13 Neuroscience ICU Therapeutics

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13.1 INTRODUCTION

Neurotrauma, neurosurgical intervention, and cerebrovascular disease all involve combinations of immediate or primary injury and delayed or secondary injury (see Chapter 4 for information on cellular treatments of stroke and hypoxia/ischemia). The primary injury occurs at the time of or a few minutes after a trauma, brain procedure or vascular insult. The secondary injury evolves over time — usually hours to several days.
The primary injury may be optimally influenced by care provided to prevent the trauma (i.e., seatbelt use in cars and other injury prevention schemes), prevent intra-operative complications, or manage medical problems such as diabetes and hypertension that may predispose a patient to stroke occurrence. Intensive care unit (ICU) therapeutic measures focus on preventing, treating, and reversing the evolving secondary effects of brain damage and its systemic complications following primary events.1

In order to improve treatment options, much attention has been directed to more sensitive monitoring methods to prevent further injury in addition to standard comprehensive medical care and prevention of systemic problems.2 This chapter reviews the current hypotheses in neuroscience ICU therapeutics and discusses promising lines of bench research that will make their way into ICUs within the next 5 years. It also includes a brief review of the modest strides made in management of head injury, postoperative issues, and cerebrovascular problems, including subarachnoid hemorrhage and ischemic stroke.

13.2 CLINICAL PROBLEMS AMENABLE TO ICU MANAGEMENT

13.2.1 BRAIN TRAUMA

The two distinct types of severe brain injuries are cerebral contusions or gray matter injuries and diffuse axonal shears or white matter injuries. The evolution over time after injury varies by type of injury, although many patients have combinations of different injury types.2

Cerebral contusions are commonly present following a variety of different injury mechanisms, and often the patient is nearly normal or only slightly disoriented initially. Computerized tomography (CT) scans may show little initial evidence of the extent of cerebral contusion although some swelling or mild hemorrhage may often be present. A common pattern is the coup–contrecoup injury in which a contusion appears under the skull at the location of the impact and also opposite the area of injury. The typical evolution is that local swelling and cortical irritation occur, often with focal or punctate hemorrhages within the cortex over 2 to 3 days. Occasionally these small hemorrhages (observed on CT scans as diffuse salt-and-pepper areas of hemorrhage) will coalesce to form a substantial intraparenchymal hemorrhage that may form a mass. The secondary consequences of the injury commonly include seizure, brain swelling and increased intracranial pressure, and hyponatremia. If the injured cortical areas were functioning close to normal, recovery over time is usually excellent when the intermediate problems of swelling, intracranial pressure, and seizure are managed effectively.

Shear injury or diffuse axonal injury (DAI) commonly is caused by more severe trauma. Patients can experience severe deficits from the time of injury. In several ways, DAI is similar to spinal cord injury because both involve primarily severe white matter injury and poor degrees of recovery over time. Rarely do intracranial pressure (ICP) problems consisting primarily of DAI appear because white matter does not show significant swelling after injury. These patients create less of a concern for intracranial swelling or raised pressure, although all the other ICU management
issues including preventing infection, treatment of seizures and electrolyte abnormalities, airway protection, and feeding arise. While some patients with severe DAI recover, they commonly require tracheostomy and gastrostomy for long-term care. Many long-term comatose patients in this category are maintained for years, often in low-functioning or vegetative states.

13.2.2 Postoperative Neurosurgical Care

ICU management after neurosurgical intervention has two common bases. The first is preventative management, for rapid detection of postoperative problems such as seizures, brain hemorrhages, airway problems, or systemic concerns such as blood loss replacement. The second basis is active treatment of patients with marginal brain function, immediate brain swelling or hemorrhage after vascular occlusion, and intraoperative complications. Essentially all patients undergoing open brain procedures are monitored at least overnight in an ICU due to the large number of problems that can arise.

13.2.3 Cerebrovascular Problems

Multiple forms of spontaneous cerebrovascular events resulting in brain damage, increased intracranial pressure, hydrocephalus, hypertension, and repeat subarachnoid hemorrhage (SAH) can be optimally managed via a neuroscience ICU approach (see Chapter 4 and Chapter 11). For example, patients with severe SAH may not be immediately amenable for either direct neurosurgical intervention, such as aneurysm clipping or endovascular treatment (see Chapter 12), but may still have severe deficits and require ICP monitoring, blood pressure, and volume management (such as hyperdynamic therapy).

