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Critical Care Management of Acute Ischemic Stroke

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Opinion Statement

Ischemic stroke accounts for approximately 85% of all strokes. Although severe strokes constitute a minority of cases, they are associated with a majority of the subsequent disability and death. Reperfusion therapy with intravenous tissue plasminogen activator (tPA) and/or endovascular thrombectomy is a mainstay of acute stroke management. Intensive care management of stroke is focused on reducing complications of reperfusion such as hemorrhagic transformation, and minimizing secondary brain injury, including brain edema and progressive stroke. Additionally, severe stroke patients frequently need ventilatory or hemodynamic support provided in an intensive care unit (ICU) setting. Here, we discuss the current medical and surgical ICU management aspects of acute ischemic stroke, and identify areas where ongoing studies may reveal new treatments to improve neurological recovery.

Introduction

Ischemic stroke epidemiology

Stroke is the fifth leading cause of death and a leading cause of disability in the United States, with nearly 800,000 Americans experiencing new or recurrent stroke annually [1]. Globally, stroke is the second leading cause of death, with 11.6 million incident ischemic strokes each year. While these numbers remain high, there has in fact been much progress in reducing mortality from stroke. This has been due in part to a focus on providing care in specialized stroke units. Less widely understood is the role of intensive care in stroke management, which is the focus of this review.

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There are number of types of ischemic stroke patients who may benefit from intensive care. The most obvious are those who qualify for an intensive care unit (ICU) setting based on respiratory or hemodynamic needs. In addition, specific stroke therapies place the patient at higher risk of complication in the immediate post intervention period. These include intravenous tissue plasminogen activator (tPA), which is used in 3.4–5.2% of ischemic strokes [2], and endovascular clot retrieval, which is increasing in use since the publication of multiple randomized trials demonstrating its efficacy [3–7]. These patients benefit from the close neurologic and hemodynamic monitoring provided in the ICU to minimize the risk of secondary injury, as discussed below. Separately, there is a subset of large hemispheric stroke patients who require close neuromonitoring in the ICU, in particular to watch for and intervene upon the development of malignant edema and hemorrhagic transformation.

Critical Care Neurology

Neuroscience-specific ICUs developed out of post-neurosurgical units and general intensive care units, with the first multidisciplinary unit established in the early 1980s, accompanied by publication of the first textbook of neurocritical care in 1983[8]. Since that time, neurointensive care has matured as a field, with establishment of the Neurocritical Care Society in 2002 and accreditation of neurocritical care fellowship programs starting in 2007. Conditions treated by neurointensivists include subarachnoid and other intracranial hemorrhages, head trauma, status epilepticus, severe neuromuscular and demyelinating disease, CNS infections as well as acute ischemic stroke. In addition to physicians with specialty training in neuroscience (neurology, neurosurgery, anesthesia) and intensive care, the neuro ICU is staffed by a team of neuroscience nurses, physical medicine and rehab physicians, occupational, physical, speech and respiratory therapists. There is evidence that care in a neuroscience-specific ICU leads to improved outcomes in TBI, intraparenchymal hemorrhage, and subarachnoid hemorrhage [9] and reduced cost of care for neurosurgical patients [10]. There is less direct evidence to support an outcome benefit of ICU care in ischemic stroke, but the association between care at a specialized stroke center and outcome is well established [11]. As this review will discuss, there is a significant subset of these ischemic stroke patients who are at risk for secondary brain injury (Table 1) and may benefit from critical care monitoring and interventions.

Treatment

Airway management/ventilatory support

Indications for Endotracheal Intubation

- As with any critically ill patient, a failure in adequate oxygenation or ventilation is an indication for endotracheal intubation following acute ischemic stroke.
- More commonly, stroke patients require intubation due to failure to protect the airway. Reduced level of consciousness (Glasgow coma scale < 8), either due to edema with resulting midline shift or due to thalamic or brainstem stroke, may also necessitate endotracheal tube placement. Other patients may have preserved consciousness, but have impaired oropharyngeal function due to the stroke injury itself. This is common with cerebellar, brainstem, and large hemispheric strokes.

