

critical care review

Management of Head Trauma*

Paul E. Marik, MD, FCCP; Joseph Varon, MD, FCCP; and Todd Trask, MD

Traumatic brain injury (TBI) is a major cause of disability and death in most Western nations and consumes an estimated \$100 billion annually in the United States alone. In the last 2 decades, the management of TBI has evolved dramatically, as a result of a more thorough understanding of the physiologic events leading to secondary neuronal injury as well as advances in the care of critically ill patients. However, it is likely that many patients with TBI are not treated according to current treatment principles. This article presents an overview of the current management of patients with TBI. (CHEST 2002; 122:699-711)

Key words: critical care; CT scanning; epidural hematoma; head injury; hypertonic saline solution; ICU; intracranial pressure; mannitol; subdural hematoma; trauma

Abbreviations: CBF = cerebral blood flow; CPP = cerebral perfusion pressure; CSF = cerebrospinal fluid; GCS = Glasgow Coma Scale; ICP = intracranial pressure; TBI = traumatic brain injury

The management of traumatic brain injury (TBI) has evolved dramatically in the last 2 decades. This is the result of a more thorough understanding of the physiologic events leading to secondary neuronal injury after TBI, as well as advances in the care of critically ill patients. Despite enormous progress in the understanding of TBI, current opinion suggests that the majority of patients are not treated according to current treatment guidelines.^{1,2} This article presents an overview of the current management of patients with TBI.

EPIDEMIOLOGY

TBI is a leading cause of death and disability in children and adults in their most productive years. It is estimated that there are nearly 1.6 million head injuries every year in the United States, with > 250,000 of these patients being admitted to the hospital.^{3,4} Overall, each year there are approximately 60,000 deaths from TBI and an estimated

70,000 to 90,000 patients are left with permanent neurologic disabilities.^{3,5,6} The financial burden of TBI in terms of both lost productivity and the cost of medical care is estimated to be approximately \$100 billion annually in the United States alone.^{3,5,6} Motor vehicle accidents are the most common cause of closed head injuries and are especially common in teenagers and young adults.⁷ Falls are responsible for the next largest group of injuries and are more common at the extremes of age. Alcohol has been shown to be a contributing factor in approximately 40% of all severe head injuries.⁷

PATHOPHYSIOLOGY

Primary Brain Injury

The pathophysiology of primary brain injury can be divided into focal and diffuse lesions. Focal brain injury is typically associated with blows to the head that typically produce cerebral contusions and hematomas. Focal injuries impact morbidity and mortality based on their location, size, and overall progression. Diffuse axonal injury is caused by inertial forces that are commonly produced by motor vehicle accidents. In clinical practice, diffuse axonal injury and focal brain lesions frequently coexist. The common types of primary head injuries are discussed below:

*From the Department of Critical Care Medicine (Dr. Marik), University of Pittsburgh, Pittsburgh, PA; and the Department of Emergency Services (Dr. Varon) and Neurosurgical ICU (Dr. Trask), The Methodist Hospital, Houston, TX. Manuscript received October 23, 2001; revision accepted January 14, 2002.

Correspondence to: Paul Marik, MD, FCCP, Department of Critical Care Medicine, University of Pittsburgh, 640A Scaife Hall, 3550 Terrace St, Pittsburgh, PA 15261; e-mail: maripe@ccm.upmc.edu

Skull Fractures: Skull fractures may be seen in the cranial vault or skull base, may be linear or stellate, and may be depressed or nondepressed. The presence of a skull fracture implies that a large amount of force was transmitted to the patient's head. A linear vault fracture increases the likelihood of the presence of an intracranial hematoma. Basilar fractures may manifest as hemotympanum, postauricular ecchymosis (Battle sign), periorbital ecchymosis, and possible cranial nerve palsies.

Epidural Hematomas: Epidural hematomas are relatively uncommon, being present in < 1% of all head-injured patients and in < 10% of those who are comatose. Epidural hematomas are located outside the dura but within the skull, and are typically biconvex or lenticular in shape (Fig 1). They are most often located in the temporal or temporoparietal region, and often result from laceration of the middle meningeal artery caused by a fracture. In many cases, but not always, there is loss of consciousness followed by a period of lucency, followed by neuro-

logic deterioration. With prompt evacuation, patients usually have a relatively favorable outcome.

Subdural Hematomas: Subdural hematomas are more common than epidural hematomas, occurring in approximately 30% of severe head injuries. They result most frequently from tearing of a bridging vein between the cerebral cortex and a draining venous sinus. With subdural hematomas, the force of impact is often transmitted to the brain itself. In approximately 80% of subdural hematomas, it is the underlying brain injury that determines the patient's course and outcome. A subdural hematoma will appear on a CT scan as a crescent-shaped blood collection between the brain and the dura (Fig 2). There is frequently an adjacent parenchymal contusion, and if large may cause a midline shift.

Intracerebral Hematomas: Intracranial hemorrhage occurs commonly in association with moderate and severe head injuries and usually produces mass lesions. The majority of lesions occur in the frontal and temporal lobes. During sudden rotations of the

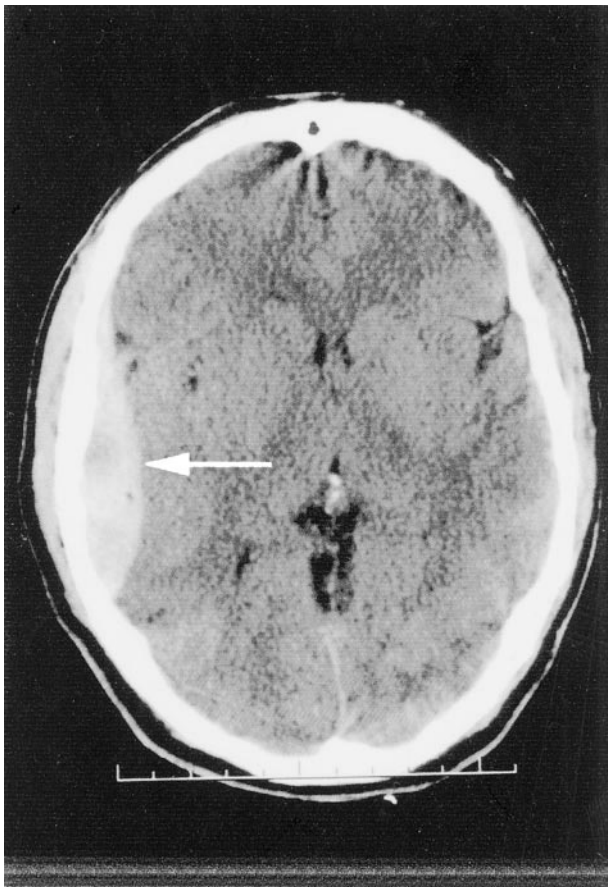


FIGURE 1. CT scan demonstrating a right temporal epidural hematoma (arrow).

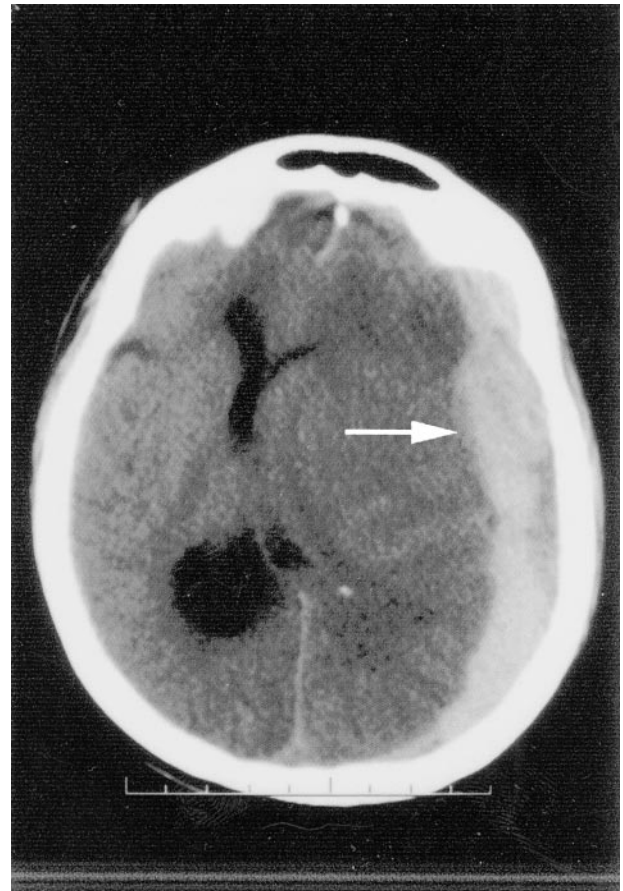


FIGURE 2. CT scan demonstrating a large right subdural hematoma with midline shift (arrow).

head, these regions impact on the rough surface of the underlying skull base, causing so called “gliding contusions.” Blood within the parenchyma of the brain will be seen as a hyperdense areas on the CT scan (Fig 3). Many intraparenchymal hematomas may be delayed, appearing on the CT scan ≥ 24 h after the initial insult.^{8–10} Therefore, clinical deterioration or progressive uncontrolled intracranial hypertension should prompt repeat CT scanning.

