Intensive Care Management of Acute Ischemic Stroke

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INTRODUCTION

In a typical ischemic stroke, neurons die at a rate of about 2 million per minute.\textsuperscript{1} Although acute reperfusion therapies are currently the best way to minimize the volume of infarcted brain and optimize outcomes,\textsuperscript{2} few acute stroke patients receive such treatment.\textsuperscript{3} Even patients who receive reperfusion therapy remain at risk for

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KEYWORDS

- Acute ischemic stroke
- Neurocritical care
- Blood pressure control
- Cerebral edema
- Induced normothermia
- Pneumonia
- Prophylaxis

KEY POINTS

- The goal of neurocritical care for the patient with acute ischemic stroke is to optimize long-term outcomes by minimizing the amount of brain tissue that is lost to secondary injury.
- Emergency department management of hypertension in acute ischemic stroke should follow a strategy of “permissive hypertension”, with treatment when the blood pressure exceeds 220/120 mm Hg in patients not treated with tPA, 180/105 mm Hg in patients who have been treated with tPA, and in any patient who shows signs of acute end-organ dysfunction.
- Neurosurgical consultation for possible decompressive surgery should be considered early for patients with large middle cerebral artery or cerebellar infarctions.
- Normal saline is the intravenous solution of choice for patients with acute ischemic stroke as more hypotonic solutions can worsen cerebral edema and do not augment intravascular volume as well.
- Sufficient uncertainty surrounds early prognostication in acute ischemic stroke that it is generally not advisable to make definitive neurologic prognoses in the emergency room setting regarding such patients.
further neuronal death through progressive infarction and secondary injury mechanisms. The goal of neurocritical care for the patient with acute ischemic stroke (AIS) is to optimize long-term functional outcomes and quality of life by minimizing the amount of brain tissue that is lost to these processes. This is accomplished by optimizing brain perfusion, limiting secondary brain injury, and compensating for associated dysfunction in other organ systems. Because of the rapid and irreversible nature of ischemic brain injury, it is crucial for best neurocritical care practices to begin as early as possible. Given data indicating that acute stroke patients might spend an average of 5 hours in the emergency department (ED), it is clear that optimal neurocritical care should begin in the ED and not be delayed until the patient arrives in the intensive care unit (ICU). This article will discuss optimal, pragmatic neurocritical care management of patients with AIS during the golden ED hours from the perspective of the neurointensivist.

PRELIMINARY CONSIDERATIONS

Triage

Determination of what constitutes critical illness in the AIS patient can be challenging. AIS patients have markers of the need for critical care that are unique to AIS in the absence of the more typical signs of respiratory or hemodynamic instability. Chief among these is the potential for neurologic decline, which can be caused by progression of the initial stroke, early recurrent stroke in a different vascular territory, progressive cerebral edema with tissue shifts, and severe reperfusion injury. Early in the course of evaluation of a patient with AIS, it can be difficult to accurately gauge an individual patient’s risk for neurologic decline. At the same time, compared with other organs, the brain is exquisitely sensitive to ischemia and other physiologic perturbations; once injured, the adult brain heals very poorly. For these reasons, reactive management strategies are far less effective in patients with critical brain injuries than in illness primarily involving other organ systems. Optimal care for AIS patients, therefore, requires a hypervigilant strategy of prevention, early detection, and ultra-rapid treatment of neurologic decline. It follows that all AIS patients should be considered to be critically ill, at least while they remain in the ED.

Physiologic Monitoring

Cardiovascular monitoring and respiratory monitoring in AIS do not differ significantly from that required for any other critically ill patient in the ED. Continuous cardiac telemetry and blood pressure monitoring every 5 to 10 minutes with an automated cuff are sufficient in most patients. In patients who require continuous antihypertensive or vasopressor infusions, an arterial catheter is the preferred method of blood pressure monitoring. Pulse oximetry and quantification of the respiratory rate are sufficient for most patients. However, due to the rapidity by which hypercapnia can develop and critically worsen cerebral edema and intracranial pressure (ICP), there should be a low threshold for the determination of the arterial partial pressure of carbon dioxide (CO2) by arterial blood gas. Similarly, intubated AIS patients in the ED should ideally have the end–tidal CO2 continuously monitored.

Several devices are currently available for continuous monitoring of key parameters of cerebral physiology beyond ICP, including brain tissue oxygen tension, cerebral blood flow, and electrical activity. Cerebral microdialysis allows for the monitoring of the concentration of numerous small molecules in the hemispheric interstitium, giving a very precise picture of neuronal metabolic milieu. Most of these devices are invasive, introduced into the brain through a small burr hole craniotomy in a fashion...
identical to the technique used to place the more familiar fiberoptic Camino ICP monitors (Integra LifeSciences, Plainsboro, New Jersey) and external ventricular drains. Despite solid physiologic underpinnings and early evidence of clinical utility, these devices have a number of limitations precluding their widespread use in contemporary clinical practice, especially in the ED setting. These include the time and expertise necessary to place the devices and interpret their results, the small associated risks of hemorrhage and infection, the relatively small volume of brain tissue that can be monitored, and, with the exception of intracranial and cerebral perfusion pressure, a lack of evidence that clearly supports benefit to the patient.

The neurologic examination, therefore, remains the most important tool for monitoring the nervous system in patients with AIS. As with other physiologic parameters, serial measurements using a validated, reproducible, and easy technique provide the most valuable information. This can be accomplished by examining the patient every 15 minutes using the National Institutes of Health (NIH) Stroke Scale (NIHSS), which is essentially an efficient, abbreviated neurologic examination focused on the most salient features in stroke patients. An increase by 2 or more points on the NIHSS can generally be used as a threshold for clinically significant neurologic decline that should trigger repeat imaging of the brain and relevant vessels.8

The NIHSS is of limited utility for patients with more than mildly diminished arousal, who are more appropriately assessed with the use of a clinical scale specifically designed for coma. The Glasgow Coma Scale (GCS) has a significant floor phenomenon, providing little useful neurologic information about patients with the lowest levels of consciousness. The Full Outline of UnResponsiveness (FOUR Score),9 which incorporates more detailed testing of brainstem functions and assesses receptive rather than expressive language (as tested by the GCS), is a superior clinical assessment scale for comatose patients with AIS (Fig. 1). It is only slightly more complicated to learn and perform than the GCS, and it has been shown to be valid and reliable when performed in the ED by emergency physicians and nurses and in AIS patients.10–12 A decline of 1 point on the FOUR Score should be considered clinically significant and trigger repeat imaging of the brain and relevant vessels.

CEREBRAL PERFUSION OPTIMIZATION

Few AIS patients undergo an acute reperfusion therapy.3 Most AIS patients, therefore, are dependent on less direct measures of perfusion optimization to protect at-risk brain from progressing to infarction. These measures form the foundation of neurocritical care for AIS and consist of careful blood pressure management with a preference for higher pressures, intravascular volume augmentation, and keeping the patient’s head of bed low.

Treatment of Hypertension

The guiding principle of hemodynamic management for AIS patients in the first 24 hours after onset is that, in general, higher blood pressures are better than lower blood pressures.2 Two pathophysiologic issues underlie this approach. First, to reach the ischemic penumbra, blood must either flow through the significant stenosis in the native circulation that is causing the stroke or travel through probably higher-resistance collateral routes in the case of occlusion of the native artery. Second, autoregulation in ischemic brain is impaired, thus making flow (and therefore oxygen delivery) entirely dependent on perfusion pressure.13 It is not surprising then, that both very high and very low initial blood pressures are associated with poor outcomes in AIS.2,14 Most notably, a substantial body of evidence from clinical trials and
Fig. 1. The Full Outline of UnResponsiveness (FOUR) score. Four components of neurologic function are assessed: eye response (E), motor response (M), brainstem reflexes (B), and respiration (R). Each component is graded 0 to 4, with lower scores indicating more severe brain dysfunction. Instructions for using the scale can be found in the following reference.