The need for intubation can at times be anticipated based on the location of the infarct, but more reliable are clinical indicators such as dysarthria and inability to manage secretions.

Management of Aspiration

- Even those stroke patients without obvious difficulty protecting their airway may have more subtle oropharyngeal dysfunction and are at risk for aspiration. For this reason, it is imperative to keep all acute stroke patients strictly nothing-by-mouth until a swallow screening can be performed. Patients at risk for airway obstruction or aspiration should be maintained with the head of bed elevated 15–30 degrees.
- Initial fever, leukocytosis, and chest x-ray findings after an aspiration can be due to a chemical pneumonitis rather than true pneumonia and can at times be managed conservatively. Persistent fever, sputum production, and increasing oxygen requirement are all suggestive of developing aspiration pneumonia and should prompt empiric treatment for community- or hospital-acquired organisms, as appropriate [12, 13].

Extubation vs. Tracheostomy Placement

- Acute stroke patients typically require little in the way of mechanical ventilatory support, such that the limiting factor in extubation is oropharyngeal control and the timing and pace of neurologic recovery. In those patients with large hemispheric (middle cerebral artery or MCA) stroke, a GCS ≥ 8 was associated with successful extubation [14]. Similar results were seen in posterior fossa stroke, where GCS > 6 at the time of intubation combined mechanical ventilation time of less than 7 days were associated with success [15]. It is likely that more fined-grained examination can provide better predictive value, as evidenced by a study of a mixed group of neuro ICU patients (including ischemic stroke), showing that the ability to follow four separate commands was predictive of extubation success, more so than GCS alone [16].
- In those patients who fail extubation, or who are not expected to recover oropharyngeal function for a prolonged period of time, tracheostomy surgery is an appropriate bridge to allow for rehabilitation. While the overall rate of tracheostomy following stroke is low, it can be required in up to a third of patients with large stroke who require hemicraniectomy [17]. Optimal timing of tracheostomy is not clear, and is the subject of ongoing studies [18, 19].

Blood pressure management

Autoregulation

- Blood pressure is frequently elevated in the acute phase of ischemic stroke, with the intent to maximize perfusion of the ischemic tissue. There is evidence that lower blood pressure in the acute setting after stroke is associated with worsening of neurologic outcome [20, 21]. Similarly, highly elevated blood

pressure is considered detrimental [22]. As a result, it is advisable to avoid extremes of blood pressure while allowing for autoregulation of systolic blood pressure (SBP) in the initial 24 hours after stroke onset. Current guidelines recommend a target SBP <220mmHg [22], but a lower goal is appropriate, particularly if there are signs of cardiac strain or if there are comorbid conditions such as acute myocardial infarction, heart failure or aortic dissection in which a lower blood pressure target would be clearly beneficial.

Induced hypertension

- In the initial hours after onset of stroke, rare patients may show fluctuation in their exam associated with changes in blood pressure. These patients may benefit from ICU monitoring, and in some cases from induced hypertension. Case reports have shown that artificial augmentation of blood pressure can improve cerebral blood flow [23] and recruit collaterals [24]. It appears safe [25], but only small series have shown an associated improvement in neurological exam [26]. While larger trials are needed, induced hypertension may be appropriate in the right clinical scenario.

Special considerations in the post-thrombolysis/endovascular therapy patient

- To be eligible for treatment with intravenous tissue plasminogen activator (tPA), patients must have a blood pressure less than 185/110 [27, 28]. This can be achieved by treatment with intravenous antihypertensives within the acute period. After administration of tPA, patients should be maintained below 180/105 to minimize the risk of hemorrhagic conversion. A similar approach is taken with patients following endovascular thrombectomy, many of whom will have also received IV tPA. There may be a role for further blood pressure decrease after clot retrieval, an an effort to limited potential reperfusion hyperemia, however this has not been systematically examined.