Diffuse Axonal Injury: Diffuse axonal injury is caused by shearing forces affecting axons that traverse large areas of the brainstem, leading to dysfunction of the reticular activating system.¹¹ It is believed that axons are not torn at the moment of injury but rather undergo sequential, focal changes that lead to swelling and disconnection over multiple hours after injury.^{12,13} As a consequence of this disconnection, the downstream disconnected fibers degenerate leading to diffuse deafferentation of target sites.^{12–14} Evidence suggests that the traumatic axon injury results from damage to the axolemma,

allowing for calcium influx, triggering local intra-axonal cytoskeletal and mitochondrial damage.^{15,16} In addition, an increase in intra-axonal caspase-3 suggests that apoptosis may play a role in the demise of the axonal appendage.¹⁶ Diffuse axonal injury may cause immediate and prolonged unconsciousness. Affected patients have a high mortality, and if they survive, a high morbidity, often improving only to a persistent vegetative state. Diffuse axonal injury may be identified by diffusion-weighted MRI.¹⁷

Secondary Brain Injury

The primary brain injury is the result of direct mechanical damage that occurs at the time of trauma.¹⁸ Secondary brain injury occurs after the initial trauma and is defined as the damage to neurons due to the systemic physiologic responses to the initial injury.¹⁹ A number of biochemical substances have been postulated to play a role in the propagation of neural injury following TBI. The release of these substances initiates a deleterious cascade of continued cell membrane breakdown and ionic shifts that further harms the injured brain. These substances include the excitatory amino acids glutamate and aspartate, cytokines, and free radicals.^{20,21}

The importance of hypotension and hypoxia as major causes of secondary brain injury have become recognized. Seminal studies published in 1978 and 1982 by Miller and colleagues^{22,23} established that hypotension and hypoxia occurring during the early posttraumatic period were primary determinants of outcome. These observations were confirmed by the Traumatic Coma Data Bank study,²⁴ which demonstrated that prehospital hypotension was an independent predictor of poor outcome. During the first 24 h after head injury, cerebral blood flow (CBF) is less than half of that of normal individuals and may approach the ischemic threshold.^{25–27} Furthermore, CBF in the vicinity of the posttraumatic contusions and subdural hematoma is reduced even further than global CBF.^{28,29} The reduction in CBF following trauma together with the vulnerability of the traumatized brain to ischemia makes hypotension a potentially lethal complication.³⁰ In patients who have died from head injury, posttraumatic ischemic lesions have been reported in up to 80% of patients at autopsy.³⁰

Role of Intracranial Pressure and Cerebral Perfusion Pressure

The cranial vault is a fixed space (closed box) that contains brain tissue, cerebrospinal fluid (CSF), extracellular fluid, and blood. These tissues are largely incompressible. After head trauma, the vol-

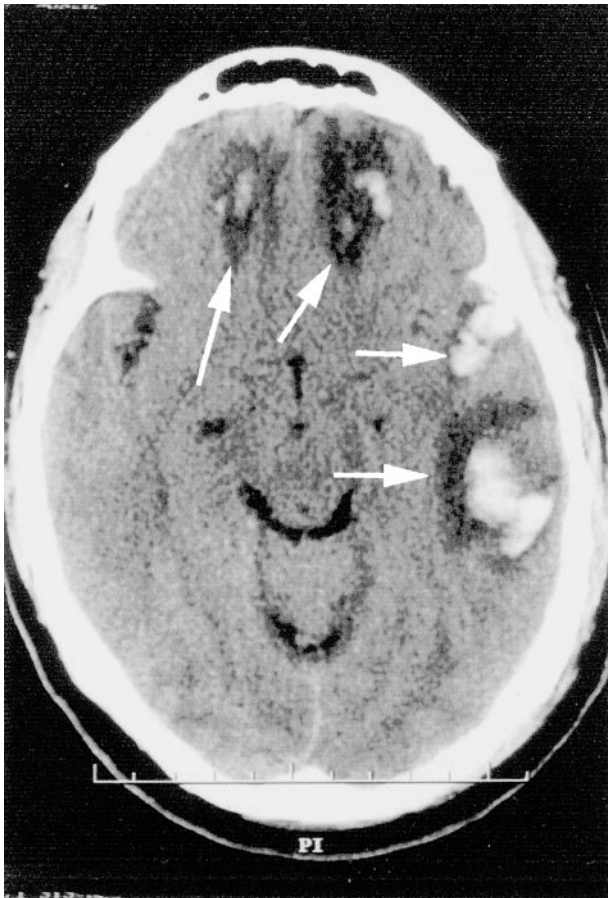


FIGURE 3. CT scan demonstrating multiple hemorrhagic contusions in the bifrontal region, and left temporal and parietal region with surrounding edema (arrows).

ume within the intracranial compartment increases due to blood and tissue edema. Initially, small increases in intracranial volume can be accommodated by the movement of blood and CSF out of the vault. However, with further expansion of its contents, intracranial pressure (ICP) increases sharply. Intracranial hypertension itself is not harmful unless it increases to the point that the cerebral perfusion pressure falls below a critical value. Cerebral ischemia leads to neuronal injury and cerebral edema, which further increases ICP, progressing to irreversible neurologic damage. Raised ICP may also result in pressure gradients that lead to displacement and herniation of brain from areas of higher to areas of lower pressure.

CBF in humans averages approximately 50 mL/100 g of brain tissue per minute. Irreversible neuronal damage occurs if CBF drops < 18 mL/100 g of brain tissue per minute for a prolonged period of time.³¹ CBF is equal to the cerebral perfusion pressure (CPP), which is defined as the difference between the mean arterial BP and the ICP, divided by the cerebral vascular resistance. Because the CBF is difficult to measure clinically, the CPP is used as a guide to assessing the adequacy of cerebral perfusion. The normal ICP is between 0 mm Hg and 10 mm Hg. Increased ICP has been defined as a pressure > 20 mm Hg persisting for ≥ 5 min.^{32,33} Normal human values for CPP are between 70 mm Hg and 100 mm Hg. However, as a result of autoregulation, CBF remains relatively constant when CPP is between 40 mm Hg and 140 mm Hg (Fig 4).³⁴ This phenomenon is due to changes in cerebrovascular resistance probably brought about by a local effect of hydrogen ions on cerebral vessels.³⁴ Thus, low flow states leading to hypoxia or hypercapnia result in an acidosis that causes cerebral vasodilation and increased blood flow. Chronic

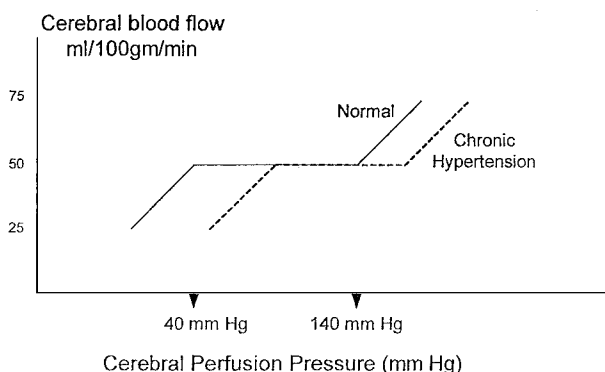


FIGURE 4. Cerebral autoregulation in normal subjects and patients with chronic hypertension.

hypertension shifts the autoregulation curve to the right, making hypertensive patients susceptible to ischemia at a CPP normally well tolerated by healthy subjects (Fig 4). Cerebrovascular autoregulatory mechanisms are disrupted following head trauma, with CBF dependent largely on the CPP.

While earlier studies and recommendations centered on the importance of the ICP *per se* in the head-injured patient,³⁵ current guidelines emphasize the importance of the CPP.³⁶⁻³⁸ The guidelines proposed by the Brain Trauma Foundation recommend that the CPP should be maintained at a minimum of 70 mm Hg in the brain-injured patient, although the exact target number and methodology for achieving that target remains controversial.¹ A higher threshold may be required in patients with chronic hypertension.