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observational studies indicates that actively lowering the blood pressure in AIS patients in the first hours after onset is associated with acute neurologic deterioration and worse clinical outcomes.14–17

Based on this information, the most recent American Heart Association/American Stroke Association (AHA/ASA) guidelines for the treatment of AIS recommend a strategy of permissive hypertension. The blood pressure is allowed to rise to as high as 220/120 mm Hg before treatment is started unless the patient develops signs of end organ dysfunction due to hypertension (myocardial ischemia, congestive heart failure [CHF], renal failure, cerebral edema, intracerebral hemorrhage [ICH], retinal injury), in which case the blood pressure should be lowered to the highest level that is safely tolerated by the injured organ (a mean arterial pressure [MAP] reduction of about 10% to 20% of maximum for most patients).2 For patients who have received intravenous rt-PA, the blood pressure must be kept strictly below 180/105 mm Hg in the first 24 hours after treatment to minimize the risk of ICH.2

Defining a target blood pressure for patients who have undergone acute endovascular revascularization is a difficult, empiric process that is different for each patient and for which there are no published data available for guidance. It is crucial to determine the goal blood pressure jointly with the endovascular specialist. Due to the empiric nature of determining a target blood pressure in these patients, meticulous attention must be paid to monitoring for signs of cerebral hypoperfusion (new or worsening deficits referable to the territory of the original stroke) and cerebral hyperperfusion (similar to hypoperfusion, but in addition headache, visual blurring, depressed arousal, and seizures).18 Although treatment must be individualized for each patient, the authors’ general blood pressure targets in hypertensive AIS patients are found in Table 1. Box 1 summarizes their approach to acute antihypertensive management in AIS.13,14,19

**Induced Hypertension**

There is no strong evidence to support the use of induced hypertension in any population of AIS patients. However, case reports, case series, and 2 very small prospective studies provide preliminary evidence of safety and effectiveness when induced hypertension is applied carefully in highly selected patients. Markers of potential responsiveness to induced hypertension are listed in Box 2.20

The authors begin hemodynamic augmentation with augmentation of intravascular volume. Determining the optimal blood pressure is empiric. The authors typically raise the mean arterial pressure by 10% to 20% and then reassess 15 to 20 minutes later. If insufficient neurologic improvement has occurred, and the patient is tolerating the treatment, the authors will raise it by another 10%, to a maximum systolic blood

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<th>Table 1</th>
<th>Blood pressure targets when treating hypertension in AIS</th>
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<tr>
<td>Clinical Scenario</td>
<td>Blood Pressure Trigger for Treatment</td>
</tr>
<tr>
<td>No end-organ dysfunction, no rt-PA</td>
<td>&gt;220/110 mm Hg</td>
</tr>
<tr>
<td>First 24 h after rt-PA</td>
<td>180/105 mm Hg</td>
</tr>
<tr>
<td>Evidence of end-organ dysfunction</td>
<td>NA</td>
</tr>
<tr>
<td>Postendovascular therapy</td>
<td>Individualized (see text)</td>
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**Abbreviation:** SBP, systolic blood pressure.
pressure of 180 mm Hg. Phenylephrine is the vasopressor of choice in this situation due to its relative safety when administered at low doses through peripheral veins, its favorable effect on the cerebral circulation, and fewer cardiotoxic effects compared with other vasopressors. Careful monitoring for cerebral hyperperfusion; ischemia of the heart, kidneys, gut, skin, and extremities; and cardiac arrhythmias is essential. Treatment should be decreased in intensity or aborted if any of these occur. The authors do not begin induced hypertension in patients at high risk for any of these complications. Because of the narrow risk–benefit margin, induced hypertension should only be undertaken under the direction of a vascular neurologist or neurointensivist.

**Intravascular Volume Repletion**

Many AIS patients, especially those who are elderly, may be hypovolemic due to dehydration. Reasons for this association are unclear, and the causal relationship may be bidirectional. Impairments in consciousness, swallowing, motor function, and central mechanisms of volume and osmoregulation due to the stroke may predispose AIS patients to hypovolemia. Conversely, hypovolemia may promote AIS by decreasing cerebral blood flow, particularly through stenotic vessels, due to decreased cardiac output and increased blood viscosity. A prothrombotic state may additionally be created by hypovolemia. These theoretical concerns may have important consequences: in at least 1 study, hypovolemia on admission, as

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**Box 1**
**Acute antihypertensive drug management in AIS**

- Decrease by 50% to 75% the following preadmission antihypertensives to avoid rebound tachycardia: beta-blockers, clonidine, and rate control agents in patients with atrial fibrillation
- Discontinue all other preadmission antihypertensives
- If blood pressure is greater than the patient’s target, begin treatment with intermittent intravenous bolus doses of labetalol or hydralazine
- If blood pressure is not controlled with intermittent intravenous boluses within 30 minutes or in patients who require very precise control, use a continuous intravenous infusion of nicardipine
- Labetalol infusions can be used, but due to labetalol’s longer half-life compared with nicardipine, control tends to be less precise
- Avoid sodium nitroprusside and pure beta-blockers due to their undesirable adverse effects and association with neurologic worsening, respectively
- Constantly monitor for signs of neurologic worsening as well as dysfunction of other organs (particularly low urine output due to renal hypoperfusion) that indicate that the blood pressure has been excessively lowered.

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**Box 2**
**Markers of potential responsiveness to induced hypertension**

- Acute stroke in the territory of a severely stenotic or occluded internal carotid, middle cerebral, vertebral, or basilar artery
- Fluctuating neurologic signs and symptoms
- Systolic blood pressure <150 mm Hg
indicated by an elevated plasma osmolality, was associated with an increased risk of 3-month mortality after AIS.\textsuperscript{22} However, treatment of the AIS patient with hypervolemic hemodilution to counter dehydration, while not harmful, has not been shown to be beneficial.\textsuperscript{23} Based on these limited data, the authors’ practice is to ensure euvolemia early by administering 2 to 3L of normal saline intravenously over the first 1 to 4 hours after presentation to all AIS patients except those with clear contraindications to modest volume loading.

**Head of Bed Manipulation**

Cerebral blood flow, particularly in ischemic territories, can be augmented by lowering the head relative to the heart.\textsuperscript{24,25} The underlying mechanism is not clear, but may be related to changes in the influence of gravity on blood flow between the heart and brain. In the authors’ experience, lowering the head of bed (HOB) to 0\degree appears to be most effective in patients with fixed large vessel stenoses, but the benefits are not clearly limited to this population. The potential benefit of lowering the HOB must be balanced against its well-known negative effects, including increasing ICP\textsuperscript{25} as well as the risk for aspiration and pneumonia.\textsuperscript{26} Additionally, there are no clinical data that show HOB lowering to have beneficial effects on functional outcomes or mortality. Thus, its use must be carefully considered in each AIS patient. The authors initially try keeping the HOB flat in all AIS patients except for those at high risk for intracranial hypertension or hydrocephalus (large hemispheric or cerebellar infarct), aspiration (severe bulbar dysfunction), or orthopnea (acutely active pulmonary disease such as pulmonary edema, pneumonia, or exacerbation of chronic obstructive pulmonary disease).

**CEREBRAL EDEMA, ICP, AND TISSUE SHIFTS**

**Overview**

Infarcted brain swells, and this swollen tissue, if of sufficient volume, can injure surrounding, healthy brain by increasing ICP and by causing brain tissue to shift into abnormal positions. Intracranial hypertension is thought to cause secondary injury primarily by decreasing the cerebral perfusion pressure, thereby causing global cerebral ischemia. Tissue shifts, on the other hand, lead to secondary injury by way of the ischemia that is caused by (1) separation of the shifting brain from the relatively fixed dural origins of its arteries and veins and (2) direct compression of vascular structures by the shifting brain.\textsuperscript{27} Because peak cerebral edema typically occurs at least 24 hours after the onset of AIS,\textsuperscript{28–30} these problems only rarely become an issue in the ED. Nonetheless, in patients who present in delayed fashion, patients who have undergone reperfusion therapy, and some young patients, malignant edema can develop early enough to become problematic in the ED. The emergency physician must be able to anticipate, rapidly detect, and swiftly and effectively treat this serious complication.

