endovascular means. The superiority of endovascular cooling is probable but still under evaluation. Target core temperature is usually 32–34°C, measured with thermistors placed inside the urinary bladder. The value of guiding hypothermic therapy using brain temperature probes deserves investigation. Shivering must be prevented using deep sedation and neuromuscular paralysis when necessary; the combination of oral buspirone (60 mg) and intravenous meperidine (50 to 75 mg loading dose followed by an infusion of 25–35 mg/h) may be an effective and safer alternative option.[157] Hypothermia is usually maintained for 12–72 hours, followed by a period of controlled rewarming over 12–24 hours.

Induction of hypothermia is associated with several potential complications. The most frequent and dangerous are sepsis (particularly from pneumonia), cardiac arrhythmias and hemodynamic instability (often seen during rewarming), coagulopathy (especially thrombocytopenia), and electrolyte disturbances (potassium, magnesium, calcium, phosphate).[153]

In patients with intracranial pressure (ICP) elevation, cerebrospinal fluid drainage is a fast and highly effective treatment measure.

Surgical Interventions

In patients with ICP elevation, cerebrospinal fluid drainage is a fast and highly effective treatment measure. This assertion holds true even in the absence of hydrocephalus. Unfortunately, external ventricular drainage carries a substantial risk of ventriculitis, even under the best care. Controlled lumbar drainage may be a safe alternative in patients with discernible basilar cisterns on CT scan[160]; yet, since the experience with lumbar catheters in patients with brain edema is very limited, its use should be accompanied by extreme caution.

A comprehensive and very updated discussion on the value of hemicraniectomy to treat ischemic brain edema associated with massive hemispheric strokes has been recently published.[154] While it is clear that hemicraniectomy can be lifesaving, its beneficial impact on the long-term functional outcome of survivors remains unproven. Older age clearly predicts very poor recovery,[161] and, in my opinion, hemicraniectomy should only be offered to stroke patients younger than 50–55 years. An example of this surgical intervention is presented in Figure 4.

In patients with critical, recalcitrant intracranial hypertension after head trauma who fail to respond to all other therapeutic measures, craniectomy with duraplasty may be a valuable alternative.[162] Hemicraniectomy may be preferable in patients with focal lesions, such as hemorrhagic contusions, but holocraniectomy is necessary in patients with massive global brain edema. Good long-term functional outcomes have been reported in 25–56% of young patients after this surgery. Although the optimal timing and indications for this intervention are not well established, the expeditious decision by an experienced neurosurgeon to proceed with holocraniectomy in a young patient with massive intractable traumatic brain edema should probably not be delayed by attempts to keep trying additional medical options.

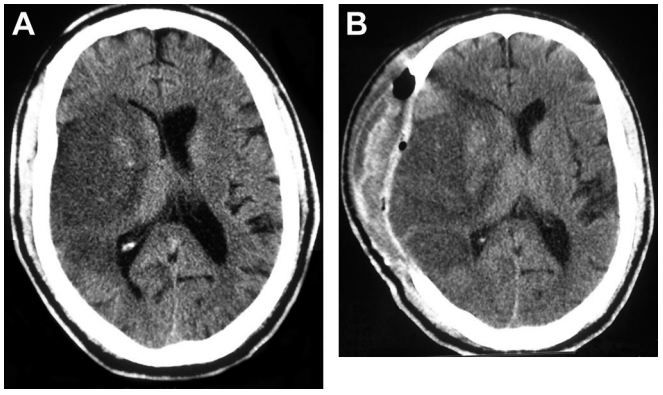

FIGURE 4. A 58-year-old man presented with acute neurologic deficits related to a large right middle cerebral artery infarction. After 36 hours, he became slightly more lethargic and developed bilateral cerebral ptosis. At that stage, his CT scan (shown in A) showed mass effect from the swollen infarction with early hemorrhagic transformation and shift of midline structures. Hemicraniectomy was promptly performed without complications. Postoperative CT scan (shown in B) demonstrated partial decompression of the mass effect with herniation of infracted tissue through the skull defect. The patient survived but remained functionally dependent 1 year later.

Conclusions

The treatment of cerebral edema remains largely empirical. Options are relatively limited, and the mechanisms of action of most of the therapeutic agents and interventions currently used are not fully elucidated. Although protocols and algorithms exist to treat brain edema associated with specific neurologic entities, these are not based on rigorous scientific data. Current uncertainties and deficiencies must be resolved by continuing research, fueled by our growing understanding of the pathophysiological processes responsible for the formation of the different forms of brain edema.

