

## **Recommendations for the Management of Cerebral and Cerebellar Infarction With Swelling: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association**

Eelco F. M. Wijdicks, Kevin N. Sheth, Bob S. Carter, David M. Greer, Scott E. Kasner, W. Taylor Kimberly, Stefan Schwab, Eric E. Smith, Rafael J. Tamargo and Max Wintermark

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## Recommendations for the Management of Cerebral and Cerebellar Infarction With Swelling

### A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

*The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.*

*Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons*

*Endorsed by the Neurocritical Care Society*

Eelco F. M. Wijdicks, MD, PhD, FAHA, Chair; Kevin N. Sheth, MD, FAHA, Co-Chair;

Bob S. Carter, MD, PhD; David M. Greer, MD, MA, FAHA;

Scott E. Kasner, MD, FAHA; W. Taylor Kimberly, MD, PhD; Stefan Schwab, MD;

Eric E. Smith, MD, MPH, FAHA; Rafael J. Tamargo, MD, FAANS;

Max Wintermark, MD, MAS; on behalf of the American Heart Association Stroke Council

**Background and Purpose**—There are uncertainties surrounding the optimal management of patients with brain swelling after an ischemic stroke. Guidelines are needed on how to manage this major complication, how to provide the best comprehensive neurological and medical care, and how to best inform families facing complex decisions on surgical intervention in deteriorating patients. This scientific statement addresses the early approach to the patient with a swollen ischemic stroke in a cerebral or cerebellar hemisphere.

**Methods**—The writing group used systematic literature reviews, references to published clinical and epidemiology studies, morbidity and mortality reports, clinical and public health guidelines, authoritative statements, personal files, and expert opinion to summarize existing evidence and to indicate gaps in current knowledge. The panel reviewed the most relevant articles on adults through computerized searches of the medical literature using MEDLINE, EMBASE, and Web of Science through March 2013. The evidence is organized within the context of the American Heart Association framework and is classified according to the joint American Heart Association/American College of Cardiology Foundation and supplementary American Heart Association Stroke Council methods of classifying the level of certainty and the class and level of evidence. The document underwent extensive American Heart Association internal peer review.

**Results**—Clinical criteria are available for hemispheric (involving the entire middle cerebral artery territory or more) and cerebellar (involving the posterior inferior cerebellar artery or superior cerebellar artery) swelling caused by ischemic infarction. Clinical signs that signify deterioration in swollen supratentorial hemispheric ischemic stroke include new or further impairment of consciousness, cerebral ptosis, and changes in pupillary size. In swollen cerebellar infarction, a decrease in level of consciousness occurs as a result of brainstem compression and therefore may include early loss of corneal reflexes and the development of miosis. Standardized definitions should be established to facilitate multicenter and population-based studies of incidence, prevalence, risk factors, and outcomes. Identification of patients at high risk for brain swelling should include clinical and neuroimaging data. If a full resuscitative status is warranted in a patient with a large territorial stroke, admission to a unit with neurological monitoring capabilities is needed. These patients are

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best admitted to intensive care or stroke units attended by skilled and experienced physicians such as neurointensivists or vascular neurologists. Complex medical care includes airway management and mechanical ventilation, blood pressure control, fluid management, and glucose and temperature control. In swollen supratentorial hemispheric ischemic stroke, routine intracranial pressure monitoring or cerebrospinal fluid diversion is not indicated, but decompressive craniectomy with dural expansion should be considered in patients who continue to deteriorate neurologically. There is uncertainty about the efficacy of decompressive craniectomy in patients  $\geq 60$  years of age. In swollen cerebellar stroke, suboccipital craniectomy with dural expansion should be performed in patients who deteriorate neurologically. Ventriculostomy to relieve obstructive hydrocephalus after a cerebellar infarct should be accompanied by decompressive suboccipital craniectomy to avoid deterioration from upward cerebellar displacement. In swollen hemispheric supratentorial infarcts, outcome can be satisfactory, but one should anticipate that one third of patients will be severely disabled and fully dependent on care even after decompressive craniectomy. Surgery after a cerebellar infarct leads to acceptable functional outcome in most patients.

**Conclusions**—Swollen cerebral and cerebellar infarcts are critical conditions that warrant immediate, specialized neurointensive care and often neurosurgical intervention. Decompressive craniectomy is a necessary option in many patients. Selected patients may benefit greatly from such an approach, and although disabled, they may be functionally independent. (*Stroke*. 2014;45:00-00.)