ICP monitors are uncommonly placed in AIS patients, particularly while they remain in the ED. Furthermore, transtentorial herniation can occur in the absence of globally elevated ICP.\textsuperscript{31} Accordingly, diagnosis of cerebral edema and brain herniation is based on the neurologic examination and imaging findings. There are 2 main scenarios in which malignant cerebral edema that causes significant secondary brain injury may occur in AIS: large infarctions of the middle cerebral artery (MCA) territory and large cerebellar infarctions.

**Malignant MCA Syndrome**

The malignant MCA syndrome refers to the condition in which a large MCA infarction causes major tissue shifts and transtentorial herniation.\textsuperscript{29} As the infarct swells, it
displaces surrounding tissue, leading to horizontal displacement of the falx cerebri and horizontal and caudal shift of the thalamus and midbrain (Fig. 2). Clinical manifestations of these tissue shifts are listed in Table 2. Box 3 lists markers of increased risk for development of the malignant MCA syndrome.

Mortality and morbidity in the malignant MCA syndrome are substantial. When treated with aggressive critical care—but without decompressive surgery—mortality is between 55% and 80%, and a large proportion of survivors have substantial neurologic deficits. The first priorities of critical care management for patients at risk of developing this syndrome are prevention and early detection. Minimization of cerebral edema involves careful management of sedation and analgesia, fluid status, body temperature, and blood glucose. The patient’s HOB should be elevated to 30°. If signs of herniation develop, the authors employ a step-wise medical management algorithm (Box 4).

In the ED setting, the choice between mannitol and hypertonic saline is largely settled by which agent can be administered more quickly to the patient. Mannitol is more widely available, more familiar, and can be safely given through peripheral veins. It ultimately depletes intravascular volume through its diuretic effects, however, in contrast with hypertonic saline’s potent volume-augmenting effects. Thus, hypertonic saline is preferred in patients who have intravascular volume depletion. Regarding the primary effect of lowering ICP, insufficient data exist to validly compare the effects of mannitol and hypertonic saline in the setting of AIS. A recent meta-analysis of 5 trials that compared the effect of equiosmolar doses of these agents in patients with mostly traumatic brain injury suggests that hypertonic saline may be somewhat more effective, but these are not conclusive data.

Because medical treatment frequently fails to control edema and reverse or arrest tissue shift in large MCA infarcts, decompressive hemicraniectomy should be considered as soon as a patient manifests any signs of malignant edema. This treatment has recently been studied in 3 European randomized, prospective studies that included patients 18 to 60 years old. Meta-analysis of pooled data from these studies indicates that, when performed within 48 hours of stroke onset, hemicraniectomy decreases 12-month mortality by about 50%. This effect does not differ if the infarct is in the dominant or nondominant hemisphere. The gain in survival, unfortunately,
comes at the expense of a significant likelihood of surviving with severe disability; in the same meta-analysis, there was no significant effect of hemicraniectomy on reducing the proportion of patients with the combined outcome of death or severe disability.\textsuperscript{35} Given these limitations, the authors typically offer decompressive hemi-
craniectomy only to patients 60 years old and younger who are in generally good
health and who have no significant neurologic disability before the stroke. They are
careful to inform surrogate decision makers that the goal of the operation is to increase
the likelihood of survival and not necessarily to improve functional outcome, which
may well be poor. Due to the lack of clear benefit when performed more than 48 hours
after stroke onset,\textsuperscript{35} the authors involve the neurosurgery team early in patients at risk
for malignant MCA syndrome to facilitate operation at the earliest indication.

**Massive Cerebellar Infarction**

The posterior fossa contains little excess space to accommodate the additional mass
of a swelling cerebellar infarct, to which the vital structures of the brainstem lie in close
proximity (Fig. 3). Significant neurologic deterioration, therefore, is both common and
can be rapidly fatal in patients with large infarctions of the cerebellum. These conse-
quences occur by 2 main mechanisms of mass effect, which often develop in parallel:

- Obstructive hydrocephalus caused by compression of the fourth ventricle and its
  outlet foramina
- Direct compression of the brainstem, most typically the pontine tegmentum

Deterioration due to brainstem compression and hydrocephalus occurs in about
10% to 25% of patients with cerebellar infarction.\textsuperscript{41–44} This decline most often occurs

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<td>Clinical manifestations of brain tissue shift and herniation in the malignant MCA syndrome</td>
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<tr>
<td><strong>Clinical Manifestation</strong></td>
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<tr>
<td>---------------------------</td>
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<tr>
<td>Progressive decline in arousal</td>
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<tr>
<td>Upgoing toe, then frank weakness on the side of the body ipsilateral to the infarct</td>
</tr>
<tr>
<td>Unilateral dilated, poorly reactive pupil</td>
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<td>Extensor posturing</td>
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<th>Box 3</th>
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<tr>
<td>Markers of increased risk for the malignant MCA syndrome</td>
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<tr>
<td><strong>Clinical</strong>: NIHSS greater than 15</td>
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<tr>
<td><strong>Computed tomography (CT) scan</strong>:</td>
</tr>
<tr>
<td>▪ Hypodensity in greater than 50% of the MCA territory</td>
</tr>
<tr>
<td>▪ Hyperdense MCA sign</td>
</tr>
<tr>
<td>▪ 2 of the following 3 signs: hypodense basal ganglia, hypodense insular ribbon, and effacement of hemispheric sulci</td>
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on the third day after symptom onset, but it can occur within the first 24 hours.\textsuperscript{28,42,45}

No historical or neurologic examination findings reliably identify those patients who present without signs of brainstem compression who are at highest risk for deterioration. Imaging findings, however, can be helpful. Not surprisingly, larger infarctions are associated with higher risk. Imaging markers of increased risk of clinical deterioration are listed in Box 5.\textsuperscript{41,42} Clinical signs of brainstem compression or hydrocephalus are listed in Table 3.\textsuperscript{28,42} Patients with any of these clinical and imaging markers of

### Box 4
**Medical management of cerebral herniation**

- Seek and treat easily reversible causes of elevated ICP (pain, agitation, seizure, blood pressure too high or too low, inadequate oxygenation and ventilation)
- Osmotherapy
  - Mannitol
    - Initial dose 1–1.5 g/kg intravenously
    - Subsequent doses 0.25–1 g/kg intravenously
    - Administer via peripheral or central vein over 10 to 20 minutes
    - Replace intravascular volume lost through diuresis with normal saline to avoid hypotension and kidney injury
    - Monitor electrolytes and serum osmolality
      - Do not repeat doses if serum osmolality greater than 325 or sodium greater than 155
      - Replace potassium and magnesium lost through diuresis
  - Hypertonic saline
    - Formulations
      - 3% saline
        - 250 to 300 mL bolus over 10 to 20 minutes
        - Administer via central vein ideally, but peripheral is possible
      - 23.4% saline
        - 30 to 60 mL bolus over 10 to 20 minutes
        - Must be administered by central vein
    - Monitor serum sodium
      - Avoid raising by more than 12 mEq/L in 24 h or beyond 160 mEq/L
- Hyperventilation
  - Best performed by increasing the respiratory rate
  - Goal PaCO\textsubscript{2} is 30 mm Hg
  - Onset of effect is extremely rapid (minutes)
  - Only useful as a very temporary measure until more definitive therapy is implemented (usually surgical decompression) in severe herniation syndromes
    - Duration of effect is only 30 to 120 minutes
    - Can worsen ischemic brain injury by causing cerebral vasoconstriction when prolonged
  - Should be weaned over hours, in increments of 1 to 2 breaths/minute, to avoid rebound intracranial hypertension
Elevated risk for deterioration should be admitted to an ICU for continuous neurologic observation.