ACKNOWLEDGMENTS

I would like to thank Dr Steven Resnick for his generous contribution of graphic material for this manuscript.

REFERENCES

1. Fishman RA. Brain edema. *N Engl J Med*. 1975;293:706–711.
2. Rabinstein AA. Found comatose. In: Rabinstein AA, Wijdicks EFM, eds. *Tough Calls in Acute Neurology*. Philadelphia, PA: Elsevier; 2004;3–18.
3. Bullock R, Chesnut RM, Clifton G, et al. Guidelines for the management of severe head injury: Brain Trauma Foundation. *Eur J Emerg Med*. 1996;3:109–127.
4. Feldman Z, Kanter MJ, Robertson CS, et al. Effect of head elevation on intracranial pressure, cerebral perfusion pressure, and cerebral blood flow in head-injured patients. *J Neurosurg*. 1992;76:207–211.
5. Ropper AH, O'Rourke D, Kennedy SK. Head position, intracranial pressure, and compliance. *Neurology*. 1982;32:1288–1291.
6. Rosner MJ, Coley IB. Cerebral perfusion pressure, intracranial pressure, and head elevation. *J Neurosurg*. 1986;65:636–641.
7. Meixensberger J, Baunach S, Amschler J, et al. Influence of body position on tissue-pO_2, cerebral perfusion pressure and intracranial pressure in patients with acute brain injury. *Neurol Res*. 1997;19:249–253.
8. Ng I, Lim J, Wong HB. Effects of head posture on cerebral hemodynamics: its influences on intracranial pressure, cerebral perfusion pressure, and cerebral oxygenation. *Neurosurgery*. 2004;54:593–597.
9. Schneider GH, von Helden GH, Franke R, et al. Influence of body position on jugular venous oxygen saturation, intracranial pressure and cerebral perfusion pressure. *Acta Neurochir Suppl (Wien)*. 1993;59:107–112.
10. Moraine JJ, Berre J, Melot C. Is cerebral perfusion pressure a major determinant of cerebral blood flow during head elevation in comatose patients with severe intracranial lesions? *J Neurosurg*. 2000;92:606–614.
11. Schwarz S, Georgiadis D, Aschoff A, et al. Effects of body position on intracranial pressure and cerebral perfusion in patients with large hemispheric stroke. *Stroke*. 2002;33:497–501.
12. Sperry RJ, Bailey PL, Reichman MV, et al. Fentanyl and sufentanil increase intracranial pressure in head trauma patients. *Anesthesiology*. 1992;77:416–420.
13. Lauer KK, Connolly LA, Schmeling WT. Opioid sedation does not