Common forms of stroke include ischemic stroke, such as major coronary artery occlusion, after which patients often develop severe brain swelling. This swelling can in some cases be ameliorated with ICP monitoring and occasionally by decompressive craniectomy. Deep intracerebral hemorrhages due to hypertension often also result in severe neurological deficits requiring intensive management, secondary medical problems, and hydrocephalus. Mortality can be as high as 85%. All of these possibilities represent common reasons to stabilize and treat patients in a neuroscience ICU setting.

13.2.4 Inappropriate Clinical Care Situations

Neuroscience ICU care intuitively is life-saving, and can function as a key bridge between difficult neurological problems and their recovery over time. However, in many instances recovery is very unlikely, in spite of intensive care capabilities. For example, terminal care in patients with poor prognosis or brain death does not require ICU care, nor would patients in a permanent vegetative state who are stable. Also, physiologically stable patients may not require an ICU environment, because no critical treatment issues may exist. In most hospitals ICU are a scarce resource, and such a resource must be managed wisely, considering which patients may optimally benefit from expensive care and resources.
13.3 MODALITIES OF NEUROSCIENCE ICU MANAGEMENT

Neuroscience ICU management includes a number of key modalities of care including frequent and sensitive neurological examination, specific concern for brain or spinal cord-related deterioration, various forms of monitoring of brain and systemic function, and attention to the details of healing, nutrition, airway management, and prevention of complications.1,2 These various modalities will be discussed individually.

13.3.1 SPECIFIC NEUROLOGICAL AND GENERAL CARE

The mainstay of neuroscience ICU management is careful neurological assessment. Most neuroscience ICUs use detailed flowsheets to help monitor neurological function, including assessment on the Glasgow coma scale for brain function, spinal cord function, and particularly detailed responses to environmental stimuli. Intensive neurological exams are usually performed at least every 2 hours by nurses specialized in neurological assessment. Detection of specific neurological events including seizures, herniation syndromes, changes in levels of consciousness and awareness, and spinal cord functions is critical. A key point is that detection of worsening may imply a cascade of pathological alterations that may be prevented by prompt treatment and management.

In addition to neurological assessment, excellent general medical care is also critical and should include assessment of airway problems, need for continued intubation, nutrition, and methods of diet supplementation. In addition, maintenance of normal temperature, or in some cases lower than normal temperature (as in cooling), requires vigilance and possibly cooling blankets. Since most patients with severe brain alterations typically have intact gastrointestinal function, rapid resumption of nutrition is usually possible, initially through an orogastric or nasal tube into the small bowel. In many cases, a gastrostomy can be helpful for long-term nutritional supplementation. Prevention of infection, skin ulceration, and other medical problems is critical because these conditions may significantly slow recovery.

13.3.2 MONITORING TECHNIQUES

Many noninvasive and invasive monitoring techniques are currently used in the ICU setting.2,3 Almost any physiological function can be intermittently or continuously monitored, depending on the need for rapid intervention. Many monitoring functions such as arterial and intracranial pressures are viewed as analog signals and converted to numbers in the case of pulse rate, systolic and diastolic pressures, cerebral perfusion pressures, levels of oxygenation, etc.

Typical systemic monitoring functions include cardiac pulse and blood pressure, temperature, weight, cardiac output, ventricular pressures, oxygenation and arterial blood gases, systemic electrolytes, and blood counts. Additional modalities specific to the neuroscience ICU setting include ICP measurement, cerebral oxygen and substrate levels, cerebral blood flow and transcranial Doppler monitoring, cerebral metabolism, electroencephalographic monitoring of seizure and electrical activity of the brain, and level of sedation.3
Other types of monitoring include structural assessments of the brain and spinal cord via CT and magnetic resonance imaging (MRI) scans. While most of these general and neurological modalities of monitoring are common, new methods of monitoring brain function continuously arise. Many monitoring procedures involve an overlap between monitoring and treatment capabilities, for example, ICP monitoring and drainage. The major forms of monitoring are discussed next.