Examination findings caused by hydrocephalus and those due to brainstem compression overlap substantially, making it very difficult to determine if one or the other is the primary cause of decline. Once any sign of deterioration manifests, the likelihood and rate of progression to severe brainstem compression with coma, cardiorespiratory instability and loss of brainstem reflexes are unpredictable. Progression from the first signs of brainstem compression to coma tends to occur rapidly, over the course of as little as 1 hour and almost always within 24 hours. Accordingly, once any risk factor for deterioration due to edema has been identified—and ideally before the first clinical sign of deterioration occurs—neurosurgical consultation must be obtained immediately with the expectation that the patient may need emergent decompression within hours.

Decompressive surgery—external ventricular drainage (EVD) through lateral ventriculostomy and/or suboccipital decompressive craniectomy (SDC)—is life-saving and is the most effective treatment for malignant edema due to a cerebellar infarction. Without surgery, approximately 80% of patients who show signs of brainstem compression die in the short term. In contrast, mortality for patients in coma at the time of surgery who undergo SDC is about 20%, and good short-term

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Box 5

**Imaging markers of increased risk of clinical deterioration due to massive cerebellar infarction**

- Complete territorial infarction or infarction of the median vermic branches of the posterior inferior cerebellar artery (PICA) or the superior cerebellar artery (SCA)
- Hydrocephalus
- Shift of the fourth ventricle away from the side of infarction
- Deformity or anterior displacement of the brainstem
- Effacement of the basal cisterns
functional outcomes occur in 40% to 50% of patients.\textsuperscript{28,45} Medical therapy is used only as a way to temporize until definitive surgical therapy takes place. Osmotherapy, as described previously for the malignant MCA syndrome, should be implemented promptly upon the first signs of decline. Hyperventilation is reserved for patients who rapidly decline to coma. The specifics of when to operate and which operation(s) to perform remain controversial due to a lack of high quality data. Available data indicate 3 major themes: (1) EVD alone is frequently insufficient\textsuperscript{28,45}; (2) SDC is a safe procedure\textsuperscript{47,48}; and (3) outcomes after surgery are best for patients who are operated on before the onset of coma.\textsuperscript{28,45} One reasonable strategy based on the available data is to proceed directly to SDC with or without EVD once the level of arousal has consistently declined to worse than a GCS eye score less than 3 or FOUR eye score less than 2, or sooner if the progression of decline is rapid.

Deterioration in patients with cerebellar infarctions can occur due to progressive brainstem infarction caused by the vertebrobasilar thrombotic process that led to the cerebellar infarct in the first place.\textsuperscript{49} Such patients may rapidly develop decline in arousal, pupillary abnormalities, and hemi- or tetraparesis in the absence of significant brainstem compression, or hydrocephalus on imaging. Their prognosis is far worse than patients whose decline is due to mass effect alone. In practice, it can be extremely difficult to decipher deterioration due to compression of the brainstem from that due to brainstem infarction, particularly in the short time window in which one must decide whether to proceed to decompressive surgery. Although magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) is best for making this distinction, it is often impossible to obtain in this very brief time window. A compromise solution may be to perform CT and CT angiogram, proceeding to surgical decompression if there is no new occlusion in the vertebrobasilar system on which the decline can be blamed.

### POST-THROMBOLYTIC CARE

The use of intravenous thrombolytic agents to treat AIS began in the 1950s, but it was not until the National Institute of Neurologic Disorders and Stroke (NINDS) trial of rt-PA, published in 1995, that any trial clearly demonstrated net clinical benefit.\textsuperscript{50–52} Much of this success may be due to the NINDS trial’s careful exclusion of patients at high risk for ICH as well as careful control of ICH risk factors once rt-PA was administered. Accordingly, contemporary post-thrombolytic care is carefully modeled after the NINDS trial protocol and is centered on the goal of minimizing hemorrhagic complications, especially ICH. Key post-tPA precautions are listed in Box 6.\textsuperscript{2}
most important element of post-thrombolytic care is careful blood pressure management, which has been discussed in detail. Deviations from this strategy have proven to be substantially problematic.53

Treatment of rt-PA-associated ICH is discussed in another article in this issue. Intravenous thrombolysis is associated with 3 other major complications: extracranial hemorrhage, angioedema, and anaphylaxis. Treatment of life-threatening extracranial hemorrhage with factor replacement should mirror proposed treatment regimens for thrombolysis-associated ICH.

Orolingual angioedema, which can occasionally be severe enough to obstruct the airway, has been reported in 2% to 5% of AIS patients who have received intravenous rt-PA.54,55 This can rarely progress to an anaphylactic reaction.56 The use of angiotensin converting enzyme (ACE) inhibitor and infarction in the frontal or insular cortex confer an increased risk.54,55 The underlying mechanism is probably rt-PA induced activation of the kinin and complement systems, the former made worse by ACE inhibitors.56 The onset of angioedema typically occurs soon after rt-PA administration, most often before the 1-hour infusion is complete. The angioedema is frequently unilateral, most often contralateral to the stroke.55 Lingual hematoma, also quite rare, is the most important element in the differential diagnosis, and can be excluded with CT.54 Treatment of angioedema consists of immediately stopping the rt-PA infusion, securing the airway with endotracheal intubation if necessary, and administration of antihistamines, corticosteroids, and, in the case of anaphylaxis, epinephrine. Early consultation of the otolaryngology service is important in case severe airway complications occur.

ACUTE ANTITHROMBOTIC THERAPY

While antithrombotic therapy is the cornerstone of secondary stroke prevention, there is actually no high-quality evidence supporting the use of any anticoagulant or antiplatelet agent in the first hours after onset of AIS.2 Therefore, perfusion optimization (including evaluation for IV rt-PA and endovascular therapy), not initiation of antithrombotic therapy, should be the focus of initial management. Once it has been determined that a patient will not be receiving intravenous rt-PA, administration of aspirin (325 mg orally or 300 mg rectally if the patient has not passed a dysphagia screen) can be considered in the ED for patients without other contraindications. In any case, this should be given within 48 hours of stroke onset.2

Anticoagulation of all-comers in the acute setting of ischemic stroke has generally been found to confer no benefit, causing a number of intracranial hemorrhages essentially equal to the number of early recurrent strokes it prevents.57 These results are
difficult to apply to individual patients, however, due to substantial heterogeneity in the anticoagulants and timing of administration across the different trials as well as heterogeneity in stroke etiology within individual trials. The last issue is crucial, as a priori pathophysiologic considerations and lower quality clinical data suggest that anticoagulation in AIS due to some etiologies—especially those associated with a high likelihood of ultraearly recurrence or progression—may be associated with a favorable risk–benefit ratio. For this reason, in consultation with an experienced vascular or critical care neurologist, the emergency physician could consider acute anticoagulation in patients who are not treated with intravenous thrombolysis or endovascular revascularization with AIS due to the mechanisms listed in Box 7.

Larger infarcts, a higher degree of anticoagulation, and higher blood pressure probably confer a higher risk of the most dreaded complication, ICH. These issues must be balanced against the estimated benefit in terms of preventing early recurrent stroke when considering acute anticoagulation in individual patients. For those rare AIS patients for whom anticoagulation is initiated in the ED, exquisite care must be taken to control modifiable factors known to influence the risk of ICH (Box 8).