alter intracranial pressure in head injured patients. *Can J Anaesth*. 1997;44:929–933.
14. Boeve BF, Wijdicks EF, Benarroch EE, et al. Paroxysmal sympathetic storms ("diencephalic seizures") after severe diffuse axonal head injury. *Mayo Clin Proc*. 1998;73:148–152.
15. Kelly DF, Goodale DB, Williams J, et al. Propofol in the treatment of moderate and severe head injury: a randomized, prospective double-blinded pilot trial. *J Neurosurg*. 1999;90:1042–1052.
16. Juul N, Morris GF, Marshall SB, et al. Neuromuscular blocking agents in neurointensive care. *Acta Neurochir Suppl*. 2000;76:467–470.
17. Segredo V, Caldwell JE, Matthay MA, et al. Persistent paralysis in critically ill patients after long-term administration of vecuronium. *N Engl J Med*. 1992;327:524–528.
18. Geller TJ, Kaiboriboon K, Fenton GA, et al. Vecuronium-associated axonal motor neuropathy: a variant of critical illness polyneuropathy? *Neuromuscul Disord*. 2001;11:579–582.
19. Caricato A, Conti G, Della CF, et al. Effects of PEEP on the intracranial system of patients with head injury and subarachnoid hemorrhage: the role of respiratory system compliance. *J Trauma*. 2005;58:571–576.
20. Huynh T, Messer M, Sing RF, et al. Positive end-expiratory pressure alters intracranial and cerebral perfusion pressure in severe traumatic brain injury. *J Trauma*. 2002;53:488–492.
21. Ramming S, Shackford SR, Zhuang J, et al. The relationship of fluid balance and sodium administration to cerebral edema formation and intracranial pressure in a porcine model of brain injury. *J Trauma*. 1994;37:705–713.
22. Clifton GL, Miller ER, Choi SC, et al. Fluid thresholds and outcome from severe brain injury. *Crit Care Med*. 2002;30:739–745.
23. Brain Trauma Foundation, American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care. Guidelines for cerebral perfusion pressure. *J Neurotrauma*. 2000;17:507–511.
24. Johnston AJ, Steiner LA, Coles JP, et al. Effect of cerebral perfusion pressure augmentation on regional oxygenation and metabolism after head injury. *Crit Care Med*. 2005;33:189–195.
25. Powers WJ, Zazulia AR, Videen TO, et al. Autoregulation of cerebral blood flow surrounding acute (6 to 22 hours) intracerebral hemorrhage. *Neurology*. 2001;57:18–24.
26. Leira R, Davalos A, Silva Y, et al. Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. *Neurology*. 2004;63:461–467.
27. Zazulia AR, Diringer MN, Derdeyn CP, et al. Progression of mass effect after intracerebral hemorrhage. *Stroke*. 1999;30:1167–1173.
28. Oliveira-Filho J, Silva SC, Trabuco CC, et al. Detrimental effect of blood pressure reduction in the first 24 hours of acute stroke onset. *Neurology*. 2003;61:1047–1051.
29. Vespa PM, O'Phelan K, Shah M, et al. Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. *Neurology*. 2003;60:1441–1446.
30. Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. *Arch Intern Med*. 1995;155:2285–2290.
31. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;54:1886–1893.
32. Ginsberg MD, Busto R. Combating hyperthermia in acute stroke: a significant clinical concern. *Stroke*. 1998;29:529–534.
33. Bruno A, Williams LS, Kent TA. How important is hyperglycemia during acute brain infarction? *Neurologist*. 2004;10:195–200.
34. Rossi S, Zanier ER, Mauri I, et al. Brain temperature, body core temperature, and intracranial pressure in acute cerebral damage. *J Neurol Neurosurg Psychiatry*. 2001;71:448–454.
35. Song EC, Chu K, Jeong SW, et al. Hyperglycemia exacerbates brain edema and perihematomal cell death after intracerebral hemorrhage. *Stroke*. 2003;34:2215–2220.
36. Diringer MN, Zazulia AR. Osmotic therapy: fact or fiction? *Neurocrit Care*. 2004;1:219–234.
37. Hartwell RC, Sutton LN. Mannitol, intracranial pressure, and vasogenic edema. *Neurosurgery*. 1993;32:444–450.
38. Paczynski RP, Venkatesan R, Diringer MN, et al. Effects of fluid management on edema volume and midline shift in a rat model of ischemic stroke. *Stroke*. 2000;31:1702–1708.
39. Nath F, Galbraith S. The effect of mannitol on cerebral white matter water content. *J Neurosurg*. 1986;65:41–43.