13.4 INTRACRANIAL PRESSURE MEASUREMENTS

Intracranial pressures (ICP) reflect a combination of the brain’s pulsatile response to incoming arterial blood with each cardiac cycle and its compliance.4–7 The shape of the ICP waveform closely resembles that of the arterial blood pressure waveform, but with a delay and smaller amplitude. This fact led to the development of waveform analysis to reveal the compliance of the brain in response to incoming cardiac pulsation and to demonstrate whether pathological changes within the brain alter this compliance and lead to increased ICP.4,8–10 While many types of ICP measurements are in common clinical use, no data indicate whether they actually improve outcomes, as compared to empirical treatment of presumed ICP elevations.

13.4.1 CSF AND INTRACRANIAL PRESSURE

Cerebrospinal fluid (CSF) normally completely surrounds the brain and occupies the subarachnoid space. The freely diffusible CSF normally equilibrates the ICP around the brain rapidly and buffers the brain mechanically. Because CSF drains into veins with positive pressures (4 to 6 mmHg above sagittal sinus pressure), the usual pressure is 10 to 12 mmHg in a lateral horizontal position. As long as CSF can circulate freely, elevated ICP has no deleterious consequences on brain function, assuming that cerebral perfusion pressure remains in the normal range (65 to 70 mmHg typically). However, secondary systemic hypertension may occur as a reflex in order to maintain cerebral perfusion pressure if the ICP is elevated.

This is clearly observed in the example of benign intracranial hypertension (BIH; formerly called pseudotumor cerebri prior to CT and MRI imaging). A CSF absorption deficit is commonly present in BIH, but because normal CSF production continues, CSF pressures can rise. Interestingly, since BIH commonly occurs in young patients with normal ventricular size (rather than hydrocephalus), the ventricles typically do not dilate. The brain typically resists the increased pressure, but papilledema can result. Long-standing papilledema can lead to loss of visual function. Visual loss and headaches are the only discernable abnormalities from high ICP in the absence of a mass, often up to 50 mmHg. However, if a mass is present and CSF circulation around the brain is disturbed because of the mass (from shift, loculation, etc.), the CSF cannot equilibrate the pressure. CSF can accumulate on the side of the mass, enhancing the brain shift and mass effect, creating a vicious cycle of increasing mass. In such cases, ICP monitoring can be very helpful for discerning whether such brain shift and ICP buildup are occurring. Additionally, CSF drainage through an intraventricular catheter can effectively treat the mass effect and prevent additional untoward consequences in many cases.
13.4.2 Types of Intracranial Pressure Monitors

ICP monitoring catheters include those that have drainage channels (and hence are placed in locations where CSF can be drained, for example, in lateral ventricles), and those that only monitor pressure. Potential locations for catheters include epidural, subdural, intraparenchymal, and intraventricular, as well as lumbar subarachnoid spaces. Epidural and subdural catheters are not as popular due to the dearth of reliable data. Intraventricular catheters remain the most popular because of their ability to measure pressure and drain CSF. The intraparenchymal catheter has changed little in the past 20 years and includes a device such as a moveable diaphragm on the tip of the catheter that will transduce brain pressure. The fiberoptics that relay signals through the catheter have improved and less drift occurs over time when these catheters are used.

Intraventricular catheters have also been combined with fiberoptic catheters that allow continuous monitoring when draining. Most intraventricular catheters can be tunneled under the skin away from the site of insertion. This decreases infection rates and allows longer catheter use time in vivo. However, most parenchymal catheters are stiff and cannot be tunneled and are thus more subject to damage or shear.

Because the brain is soft and does not transmit pressure well, ICP may vary from location to location, as demonstrated by several studies with multiple catheter locations and the resulting disparate pressure measurements. This is particularly true when CSF circulation is impeded by mass or shift, leading to pressure gradients in the brain that are then not equalized by CSF movement. Thus, intracranial pressure measurement in a distal location (such as contralateral to a mass) may be misleading and may show apparent low value that could potentially misinform a clinician about a patient’s true status.

13.4.3 Intracranial Pressure and Waveform Monitoring

Although ICP recordings are commonly used to monitor increased pressure, clinical interpretation of increased mean ICP has major limitations because it is an indirect measure of potential neurological deterioration; a high degree of variability of mean ICP levels exists among patients. Consistently increased mean ICP values (>40 mmHg) correlate well with poor clinical status and outcome in compromised patients, but this relationship is less predictable in patients with moderately increased values between 20 and 30 mmHg. Theoretically, the volume–pressure relationship provides a measure of the compensatory reserve and the likelihood of neurological deterioration. However, no reliable and safe direct clinical method of calculating intracranial compliance or elastance (the inverse of compliance) allows full reconstruction of the volume–pressure curve.