**POSTSTROKE SEIZURES**

Approximately 5% of AIS patients have a seizure within 7 to 14 days of stroke onset. Most of these seizures are partial, and status epilepticus is particularly uncommon, occurring in less than 1% of patients with AIS. Cortical infarction and higher stroke severity are the only known risk factors for seizures after AIS. It is not clear if the occurrence of early poststroke seizures affects outcome, and the effect of antiseizure prophylaxis has not been well-studied in AIS. On the other hand, some data indicate that exposure to common antiepileptic medications, including phenytoin and benzodiazepines, after AIS seems to worsen long-term neurologic outcome. Routine seizure prophylaxis is therefore not recommended after AIS, even in patients with large cortical infarctions. The authors typically treat patients after a first early poststroke seizure with levetiracetam due to its ease of administration, infrequent drug–drug and metabolic interactions, and possible action as a neuroprotective agent. Because of its association with poor neurologic outcomes after stroke, the authors reserve phenytoin for those rare patients with poststroke status epilepticus. The authors' treatment of status epilepticus in AIS patients does not differ from the way they treat this disorder in other patient groups.

**SEDATION AND ANALGESIA**

Because of the primacy of the neurologic examination in monitoring the physiology of the brain, every reasonable effort must be made to avoid confounding it with sedatives and analgesics. For many AIS patients, this is not an issue as, in the absence of

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**Box 7**

**Possible indications for acute anticoagulation in AIS**

- Symptomatic stenosis or acute occlusion of cervical or large intracranial arteries (internal carotid, vertebral, middle cerebral, and basilar arteries)
- Dissection of a cervical vertebral or internal carotid artery
- Cardoembolism due to mechanical heart valve or intracardiac thrombus (noninfectious etiologies)
endotracheal intubation, significant pain and agitation are uncommon problems. Careful thought should be given to the indications for and manner by which sedation and analgesia are achieved in the intubated AIS patient. Many AIS patients, for example, are intubated at least in part due to decreased level of arousal. These patients frequently do not show signs of pain or agitation and should not receive sedatives or analgesics. For those patients who do have significant pain or agitation, nonpharmacologic measures such as optimizing ventilation, treating urinary obstruction, minimizing stimulation, offering reassurance, and when possible, allowing the presence of a person familiar to the patient, should be attempted first.

If these are unsuccessful, the patient should be assessed for pain and, if present, treated with analgesics. The minimal necessary dose of short-acting agents that have the least effect on the neurologic examination should be used. Extreme care should be taken to avoid or counteract the potentially significant hypotensive effects possessed by most of the commonly used sedatives and analgesics. The authors find a step-wise approach that begins with nonsedating agents such as acetaminophen and tramadol to be useful. Revised goals are often necessary for treatment of severe pain in patients with acute brain injuries, as treatment to zero pain without significant alteration of the neurologic examination caused by the analgesics is rarely possible.

If these methods fail to calm an agitated patient, the authors use sedatives following the same basic principles as treatment of pain: start low and go slow. For nonintubated patients, very low doses of antipsychotics or short-acting benzodiazepines are useful. Antipsychotics are the authors’ drug of choice owing to their lesser propensity for causing significant sedation, respiratory compromise, and delirium than benzodiazepines. The authors find low-dose quetiapine (12.5 to 25 mg) to be particularly useful. This drug is less likely than haloperidol to cause corrected QT interval prolongation and extrapyramidal symptoms, and has been shown to be quite useful for treating ICU delirium in small studies of non-neurologic patients. For patients who do not have enteral access, haloperidol starting at 0.5 to 1.5 mg IM or intravenous every 15 to 30 minutes, with slow dose escalation if the preceding dose was ineffective, can be used. If the agitation appears to be caused predominantly by anxiety, the authors may administer 0.5 to 1 mg of lorazepam intravenously. If this is ineffective after 15 minutes, they will occasionally repeat the dose once more. The authors generally do not give more benzodiazepines than this because of their propensity to significantly confound the neurologic examination.

Propofol is probably the most widely used sedative in neurocritical care for intubated patients because of its extremely short duration of action. When propofol is used in
the AIS patient, one must anticipate hypotension and not allow the MAP to drop by more than about 10%. Decreasing the rate of propofol infusion, intravenous boluses of normal saline and vasopressors may be required. The authors avoid midazolam when possible because of its prolonged duration of effect when used as a continuous infusion, particularly in patients with renal or hepatic dysfunction.\textsuperscript{76} Dexmedetomidine is a central alpha-2 adrenergic receptor agonist that has nearly ideal properties as a sedating agent for AIS patients; it effectively diminishes agitation and anxiety while depressing consciousness far less than propofol or midazolam, does not significantly blunt respiratory drive, has analgesic properties, and does not frequently lead to significant hypotension.\textsuperscript{77} In a number of studies, including 2 large, blinded, randomized, controlled trials, when compared with lorazepam and midazolam for sedation in the general ICU patients, dexmedetomidine has been shown to decrease time with delirium, coma, and mechanical ventilation.\textsuperscript{77} It has also been shown to be safe and effective in small studies in critically ill neurologic and neurosurgical patients.\textsuperscript{78,79} The main adverse effect of dexmedetomidine is bradycardia, which rarely can be severe. Because dexmedetomidine has not been well-studied, specifically in AIS and other acutely brain-injured patients and these patients may be prone to autonomic instability, vigilance for bradycardia and a low threshold for discontinuation of the drug if bradycardia occurs seem warranted in this context.\textsuperscript{80}

**CARDIAC CONSIDERATIONS**

Cardiac complications are common and explain up to 20% of the early mortality after ischemic stroke.\textsuperscript{81,82} Patients with ischemic stroke are at risk for cardiac complications not only due to shared risk factors, but also due to neurogenic factors. One example of the latter would be a patient with a right middle cerebral artery stroke involving the insular cortex, which is associated with a higher risk of cardiac complications thought to be related to disruption of the autonomic nervous system.

An electrocardiogram (EKG) is recommended in all AIS patients due to the high incidence of concomitant heart disease.\textsuperscript{2} While EKG abnormalities occur in up to 90% of stroke patients, potentially life-threatening arrhythmias occur in less than 10% of patients.\textsuperscript{83} EKG changes such as ST segment and T wave changes are very common in the setting of a stroke and may be difficult to distinguish from acute myocardial infarction. Approximately 13% of ischemic stroke patients have a concomitant myocardial infarction.\textsuperscript{83} Particularly for patients who present within the time window for thrombolytic or endovascular therapy, obtaining an EKG should not be allowed to prolong the time to head CT.

Cardiac troponin levels may be elevated in 17% of patients with ischemic stroke and are associated with higher risk of in-hospital cardiac complications and death.\textsuperscript{84} Troponin release may either be due to autonomic activation after AIS (particularly involving the insular cortex) or be due to comorbid coronary artery disease with myocardial ischemia. The TRELAS (TRoponin ELevation in Acute ischemic Stroke) trial will prospectively determine the frequency and potential etiology of troponin elevation in a large cohort of ischemic stroke patients with the intention of providing recommendations for cardiac evaluation of these patients.\textsuperscript{85}

**Atrial Fibrillation**

Atrial fibrillation, which may be either the cause of or the result of the stroke, is probably the most common arrhythmia associated with AIS. Other arrhythmias such as sinus tachycardia and premature ventricular or atrial complexes may be nearly as common. Atrial fibrillation often suggests underlying disease such as myocardial infarction, thyrotoxicosis, and acute lung disease. Atrial fibrillation is associated with
higher mortality after AIS. A retrospective review of the Virtual International Stroke Trials Archive-Acute database containing patients from 30 acute stroke trials revealed that atrial fibrillation was associated with a significantly higher rate of serious cardiac complications including heart failure, ventricular tachycardia or fibrillation, and cardiac mortality. Given the higher rate of potentially preventable cardiac complications, close surveillance of those patients with atrial fibrillation is suggested.

Although there are no clinical trials looking at the value of cardiac monitoring in acute stroke patients, AHA/ASA guidelines state that at least 24 hours of telemetry monitoring are warranted to screen for atrial fibrillation or other serious arrhythmias.