40. Cascino T, Baglivo J, Conti J, et al. Quantitative CT assessment of furosemide- and mannitol-induced changes in brain water content. *Neurology*. 1983;33:898–903.
41. Bell BA, Smith MA, Kean DM, et al. Brain water measured by magnetic resonance imaging: correlation with direct estimation and changes after mannitol and dexamethasone. *Lancet*. 1987;1:66–69.
42. Manno EM, Adams RE, Derdeyn CP, et al. The effects of mannitol on cerebral edema after large hemispheric cerebral infarct. *Neurology*. 1999;52:583–587.
43. Videen TO, Zazulia AR, Manno EM, et al. Mannitol bolus preferentially shrinks non-infarcted brain in patients with ischemic stroke. *Neurology*. 2001;57:2120–2122.
44. Muizelaar JP, Lutz HA III, Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. *J Neurosurg*. 1984;61:700–706.
45. Rosner MJ, Coley I. Cerebral perfusion pressure: a hemodynamic mechanism of mannitol and the postmannitol hemogram. *Neurosurgery*. 1987;21:147–156.
46. Burke AM, Quest DO, Chien S, et al. The effects of mannitol on blood viscosity. *J Neurosurg*. 1981;55:550–553.
47. Ravussin P, Archer DP, Tyler JL, et al. Effects of rapid mannitol infusion on cerebral blood volume: a positron emission tomographic study in dogs and man. *J Neurosurg*. 1986;64:104–113.
48. Alvarez B, Ferrer-Sueta G, Radi R. Slowing of peroxynitrite decomposition in the presence of mannitol and ethanol. *Free Radic Biol Med*. 1998;24:1331–1337.
49. Korenkov AI, Pahnke J, Frei K, et al. Treatment with nimodipine or mannitol reduces programmed cell death and infarct size following focal cerebral ischemia. *Neurosurg Rev*. 2000;23:145–150.
50. Schrot RJ, Muizelaar JP. Mannitol in acute traumatic brain injury. *Lancet*. 2002;359:1633–1634.
51. McManus ML, Soriano SG. Rebound swelling of astroglial cells exposed to hypertonic mannitol. *Anesthesiology*. 1998;88:1586–1591.
52. Kaufmann AM, Cardoso ER. Aggravation of vasogenic cerebral edema by multiple-dose mannitol. *J Neurosurg*. 1992;77:584–589.
53. Garcia-Morales EJ, Cariappa R, Parvin CA, et al. Osmole gap in neurologic-neurosurgical intensive care unit: its normal value, calculation, and relationship with mannitol serum concentrations. *Crit Care Med*. 2004;32:986–991.
54. Suarez JI. Hypertonic saline for cerebral edema and elevated intracranial pressure. *Cleve Clin J Med*. 2004;71(suppl 1):S9–13.
55. Qureshi AI, Suarez JI. Use of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension. *Crit Care Med*. 2000;28:3301–3313.
56. Tseng MY, Al Rawi PG, Pickard JD, et al. Effect of hypertonic saline on cerebral blood flow in poor-grade patients with subarachnoid hemorrhage. *Stroke*. 2003;34:1389–1396.
57. Shackford SR, Schmoker JD, Zhuang J. The effect of hypertonic resuscitation on pial arteriolar tone after brain injury and shock. *J Trauma*. 1994;37:899–908.
58. Munar F, Ferrer AM, de Nadal M, et al. Cerebral hemodynamic effects of 7.2% hypertonic saline in patients with head injury and raised intracranial pressure. *J Neurotrauma*. 2000;17:41–51.
59. Hartl R, Medary MB, Ruge M, et al. Hypertonic/hyperoncotic saline attenuates microcirculatory disturbances after traumatic brain injury. *J Trauma*. 1997;42(5 suppl):S41–S47.
60. Toung TJ, Chang Y, Lin J, et al. Increases in lung and brain water following experimental stroke: effect of mannitol and hypertonic saline. *Crit Care Med*. 2005;33:203–208.
61. Bacher A, Wei J, Grafe MR, et al. Serial determinations of cerebral water content by magnetic resonance imaging after an infusion of hypertonic saline. *Crit Care Med*. 1998;26:108–114.
62. Berger S, Schurer L, Hartl R, et al. Reduction of post-traumatic intracranial hypertension by hypertonic/hyperoncotic saline/dextran and hypertonic mannitol. *Neurosurgery*. 1995;37:98–107.
63. Zornow MH, Oh YS, Scheller MS. A comparison of the cerebral and haemodynamic effects of mannitol and hypertonic saline in an animal model of brain injury. *Acta Neurochir Suppl (Wien)*. 1990;51:324–325.
64. Qureshi AI, Wilson DA, Traystman RJ. Treatment of elevated intracranial