One technique proposed to provide additional information about neurological status is spectral analysis of arterial blood pressure (ABP) in the intracranial cavity as an input function and analysis of the ICP waveform as an output function. The ratio of the frequency components of the ICP and ABP spectra yields a transfer function that includes both cerebrovascular and brain compliance components. ICP
waveforms have been analyzed in this manner using a variety of models and techniques, generally across multiple cardiac cycles. The influence of respiratory cycles and central venous pressures (CVP) and their relationship to ICP may also be important in understanding ICP.

A normal ICP recording consists of a pulsatile waveform with two components: one corresponding to arterial pulsations, the other corresponding to the much slower respiratory excursions, related most closely to changes in CVP.9 The pulsatile waveform has been analyzed by the inflections and components as well as by fractionating the frequency components using the Fourier transform. This can done on a cycle-by-cycle basis to provide an almost instantaneous measure of cerebral compliance for each cardiac pulse.8 This type of analysis will require further clinical studies to assess its overall usefulness and predictive value.

13.5 ADDITIONAL MONITORING MODALITIES

13.5.1 CEREBRAL BLOOD FLOW

Cerebral blood flow (CBF) is the velocity of blood through the cerebral circulation,1 together with estimates of the total blood volume in the various arterial and venous compartments. Many metabolic parameters are dependent on knowing the CBF. Changing the CBF at different times can help treat patients, particularly in low-flow situations, such as after occlusion of a major trunk artery. CBF follows Poiseulle’s law that essentially identifies three variables the clinician can affect: (1) perfusion pressure, (2) vascular radius, and (3) blood viscosity.

During different physiologic states such as vasospasm or after an ischemic infarct, perfusion pressure may be increased for greater blood flow and enhancement of collateral formation. In addition, blood may be diluted to decrease viscosity to an optimal hematocrit in the range of 30 to 33%. Cerebral autoregulation primarily functions to maintain constant CBF during fluctuations in cerebral perfusion pressure within a wide normal-range systemic blood pressure (approximately 60 through 180 mmHg).

Diminished CBF can indicate ischemia, which may lead to damage to regions of the brain. Thus, measurements of CBF can allow a physician to change treatment paradigms. Multiple techniques of direct or indirect measurement of CBF have been developed. A simple method such as the Kety–Schmidt nitrous oxide technique can be used at the bedside. Only arterial and venous samples are needed to measure nitrous oxide differences. Radiological imaging can also be used to determine blood flow via many modalities, classically by using radioactive monitors over the skull to measure the amount of radioactive xenon coursing through blood vessels of the brain after inhalation. Because the number of surface monitors is limited, this type of crude blood-flow assessment is rarely done.

Recently, MR diffusion and perfusion were used to measure the diffusion coefficient of water, which relates areas of low blood flow and/or evolving ischemic infarct. Perfusion can be used with contrast to determine areas of low-blood volume. CT can also be used to measure flow by looking at specific tracers that provide quantitative measurements. The most common form of this CT blood-flow approach

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is the use of inhaled xenon (up to 40% by mask). Because xenon is a heavier molecule than iodine (the most common CT contrast agent), xenon provides excellent visualization in vessels for measuring both blood volume and flow. Unfortunately, the dose of xenon needed by inhalation for this technique is at the level for achieving anesthesia, leading to confusion and sedation. Single photon emission computed tomography (SPECT) can also be used for blood-flow studies in stroke, brain death determination, and epilepsy. All these techniques can be used to determine areas of decreased blood flow.

13.5.2 Brain Oximetry

Two modalities of brain oximetry are currently in limited use for assessing regional oxygen levels.12 Near-infrared spectroscopy (NIRS) is a noninvasive method that can be used in the operating room and ICU to observe changes in brain oxygen demand. This technique is based on using oxyhemoglobin concentration as a tracer to determine CBF. However, since NIRS depends on the ability of infrared light to cross the scalp and dura to reach the brain when the skull is closed, it can only be used in infants with thin skulls or through the fontanelle. Even then, controlled studies to determine the validity and accuracy of this indirect measure are needed, particularly because no method clearly distinguishes scalp blood oxygen levels from blood oxygen levels in the brain.