**Congestive Heart Failure**

In AIS, acute myocardial infarction and heart failure have been found to be associated with increased mortality at 3 months. Factors associated with higher risk of in-hospital myocardial infarction or heart failure include history of angina, myocardial infarction in the 3 months before admission, admission hyperglycemia, and high admission NIHSS score. Awareness of these risk factors for cardiac complications may help with timely management and possibly improve clinical outcome.

Similar to findings in other studies, a prospective cohort of over 500 patients with ischemic stroke found elevated serum brain natriuretic peptide (BNP) levels were associated with cardioembolic stroke, lower ejection fraction, left atrial dilatation, and atrial fibrillation. Among those with cardioembolic stroke, elevated BNP was associated with higher mortality and lower likelihood of good functional outcome at 6 months. BNP testing might be considered for prognostication as well as to help determine aggressiveness of heart failure treatment and intensity of monitoring.

**Neurogenic Stunned Myocardium**

Neurogenic stunned myocardium is a reversible cause of cardiac dysfunction seen more frequently with subarachnoid hemorrhage, but it can occur with other acute intracranial disorders such as ischemic stroke. It is characterized by globally decreased myocardial wall motion not caused by coronary disease, and it is more likely to occur in women and in those with a more severe neurologic injury. It is thought to be caused by a catecholamine surge, which leads to contraction band necrosis. It has been described as tako-tsubo cardiomyopathy due to its appearance similar to that of an octopus fishing pot. Diffuse - as opposed to focal - EKG changes, echocardiographically determined wall-motion abnormalities that do not correlate with a coronary vascular territory, and cardiac troponin levels that are disproportionately low for the degree of ST-segment changes and wall-motion abnormalities can distinguish this reversible condition from a myocardial infarction.

**Summary of Cardiac Considerations**

Awareness and early recognition of these potential cardiac complications are imperative to avoid delays in treatment. For arrhythmias, treatment would be similar to their treatment in nonstroke patients. Beta-blockers and calcium channel blockers are generally used to reduce a rapid ventricular rate. Cardiology consultation should be considered. For neurogenic stunned myocardium with significant depression of left ventricular function, avoidance of fluid overload, supportive care including in rare cases inotropic drugs, and treatment of causal neurologic issues such as intracranial hypertension may be helpful. If inotropic support is needed, milrinone offers the theoretical advantage over dobutamine in that it is not an adrenergic receptor agonist, a potentially important consideration given the role of catecholamine excess in the generation of neurogenic stress myocardium.
PULMONARY CONSIDERATIONS

Respiratory Failure

Respiratory failure occurs in about 5% to 10% of AIS patients, and up to 25% of patients with infarction in the MCA territory. It is most frequently caused by loss of airway control, itself the result of a combination of decreased arousal and oropharyngeal incoordination. These lead to impaired handling of secretions and inefficient respiratory mechanics due to collapse of the upper airway. Patients with basilar territory infarctions additionally may have central hypoventilation with periods of apnea. Pulmonary parenchymal disease is less common and is typically due to aspiration pneumonitis/pneumonia, and rarely neurogenic pulmonary edema.

Respiratory failure has critical consequences for AIS patients, as both hypercapnea and hypoxemia can worsen brain injury through worsening ischemic injury and raising the ICP. Accordingly, it must be detected and reversed as early as possible. This is made challenging by the fact that the presentation and evolution of respiratory failure in AIS often differ considerably from that seen in patients with acute pulmonary disease. Rather than manifesting obvious signs such as anxiety, tachypnea, increased respiratory effort, and low oxygen saturation, AIS patients in respiratory failure frequently have depressed arousal, a respiratory pattern that may not appear labored, and, as long as supplemental oxygen is supplied, oxygen saturation readings that can remain normal until late. If allowed to continue, through a vicious cycle of hypoventilation, secretion accumulation, atelectasis, hypoxemia, and hypercapnea, this process can insidiously lead to cardiopulmonary collapse with refractory hypoxemia, bradycardia, hypotension, and cardiac arrest.

Determination of the need for endotracheal intubation in AIS, therefore, is based largely on indications other than oxygen saturation and findings on chest imaging and arterial blood gas testing. Thus far, there are no evidence-based guidelines for the optimal timing and specific indications for intubation in AIS, and the decision remains based on clinical judgment. Specific relative indications are listed in Box 9.

Once the AIS patient has been determined to have respiratory failure, if a rapidly correctable cause is not present, he or she should undergo endotracheal intubation. Noninvasive positive pressure ventilation should not be used in these patients, as it does not correct the underlying problems with airway control and, in fact, can exacerbate them.

Technique of Rapid Sequence Intubation

The consequences of the physiologic disturbances that commonly occur during rapid sequence intubation are amplified in the AIS patient. Hypoxemia, hypercapnea, hypertension, and hypotension can all exacerbate ischemic brain injury. Additionally,

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<th>Box 9</th>
<th>Relative indications for tracheal intubation in AIS patients</th>
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<td>• Decreased or rapidly progressive decline in level of arousal. A GCS of 8 to 10 has been proposed as a trigger, but the GCS is not an ideal measurement tool in AIS patients.</td>
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<td>• Weakness or incoordination of the facial, oral, lingual, and pharyngeal musculature and reflexes. Key signs on examination include prominent facial weakness, severe dysarthria, obstructed respiratory pattern/sounds, weak/absent cough, and poor handling of oral secretions (drooling, pharyngeal pooling)</td>
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<td>• Large hemispheric or cerebellar infarctions</td>
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<td>• Brainstem infarctions, especially in the pons</td>
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airway manipulation and succinylcholine have the potential to transiently lead to significant elevation of the ICP,\textsuperscript{100,101} a crucial concern for patients with space-occupying infarcts. Intubation techniques generally do not differ for AIS patients and are beyond the scope of this article. However, a few issues surrounding the choice of drugs in RSI for AIS are worth noting (\textit{Table 4}).\textsuperscript{100–104}

\textbf{Strategies for Mechanical Ventilation}

Mechanical ventilation of AIS patients is generally simple due to their typical lack of coexisting acute pulmonary disease.\textsuperscript{96} Oxygenation is paramount. Although there is no clear evidence to support any specific oxygenation targets, the authors aim to keep the oxygen saturation greater than 94\% and the PaO\textsubscript{2} greater than 80 mm Hg to facilitate oxygen delivery to ischemic brain. Hyperoxygenation with normobaric

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\textbf{Phase of Rapid Sequence Intubation} & \textbf{Issues} \\
\hline
Premedication & Airway manipulation can potently elevate ICP. Premedication with lidocaine (1.5 mg/kg intravenously) and fentanyl (2.5–3.0 \textmu g/kg intravenously) can significantly blunt this response and should be performed when possible. Higher dose fentanyl boluses, which have been associated with transient but substantial increases in ICP and decreases in cerebral perfusion pressure, should not be used. \\
\hline
Induction & Etomidate is the ideal induction agent for most AIS patients owing to its minimal hemodynamic effects while remaining effective at creating favorable intubating conditions. Ketamine, which generally raises the blood pressure by way of sympathetic stimulation, is an alternative that can be considered in hypotensive patients. Older evidence indicating that ketamine causes an elevation in ICP has been contradicted by newer studies, although none have examined ketamine’s effect on ICP specifically during RSI. \\
\hline
Paralysis & Succinylcholine has been associated with elevations in ICP. While this issue is controversial, it deserves consideration in patients with large, space-occupying infarctions, for whom this effect could at least theoretically lead to significant intracranial hypertension, cerebral hypoperfusion, and even herniation. Additionally, AIS patients not infrequently present to the ED after having been down in the field for prolonged times, placing them at risk for rhabdomyolysis, an important contraindication to the use of succinylcholine. In either of these 2 scenarios, consideration should be given to either using a defasciculating dose of a nondepolarizing agent before paralysis with succinylcholine or to using a rapid-onset nondepolarizing agent such as rocuronium. \\
\hline
\end{tabular}
\caption{Issues regarding rapid sequence intubation technique in AIS}
\end{table}
and hyperbaric techniques are currently being investigated as therapies for AIS. Because thus far there is no high-quality supportive clinical evidence, these techniques should not be used outside of research protocols.105

Even in patients with considerable cerebral edema, prophylactic hyperventilation is not useful and potentially harmful due to, respectively, its short-lived effect on intracranial pressure and potential to exacerbate cerebral ischemia. Hypercapnea, a potent cause of increased ICP, must be fastidiously avoided. The authors’ PaCO2 goal in mechanically ventilated patients, therefore, is in the low normal range of 37 to 42 mm Hg.