**Key Words:** AHA Scientific Statements ■ brain edema ■ decompressive craniectomy ■ infarction  
■ patient care management ■ prognosis ■ stroke

The emergence of brain swelling is the most troublesome and even life-threatening consequence of a large-territory ischemic stroke. Brain swelling occurs as a result of loss of function of membrane transporters, causing sodium and water influx into the necrotic or ischemic cell, leading to cytotoxic edema. Unrelenting swelling disrupts the blood-brain barrier (BBB); therefore, a component of vasogenic edema may coexist.<sup>1</sup>

The development of clinically significant cerebral edema is expected only in large-territory cerebral infarcts and can be observed by the clinician in 3 ways: a rapid and fulminant course (within 24–36 hours), a gradually progressive course (over several days), or an initially worsening course followed by a plateau and resolution (about a week).<sup>2–5</sup> Currently, no methods are available to predict the course of brain swelling reliably. There is a clinical perception that when brain swelling occurs in the cerebral or cerebellar hemisphere, medical management to reduce brain swelling is not successful in changing outcome.<sup>4,6</sup> Therefore, a decompressive craniectomy is offered to relieve the mass effect of the swollen hemisphere on the thalamus, brainstem, and network projections to the cortex, manifested mainly by a decreased level of arousal. Decompressive craniectomy for cerebral edema after ischemic hemispheric stroke has significantly increased in US hospitals.<sup>7</sup>

Clinical experience has matured over the years, but there are uncertainties about how to approach a patient with neuroimaging and clinical evidence of emerging brain swelling after an ischemic stroke. These include recognition of key warning neurological signs, comprehensive evaluation of changing neuroimaging patterns, prevention of clinically significant swelling, options for reducing cerebral edema by pharmacological means, and selection of patients for decompressive craniectomy and methods to measure the degree of postoperative morbidity. This scientific statement addresses the early approach to the patient with a swollen ischemic stroke in the cerebellum and cerebral hemisphere. It provides a guideline on how to provide the best comprehensive care and how to manage this complication. Communicating prognosis with family members is also discussed. The level of evidence is rated for all recommendations.

## Methods

Writing group members were nominated by the committee chair and co-chair because of their previous work in relevant topic areas and were approved by the American Heart Association (AHA) Stroke Council's Scientific Statement Oversight Committee and the AHA's Manuscript Oversight Committee. The writers used systematic literature reviews, references to published clinical and epidemiological studies, morbidity and mortality reports, clinical and public health guidelines, authoritative statements, personal files, and expert opinion to summarize existing evidence and to indicate gaps in current knowledge. The panel reviewed the most relevant articles on adults through computerized searches of the medical literature using MEDLINE, EMBASE, and Web of Science through March 2013. The evidence is organized within the context of the AHA framework and is classified according to the joint AHA/American College of Cardiology and supplementary AHA Stroke Council methods of classifying the level of certainty and the class and level of evidence (Tables 1 and 2). All members of the writing group approved the final version of this document. The document underwent extensive AHA internal peer review, Stroke Council Leadership review, and Scientific Statements Oversight Committee review before consideration and approval by the AHA Science Advisory and Coordinating Committee.

## Epidemiology

Variation in terminology complicates the accurate estimation of the incidence of severe brain edema caused by massive infarction. The estimated prevalence of severe stroke may be affected by referral patterns because most data come from single tertiary care hospitals and thus may not be representative of the population as a whole. The term malignant middle cerebral artery (MCA) infarction, introduced in 1996, was originally defined as infarction of the entire MCA territory appearing on computed tomography (CT) within 48 hours, with or without infarction in other vascular territories.<sup>4</sup> This term has been used frequently in the subsequent literature, along with closely related terms such as large hemispheric infarction, but almost