Intraparenchymal oxygen tension catheters for human use based on the Clark style oxygen electrode (Licox, Integra Neurosciences, Plainsboro, NJ) have become available recently.13–16 The principle of this electrode that dates back to the 1930s is the use of a gold sensor sensitive to oxygen and diffusion of oxygen through a dialysis membrane into an internal electrolyte solution. The impermeable dialysis membrane allows a small (1 mm in diameter) catheter to be sterilized. Despite some preliminary experience, the indications for use are not yet clear, but the device seems promising. The device has been used to ensure adequate oxygenation of injured tissue in traumatic injury.2,17–19 Several studies suggest that normal brain oxygen levels in the extracellular space range from 30 to 40 mmHg, and that brain levels rise considerably with systemic oxygen challenges to 100% inspired oxygen.19 Levels below 20 mmHg are considered hypoxic and increased oxygen or increased cerebral perfusion may be used to reverse a trend toward hypoxia in brain regions.15

Our institution has used the Licox catheter in a small number of patients. The catheter is placed similarly to a frontal intraparenchymal bolt. Continuous recording of brain oxygen tension is performed. When values fall below a certain level, the percent of inhaled oxygen is increased. The thought is that damaged tissue may be more sensitive to lowered levels of oxygen, with permanent damage caused by periods of hypoxia. The overall hypothesis for Licox use is that by ensuring adequate oxygenation of the brain, marginal areas may be prevented from cell death. In an observational study in the Netherlands, patients had catheters placed without any major complications. The patients were observed for partial oxygen pressure and outcome. The study determined that the depth and duration of brain tissue hypoxia correlated well with outcome and they proved to be independent predictors of unfavorable outcomes.17
In addition, the catheter can also be used to manage partial pressure of carbon dioxide and ventilation. Hyperventilation is a useful tool in the armamentarium of ICP management. However, cerebral autoregulation is usually disturbed in injured states. Because blood vessels may severely constrict at a pCO₂ level below 25 to 28 mmHg, the possible risk of causing ischemia with excessive hypocarbia is real. With a partial oxygen pressure reading, ventilation can be titrated so as not to cause ischemia while controlling ICP. This relationship of brain oxygen tension and blood gas carbon dioxide levels was confirmed in the laboratory using swine and Licox catheters.13

Jugular bulb oximetry is a recent method of assessing oxygen extraction that has fallen out of favor due to difficulty in its application and unreliable data. It is used to estimate the brain’s metabolic needs because arterio–venous oxygen differences (oxygen extraction in a global sense) can be roughly determined. Because the jugular vein has a highly variable distribution of brain blood drainage, this method only hints at global brain metabolism and is highly nonspecific. Normal values range from 60 to 80%. Low levels can signify ischemia secondary to hyperventilation, increased metabolic demand, agitation, or seizure, suggesting increased oxygen extraction due to demand. Conversely, high levels can signify hypercarbia, hyperemia, late ischemia, or cerebral blood flow cessation. Difficulties with the catheters include migration, extracerebral contribution to jugular venous blood causing contamination, and low resolution to identifying areas of decreased metabolism.1,12

Overall, the tissue levels of oxygen in the brain are now well defined through both preclinical and human studies. In several early human studies, the low levels of oxygen were thought to be due to ischemia, but it has since become clear that oxygen is tightly regulated within the brain at fairly low levels. Supply is coupled to demand through vascular control and autoregulation.19 However, a clear hypoxic threshold (oxygen level below which local ischemia or cell death occurs) has not yet been determined.15 Rather, a loose clinical correlation between brain oxygen levels and survival exists, but these two disparate factors may or may not be correlated.