pressure in experimental intracerebral hemorrhage: comparison between mannitol and hypertonic saline. *Neurosurgery*. 1999;44:1055–1063.
65. Toung TJ, Hurn PD, Traystman RJ, et al. Global brain water increases after experimental focal cerebral ischemia: effect of hypertonic saline. *Crit Care Med*. 2002;30:644–649.
66. Mirski AM, Denchev ID, Schnitzer SM, et al. Comparison between hypertonic saline and mannitol in the reduction of elevated intracranial pressure in a rodent model of acute cerebral injury. *J Neurosurg Anesthesiol*. 2000;12:334–344.
67. Hartl R, Bardt TF, Kiening KL, et al. Mannitol decreases ICP but does not improve brain-tissue pO_2 in severely head-injured patients with intracranial hypertension. *Acta Neurochir Suppl*. 1997;70:40–42.
68. DeWitt DS, Prough DS, Deal DD, et al. Hypertonic saline does not improve cerebral oxygen delivery after head injury and mild hemorrhage in cats. *Crit Care Med*. 1996;24:109–117.
69. Vassar MJ, Fischer RP, O'Brien PE, et al. A multicenter trial for resuscitation of injured patients with 7.5% sodium chloride: the effect of added dextran 70: the Multicenter Group for the Study of Hypertonic Saline in Trauma Patients. *Arch Surg*. 1993;128:1003–1011.
70. Battistella FD, Wisner DH. Combined hemorrhagic shock and head injury: effects of hypertonic saline (7.5%) resuscitation. *J Trauma*. 1991;31:182–188.
71. Cooper DJ, Myles PS, McDermott FT, et al. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. *JAMA*. 2004;291:1350–1357.
72. Qureshi AI, Suarez JI, Bhardwaj A, et al. Use of hypertonic (3%) saline/acetate infusion in the treatment of cerebral edema: effect on intracranial pressure and lateral displacement of the brain. *Crit Care Med*. 1998;26:440–446.
73. Bentsen G, Breivik H, Lundar T, et al. Predictable reduction of intracranial hypertension with hypertonic saline hydroxyethyl starch: a prospective clinical trial in critically ill patients with subarachnoid haemorrhage. *Acta Anaesthesiol Scand*. 2004;48:1089–1095.
74. Suarez JI, Qureshi AI, Bhardwaj A, et al. Treatment of refractory intracranial hypertension with 23.4% saline. *Crit Care Med*. 1998;26:1118–1122.
75. Horn P, Munch E, Vajkoczy P, et al. Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. *Neurol Res*. 1999;21:758–764.
76. Khanna S, Davis D, Peterson B, et al. Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. *Crit Care Med*. 2000;28:1144–1151.
77. Qureshi AI, Suarez JI, Bhardwaj A. Malignant cerebral edema in patients with hypertensive intracerebral hemorrhage associated with hypertonic saline infusion: a rebound phenomenon? *J Neurosurg Anesthesiol*. 1998;10:188–192.
78. Reed RL, Johnston TD, Chen Y, et al. Hypertonic saline alters plasma clotting times and platelet aggregation. *J Trauma*. 1991;31:8–14.
79. French LA, Galicich JH. The use of steroids for control of cerebral edema. *Clin Neurosurg*. 1964;10:212–223.
80. Papadopoulos MC, Saadoun S, Binder DK, et al. Molecular mechanisms of brain tumor edema. *Neuroscience*. 2004;129:1011–1020.
81. Kaal EC, Vecht CJ. The management of brain edema in brain tumors. *Curr Opin Oncol*. 2004;16:593–600.
82. Sinha S, Bastin ME, Wardlaw JM, et al. Effects of dexamethasone on peritumoural oedematous brain: a DT-MRI study. *J Neurol Neurosurg Psychiatry*. 2004;75:1632–1635.
83. Andersen C, Jensen FT. Differences in blood-tumour-barrier leakage of human intracranial tumours: quantitative monitoring of vasogenic oedema and its response to glucocorticoid treatment. *Acta Neurochir (Wien)*. 1998;140:919–924.
84. Long DM, Hartmann JF, French LA. The response of human cerebral edema to glucosteroid administration: an electron microscopic study. *Neurology*. 1966;16:521–528.
85. Chumas P, Condon B, Oluoch-Olunya D, et al. Early changes in peritumorous oedema and contralateral white matter after dexamethasone: a study using proton magnetic resonance spectroscopy. *J Neurol Neurosurg Psychiatry*. 1997;62:590–595.