RENAL CONSIDERATIONS

Intravascular Volume Targets

The importance of adequate intravascular volume in AIS has already been discussed. The goal for fluid management is euvolemia, as hypervolemia has enough negative consequences for the pulmonary and nervous systems to make it nearly as undesirable as hypovolemia. As in other critically ill patients, determination of intravascular euvolemia can be difficult in AIS patients. Blood pressure in the target range for the patient, heart rate less than 100 beats per minute, normal serum urea nitrogen (BUN) and creatinine, a BUN–creatinine ratio less than 20, and urine output at least 0.5 mL/kg/h are all markers of euvolemia. Consistent with studies in other types of critically ill patients, the authors do not find that measurement of central venous pressure or hemodynamic indices obtained from a pulmonary artery catheter is useful in managing the volume status and hemodynamics of AIS patients who do not have concomitant major derangements of cardiovascular system function.106,107

Choice of Intravenous Fluid Solution

Normal saline is essentially the only intravenous fluid solution that should be used for intravascular volume augmentation and maintenance in AIS patients. More hypotonic formulations, such as 0.45% saline and Lactated Ringer solution, are almost never used, because they do not augment or maintain intravascular volume as well as normal saline and, by virtue of their lower osmolality, can worsen cerebral edema.108,109 While intermittent bolus administration of hypertonic saline solutions such as 3% saline can be useful for treating intracranial hypertension, their value as a continuous infusion is unclear.110,111 The authors reserve continuous infusions of hypertonic saline for the treatment of severe hyponatremia. Dextrose-containing solutions of any osmolality should be reserved for the treatment of hypoglycemia because of the well-established and diverse deleterious effects of elevated serum glucose on acute cerebral infarctions. There is at present no role for routine administration of intravenous colloid solutions. Although the effectiveness of albumin infusion early in AIS as a neuroprotective therapy is currently being investigated, lack of high-quality human clinical data indicating benefit and possible problems with safety preclude the use of albumin infusions in the routine care of AIS patients.112

Electrolyte Management

Magnesium has been shown to have neuroprotective effects in a number of animal models. Clear clinical evidence of the effectiveness of magnesium supplementation in improving outcomes after AIS is thus far lacking. Safety of moderate magnesium supplementation, on the other hand, appears to be acceptable.113 Accordingly, it is the authors’ practice to maintain high-normal magnesium concentrations of 2 to 2.5 mg/dL in AIS patients through the use of intravenous magnesium sulfate infusions.
The effect, if any, of serum potassium concentration on AIS outcomes has not been well investigated. Extrapolating from epidemiologic data linking low serum potassium concentration with increased risk of stroke mortality as well as recent data linking increased mortality in acute myocardial infarction with serum potassium concentrations less than 3.5 mEq/L or greater than 4.5 mEq/L, the authors aim to maintain a serum potassium concentration of 3.5 to 4.5 mEq/L in their AIS patients. Because of changes in osmolality associated with changes in serum sodium concentration, serum sodium levels should be maintained within normal limits. Sodium concentration abnormalities are common in AIS, but a detailed discussion of their diagnosis and management is beyond the scope of this article. Interested readers are referred to the review by Rabinstein and Wijdicks.

TEMPERATURE CONTROL

Induced hypothermia has been recognized as being potentially beneficial in limiting secondary injury after acute brain injury since the middle of the 20th century. More recently, human and animal data have consistently shown that even low levels of fever can significantly worsen ischemic brain injury. In the Copenhagen Stroke Study, a large prospective cohort study of predominantly AIS patients, a 1°C increase in body temperature on admission doubled the odds of in-hospital death or poor neurologic outcome at discharge, independent of other, known predictors of outcome. These observations are explained by the fact that most of the key cellular and molecular processes underlying secondary brain injury—including apoptosis, mitochondrial dysfunction, endothelial dysfunction, inflammation, and excitotoxicity—are temperature-dependent. These facts, along with the success of therapeutic hypothermia in improving outcomes after cardiac arrest and perinatal asphyxia, have intensified investigation of induced normothermia (IN) and therapeutic hypothermia (TH) as treatments for AIS.

Induced Normothermia

IN is the use of pharmacologic fever control and physical cooling therapies to maintain normothermia (37 to 37.5°C) in patients with fever. Small, preliminary human clinical studies of IN in patients with severe brain injury of various types have shown the therapy to reduce intracranial pressure and microdialysis markers of cerebral metabolic distress. Nonetheless, there are at present no clinical data directly relating the effect of IN on neurologic outcome in patients with brain injury of any type, including AIS. Accordingly, the indirect evidence provided by studies identifying fever as a strong risk factor for poor neurologic outcome along with the relative ease and safety of application of IN with recently developed surface and endovascular cooling devices underlie the rationale for using IN in AIS patients.

IN is associated with adverse effects that are similar to those seen with TH, perhaps the most important of which is shivering. Shivering, caused by activation of the sympathetic nervous system, not only limits the effectiveness of fever control therapies in lowering body temperature, but also increases the total body metabolic rate by as much as a factor of 3; additionally, it is associated with a rise in mean arterial pressure of about 10 mm Hg. Although these responses are most common and potent in young, male patients, they are of the most consequence in older patients of either sex, in whom the hemodynamic consequences of these physiologic changes can have serious cardiovascular consequences. In addition, shivering may increase the cerebral metabolic rate, and in patients with severe brain injury, shivering is associated with increased intracranial pressure and decreased brain tissue oxygenation. For all of these reasons, effective shiver control is paramount to effectively employing...
IN. The masking of fever as an indication of new or worsening infection and the possibility of worsening of existing infections are other important adverse effects of IN.

The authors employ IN in patients with large ischemic strokes for neuroprotection and to limit cerebral edema using a step-wise approach. The first step, which can be easily employed in the ED, involves simple environmental interventions (minimal clothing/bed clothes on the patient and a cool room) and administration of acetaminophen. The authors do not use a typical cooling blanket as, in their experience, these often produce shivering without significantly lowering the core temperature. The next step is active temperature control using the Arctic Sun external cooling device (Medi-vance, Louisville, Colorado). At this point, an antishivering protocol based on the Columbia ant-shivering protocol is used. Given the lack of clear benefit of IN, the authors abort the treatment if shivering cannot be controlled without the use of neuromuscular blocking agents unless it appears to be controlling potentially malignant cerebral edema. Given its complexity, labor-intensive nature, potentially narrow therapeutic index with shivering, and unknown benefits, the authors do not take IN beyond environmental measures and acetaminophen in the ED.

**Therapeutic Hypothermia**

There are 2 potential uses for TH in AIS: general neuroprotection and control of malignant cerebral edema. Despite substantial animal evidence for effectiveness in neuroprotection, there are as yet insufficient human clinical data to support the broad use of TH in AIS outside of clinical trials. As of the writing of Polderman’s 2008 review, only 145 subjects had been included in 7 small studies of the use of TH in AIS. Since then, the only study of significance published on the topic, the Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke trial, included 59 patients. These existing studies indicate that implementation of TH for AIS patients is feasible, not prohibitively unsafe, and can be combined with intravenous thrombolysis without major hemorrhagic complications. Major problems limiting the conclusions that can be drawn from these studies include insufficient numbers of patients for determining effects on clinical outcomes; an excess of potentially preventable adverse effects in treated patients, including infections (mostly pneumonia) and rebound intracranial hypertension during rewarming; differences in duration of hypothermia; and a wide variety of methods and protocols used to control body temperature and shivering and protect against known complications of the therapy. Furthermore, in many studies hypothermia may have been achieved too late to be effective. Based on animal data, this window may be as short as 1 hour, and at its longest probably is not longer than 6 hours. Given the widespread experience and success achieved with the use of TH for coma after cardiac arrest and the lessons learned in these preliminary studies, the time is ripe for a large-scale trial of TH for AIS.