CLINICAL EVALUATION OF THE HEAD-INJURED PATIENT

Primary Trauma Survey

The first priority in any injured patient is to stabilize the cervical spine, establish an adequate airway (A, airway), ensure adequate ventilation (B, breathing), and gain venous access to initiate volume resuscitation (C, circulation).³⁹ These steps are crucial in the head-injured patient to avoid both hypoxia and hypotension, the most important causes of secondary brain insults. The primary survey should conclude with a determination of the level of consciousness and an examination of the pupils (D, disability).

Secondary Trauma Survey

A secondary survey is completed once the patient is relatively stable and includes a complete neurologic examination.³⁹ The severity of the head injury is classified clinically by the Glasgow Coma Scale (GCS)⁴⁰ [Table 1]. A GCS score of 13 to 15 is classified as a mild head injury, as score of 9 to 12 as moderate, and a score of ≤ 8 as severe. Caution should be used in evaluating patients suspected of intoxication with alcohol or other drugs. All too often, an obtunded state in such patients is attributed to the abused substance, when in fact the intoxication may be masking an expanding intracranial mass lesion.

INITIAL MANAGEMENT

The primary brain injuries sustained at the time of trauma cannot be reversed. In order to minimize

Table 1—GSC

Signs	Score
Eye opening	
Spontaneous	4
To verbal command	3
To pain	2
No response	1
Best motor response	
Obeys verbal commands	6
Localizes to pain	5
Withdraws to pain	4
Flexion response to pain	3
Extension response to pain	2
No response	1
Best verbal response	
Orientated	5
Confused	4
Inappropriate words	3
Nonspecific sounds	2
No response	1

secondary brain damage, the initial management of any patient with TBI is to prevent hypoxia, maintain an adequate BP (*ie*, CPP), and to recognize and treat surgically correctable intracranial lesions. In addition, other concomitant injuries should be recognized and stabilized.

Prehospital Phase

The prehospital phase is perhaps the most important interval in determining the ultimate outcome after TBI. The initial goals are to maintain a patent airway, begin fluid resuscitation, immobilize the cervical and thoracolumbar spine, and assess the level of consciousness, followed by the expeditious transport to a trauma center with neurologic services.

Approximately 50% of TBI patients are reported to be hypoxic in the field; this finding is associated with an increased mortality.^{41–43} A retrospective case control study⁴⁴ suggested that prehospital intubation was associated with a significant reduction in mortality of patients with TBI. Early orotracheal intubation is therefore recommended in patients with a GCS score ≤ 8 . Intubation can usually be accomplished without sedation and chemical paralysis. Paralytic agents should only be used by emergency personnel who are skilled in endotracheal intubation, who have been adequately trained and certified, and who are able to perform a surgical airway.⁴⁵ Sedation and neuromuscular blockade can be useful in optimizing transport of the head-injured patients; however, both treatments interfere with the neurologic examination and influence the initial evaluation and management of the neurotrauma patient.⁴⁶

Patients with a systolic BP of < 110 mm Hg

require fluid resuscitation. While lactated Ringer's solution is generally recommended,^{1,39} small volume resuscitation (250 mL) with hypertonic saline solution appears very promising in this situation.^{47,48} In patients with penetrating truncal trauma, Bickell et al⁴⁹ reported that volume resuscitation initiated only after arrival at the hospital was associated with an improvement in survival compared to immediate prehospital resuscitation. This approach to fluid resuscitation is not applicable to hypotensive patients with TBI who are usually victims of blunt trauma. Delayed volume resuscitation in patients with head injuries is likely to increase the extent of secondary brain injuries.

Early Hospital Management

Patients who have not been intubated in the field and have a GCS score ≤ 8 or are unable to protect their airway should be intubated early. Precautions in intubation need to be taken in the patient with an uncleared cervical spine, because the incidence of concomitant spine injury in head-injury patients ranges from 6 to 8%.^{50,51} Rapid-sequence induction anesthesia is recommended to avoid the increases in ICP that may occur with airway stimulation associated with laryngoscopy and intubation. Hypnotic agents that reduce vascular tone should be avoided. Etomidate, 0.2 to 0.4 mg/kg, a rapidly acting hypnotic agent with a short duration of action and minimal hemodynamic effects, is the preferred agent.^{52–54} Rocuronium is a short-acting, nondepolarizing muscle relaxant that is devoid of significant hemodynamic effects and does not increase ICP.^{55,56} Rocuronium is considered the drug of choice for rapid-sequence induction in many trauma facilities.^{55–57} Etomidate has no analgesic properties and does not blunt the sympathetic response to endotracheal intubation.⁵² Esmolol, 20 to 40 mg, or fentanyl, 50 to 100 μ g, are therefore suggested in combination with etomidate.⁵⁸

Once the patient is intubated, the patient should be placed on 100% oxygen, with the inspired fraction of oxygen only titrated down once the patient has been transferred to the ICUs. Aggressive hyperventilation (PaCO₂ of 25 mm Hg) has traditionally been considered a cornerstone in the management of TBI because it causes a rapid reduction in ICP. However, hyperventilation reduces ICP by causing cerebral vasoconstriction with a subsequent reduction in CBF. Skippen and colleagues,²⁷ using xenon-enhanced CT and CBF studies, demonstrated a 2.5-fold increase in the number of regions of brain ischemia in children with TBI who were hyperventilated. In 1991, Muizelaar and colleagues⁵⁹ published the results of a prospective randomized

clinical study in which they demonstrated that hyperventilation after head injury was associated with a significantly worse neurologic outcome when compared to patients who were kept normocapnic. Based on this data, long-term hyperventilation is no longer recommended.^{1,60} Initial target PCO₂ should be 35 to 40 mm Hg.^{1,60} Short-term hyperventilation, however, may have a role in reducing ICP in patients who are rapidly deteriorating before other measures can be instituted.⁶¹

After the establishment of an airway and ventilation, the restoration of BP and normal circulating volume is of utmost importance. According to the Brain Trauma Foundation guidelines for the management of severe head injury, a mean arterial pressure of ≥ 90 mm Hg should be targeted; this was chosen based on attaining cerebral perfusion pressures > 70 mm Hg.¹ These guidelines use 20 mm Hg as the threshold for intracranial hypertension.¹

Previous guidelines⁶² recommended moderate-to-severe dehydration in the treatment of TBI on the basis that this would decrease cerebral edema. However, experimental studies^{63,64} demonstrated that cerebral water content and cerebral edema were not altered by hydration status. Furthermore, this approach failed to recognize the importance of the CPP in preventing secondary brain ischemia. Volume resuscitation with restoration of a normal intravascular volume is therefore essential in all patients with acute cerebral insults.

Currently, lactated Ringer's solution or normal saline solution are recommended for volume resuscitation in head-injured patients.³⁹ Hypotonic solutions should not be administered, as these will increase cerebral edema.^{65,66} Hypertonic saline solution has a number of beneficial effects in head-injured patients, including the expansion of intravascular volume, the extraction of water from the intracellular space, a decrease in the ICP, and increase in cardiac contractility.⁶⁷⁻⁷⁰ Despite serum sodium concentrations as high as 170 mEq/L, hypertonic saline solution is well tolerated in head-injured patients.⁷¹⁻⁷³ Wade and colleagues⁷⁴ performed a cohort analysis of individual patient data from prospective, randomized, double-blind trials to evaluate the effect on survival after initial treatment with hypertonic saline solution in patients with TBI. Using logistic regression analysis, these authors⁷⁴ concluded that hypertonic saline solution significantly improved survival (odds ratio, 2.12; $p = 0.048$). The indications as well as the optimal timing, concentration, and volume of hypertonic saline solution have yet to be determined by prospective clinical studies. However, hypertonic saline solution appears to have promise in the initial resuscitation of head-injured patients. The prophyl-

actic use of mannitol is not recommended due to its volume-depleting diuretic effect.⁷⁵ Mannitol should only be used initially in patients demonstrating signs of transtentorial herniation.⁶¹

Diagnostic Studies: Historically, imaging of the head-injured patient relied on skull radiographs.⁷⁶ With the widespread availability and advancement of head CT scanning, the CT scan has become the diagnostic procedure of choice when evaluating acute head trauma. CT scanning is recommended in patients considered to be at high risk for intracranial injury. This includes all patients with a GCS score < 15 and patients with focal neurologic deficits or clinical signs of basilar or depressed skull fractures. While it is generally recommended to scan patients with a GCS score of 15 and a history of loss of consciousness or amnesia, not all investigators believe this to be a cost-effective approach.⁷⁷⁻⁷⁹ A CT scan without contrast will enable visualization of most major types of injuries.