86. Rommel T, Bodsch W. Glucocorticosteroid treatment of vasogenic oedema. *Acta Neurochir Suppl (Wien)*. 1988;43:145–148.
87. Renaudin J, Fewer D, Wilson CB, et al. Dose dependency of Decadron in patients with partially excised brain tumors. *J Neurosurg*. 1973;39:302–305.
88. El Shehaby A, Ganz JC, Reda WA, et al. Temporary symptomatic swelling of meningiomas following gamma knife surgery: report of two cases. *J Neurosurg*. 2005;102(suppl):293–296.
89. Plowman PN. Stereotactic radiosurgery, VIII: the classification of postradiation reactions. *Br J Neurosurg*. 1999;13:256–264.
90. Kondziolka D, Somaza S, Martinez AJ, et al. Radioprotective effects of the 21-aminosteroid U-74389G for stereotactic radiosurgery. *Neurosurgery*. 1997;41:203–208.
91. Tauber MG, Khayam-Bashi H, Sande MA. Effects of ampicillin and corticosteroids on brain water content, cerebrospinal fluid pressure, and cerebrospinal fluid lactate levels in experimental pneumococcal meningitis. *J Infect Dis*. 1985;151:528–534.
92. Syrogiannopoulos GA, Al Sabbagh A, Olsen KD, et al. Pharmacokinetics and bacteriological efficacy of ticarcillin-clavulanic acid (Timentin) in experimental *Escherichia coli* K-1 and *Haemophilus influenzae* type b meningitis. *Antimicrob Agents Chemother*. 1987;31:1296–1300.
93. Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. *N Engl J Med*. 1997;336:708–716.
94. Molyneux EM, Walsh AL, Forsyth H, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. Lancet 2002;360:211–218.
95. Cabellos C, Martinez-Lacasa J, Tubau F, et al. Evaluation of combined ceftriaxone and dexamethasone therapy in experimental cephalosporin-resistant pneumococcal meningitis. *J Antimicrob Chemother*. 2000;45:315–320.
96. Martinez-Lacasa J, Cabellos C, Martos A, et al. Experimental study of the efficacy of vancomycin, rifampicin and dexamethasone in the therapy of pneumococcal meningitis. *J Antimicrob Chemother*. 2002;49:507–513.
97. Thomas R, Le Tulzo Y, Bouget J, et al. Trial of dexamethasone treatment for severe bacterial meningitis in adults: Adult Meningitis Steroid Group. *Intensive Care Med*. 1999;25:475–480.
98. Girgis NI, Farid Z, Mikhail IA, et al. Dexamethasone treatment for bacterial meningitis in children and adults. *Pediatr Infect Dis J*. 1989;8:848–851.
99. de Gans J, van de BD. Dexamethasone in adults with bacterial meningitis. *N Engl J Med*. 2002;347:1549–1556.
100. van de Beek D, de Gans J, McIntyre P, et al. Steroids in adults with acute bacterial meningitis: a systematic review. *Lancet Infect Dis*. 2004;4:139–143.
101. Abril V, Ortega E. Dexamethasone in adults with bacterial meningitis. *N Engl J Med*. 2003;348:954–957.
102. The Brain Trauma Foundation, American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care. Role of steroids. *J Neurotrauma*. 2000;17:531–535.
103. Braakman R, Schouten HJ, Blaauw-van Dishoeck M, et al. Megadose steroids in severe head injury: results of a prospective double-blind clinical trial. *J Neurosurg*. 1983;58:326–330.
104. Cooper PR, Moody S, Clark WK, et al. Dexamethasone and severe head injury: a prospective double-blind study. *J Neurosurg*. 1979;51:307–316.
105. Dearden NM, Gibson JS, McDowall DG, et al. Effect of high-dose dexamethasone on outcome from severe head injury. *J Neurosurg*. 1986;64:81–88.
106. Giannotta SL, Weiss MH, Apuzzo ML, et al. High dose glucocorticoids in the management of severe head injury. *Neurosurgery*. 1984;15:497–501.
107. Roberts I, Yates D, Sandercock P, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet*. 2004;364:1321–1328.
108. Lam AM, Winn HR, Cullen BF, et al. Hyperglycemia and neurological outcome in patients with head injury. *J Neurosurg*. 1991;75:545–551.
109. Rovlias A, Kotsou S. The influence of hyperglycemia on neurological outcome in patients with severe head injury. *Neurosurgery*. 2000;46:335–342.
110. Bauer RB, Tellez H. Dexamethasone as treatment in cerebrovascular