Management of Cerebral Edema

Overview and Risk Factors

- Ischemic brain injury following stroke leads to an initial cytotoxic injury that can lead to the influx of water and development of tissue edema. While there is evidence that such swelling can impact outcome even in small infarcts [29], most concerning is the malignant edema that can occur following large hemispheric infarction. While this complication affects only an estimated 2–8% of ischemic stroke admissions annually, the mortality is high at 40–80% [30].
- Clinical factors associated with development of ischemic cerebral edema include young age [31], NIHSS ≥ 20 for dominant or ≥ 15 for non-dominant lesions, nausea/vomiting within 24 hours, systolic BP > 180mmHg within 12 hours [32], and an early decrease in level of alertness [33].
- Imaging can be helpful in predicting the risk of early cerebral edema. Head CT scanning within 6 hours that reveals hypodensity in >50% of the MCA territory

or involvement of multiple vascular territories is associated with subsequent malignant edema [34]. The presence of a diffusion weighted imaging (DWI) lesion of >82 cm^3 within 6 hours of symptom onset alongside known vessel occlusion is a specific, but not sensitive, marker for the prediction of malignant edema [35]. Sensitivity can be improved when a large early DWI lesion is combined with high NIHSS at 24 hours [36]. The degree of restriction on apparent diffusion coefficient (ADC) imaging, has been associated with edema [29] and outcome [37] after small stroke, but applicability to large stroke has not yet been reported.

Management and Monitoring of Elevated ICP

- While invasive ICP monitoring has a role following traumatic brain injury and is used for subarachnoid and intraparenchymal/intraventricular hemorrhage [38], it is not typically used in ischemic stroke. There is evidence that ICP can be elevated following decompressive hemicraniectomy [39], however the effect of monitoring and treating that ICP on outcome is unknown. It is possible that use of invasive ICP monitors, particularly as part of a multimodal monitoring strategy including cerebral blood flow, tissue oxygen and other sensors may play a role in stroke management at some point in the future, but current data does not support the routine use of such monitors.
- In addition to specific therapies for managing ICP, a number of conservative measures can be used to maximize cerebral venous outflow thereby minimizing the blood volume contribution to ICP. The head of bed should be elevated to at least 30 degrees with the head positioned midline to ensure patency of the internal jugular veins bilaterally. When central access is required, a subclavian site may avoid the potential risk of IJ thrombosis and occlusion, but is associated with higher rate of pneumothorax [40]. In ventilated patients, PEEP should be minimized to reduce intrathoracic pressure and improve venous return. Similarly, patients at risk for elevated ICP should be placed on a standing bowel regimen to avoid the increased abdominal (and therefore thoracic) pressure that can result from constipation.

Sodium management/Hyperosmolar therapy

- Given the potential for low serum sodium to contribute to cerebral edema, we maintain eunatremia (135–145mmol/L) in patients at risk for swelling after ischemic stroke. While sustained hypernatremia through the use of continuous 3% saline infusion is sometimes employed as an anti-edema measure, evidence for its clinical efficacy is lacking [41]. There is some evidence, particularly in subarachnoid hemorrhage, that sustained hypernatremia is associated with adverse cardiac events and poor neurologic outcome [42], however the causality of this relationship has not been established. Sustained hypernatremia may also theoretically lessen the effect of bolus hyperosmolar therapy by reducing the gradient across which water can be pulled out of tissue.