Abnormalities noted on CT imaging associated with intracranial hypertension include subdural hematomas, subarachnoid hemorrhage, intracerebral hematomas, cerebral infarcts, diffuse brain injury, and generalized cerebral edema often with shift of midline structures, effacement of cortical sulci, and ventricular compression.⁸⁰⁻⁸² However, it should be emphasized that a normal initial CT scan does not exclude significant intracranial hypertension.^{17,82}

Neurosurgical Consultation: Once the patient's condition is stabilized, neurosurgical consultation is required. The critical factors in deciding whether to proceed directly with surgical evacuation of an intracranial hematoma are the patient's neurologic status and the CT scan findings. In general, all acute traumatic extra-axial hematoma ≥ 1 cm in thickness warrant evacuation; a subdural or epidural hematoma > 5 mm in thickness with an equivalent midline shift in a comatose patient (GCS score ≤ 8) should also be evacuated urgently. Surgical evacuation has been recommended in patients with intracerebral hematomas > 20 mL with mass effect.^{83,84} Surgical repair is also required in patients with depressed, open, and compound skull fractures.

Disposition: Head-injured patients with no loss of consciousness, no amnesia, no palpable fractures, and a GCS score of 15 can be discharged home to a reliable caretaker without brain imaging. Written instructions on how to evaluate the patient at home should be given. The patient should undergo follow-up with his primary care physician, with instructions to return to the emergency department if there

are any signs indicating increased ICP, such as change in mental status.

Patients with loss of consciousness, amnesia, or a GCS score of 13 to 14 must undergo an immediate head CT. If this noncontrast study finding is negative, the patient can be discharged with instructions as above. If there is a focal neurologic examination, GCS score < 13, or an intracranial lesion on head CT, the patient should be admitted to an ICU or neurologic observation unit for continuing care.

Continuing Management in the ICU

Once the patient is stabilized and has been transferred to the ICU, the establishment of physiologic monitoring facilitates and directs the further management of these patients. Although no randomized controlled studies have been performed demonstrating that ICP monitoring improves outcome, ICP monitoring has become an integral part of the management of patients with severe head injuries in virtually all trauma centers in the United States. The improved outcome of patients with severe head injuries in the United States has been ascribed to intensive management protocols that include ICP monitoring.⁸⁵⁻⁸⁷ Furthermore, several studies have shown that under conditions of aggressive ICP management, the probability of a good outcome is inversely proportional to the maximum ICP and the percentage of the time spent at levels of > 20 mm Hg.⁸⁸ ICP monitoring is therefore recommended in patients with a GCS score < 8, since intracranial hypertension in this population is > 60%.⁸² Currently, available methods for ICP monitoring include extradural, subdural, intraparenchymal, and intraventricular catheters.^{89,90} Intraventricular catheters are preferred when possible, as these allow for continuous measurement of ICP and for drainage of CSF to control raised ICP.⁹¹ The role of continuous monitoring of jugular venous oxygen saturation in head injured patients is unclear.^{92,93}

Patients should undergo aggressive fluid resuscitation to maintain the mean arterial BP > 90 mm Hg. Volume replacement with Ringer's lactate or normal saline solution is suggested. The central venous pressure should not be used as a guide to fluid replacement, as there is no correlation between central venous pressure and intravascular volume.⁹⁴⁻⁹⁷ A volumetric pulmonary artery catheter is recommended in patients who respond poorly to volume expansion, demonstrate hemodynamic instability, or have underlying cardiovascular disease.⁹⁸ The role of vasopressor agents in TBI is controversial. While the data suggests that a decline in BP should be avoided in the head-injured patient, even when the baseline BP is high, induced hypertension

may either increase or decrease ICP depending on the ability of the cerebral circulation to autoregulate.⁹⁹ Furthermore, because of their potential vasoconstrictory effect on intracerebral vessels, vasopressors might impair local CBF, despite adequate CPP elevation. Induced hypertension with vasopressor agents should, therefore, be used with extreme caution and only with invasive hemodynamic monitoring. Dopamine is the preferred pressor, as experimental data have shown this agent to increase CBF within and around the injured brain without increasing ICP or cerebral edema.¹⁰⁰ Phenylephrine, however, may increase ICP and decrease cardiac output.¹⁰¹ A potentially promising approach to increasing CBF in head-injured patients is the use of cerebral vasodilators, such as L-arginine.^{101,102}

Colloid solutions do not reduce ICP or cerebral water content.^{103,104} This is because cerebral capillaries have extremely tight intercellular junctions and few microvesicles and, as such, are impermeable to most ions. It is the osmolality, rather than the plasma oncotic pressure, that is the major determinant of water movement between the vascular and the extravascular compartments of those areas where the blood-brain barrier is intact. In patients with leaky capillaries, albumin has been demonstrated to increase interstitial fluid volume.¹⁰⁵ Albumin administration may therefore leak into the interstitium in areas where the blood-brain barrier is compromised and increase ICP. Furthermore, as albumin has been associated with an increased mortality in critically ill patients, this solution cannot be recommended.^{103,106}

The ventilator settings should be adjusted to maintain the PaCO₂ between 35 mm Hg and 40 mm Hg and the PaO₂ > 70 mm Hg. While it has been suggested that a high PaO₂ may improve brain tissue oxygenation,¹⁰⁷ this goes against our understanding of human physiology, as tissue oxygen unloading is dependant primarily on the hemoglobin concentration, the position of the oxygen dissociation curve (partial pressure at which hemoglobin is 50% saturated), and the hemoglobin saturation. The dissolved oxygen fraction makes an insignificant contribution to oxygen transport. A high fraction of inspired oxygen may, however, promote the formation of reactive oxygen species and increase lipid peroxidation. While it has been suggested that positive end-expiratory pressure and modes of ventilation that increase mean intrathoracic pressure be avoided in patients with elevated ICP,^{108,109} studies^{110,111} do not support this contention. However, in accord with current guidelines,¹¹²⁻¹¹⁴ the lowest level of positive end-expiratory pressure that maintains adequate oxygenation and prevents end-expiratory alveolar collapse should be used. Continuous pulse oximetry is recommended, with the arterial saturation main-

tained > 94%. Although endotracheal suctioning does cause a transient rise in ICP, it does not produce cerebral ischemia and is required to prevent atelectasis.¹¹⁵

Even though head-injured patients may be comatose, they require analgesia and sedation as they still respond to painful and noxious stimuli, often with an increase in ICP and BP. Narcotics (morphine or fentanyl) should be considered first-line therapy since they provide both analgesia and depression of airway reflexes, which is required in the intubated patient. Fentanyl has the advantage of having minimal hemodynamic effects. Propofol is the hypnotic agent of choice in patients with an acute neurologic insult, as it is easily titratable and rapidly reversible once discontinued. These properties permit predictable sedation yet allow for periodic neurologic evaluation of the patient.^{116,117} Propofol has additional properties that may be beneficial in the head-injured patient, including a decrease in cerebral metabolic rate, potentiation of γ -aminobutyrate A (GABAergic) inhibition, and inhibition of methyl-D-aspartate glutamate receptors and voltage-dependent calcium channels.¹¹⁸ Propofol is also a potent antioxidant and inhibitor of lipid peroxidation.¹¹⁹

Paralytic agents have traditionally been used in patients receiving mechanical ventilation. There are, however, no data to support this practice. Indeed, in patients with TBI, paralytic agents have been demonstrated to increase the risk of pneumonia.¹²⁰ In addition, paralytic agents are associated with significant neuromuscular complications.¹²¹ The use of adequate doses of propofol together with fentanyl may obviate the need for paralysis. The routine paralysis of patients with TBI can no longer be recommended.¹²² However, as it may take up to 30 min to carefully load a patient with sufficient sedation and analgesia to control airway reflexes in response to mechanical ventilation, early paralysis may be helpful in preventing ventilator dyssynchrony with gagging and coughing that produce ICP surges. However, once the patient has been stabilized and adequate sedation and analgesia achieved, the neuromuscular blocker should be stopped.

Other general principles in the management of patients with head injury include lowering the body temperature of patients with fever and prevention of jugular venous outflow obstruction (keeping the patient's head midline, avoiding extrinsic compression of the jugular veins by hematomas, masses). While some studies^{37,123} have suggested that CPP is optimal when patients are nursed flat, others¹²⁴ have demonstrated that head elevation to 30° lowers ICP without decreasing CPP or CBF. However, elevation of the head of the bed (to 30°) has been demonstrated to reduce the risk of ventilator-associated

pneumonia.¹²⁵ Erosive GI lesions are common after severe head injury; therefore, routine stress ulcer prophylaxis is required.¹²⁶ Seizure prophylaxis is currently recommended for 7 days following the injury in patients with severe TBI.¹²⁷ The agent most commonly recommended is phenytoin, with a loading dose of 18 mg/kg and usual maintenance dose of 5 mg/kg/d following serum drug levels to a goal of 10 to 20 mg/L.