While the utility of routine use of TH in AIS is unknown, existing data rather clearly show that malignant cerebral edema and elevated ICP can be effectively controlled by TH. Accordingly, TH may be useful in treating AIS patients with malignant edema who either cannot undergo hemicraniectomy or for whom hemicraniectomy fails to control intracranial hypertension or shift. Rebound intracranial hypertension during rewarming is particularly common and dangerous in such patients. Very slow, controlled rewarming at a rate of 0.1 °C per hour may prevent this.

**GLYCEMIC CONTROL**

Hyperglycemia is common in patients arriving to the ED with stroke. Serum glucose greater than 200 mg/dL is associated with a worsened prognosis and has been associated with
increased risk of hemorrhagic transformation after thrombolysis.\textsuperscript{130,131} Hyperglycemia may be harmful due to increased tissue acidosis, free radical production, impairment of the blood–brain barrier, augmentation of cerebral edema, and higher risk of hemorrhagic transformation of the stroke.\textsuperscript{130,132} Another consideration, however, is that hyperglycemia may simply be an epiphenomenon or marker of a more severe stroke.\textsuperscript{133}

Persistent hyperglycemia greater than 200 mg/dL during the first 24 hours after a stroke has been shown to predict expansion of the infarct size and poor neurologic outcome.\textsuperscript{134} This implies that acute management of hyperglycemia might benefit the AIS patient. The exact blood glucose level that should be targeted, however, is not entirely clear. In the AHA/ASA ischemic stroke guideline, a class 2a, level C evidence recommendation is to administer insulin when serum glucose concentration is greater than 140 to 185 mg/dL.\textsuperscript{2} However, since that guideline was published, the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm) trial of critically ill medical and surgical patients found higher mortality with target blood glucose levels of 80 to 110 mg/dL compared with levels of 140 to 180 mg/dL.\textsuperscript{135} This trial did not, however, report inclusion of ischemic stroke patients. One small prospective randomized trial of insulin for glycemic control in critically ill neurologic patients (including ischemic stroke patients) found no difference in neurologic outcome when a goal of serum glucose less than 151 mg/dL was compared with a goal of 80 to 110 mg/dL. There was a higher incidence of hypoglycemia in the group with the lower goal glucose concentration.\textsuperscript{136} It is hoped that further evidence from ongoing trials, such as the Stroke Hyperglycemia Insulin Network Effort (SHINE) trial will clarify the risk–benefit analysis of glycemic control in AIS.

Because hypoglycemia can mimic AIS signs and can lead to irreversible brain injury, close monitoring for this complication and rapid treatment when it is detected are essential. Concerns have been raised in microdialysis studies that intensive glycemic control may lead to low cerebral extracellular glucose and be detrimental to severely brain injured patients.\textsuperscript{137} Given the dual concerns of potential hypoglycemia and its consequences with intensive insulin therapy on the 1 hand, and the importance of avoiding severe hyperglycemia on the other, the authors’ approach is to administer insulin aiming for a blood glucose level of 120 to 180 mg/dL with close glucose monitoring. A continuous infusion of intravenous insulin is preferred in critically ill patients, while subcutaneous insulin may be appropriate in most other patients.

PROPHYLAXIS

Pneumonia

Pneumonia develops in about 13% of AIS patients, and causes approximately 35% of deaths after AIS.\textsuperscript{138} Fortunately, this is largely a preventable complication. Dysphagia, which may occur in up to 78% of stroke patients, is thought to be responsible for a large proportion of poststroke pneumonia by way of aspiration of oral and gastric contents.\textsuperscript{138,139} Despite well-established risk factors, poststroke aspiration is infrequently clinically obvious, and many patients without overt oropharyngeal dysfunction are at risk for clinically significant dysphagia and aspiration.\textsuperscript{138,139} Hinchey and colleagues demonstrated that use of a formal dysphagia screen, leading to withholding or modification of oral intake for patients with dysphagia, was associated with a >50% reduction in poststroke pneumonia.\textsuperscript{138} As stroke-related dysphagia tends to be worst early in the illness, it is crucial for its detection to occur as early in a patient’s hospital course as possible. This makes the ED the ideal place for dysphagia screening. Dysphagia screening is simple, consisting of observing a patient swallow a small amount of water.\textsuperscript{140} It can be performed at the bedside by any nurse
or physician trained in the evaluation. Current AHA/ASA guidelines recommend that no oral intake, including medications such as aspirin, be allowed in AIS unless the patient passes a bedside dysphagia screen. Adherence to this recommendation is an important quality indicator for AIS stroke care. For patients who fail the bedside dysphagia screen, consideration should be given to placing a nasogastric tube in the ED (contraindicated if the patient has received rt-PA) if oral medications are necessary.

**Venous Thromboembolism**

In the absence of venous thromboembolism (VTE) prophylaxis, approximately 25% to 68% of AIS patients will develop a deep venous thrombosis (DVT) or pulmonary embolus (PE). This risk increases up to 75% in patients with hemiplegia. DVTs may develop as early as poststroke day 2, with peak incidence occurring between poststroke days 2 and 7. Pulmonary emboli account for about 20% of VTE complications in AIS and are estimated to cause 25% of early deaths following AIS. Accordingly, careful, early VTE prophylaxis is crucial. The use of subcutaneous unfractionated heparin (UFH) or LMWH has been associated with a 79% decrease in risk of DVT and a 40% decrease in risk of symptomatic PE. The effectiveness of intermittent sequential compression devices (SCDs) in AIS is unclear, but they have few adverse effects. VTE prophylaxis should consist of immediate application of SCDs to the lower limbs and early (generally beginning 12 to 24 hours after admission) mobilization with at least passive range of motion exercises. Prophylactic subcutaneous UFH or LMWH should begin immediately for all patients except those with strong contraindications. Patients who received intravenous rt-PA should receive a first dose of prophylactic UFH or LMWH 24 hours after the rt-PA was administered, provided there is no major hemorrhagic transformation on follow-up CT.

**Stress Ulcer**

Critically ill AIS patients are under the influence of similar physiologic stressors as other critically ill patients. They may actually have increased gastric mucosal destruction associated with increased vagal tone and greater gastric acid production. While there is a relative paucity of data related specifically to the risk of stress ulcers and effectiveness of prophylaxis in stroke patients, it is reasonable to extrapolate from the general ICU and traumatic brain injury data and conclude that critically ill AIS patients are at high enough risk to warrant active prophylaxis. Such prophylaxis should consist of the use of either a proton pump inhibitor or histamine type-2 receptor antagonist and early (within 24 hours of admission) enteral feeding.

**PROGNOSIS**

Early prognostication in the setting of AIS lacks precision and accuracy. The consequences of early rendering of a dismal prognosis, however, can be absolute, influencing decisions about level and aggression of care for the patient’s family as well as for other members of the medical team. Even in the setting of more severe ischemic stroke syndromes, including the malignant MCA syndrome or basilar artery occlusion, poor outcomes are not guaranteed. Early establishment of a poor prognosis in the ED might lead to premature limitations in treatment or early withdrawal of care, resulting in a self-fulfilling prophecy of poor outcome. Although one can never be sure that if such patients were offered more aggressive treatment their outcomes would be better, enough uncertainty surrounds early prognostication that
it is generally not advisable to make definitive neurologic prognoses in the emergency room setting regarding AIS patients.

REFERENCES


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