- Intermittent administration of hyperosmolar agents (such as 20% mannitol and 23.4% saline) is the mainstay of cerebral edema treatment in large ischemic stroke. A meta-analysis has shown a slight benefit for hypertonic saline in TBI patients [43], but the effect was modest and randomized trials do not yet exist. As a result, we tend to use mannitol and 23.4% saline interchangeably following ischemic stroke and choice of agent is driven by other patient factors. Mannitol is renally cleared and thus its use should be limited in those with acute or chronic kidney injury. Hypertonic saline requires central access for administration, and thus mannitol is often used as a first agent until such access can be established. Hypertonic saline also represents a greater volume challenge, and thus should be avoided in patients with congestive heart failure.
- Mannitol is given as a 20% solution at a dose of 1g/kg body weight every six hours. Serum osmolarity, BUN, sodium and glucose are monitored to allow for calculation of the osmolal gap according to the formula: Osm gap = Measured osm – (1.86(Na + K [mmol/L]) + glucose[mg/dL]/18 + BUN[mg/dL]/2.8). Osm gap > 10 suggests that mannitol is no longer being adequately cleared, and therefore additional doses should be held until the osmolal gap has closed to < 10.
- 23.4% saline is given as a bolus of 30mL every six hours. Serum sodium is monitored, and additional boluses are typically held if sodium is greater than 160mmol/L.
- In cases of severe, refractory edema, mannitol and hypertonic saline can be given in an alternating regimen. This is done in a “2/2/2” scheme, whereby mannitol is given at hour 0, 23.4% saline at hour 2, and then labs are checked at hour 4 in preparation for repeating the cycle starting at 6 hours.
- Patients receiving prolonged courses of hyperosmolar therapy will often “auto-taper” by missing doses due to exceeding laboratory parameters. In those that do not, we monitor for signs of clinical and radiographic improvement and then begin to taper treatment by spacing doses of hyperosmolar agents to every 8 or 12 hours before tapering off.

Decompressive Craniectomy

- Multiple randomized trials have demonstrated the efficacy of hemicraniectomy in improving both survival and outcome following hemispheric MCA infarction with malignant edema in patients under the age of 60 [44–46]. A more recent trial in patients ages 60–82 showed improved survival, but at the expense of more severe disability [47]. Based on these trials, our practice is to recommend hemicraniectomy within 24–48 hours of presentation in patients up to age 60 with large (>2/3 of MCA territory) hemispheric infarction and a decreased level of consciousness. For patients between the ages of 60–80, hemicraniectomy remains a life-saving procedure, however it should only be pursued if the likelihood of living with severe disability is within the patient’s goals of care.

- Similar trials have not been performed for posterior fossa stroke. However, given the potentially dire consequences of edema in this region, suboccipital craniectomy should be considered for any large cerebellar infarct. In particular, if brainstem compression is avoided through surgery, neurological outcome from the cerebellar infarction typically is good. Indicators for decompression have primarily been studied in cerebellar hemorrhage, but one can extrapolate from that data to consider craniectomy after cerebellar stroke in patients with development of new cranial nerve findings, reduced level of consciousness, evidence of brainstem compression, hydrocephalus, and/or with lesions > 3cm in diameter [48, 49].

Anti-edema pharmacotherapy

- There is no currently approved treatment to prevent the development of ischemic cerebral edema. A randomized, double-blind phase II trial of intravenous glyburide for the prevention of malignant edema found the drug to be well tolerated, to limit the development of midline shift, and to reduce mortality. However, glyburide did not impact the primary outcome of mRS at 90 days without hemicraniectomy [50]. A phase III trial is planned.

Management of Hemorrhagic Transformation

Hemorrhage risk factors and classification

- The most reliable predictor of hemorrhagic transformation is infarct size, with review of multiple studies showing that larger infarcts are associated with higher risk of transformation [51]. Level of matrix metalloproteinase 9 [52] has been associated with hemorrhagic transformation, particularly after tPA [53], but this marker is not sensitive or specific enough for routine clinical use.
- Post-stroke hemorrhagic conversion is typically classified using the categories established by the European Cooperative Acute Stroke Study (ECASS) criteria (Table 2) [27]. Hemorrhagic Infarction (HI) is defined as punctate or variable CT hyperdensity within the infarct. It is further subdivided into HI1 (small petechiae) or HI2 (more confluent). Parenchymal hematoma (PH) is an organized clot with mass effect, with PH1 defined as occupying <30% of the infarct territory with mild mass effect while PH2 occupies >30% of the infarct and has significant mass effect. Classification of hemorrhage type is important because it make dictate further plan of care, with those larger or symptomatic bleeds requiring aggressive treatment of coagulopathy and blood pressure while petechial hemorrhage can often be observed.