In patients with TBI, corticosteroids have been shown to lack efficacy and carry the risks of potential side effects (*ie*, hyperglycemia, increased risk of infections), and their use must be avoided.^{128–130} Experimental and initial clinical data suggested that moderate hypothermia (33°C) for 24 h after severe head injury may improve outcome.^{131–133} However, a recently completed, randomized, placebo-controlled, multicenter study¹³⁴ demonstrated that hypothermia initiated within 8 h after injury was ineffective in improving outcomes in patients with severe brain injury. The lack of efficacy of induced hypothermia may be related to the use of neuromuscular blockers (to prevent shivering) in the hypothermic group. However, the active warming of patients who are hypothermic on hospital admission may be detrimental, and is therefore not recommended.¹³⁴

Management of Established Intracranial Hypertension: If the ICP remains > 20 mm Hg, despite adequate sedation and elevation of the head of the bed (to 30°), additional measures are required to lower the ICP.¹³⁵ When a ventricular catheter is being used for ICP monitoring, CSF drainage should be used for ICP elevations.¹³⁶ If CSF drainage is ineffective, a hyperosmotic agent such as mannitol should be used next.^{136,137} The dose used is 0.25 to 0.5g/kg administered every 2 to 6 h to increase the serum osmolarity to 310 to 320 mOsm/kg H₂O.¹³⁸ Mannitol acts acutely by expanding intravascular volume and decreasing blood viscosity, thereby increasing CBF.^{139,140} The osmotic movement of fluid out of the cellular compartment is followed by a diuresis that is delayed for 15 to 30 min while gradients are established between plasma and cells.¹⁴¹ The osmotic diuresis following mannitol lasts between 90 min and 6 h.^{142,143} The prolonged administration of mannitol may lead to intravascular dehydration, hypotension, and prerenal azotemia.¹⁴⁴ The benefit of mannitol in head-injured patients has yet to be determined, and remarkably only one placebo-controlled study has been reported to date.¹⁴⁵ In this study, which compared the prehospital administration of mannitol against placebo, mannitol was associated with an increased relative risk for death (1.59; 95% confidence interval, 0.44 to 5.79). Mannitol, in common with other osmotically

active agents, is known to cause “opening” of the blood brain barrier, meaning that both mannitol and other small molecules may pass into the brain.^{146,147} This effect becomes harmful after many doses have been administered because mannitol may accumulate in the brain, causing a reverse osmotic shift and raising brain osmolarity, thus theoretically exacerbating ICP. The accumulation of mannitol in the brain may be most marked when mannitol is in the circulation for long periods, as occurs with continuous infusion administration. Thus it has been recommended that mannitol should be administered as repeated boluses rather than as a continuous infusion.¹⁴⁸ Hypertonic saline solution has been demonstrated to decrease ICP and increase CPP in patients with refractory intracranial hypertension, and should be considered an alternative to treatment with mannitol.^{71–73} High-dose barbiturate coma may be used as last resorts in patients with persistently elevated ICP; however, this therapy has not been proven to change neurologic outcome.¹⁴⁹ Indeed, in the University of Toronto Head Injury Study,¹⁵⁰ those patients with an elevated ICP and no intracranial hematoma who were treated with pentobarbital had a 77% mortality rate, compared to a 41% mortality for those patients treated initially with mannitol. Finally, there is a resurgence of interest in decompressive craniectomy for intractable ICP elevations, and craniectomy is an option to consider in selected cases.

Experimental Drug Therapies

There have been many attempts to reduce brain damage after severe head trauma using pharmacologic therapy. Free-radical scavengers, aminosteroids, calcium antagonists, glutamate antagonists, ion-channel blockers, and adenosine agonists have been evaluated in patients with TBI.¹⁵¹ To date, none of these agents have been demonstrated to be beneficial.¹⁵¹

Other Management Issues in the ICU

Electrolyte Derangements: Hyponatremia lowers the seizure threshold and can exacerbate cerebral edema. Hyponatremia is relatively common after head injury. The etiology of the hyponatremia is complex, with both cerebral salt wasting and the syndrome of inappropriate antidiuretic hormone being implicated.¹⁵² Urine electrolytes and osmolarity are helpful in the evaluation of hyponatremia. The distinction between these two syndromes is critical, as the former is treated with volume replacement while the latter is treated by fluid restriction.¹⁵²

Magnesium levels should be closely followed in

patients with TBI. Hypomagnesemia lowers the seizure threshold, and in experimental brain injury hinders recovery. Postinjury administration of magnesium has been shown to improve neurologic outcome in an experimental model of head injury.^{153,154}

Nutritional Support: TBI results in a generalized hypermetabolic and catabolic state. Early enteral nutrition maintains the integrity of the GI mucosa, has beneficial effects on immunocompetence, and attenuates the metabolic response to stress. A meta-analysis¹⁵⁵ that compared early (within 36 h) with delayed initiation of enteral nutrition demonstrated a 55% reduction in the risk of infections in head-injured patients who received early enteral nutrition. Parenteral nutrition should be avoided, as it is associated with profound metabolic, immunologic, and GI changes and an increase in mortality.¹⁵⁶ Although gastric emptying is frequently impaired following TBI,^{157–159} this route of feeding is generally well tolerated in head-injured patients.¹⁶⁰ We recommend placement of a standard 14-gauge to 16-gauge orogastric tube followed by the immediate initiation of an immune-enhancing nutritional formula at a rate of 20 mL/h, increased at 6-h intervals by 20 mL until the nutritional goal is achieved. Additionally, we recommend erythromycin, 250 mg IV q8h, as a promotility agent at the time of initiation of tube feedings.¹⁶¹ The gastric residual volume should be checked every 6 h; a small bowel feeding tube should be placed in patients with a residual volume > 150 mL.¹⁵⁵

Deep Venous Thrombosis Prophylaxis: Deep vein thrombosis and pulmonary embolism are frequent complications in head-injured patients. The incidence of deep-venous thrombosis in patients with major head injuries who are not receiving thromboprophylaxis is reported to be as high as 54%.¹⁶² Low-dose heparin and low-molecular-weight heparin are considered to be contraindicated in patients with head injuries.^{163,164} Sequential compression devices should be used (if possible) in all patients with TBI. However, the optimal prophylactic regimen and the indications for prophylactic vena caval filter placement in these patients remains unclear.^{165–168}

CONCLUSION

The management of patients with severe head injury is complex and requires a coordinated, comprehensive, and multidisciplinary approach. Central to the management of the head-injured patient is the prevention of secondary neuronal injury by avoiding hypotension and hypoxemia. Considering the enor-

mous costs to society, we need to invest greater resources in the prevention of this pandemic.