disease, 2: a controlled study in acute cerebral infarction. *Stroke*. 1973;4:547–555.
111. Norris JW. Steroid therapy in acute cerebral infarction. *Arch Neurol*. 1976;33:69–71.
112. Norris JW, Hachinski VC. High dose steroid treatment in cerebral infarction. *BMJ (Clin Res Ed)*. 1986;292:21–23.
113. Poungvarin N. Steroids have no role in stroke therapy. *Stroke*. 2004; 35:229–230.
114. Tellez H, Bauer RB. Dexamethasone as treatment in cerebrovascular disease, 1: a controlled study in intracerebral hemorrhage. *Stroke*. 1973;4:541–546.
115. Poungvarin N, Bhoopat W, Viriyavejakul A, et al. Effects of dexamethasone in primary supratentorial intracerebral hemorrhage. *N Engl J Med*. 1987;316:1229–1233.
116. Slivka AP, Murphy EJ. High-dose methylprednisolone treatment in experimental focal cerebral ischemia. *Exp Neurol*. 2001;167:166–172.
117. de Courten-Myers GM, Kleinholz M, Wagner KR, et al. Efficacious experimental stroke treatment with high-dose methylprednisolone. *Stroke*. 1994;25:487–492.
118. Baird TA, Parsons MW, Phanh T, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke*. 2003;34:2208–2214.
119. Bruno A, Levine SR, Frankel MR, et al. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurology*. 2002; 59:669–674.
120. Leigh R, Zaidat OO, Suri MF, et al. Predictors of hyperacute clinical worsening in ischemic stroke patients receiving thrombolytic therapy. *Stroke*. 2004;35:1903–1907.
121. Alvarez-Sabin J, Molina CA, Montaner J, et al. Effects of admission hyperglycemia on stroke outcome in reperfused tissue plasminogen activator-treated patients. *Stroke*. 2003;34:1235–1241.
122. Schalen W, Messeter K, Nordstrom CH. Cerebral vasoreactivity and the prediction of outcome in severe traumatic brain lesions. *Acta Anaesthesiol Scand*. 1991;35:113–122.
123. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. *J Neurosurg*. 1991;75:731–739.
124. Carmona Suazo JA, Maas AI, van den Brink WA, et al. CO_2 reactivity and brain oxygen pressure monitoring in severe head injury. *Crit Care Med*. 2000;28:3268–3274.
125. Marion DW, Puccio A, Wisniewski SR, et al. Effect of hyperventilation on extracellular concentrations of glutamate, lactate, pyruvate, and local cerebral blood flow in patients with severe traumatic brain injury. *Crit Care Med*. 2002;30:2619–2625.
126. Diringer M. Hyperventilation in head injury: what have we learned in 43 years? *Crit Care Med*. 2002;30:2142–2143.
127. Eisenberg HM, Frankowski RF, Contant CF, et al. High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. *J Neurosurg*. 1988;69:15–23.
128. Schwartz ML, Tator CH, Rowed DW, et al. The University of Toronto head injury treatment study: a prospective, randomized comparison of pentobarbital and mannitol. *Can J Neurol Sci*. 1984;11:434–440.
129. Ward JD, Becker DP, Miller JD, et al. Failure of prophylactic barbiturate coma in the treatment of severe head injury. *J Neurosurg*. 1985;62:383–388.
130. Schalen W, Sonesson B, Messeter K, et al. Clinical outcome and cognitive impairment in patients with severe head injuries treated with barbiturate coma. *Acta Neurochir (Wien)*. 1992;117:153–159.
131. Schwab S, Spranger M, Schwarz S, et al. Barbiturate coma in severe hemispheric stroke: useful or obsolete? *Neurology*. 1997;48:1608–1613.
132. Berger C, Sakowitz OW, Kiening KL, et al. Neurochemical monitoring of glycerol therapy in patients with ischemic brain edema. *Stroke*. 2005;36:e4–e6.
133. Righetti E, Celani MG, Cantisani T, et al. Glycerol for acute stroke. *Cochrane Database Syst Rev*. 2004;(2):CD000096.
134. Sakamaki M, Igarashi H, Nishiyama Y, et al. Effect of glycerol on ischemic cerebral edema assessed by magnetic resonance imaging. *J Neurol Sci*. 2003;209:69–74.
135. Sloviter HA, Shimkin P, Suhara K. Glycerol as a substrate for brain metabolism. *Nature*. 1966;210:1334–1336.
136. Ishikawa M, Sekizuka E, Sato S, et al. Glycerol attenuates the adherence of leukocytes in rat pial venules after transient middle cerebral artery occlusion. *Neurol Res*. 1999;21:785–790.
137. Wolf AL, Levi L, Marmarou A, et al. Effect of THAM upon outcome in severe head injury: a randomized prospective clinical trial. *J Neurosurg*. 1993;78:54–59.
138. de Hooge MN, Verhoeven BH, Rutten WJ, et al. Irreversible ischemia of the hand after peripheral administration of tromethamol (THAM). *Intensive Care Med*. 2003;29:503.