13.5.3 CEREBRAL MICRODIALYSIS

Lactate, glutamate, pyruvate, glucose, and other critical metabolites within the brain play a large role in secondary injuries that occur before and after neuronal damage. Much interest now focuses on measuring levels of these compounds and correlating them to ischemic or detrimental events. The Licox catheter can also be used for microdialysis. The bolt placed into the skull for fixation is large enough to allow a two- or three-way manifold to be placed into the bolt to accommodate up to three different catheters. Often, the simplest combination is the oxygen tension monitor, ICP parenchymal monitor, and brain temperature monitor. However, one or two of these can be exchanged for a microdialysis catheter. A group in Germany recently showed that prior to a hypoxic period, glucose decreased significantly and glutamate increased three- to fourfold.18 This suggests that either a reduction in hyperventilation therapy or an increase in FiO₂ was indicated. Further research is needed to determine whether changes in treatment modalities affect outcome.
Determination of resting and stress levels of metabolites within the brain has proven very enlightening for understanding CNS metabolism and correlating human values with those obtained in preclinical studies. A popular preclinical hypothesis presented in many studies since 1997 has been the “lactate shuttle” concept, borrowed from muscle metabolism analysis. Briefly, concept suggests that one of the primary glial functions in the brain is to produce lactate from glycolytic metabolism of glucose and then excrete this lactate into the extracellular space. Neurons, according to this hypothesis, preferentially use lactate (rather than glucose) for much of the production of ATP and energy. An excellent review article critically discusses this concept and concludes that neurons may use lactate if available, but glucose is a critical fuel, particularly for membrane pumping of ions.

The levels of lactate measured within the human brain partially support the lactate shuttle concept. In a head injury study in which the Licox catheters were placed contralateral to brain lesions (in the most normal areas possible), the measured brain lactate levels exceeded 3 mM. These values were much higher than systemic lactate values near 1 mM, suggesting a complete dissociation of brain and systemic lactate due to the loss of monocarboxylate transporter activity (particularly MCT1) with maturity in the blood–brain barrier.

The relatively high level of brain lactate was initially thought to represent a high degree of anaerobic glycolysis within the brain (in other words, hypoxia), but on oxygen challenge, the lactate did not change. This finding of persistent lactate, even in a highly enriched oxygen environment, suggests a high degree of aerobic glycolysis, presumably partly within glial cells, as proposed by the lactate shuttle concept. The level of glucose measured was near 2 mM, suggesting highly limited transport into the brain, and/or high utilization by glial cells. Interestingly, the levels of pyruvate were very low (<0.2 mM), indicating that pyruvate is rapidly transported into cells and mitochondria when available, and is only a transient molecule in the extracellular space.

These results suggest an intricate interplay of metabolism between neurons and glia. Presumably neurons are the primary consumers of lactate, along with glucose for membrane pumping and other needs, whereas glia are net lactate producers, particularly because the glial citric acid cycle is primarily used for glutamine generation. The basic mechanisms of CNS metabolism appear in many ways to be radically different from those of systemic circulation, so it is not necessarily correct to borrow systemic concepts, such as, for example, lactate indicates anaerobic metabolism.

13.5.4 Serum and CSF Markers

Blood tests that could signal impending intracranial hypertension or vasospasm would be very useful and innocuous to patients in intensive care settings. Panels of serum values currently under development may help intensive care specialists discuss prognosis or heighten concern regarding vasospasm. For example, S-100 is a cytosolic calcium-binding protein normally found in striated muscle, heart, kidney, astroglial, and Schwann cells. In adults, the levels of S-100β are elevated in multiple sclerosis, intracranial tumors, subarachnoid hemorrhage, and cerebral infarction.
Similar correlations were recently validated for children. If blood was drawn within an hour of injury, a high level demonstrated 95% specificity and 86% sensitivity for predicting a poor outcome. In our own institution, McGirt et al. assessed serum markers that became elevated prior to clinical vasospasm. These markers must be better correlated with angiographic and transcranial Doppler data in a larger population. The preliminary data are promising.26

13.6 TREATMENT MODALITIES

Current innovations in actual treatment modalities are actually new investigations of old ideas. A resurgence of interest surrounds the use of hypothermia for intracranial pressure control and treatment of head injury and stroke and many metabolic support concepts are close to clinical trials. Most neuroprotectant agents have failed to win clinical approval, as outlined in Chapter 4.