REFERENCES

- 1 Bullock R, Chesnut R, Clifton G, et al. Guidelines for the management of severe head injury. New York, NY: Brain Trauma Foundation, 1996
- 2 Chesnut RM. Avoidance of hypotension: conditio sine qua non of successful severe head-injury management. *J Trauma* 1997; 42:S4–S9
- 3 Thurman D, Guerrero J. Trends in hospitalization associated with traumatic brain injury. *JAMA* 1999; 282:954–957
- 4 Guerrero JL, Thurman DJ, Sniezek JE. Emergency department visits associated with traumatic brain injury, United States, 1995–1996. *Brain Injury* 2000; 14:181–186
- 5 Karus JF. Epidemiology of head injury. In: Cooper PR, ed. *Head injury*. Baltimore, MD: Williams and Wilkins, 1993; 1–25
- 6 Sosin DM, Sniezek JE, Waxweiler RJ. Trends in death associated with traumatic brain injury, 1979 through 1992: success and failure. *JAMA* 1995; 273:1778–1780
- 7 Foulkes MA, Eisenberg HM, Jane JA, et al. The Traumatic Coma Data Bank: design, methods and baseline characteristics. *J Neurosurg* 1991; 75:S8–S13
- 8 Soloniuk D, Pitts LH, Lovely M, et al. Traumatic intracerebral hematomas: timing of appearance and indications for operative removal. *J Trauma* 1986; 26:787–794
- 9 Fukamachi A, Kohno K, Nagaseki Y, et al. The incidence of delayed traumatic intracerebral hematoma with extradural hemorrhages. *J Trauma* 1985; 25:145–149
- 10 Tabori U, Kornecki A, Sofer S, et al. Repeat computed tomographic scan within 24–48 hours of admission in children with moderate and severe head trauma. *Crit Care Med* 2000; 28:840–844
- 11 Smith DH, Nonaka M, Miller R, et al. Immediate coma following inertial brain injury dependent on axonal damage in the brainstem. *J Neurosurg* 2000; 93:315–322
- 12 Povlishock JT, Erb DE, Astruc J. Reactive axonal change, deafferentation, and neuroplasticity. *J Neurotrauma* 1992; 9:S189–S200
- 13 Pettus EH, Christman C, Giebel ML. Traumatically induced altered membrane permeability: Its relationship to traumatically induced reactive axonal change. *J Neurotrauma* 1994; 11:507–522
- 14 Xiao-sheng H, Sheng-Yu Y, Xiang Z, et al. Diffuse axonal injury due to lateral head rotation in a rat model. *J Neurosurg* 2000; 93:626–633
- 15 Buki A, Povlishock JT. Evidence for calpain-mediated spectrin proteolysis in the pathogenesis of traumatically induced axonal injury. *J Neuropathol Exp Neurol* 1999; 58:365–375
- 16 Buki A, Okonkwo DO, Wang KKW, et al. Cytochrome c releases and caspase activation in traumatic axonal injury. *J Neurosci* 2000; 20:2825–2834
- 17 Liu AY, Maldjian JA, Bagley LJ, et al. Traumatic brain injury: diffusion-weighted MR imaging findings. *AJNR Am J Neuroradiol* 1999; 20:1636–1641
- 18 Bruce DA, Raphaely RC, Goldberg AI, et al. Pathophysiology, treatment and outcome following severe head injury in children. *Childs Brain* 1979; 5:174–191
- 19 Haun S. Theories of brain resuscitation. In: Rogers MC, ed. *Textbook of pediatric intensive care*. Baltimore, MD: Williams and Wilkins, 1992; 698–732
- 20 Gourin CG, Shackford SR. Production of tumor necrosis factor- α and interleukin-1 β by human cerebral microvascular endothelium after percussive trauma. *J Trauma* 1997; 42:1101–1107
- 21 Shohami E, Gallily R, Mechoulam R, et al. Cytokine production in the brain following closed head injury: dexanabinol (HU-211) is a novel TNF- α inhibitor and an effective neuroprotectant. *J Neuroimmunol* 1997; 72:169–177
- 22 Miller JD, Sweet RC, Narayan R. Early insults to the injured brain. *JAMA* 1978; 240:439–442
- 23 Miller JD, Becker DP. Secondary insults to the injured brain. *J R Coll Surg Edinb* 1982; 27:292–298
- 24 Chesnut RM, Marshall LF, Klauber MR. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma* 1993; 34:216–222
- 25 Marion DW, Darby J, Yonas H. Acute regional cerebral blood flow changes caused by severe head injuries. *J Neurosurg* 1991; 74:407–414
- 26 Muizelaar JP, Ward JD, Marmarou A, et al. Cerebral blood flow and metabolism in severely head-injured children: part 2. autoregulation. *J Neurosurg* 1989; 71:72–76
- 27 Skippen P, Seear M, Poskitt K, et al. Effect of hyperventilation on regional cerebral blood flow in head-injured children. *Crit Care Med* 1997; 25:1402–1409
- 28 McLaughlin MR, Marion DW. Cerebral blood flow and vasoresponsivity within and around cerebral contusions. *J Neurosurg* 1996; 85:871–876
- 29 Salvant JB Jr, Muizelaar JP. Changes in cerebral blood flow and metabolism related to the presence of subdural hematoma. *Neurosurgery* 1993; 33:387–393
- 30 Graham DI, Ford I, Adams JH. Ischemic brain damage is still common in fatal non-missile head injury. *J Neurol Neurosurg Psychiatry* 1998; 52:346–350
- 31 Heiss WD, Rosner G. Functional recovery of cortical neurons as related to the degree and duration of ischemia. *Ann Neurol* 1983; 14:194–201
- 32 Miller JD, Butterworth JF, Gudeman SK, et al. Further experience in the management of severe head injury. *J Neurosurg* 1981; 54:289–299
- 33 Bullock MR, Chesnut RM, Clifton GL, et al. Intracranial pressure treatment threshold. *J Neurotrauma* 2000; 17:493–495
- 34 Kelly BJ, Luce JM. Current concepts in cerebral protection. *Chest* 1993; 103:1246–1254
- 35 Miller JD, Becker DP, Ward JD, et al. Significance of intracranial hypertension in severe head injury. *J Neurosurg* 1977; 47:503–516
- 36 Rosner MJ, Rosner SD, Johnson AH. Cerebral perfusion pressure: management protocol and clinical results. *Journal of Neurosurgery* 1995; 83:949–962
- 37 Rosner MJ, Daughton S. Cerebral perfusion pressure management in head injury. *J Trauma* 1990; 30:933–941
- 38 Guidelines for cerebral perfusion pressure. *J Neurotrauma* 2000; 17:507–511
- 39 Initial assessment and management. *Advanced trauma life support for doctors: student course manual*. Chicago, IL: American College of Surgeons, 1997; 21–46
- 40 Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet* 1974; 2:81–84
- 41 Silverston P. Pulse oximetry at the roadside: a study of pulse oximetry in immediate care. *BMJ* 1989; 298:711–713
- 42 Cooke RS, McNicholl BP, Byrnes DP. Early management of severe head injury in Northern Ireland. *Injury* 1995; 26:395–397
- 43 Stocchetti N, Furlan A, Volta F. Hypoxemia and arterial hypotension at the accident scene in head injury. *J Trauma* 1996; 40:764–767
- 44 Wittchell RJ, Hoyt DB. Endotracheal intubation in the field