Reversal of coagulopathy

- Hemorrhage in the first 24 hours after receiving tPA can be reversed with administration of either cryoprecipitate or concentrated fibrinogen. Patient fibrinogen levels can be tracked to guide therapy, and if the fibrinogen level is < 100mg/dL, we typically give 0.15 units/kg of cryoprecipitate, which can be repeated an hour later if bleeding persists. Fibrinogen concentrate is known to be

effective at achieving hemostasis in a number of settings, and may have a more favorable safety profile than cryoprecipitate [54]. Head-to-head trials against cryoprecipitate have not been reported.

- Bleeding in the setting of elevated INR from warfarin can be reversed using either fresh frozen plasma, or one of several commercially available prothrombin complex concentrates (PCC). Dosing depends on the patient's INR and the particular product used. There is evidence that four-factor PCC reverses INR more quickly [55] and its use is associated with improved outcome after primary ICH [56]. For this reason, PCC should be the first choice for INR reversal if available.
- Newer oral anticoagulants, including the direct thrombin inhibitor dabigatran and factor Xa inhibitors abixaban, rivaroxaban and edoxaban, require different strategies for reversal. Coagulopathy due to dabigatran is treated with the specific reversal agent idarucizumab [57]. The factor Xa inhibitors can all be reversed using four factor prothrombin complex concentrate [58]. In all cases of severe bleeding, non-specific strategies can also be used to reduce the effect of drug. These include early administration of activated charcoal, hemodialysis (for dabigatran), or use of an anti-fibrinolytic agent such as tranexamic acid or aminocaproic acid.

Blood pressure management

- There aren't specific trials looking at blood pressure management after hemorrhagic transformation of an ischemic stroke, so BP targets are extrapolated from studies on primary intracerebral hemorrhage (ICH). Intensive (SBP < 140) BP control after ICH is achievable and safe [59] has been associated with less hematoma growth [60] compared to standard (SBP < 180) management. Given the preference to maintain adequate perfusion pressure immediately following ischemic stroke, it is reasonable to maintain SBP < 180 following hemorrhagic transformation, unless in cases of large or expanding hematoma where the balance of risk may favor a lower BP target.

Surgical clot evacuation

- It is relatively uncommon to pursue surgical evacuation for hemorrhagic conversion of an ischemic stroke. As with blood pressure management, most data comes from trials of primary ICH. Two randomized trials found no benefit for surgical clot evacuation over medical therapy alone[61, 62]. However, both trials had high crossover rates from the medical to surgical arm, so the possibility remains for a benefit of surgery in selected circumstances.
- Surgical evacuation of hemorrhage following ischemic stroke is not routinely recommended. However, there may be isolated cases where the volume of hematoma and resulting mass effect is enough to prompt surgery. Importantly, the current trials have not examined posterior fossa hemorrhage, and so hemorrhagic transformation of a cerebellar stroke with subsequent mass effect

should be considered for decompressive suboccipital craniectomy with or without clot evacuation.

Prevention of Early Recurrent Stroke/Stroke Progression

Antiplatelet therapy

- Aspirin is the mainstay of therapy immediately following acute stroke, having been shown in two large trials to reduce recurrent stroke and improve mortality [63, 64]. Aspirin should be started as soon as possible in all acute stroke patients that do not have a contraindication. Potential reasons to hold aspirin initially include treatment with tPA (hold aspirin for 24 hours after tPA), potential for needing surgery such as hemicraniecomty or early hemorrhagic conversion.
- There is not clear evidence for changing antiplatelet agents for patients who present with stroke despite taking aspirin. While clopidogrel has shown benefit in treatment of cardiac and peripheral arterial disease, there is not a demonstrated benefit over aspirin when used as a single agent for stroke prevention [65]. A trial of the newer antiplatelet agent ticagrelor [66] also did not show any additional benefit over aspirin.
- There is evidence for using dual antiplatelet therapy for a period of time in patients with small stroke or TIA [67]. Combined aspirin and clopidogrel is also often used in those with substantial intracranial arterial atherosclerosis, based on the medical arm of the SAMMPRIS trial of intracranial stenting [68].