13.6.1 HYPOTHERMIA IN INTRACRANIAL PRESSURE MANAGEMENT

Induced hypothermia for control of ICP is currently under study as a neuroprotective tool after traumatic brain injury.27–32 Multiple theories about its mechanism exist. Possible candidates include reduction of metabolic rate, reduction of increased ICP, decrease in cerebral edema formation, attenuation in the opening of the blood–brain barrier, inhibition of inflammatory response, and a decrease in the release of glutamate, nitric oxide, and free radicals associated with traumatic brain injury.27–30

Most studies revealed modest gains with little or no statistical improvement in outcome. Evidence for this modality is still lacking and indicates an increased risk of pneumonia for this treatment.31 However, active studies continue because of the strong momentum. Many researchers feel that studies have been done inappropriately and that the treatment modality has clinical value. Most studies will take patients with a Glasgow coma scale (GCS) of eight or less within 24 hours of injury and cool to anywhere from 32 to 35°C. Patients are maintained at these temperatures for 2 to 7 days.28–30 Rewarming procedures can also be harmful, so proper protocols must be elucidated. The most favored procedure is slow or passive rewarming instead of active rewarming.

13.6.2 STROKE MANAGEMENT

Stroke management in the ICU involves a combination of problems. Most strokes are ischemic. Treatment in the acute stage is based on prompt triage so that patients may be considered candidates for tissue plasminogen activator (tPA; see Chapter 12). However, the 3-hour window is very short and only a small percentage of eligible patients reach hospitals in the required time. Outside the 3-hour window, treatment involves hyperdynamic and ICP management for large strokes (discussed in other sections) and risk factor management.

Our university and others recently started using tPA for ischemic strokes presenting within a 3- to 6-hour window after the onset of symptoms.33 The tPA is
administered intra-arterially, specifically to the site of the clot. Direct administration allows higher doses, but still carries risk of intracranial hemorrhage. This use is not currently FDA-approved, and is discussed further in Chapter 12.

Another method of clearing cerebral arteries in the acute setting involves the use of a device called the concentric retriever. The retriever underwent a Phase I trial and has just begun a Phase II trial called “mechanical embolus removal in cerebral ischemia” (MERCI). An interventional radiologist uses the device by deploying a self-expanding coil into an acute clot. The coil becomes entangled with the clot and is removed with the introduction catheter. The first trial involved seven centers across the United States. The device was used up to 8 hours after symptom onset. More than 50% of the patients had clot removed and half experienced good functional recoveries (see Chapter 12 for further discussion).

Hemorrhagic strokes constitute 15% of all strokes and usually have poor outcomes. Current treatment includes ICP management with intraventricular catheters and physical therapy. Few patients are candidates for clot removal. Ongoing trials are aimed at halting intracerebral hemorrhage as soon as it is diagnosed. Recombinant factor VIIa is administered in the emergency room for rapid hemostasis. This treatment is very early in the development phase. Efforts have also been made to remove clots medically due to their deleterious effects on the brain. Columbia University has begun a trial to place intraventricular catheters in addition to direct intraventricular thrombolytic therapy. The goal is to reduce the clot burden, thus decreasing the time that toxic blood elements are in contact with viable brain tissue.

13.6.3 Metabolic Enhancement

Several classes of agents can affect stroke or head injury. Since the glutamate hypothesis related to secondary damage following either of these events was developed, a large number of pharmacological agents have been tested for their neuroprotective capabilities. However, they have not shown efficacy, suggesting that perhaps neuroprotection is a somewhat wider area than glutamate alone (see Chapter 4). Another category of treatment in addition to tPA for vessel restoration, hypothermia, and neuroprotection, is metabolic enhancement. This concept involves getting more energy to the ischemic or hypoxic damaged brain through alternative sources other than glucose.

For example, intravenous pyruvate in high doses has been suggested for stroke treatment because pyruvate provides rapid uptake via monocarboxylate transporters and can be utilized immediately in mitochondria without conversion as long as oxygen is present. Lactate supplementation has also been suggested, in addition to creatine, magnesium, nicotinamide and other natural substances. If these metabolic substrates and cofactors can reach an ischemic or hypoxic region, then perhaps neurons can be saved by the additional metabolic support.
13.7 CONCLUSIONS

Intensive care progress specific to neurosciences has developed as a comprehensive care scheme. Many of the ideas discussed are not necessarily new and were revisited recently in attempts to improve management of difficult neurological entities. ICP management is far from resolved. Perhaps treatment for these injuries will lie in replacement therapies after the damage has been done (see Chapters 2 and 3), but the goal of the intensive care specialist must remain to reverse or minimize neurological injury in the acute setting.

New research venues in these settings must be identified because the situation involves many invasive devices and catheters that may provide specimens from the human brain environment. However, considerable expense is involved, and further definition of patient candidates for neuroscience ICU treatment will be critical.

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