- improves survival in patients with severe head injury. *Arch Surg* 1977; 132:592–597
- 45 Airway and ventilatory management. *Advanced trauma life support for doctors: student course manual*. Chicago, IL: American College of Surgeons, 1997; 59–85
 - 46 Marion DW, Carlier PM. Problems with initial Glasgow Coma Scale assessment caused by prehospital treatment of patients with head injuries: results of a national survey. *J Trauma* 1994; 36:89–95
 - 47 Vassar MJ, Perry CA, Gannaway WL, et al. 7.5% sodium chloride/dextran for resuscitation of trauma patients undergoing helicopter transport. *Arch Surg* 1991; 126:1065–1072
 - 48 Simma B, Burger R, Falk M, et al. A prospective, randomized, and controlled study of fluid management in children with severe head injury: lactated Ringer's solution versus hypertonic saline. *Crit Care Med* 1998; 26:1265–1270
 - 49 Bickell WH, Wall MJ, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994; 331:1105–1109
 - 50 Hills MW, Deane SA. Head injury and facial injury: is there an increased risk of cervical spine injury? *J Trauma* 1993; 34:549–553
 - 51 Michael DB, Guyot DR, Darmody WR. Coincidence of head and cervical spine injury. *J Neurotrauma* 1989; 6:177–189
 - 52 Bergen JM, Smith DC. A review of etomidate for rapid sequence intubation in the emergency department. *J Emerg Med* 1997; 15:221–230
 - 53 Moss E, Powell D, Gibson RM. Effect of etomidate on intracranial pressure and cerebral perfusion pressure. *Br J Anaesth* 1979; 51:347–351
 - 54 Milde LN, Milde JH, Michenfelder JD. Cerebral function, metabolic and hemodynamic effects of etomidate in dogs. *Anesthesiology* 1985; 63:371–377
 - 55 Marshall RJ, Muir AW, Sleight T, et al. An overview of the pharmacology of rocuronium bromide in experimental animals. *Eur J Anaesthesiol Suppl* 1994; 9:9–15
 - 56 Hudson ME, Rothfield KP, Tullock WC, et al. Haemodynamic effects of rocuronium bromide in adult cardiac surgical patients. *Can J Anaesth* 1998; 45:139–143
 - 57 Abrams KJ. Airway management and mechanical ventilation. *New Horiz* 1995; 3:479–487
 - 58 Feng CK, Chan KH, Liu KN, et al. A comparison of lidocaine, fentanyl, and esmolol for attenuation of cardiovascular response to laryngoscopy and tracheal intubation. *Acta Anaesthesiol Sin* 1996; 34:61–67
 - 59 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
 - 60 Brain Trauma Foundation, American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care: hyperventilation. *J Neurotrauma* 2000; 17:513–520
 - 61 Qureshi AI, Geocadin RG, Suarez JI, et al. Long-term outcome after medical reversal of transtentorial herniation in patients with supratentorial mass lesions. *Crit Care Med* 2000; 28:1556–1564
 - 62 Shenkin HA, Benzier HO, Bouzarth W. Restricted fluid intake: rational management of the neurosurgical patient. *J Neurosurg* 1976; 45:432–435
 - 63 Morse ML, Milstein JM, Haas JE, et al. Effect of hydration on experimentally induced cerebral edema. *Crit Care Med* 1985; 13:563–565
 - 64 Gaab M, Knoblich OE, Schupp J, et al. Effect of furosemide (Lasix) on acute severe experimental cerebral edema. *J Neurol* 1979; 220:185–197
 - 65 Marmarou A. Quantitative analysis of blood-brain barrier damage in two models of experimental head injury in the rat. *Acta Neurochir* 1994; 60(suppl):456–468
 - 66 Tanno H, Nockels RP, Pitts LH, et al. Breakdown of the blood-brain barrier after fluid percussive brain injury in the rat; part I: distribution and time course of protein extravasation. *J Neurotrauma* 1992; 9:21–32
 - 67 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
 - 68 Battistella FD, Wisner DH. Combined hemorrhagic shock and head injury: effects of hypertonic saline (7.5%) resuscitation. *J Trauma* 1991; 31:182–188
 - 69 Kein ND, Reitan JA, White DA. Cardiac contractility and blood flow distribution following resuscitation with 7.5% hypertonic saline in anesthetized dogs. *Circ Shock* 1991; 35:109–116
 - 70 Mazzoni MC, Borgstrom P, Arfors KE, et al. Dynamic fluid redistribution in hyperosmotic resuscitation of hypovolemic hemorrhage. *Am J Physiol* 1988; 255(3 pt 2):H629–H637
 - 71 Hartl R, Ghajar J, Hochleuthner H, et al. Hypertonic/hyperoncotic saline reliably reduces ICP in severely head-injured patients with intracranial hypertension. *Acta Neurochir Suppl* 1997; 70:126–129
 - 72 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
 - 73 Peterson B, Khanna S, Fisher B, et al. Prolonged hypernatremia controls elevated intracranial pressure in head-injured pediatric patients. *Crit Care Med* 2000; 28:1136–1143
 - 74 Wade CE, Grady JJ, Kramer GC, et al. Individual patient cohort analysis of the efficacy of hypertonic saline/dextran in patients with traumatic brain injury and hypotension. *J Trauma* 1997; 42(5 Suppl):S61–S65
 - 75 Bullock MR, Chestnut RM, Clifton GL, et al. Initial management. *J Neurotrauma* 2000; 17:463–469
 - 76 Masters SJ, McClean PM, Arcarese JS, et al. Skull x-ray examinations after head trauma: recommendations by a multidisciplinary panel and validation study. *N Engl J Med* 1987; 316:84–91
 - 77 Stein SC, Ross SE. Mild head injury: a plea for routine early CT scanning. *J Trauma* 1992; 33:11–13
 - 78 Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT head rule for patients with minor head injury. *Lancet* 2001; 357:1391–1396
 - 79 Jeret JS. Minor head injury and CT scanning [letter]. *J Trauma* 1993; 35:490–491
 - 80 Weisberg L, Nice C. *Head injury*. Philadelphia, PA: WB Saunders, 1989; 321–343
 - 81 Greenberg J. Neuroimaging in brain swelling. *Neurol Clin* 1984; 2:677–693
 - 82 Narayan RK, Kishore PR, Becker DP, et al. Intracranial pressure: to monitor or not to monitor? A review of our experience with severe head injury. *J Neurosurg* 1982; 56:650–659
 - 83 Sharp SJ, Thompson SG, Altman DG. The relation between treatment benefit and underlying risk in meta-analysis. *BMJ* 1996; 313:735–738
 - 84 Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999; 18:2693–2708
 - 85 Colohan AR, Alves WM, Gross CR. Head injury mortality in two centers with different emergency medical services and intensive care. *J Neurosurg* 1989; 71:202–207

- 86 Marshall LF, Gattille T, Klauber MR. The outcome of severe closed head injury. *J Neurosurg* 1991; 75:S28–S36
- 87 Bullock MR, Chestnut RM, Clifton GL, et al. Indications for intracranial pressure monitoring. *J Neurotrauma* 2000; 17: 479–491
- 88 Marmarou A, Anderson RL, Ward JD. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. *J Neurosurg* 1991; 75:S59–S66
- 89 Kosteljanetz M, Borgesen SE, Stjernholm P, et al. Clinical evaluation of a simple epidural pressure sensor. *Acta Neurochir* 1986; 83:108–111
- 90 Powell MP, Crockard HA. Behavior of an extradural pressure monitor in clinical use: comparison of extradural with intraventricular pressure in patients with acute and chronically raised intracranial pressure. *J Neurosurg* 1985; 63:745–749
- 91 Bullock MR, Chestnut RM, Clifton GL, et al. Recommendations for intracranial pressure monitoring technology. *J Neurotrauma* 2000; 17:497–506
- 92 Sheinberg M, Kanter MJ, Robertson CS, et al. Continuous monitoring of jugular venous oxygen saturation in head-injured patients. *J Neurosurg* 1992; 76:212–217
- 93 Cruz J. Relationship between early patterns of cerebral extraction of oxygen and outcome from severe acute traumatic brain swelling: cerebral ischemia or cerebral viability? *Crit Care Med* 1996; 24:953–956
- 94 Shippy CR, Appel PL, Shoemaker WC. Reliability of clinical monitoring to assess blood volume in critically ill patients. *Crit Care Med* 1984; 12:107–112
- 95 Godje O, Peyerl M, Seebauer T, et al. Central venous pressure, pulmonary capillary wedge pressure and intrathoracic blood volumes as preload indicators in cardiac surgery patients. *Eur J Cardiothorac Surg* 1998; 13:533–539
- 96 Diebel L, Wilson RF, Heins J, et al. End-diastolic volume versus pulmonary artery wedge pressure in evaluating cardiac preload in trauma patients. *J Trauma* 1994; 37:950–955
- 97 Chang MC, Blinman TA, Rutherford EJ, et al. Preload assessment in trauma patients during large-volume shock resuscitation. *Arch Surg* 1996; 131:728–731
- 98 Marik PE. Pulmonary artery catheterization and esophageal Doppler monitoring in the ICU. *Chest* 1999; 116:1085–1091
- 99 Bouma GJ, Muizelaar JP, Bandoh K, et al. Blood pressure and intracranial pressure-volume dynamics in severe head injury: relationship with cerebral blood flow. *J Neurosurg* 1992; 77:15–19
- 100 Kroppenstedt SN, Stover JF, Unterberg AW. Effects of dopamine on posttraumatic cerebral blood flow, brain edema, and cerebrospinal fluid glutamate and hypoxanthine concentrations. *Crit Care Med* 2000; 28:3792–3798
- 101 Cherian L, Chacko G, Goodman C, et al. Cerebral hemodynamic effects of phenylephrine and l-arginine after cortical impact injury. *Crit Care Med* 1999; 27:2512–2517
- 102 DeWitt DS, Smith TG, Deyo DJ, et al. L-arginine and superoxide dismutase prevent or reverse cerebral hypoperfusion after fluid-percussion traumatic brain injury. *J Neurotrauma* 1997; 14:223–233
- 103 Zhuang J, Shackford SR, Schmoker JD, et al. Colloid infusion after brain injury: effect on intracranial pressure, cerebral blood flow, and oxygen delivery. *Crit Care Med* 1995; 23:140–148
- 104 Kaieda R, Todd MM, Cook LN, et al. Acute effects of changing plasma osmolality and colloid oncotic pressure on the formation of brain edema after cryogenic injury. *Neurosurgery* 1989; 24:671–678
- 105 Ernest D, Belzberg AS, Dodek PM. Distribution of normal saline and 5% albumin infusions in septic patients. *Crit Care Med* 1999; 27:46–50
- 106 Human albumin administration in critically ill patients: systematic review of randomised controlled trials; Cochrane Injuries Group Albumin Reviewers. *BMJ* 1998; 317:235–240
- 107 Menzel M, Doppenberg EMR, Zauneer A, et al. Increased inspired oxygen concentration as a factor in improved brain tissue oxygenation and tissue lactate levels after severe human head injury. *J Neurosurg* 1999; 91:1–10
- 108 Cooper KR, Boswell PA, Choi SC. Safe use of PEEP in patients with severe head injury. *J Neurosurg* 1985; 63: 552–555
- 109 Shapiro HM, Marshall LF. Intracranial pressure responses to PEEP in head-injured patients. *J Trauma* 1978; 18: 254–256
- 110 Clarke JP. The effects of inverse ratio ventilation on intracranial pressure: a preliminary report. *Intensive Care Med* 1997; 23:106–109
- 111 McGuire G, Crossley D, Richards J, et al. Effects of varying levels of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure. *Crit Care Med* 1997; 25:1059–1062
- 112 Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome: Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301–1308
- 113 Amato MBP, Barbas CSV, Medeiros DM, et al. Beneficial effects of the “open lung approach” with low distending pressures in acute respiratory distress syndrome: a prospective randomized study on mechanical ventilation. *Am J Respir Crit Care Med* 1995; 152:1835–1846
- 114 Marik PE, Krikorian J. Pressure-controlled ventilation in ARDS: a practical approach. *Chest* 1997; 112:1102–1106
- 115 Kerr ME, Weber BB, Sereika SM, et al. Effect of endotracheal suctioning on cerebral oxygenation in traumatic brain-injured patients. *Crit Care Med* 1999; 27:2776–2781
- 116 Miranda J, Broyles G. Propofol as used for sedation in the ICU. *Chest* 1995; 108:539–548
- 117 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
- 118 Alkire MT, Haier RJ, Barker SJ, et al. Cerebral metabolism during propofol anesthesia in humans studies with positron emission tomography. *Anesthesiology* 1995; 82:393–403
- 119 Bao YP, Williamson G, Tew D, et al. Antioxidant effects of propofol in human hepatic microsomes: concentration effects and clinical relevance. *Br J Anaesth* 1998; 81:584–589
- 120 Hsiang JK, Chesnut RM, Crisp CB. Early, routine paralysis for intracranial pressure control in severe head injury: is it necessary? *Crit Care Med* 1994; 22:1471–1476
- 121 Marik PE. Doxacurium-corticosteroid acute myopathy: another piece to the puzzle. *Crit Care Med* 1996; 24:1266–1267
- 122 Prough DS, Joshi S. Does early neuromuscular blockade contribute to adverse outcome after acute head injury? *Crit Care Med* 1994; 22:1349–1350
- 123 Davenport A, Will EJ, Davison AM. Effect of posture on intracranial pressure and cerebral perfusion pressure in patients with fulminant hepatic and renal failure after acetaminophen self-poisoning. *Crit Care Med* 1990; 18:286–289
- 124 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
- 125 Drakulovic MB, Torres A, Bauer TT, et al. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet* 1999; 354:1851–1858