139. Steiner T, Ringleb P, Hacke W. Treatment options for large hemispheric stroke. *Neurology*. 2001;57(5 suppl 2):S61–S68.
140. Wilkinson HA, Rosenfeld SR. Furosemide and mannitol in the treatment of acute experimental intracranial hypertension. *Neurosurgery*. 1983;12:405–410.
141. Roberts PA, Pollay M, Engles C, et al. Effect on intracranial pressure of furosemide combined with varying doses and administration rates of mannitol. *J Neurosurg*. 1987;66:440–446.
142. Thenuwara K, Todd MM, Brian JE Jr. Effect of mannitol and furosemide on plasma osmolality and brain water. *Anesthesiology*. 2002; 96:416–421.
143. Gaab M, Knoblich OE, Schupp J, et al. Effect of furosemide (Lasix) on acute severe experimental cerebral edema. *J Neurol*. 1979;220:185–197.
144. Tornheim PA, McLaurin RL, Sawaya R. Effect of furosemide on experimental traumatic cerebral edema. *Neurosurgery*. 1979;4:48–52.
145. Slavik RS, Rhoney DH. Indomethacin: a review of its cerebral blood flow effects and potential use for controlling intracranial pressure in traumatic brain injury patients. *Neurol Res*. 1999;21:491–499.
146. Busto R, Dietrich WD, Globus MY, et al. Postischemic moderate hypothermia inhibits CA1 hippocampal ischemic neuronal injury. *Neurosci Lett*. 1989;101:299–304.
147. Corbett D, Hamilton M, Colbourne F. Persistent neuroprotection with prolonged postischemic hypothermia in adult rats subjected to transient middle cerebral artery occlusion. *Exp Neurol*. 2000;163:200–206.
148. Huh PW, Belayev L, Zhao W, et al. Comparative neuroprotective efficacy of prolonged moderate intraischemic and postischemic hypothermia in focal cerebral ischemia. *J Neurosurg*. 2000;92:91–99.
149. Koizumi H, Povlishock JT. Posttraumatic hypothermia in the treatment of axonal damage in an animal model of traumatic axonal injury. *J Neurosurg*. 1998;89:303–309.
150. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* 2002;346:549–556.
151. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346:557–563.
152. Holzer M, Bernard SA, Hachimi-Idrissi S, et al. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. *Crit Care Med*. 2005;33:414–418.
153. Georgiadis D, Schwab S. Hypothermia in acute stroke. *Curr Treat Options Neurol*. 2005;7:119–127.
154. Subramaniam S, Hill MD. Massive cerebral infarction. *Neurologist*. 2005;11:150–160.
155. Kammersgaard LP, Jorgensen HS, Rungby JA, et al. Admission body temperature predicts long-term mortality after acute stroke: the Copenhagen Stroke Study. *Stroke*. 2002;33:1759–1762.
156. Castillo J, Davalos A, Marrugat J, et al. Timing for fever-related brain damage in acute ischemic stroke. *Stroke*. 1998;29:2455–2460.
157. De Georgia MA, Krieger DW, Abou-Chebl A, et al. Cooling for Acute Ischemic Brain Damage (COOL AID): a feasibility trial of endovascular cooling. *Neurology*. 2004;63:312–317.
158. Schwab S, Georgiadis D, Berrouschot J, et al. Feasibility and safety of moderate hypothermia after massive hemispheric infarction. *Stroke*. 2001;32:2033–2035.
159. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med*. 2001;344:556–563.
160. Munch EC, Bauhuf C, Horn P, et al. Therapy of malignant intracranial hypertension by controlled lumbar cerebrospinal fluid drainage. *Crit Care Med*. 2001;29:976–981.
161. Gupta R, Connolly ES, Mayer S, et al. Hemicraniectomy for massive middle cerebral artery territory infarction: a systematic review. *Stroke*. 2004;35:539–543.

162. Coplin WM, Cullen NK, Policherla PN, et al. Safety and feasibility of craniectomy with duraplasty as the initial surgical intervention for severe traumatic brain injury. *J Trauma*. 2001;50:1050–1059.
163. Freshman SP, Battistella FD, Matteucci M, et al. Hypertonic saline (7.5%) versus mannitol: a comparison for treatment of acute head injuries. *J Trauma*. 1993;35:344–348.
164. Gemma M, Cozzi S, Tommasino C, et al. 7.5% Hypertonic saline versus 20% mannitol during elective neurosurgical supratentorial procedures. *J Neurosurg Anesthesiol*. 1997;9:329–334.
165. Schwarz S, Schwab S, Bertram M, et al. Effects of hypertonic saline hydroxyethyl starch solution and mannitol in patients with increased intracranial pressure after stroke. *Stroke*. 1998;29:1550–1555.
166. Vialet R, Albanese J, Thomachot L, et al. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. *Crit Care Med*. 2003;31:1683–1687.
167. Battison C, Andrews PJ, Graham C, et al. Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. *Crit Care Med*. 2005;33:196–202.