Indications for acute anticoagulation

- While acute anticoagulation with heparin has not shown a benefit over aspirin when considering all comers with acute stroke [64], or even those with known atrial fibrillation [69], there are isolated cases where anticoagulation is indicated. These patients may benefit from monitoring in the intensive care unit while anticoagulation is administered, particularly in cases of large stroke where the risk of hemorrhagic transformation is significant.
- Patients who present with artery-to-artery embolus from carotid disease may benefit from acute anticoagulation [70] based on subgroup analysis from the TOAST trial. We often use anticoagulation as a bridge to carotid endarterectomy in patients where the stroke volume is low enough that there is minimal risk of reperfusion injury.
- A recent randomized trial did not find any benefit of anticoagulation over antiplatelet for the prevention of recurrent stroke after carotid or vertebral dissection [71]. However, the rate of stroke in this trial was very low and a large proportion of patients did not have dissection radiographically confirmed by central readers. Given that anticoagulation can reduce embolization from dissection as measured by transcranial Doppler [72], there is likely still a role for anticoagulation in patients who are at high risk or who have proven ongoing embolization, but further studies are needed to appropriately select patients.

Delayed endovascular therapy

- While a trial of intracranial stenting showed no benefit over medical therapy [68], patients with intracranial stenosis and recurrent stroke or blood pressure dependence may theoretically benefit from angioplasty [73]. Dual antiplatelet or anticoagulation is often tried as an initial strategy, and endovascular therapy pursued only if medical therapy fails.
- Randomized trials of endovascular stroke therapy have focused on anterior circulation disease, and as a result little is known about the time window of intervention in the posterior circulation. However, clot retrieval is sometimes considered up to 24 hours after onset for basilar disease as well as delayed angioplasty in those with vertebrobasilar stenosis with recurrent infarct or fluctuating symptoms suggestive of hypoperfusion [74].

Other supportive care

Fever management

- Hyperthermia following ischemic stroke is associated with increased mortality [75]. In addition to identifying potential infectious sources of fever, normothermia should be maintained through the use of antipyretic medications and mechanical cooling if necessary.

Glucose control

- Hyperglycemia is correlated with poor outcome after ischemic stroke [76, 77], particularly in those patients without a history of DM [78–80]. Previous trials of tight glycemic control in stroke have thus far been inconclusive [81–83] and a large multi-center trial of glucose control is ongoing [84].
- In the absence of clear stroke-specific data on glucose control, a target of <180mg/dL is suggested, as that level was associated with improved outcome in a mixed ICU population [85].

Conclusion

Severe ischemic stroke is often complicated by factors that require intensive care management. In additional to general ICU needs such as airway and ventilatory support and post-procedure or post-thrombolysis care, several complications of acute stroke present unique challenges best addressed in a neurocritical care setting. Monitoring and management of cerebral edema and elevated ICP, early recognition and management of hemorrhagic transformation, and prevention of recurrent and progressive ischemia are the primary goals of critical care management of acute stroke. Effective treatment requires careful clinical and physiologic monitoring to support application of both medical and surgical therapies.

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Table 1.

Types of secondary injury and treatment after ischemic stroke

	ICU interventions	**References**
Cerebral edema	Osmotic therapy	[41]
	Surgical decompression	[44-46]
Hemorrhagic transformation	Continuous BP titration	[22]
	Reversal of coagulopathy	[22]
Progressive stroke	BP augmentation	extrapolation from [58, 59]
	Early antiplatelet therapy	[66, 67]

Table 2.

Types of Hemorrhagic Transformation

	Definition	**Clinical Significance**
Hemorrhagic infarction 1 (HI1)	Hemorrhagic infarction with small petechiae within the stroke	Uncertain; may be a beneficial marker of reperfusion
Hemorrhagic infarction 2 (HI2)	Hemorrhagic infarction with confluent petechiae within the stroke	Uncertain
Parenchymal hematoma 1 (PH1)	Parenchymal hematoma with an organized clot <30% of stroke and mild mass effect	Often associated with neurological deterioration
Parenchymal hematoma 2 (PH2)	Parenchymal hematoma with a large organized clot and significant mass effect	Associated with neurological deterioration from mass effect