- 126 Marik PE. Stress ulcer prophylaxis: a practical approach. *J Intensive Care Med* 1999; 14:1-8
- 127 Temkin NR, Dikmen SS, Wilensky AJ, et al. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *N Engl J Med* 1990; 323:497-502
- 128 Braakman R, Schouten HJ, Blaauw-van DM, et al. Megadose steroids in severe head injury: results of a prospective double-blind clinical trial. *J Neurosurg* 1983; 58:326-330
- 129 Cooper PR, Moody S, Clark WK, et al. Dexamethasone and severe head injury: a prospective double-blind study. *J Neurosurg* 1979; 51:307-316
- 130 Bullock MR, Chestnut RM, Clifton GL, et al. Role of steroids. *J Neurotrauma* 2000; 17:531-535
- 131 Clasen RA, Pandolfi S, Russel J, et al. Hypothermia and hypotension in experimental cerebral edema. *Arch Neurol* 1968; 19:472-486
- 132 Laskowski EJ, Klatzo I, Baldwin M. Experimental study of the effects of hypothermia on local brain injury. *Neurology* 1960; 10:499-505
- 133 Marion DW, Penrod LE, Kelsey SF, et al. Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med* 1997; 336:540-546
- 134 Clifton GL, Miller ER, Choi S, et al. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med* 2001; 344:556-563
- 135 Goldstein B, Powers KS. Head trauma in children. *Pediatr Rev* 1994; 15:213-219
- 136 Bullock MR, Chestnut RM, Clifton GL, et al. Critical pathway for the treatment of established intracranial hypertension. *J Neurotrauma* 2000; 17:537-547
- 137 Chestnut RM. The management of severe traumatic brain injury. *Emerg Med Clin North Am* 1997; 15:581-604
- 138 Marshall LF, Smith RW, Rauscher LA, et al. Mannitol dose requirements in brain-injured patients. *J Neurosurg* 1978; 48:169-172
- 139 Muizelaar JP, Wei EP, Kontos HA, et al. Mannitol causes compensatory cerebral vasoconstriction and vasodilation in response to blood viscosity changes. *J Neurosurg* 1983; 59:822-828
- 140 Rosner MJ, Coley I. Cerebral perfusion pressure: a hemodynamic mechanism of mannitol and the postmannitol hemogram. *Neurosurgery* 1987; 21:147-156
- 141 Barry KG, Berman AR. Mannitol infusion; part III: the acute effect of the intravenous infusion of mannitol on blood and plasma volume. *N Engl J Med* 1961; 264:1085-1088
- 142 Brown FD, Johns L, Jafar JJ, et al. Detailed monitoring of the effects of mannitol following experimental head injury. *J Neurosurg* 1979; 50:423-432
- 143 McGraw CP, Howard G. Effect of mannitol on increased intracranial pressure. *Neurosurgery* 1983; 13:269-271
- 144 Arai T, Tsukahara I, Nitta K, et al. Effects of mannitol on cerebral circulation after transient complete cerebral ischemia in dogs. *Crit Care Med* 1986; 14:634-637
- 145 Sayre MR, Daily SW, Stern SA, et al. Out-of-hospital administration of mannitol to head-injured patients does not change systolic blood pressure. *Acad Emerg Med* 1996; 3:840-848
- 146 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
- 147 James HE, Langfitt TW, Kumar VS, et al. Treatment of intracranial hypertension: analysis of 105 consecutive, continuous recordings of intracranial pressure. *Acta Neurochir* 1977; 36:189-200
- 148 Bullock MR, Chestnut RM, Clifton GL, et al. Use of mannitol. *J Neurotrauma* 2000; 17:521-525
- 149 Shapiro HM, Wyte SR, Loeser J. Barbiturate-augmented hypothermia for reduction of persistent intracranial hypertension. *J Neurosurg* 1974; 40:90-100
- 150 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
- 151 Dickinson K, Bunn F, Wentz R, et al. Size and quality of randomised controlled trials in head injury: review of published studies. *BMJ* 2000; 320:1308-1311
- 152 Harrigan MR. Cerebral salt wasting. *Crit Care Clin* 2001; 17:125-138
- 153 Heath DL, Vink R. Magnesium sulphate improves neurologic outcome following severe closed head injury in rats. *Neurosci Lett* 1997; 228:175-178
- 154 Heath DL, Vink R. Neuroprotective effects of MgSO₄ and MgCl₂ in closed head injury: a comparative phosphorus NMR study. *J Neurotrauma* 1998; 15:183-189
- 155 Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med* 2001; 29:2264-2270
- 156 Heyland DK, MacDonald S, Keefe L, et al. Total parenteral nutrition in the critically ill patient: a meta-analysis. *JAMA* 1998; 280:2013-2019
- 157 Ott L, Young B, Phillips R, et al. Altered gastric emptying in the head-injured patient: relationship to feeding intolerance. *J Neurosurg* 1991; 74:738-742
- 158 McArthur CJ, Gin T, McLaren IM, et al. Gastric emptying following brain injury: effects of choice of sedation and intracranial pressure. *Intensive Care Med* 1995; 21:573-576
- 159 Kao CH, ChangLai SP, Chieng PU, et al. Gastric emptying in head-injured patients. *Am J Gastroenterol* 1998; 93:1108-1112
- 160 Klodell CT, Carroll M, Carrillo E, et al. Routine intragastric feeding following traumatic brain injury is safe and well tolerated. *Am J Surg* 2000; 179:168-171
- 161 Zaloga GP, Marik P. Promotility agents in the intensive care unit. *Crit Care Med* 2000; 28:2657-2659
- 162 Geerts WH, Code KI, Jay RM, et al. A prospective study of venous thromboembolism after major trauma. *N Engl J Med* 1994; 331:1601-1606
- 163 Geerts WH, Jay RM, Code KI, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med* 1996; 335:701-707
- 164 Knudson MM, Morabito D, Paiement GD, et al. Use of low molecular weight heparin in preventing thromboembolism in trauma patients. *J Trauma* 1996; 41:446-459
- 165 Gersin K, Grindlinger GA, Lee V, et al. The efficacy of sequential compression devices in multiple trauma patients with severe head injury. *J Trauma* 1994; 37:205-208
- 166 Spain DA, Richardson JD, Polk HC, et al. Venous thromboembolism in the high-risk trauma patient: Do risks justify aggressive screening and prophylaxis? *J Trauma* 1997; 42:463-469
- 167 Rogers FB, Strindberg G, Shackford SR, et al. Five-year follow-up of prophylactic vena cava filters in high-risk trauma patients. *Arch Surg* 1998; 133:406-411
- 168 Velmahos GC, Nigro J, Tatevossian R, et al. Inability of an aggressive policy of thromboprophylaxis to prevent deep venous thrombosis (DVT) in critically injured patients: are current methods of DVT prophylaxis insufficient? *J Am Coll Surg* 1998; 187:529-533