Table 1. Applying Classification of Recommendation and Level of Evidence

		SIZE OF TREATMENT EFFECT												
		CLASS I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment <b>SHOULD</b> be performed/ administered	CLASS IIa <i>Benefit &gt;&gt; Risk</i> Additional studies with <i>focused objectives needed</i> <b>IT IS REASONABLE</b> to per- form procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>									
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"><li>■ Recommendation that procedure or treatment is useful/effective</li><li>■ Sufficient evidence from multiple randomized trials or meta-analyses</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation in favor of treatment or procedure being useful/effective</li><li>■ Some conflicting evidence from multiple randomized trials or meta-analyses</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation's usefulness/efficacy less well established</li><li>■ Greater conflicting evidence from multiple randomized trials or meta-analyses</li></ul>	<table><tr><th></th><th>Procedure/ Test</th><th>Treatment</th></tr><tr><td>COR III: No benefit</td><td>Not Helpful</td><td>No Proven Benefit</td></tr><tr><td>COR III: Harm</td><td>Excess Cost w/o Benefit or Harmful</td><td>Harmful to Patients</td></tr></table> <ul style="list-style-type: none"><li>■ Recommendation that procedure or treatment is not useful/effective and may be harmful</li><li>■ Sufficient evidence from multiple randomized trials or meta-analyses</li></ul>		Procedure/ Test	Treatment	COR III: No benefit	Not Helpful	No Proven Benefit	COR III: Harm	Excess Cost w/o Benefit or Harmful	Harmful to Patients
		Procedure/ Test	Treatment											
	COR III: No benefit	Not Helpful	No Proven Benefit											
	COR III: Harm	Excess Cost w/o Benefit or Harmful	Harmful to Patients											
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"><li>■ Recommendation that procedure or treatment is useful/effective</li><li>■ Evidence from single randomized trial or nonrandomized studies</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation in favor of treatment or procedure being useful/effective</li><li>■ Some conflicting evidence from single randomized trial or nonrandomized studies</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation's usefulness/efficacy less well established</li><li>■ Greater conflicting evidence from single randomized trial or nonrandomized studies</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation that procedure or treatment is not useful/effective and may be harmful</li><li>■ Evidence from single randomized trial or nonrandomized studies</li></ul>										
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"><li>■ Recommendation that procedure or treatment is useful/effective</li><li>■ Only expert opinion, case studies, or standard of care</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation in favor of treatment or procedure being useful/effective</li><li>■ Only diverging expert opinion, case studies, or standard of care</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation's usefulness/efficacy less well established</li><li>■ Only diverging expert opinion, case studies, or standard of care</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation that procedure or treatment is not useful/effective and may be harmful</li><li>■ Only expert opinion, case studies, or standard of care</li></ul>										
Suggested phrases for writing recommendations		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be performed/administered/other is not useful/beneficial/effective	COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/administered/other								
Comparative effectiveness phrases <sup>†</sup>		treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B											

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

\*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

always with a study-specific definition that deviated from the original. These variable definitions were based on some combination of neurological symptoms or signs,<sup>8–13</sup> MCA occlusion,<sup>10</sup> involvement of some or all of the MCA-perfused brain territory based on either CT or magnetic resonance imaging (MRI) diffusion-weighted imaging (DWI),<sup>4,8,13–16</sup> radiographic evidence of brain edema,<sup>10,12,17</sup> postadmission neurological deterioration,<sup>17,18</sup> or use of decompressive craniectomy.<sup>9,11,19</sup>

The prevalence of hemispheric MCA infarction by these variable definitions has been reported to be 2% to 8% of all hospitalized ischemic stroke,<sup>4,10,11,14,17,18</sup> 10% to 15% of all MCA territory ischemic stroke,<sup>13,20</sup> and 18% to 31% of all ischemic stroke caused by MCA occlusion.<sup>9,16,21</sup> The risk of subsequent

neurological deterioration and death is high, 40% to 80%.<sup>4,22</sup> A population-based study estimated that 0.3% of all ischemic stroke patients may be eligible for decompressive craniectomy on the basis of criteria used in randomized, controlled trials.<sup>23</sup> The actual frequency of decompressive craniectomy for malignant MCA infarction is estimated to have increased from 0.04% of all ischemic stroke admissions in 1999 to 2000 to 0.14% of all ischemic stroke admissions in 2007 to 2008.<sup>7</sup>

Data on the incidence of severe brain edema complicating cerebellar infarction and the frequency of decompressive craniectomy for cerebellar edema are sparse. Studies suggest that ~20% of patients will develop radiographic signs of mass effect accompanied by neurological deterioration.<sup>24,25</sup> One series of 84 patients

**Table 2. Definition of Classes and Levels of Evidence Used in AHA/ASA Recommendations**

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment.
Class IIb	Usefulness/efficacy is less well established by evidence or opinion.
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.
Therapeutic recommendations	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
Diagnostic recommendations	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study or one or more case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

AHA/ASA indicates American Heart Association/American Stroke Association

included 34 patients with craniectomies and 14 with ventriculostomies,<sup>26</sup> but selection criteria for surgery remain arbitrary, with many neurosurgeons operating on comatose patients.<sup>27</sup>

## Epidemiology: Recommendations

1. Standardized terms and definitions for severe hemispheric and cerebellar edema resulting from infarction should be established to facilitate multicenter and population-based studies of incidence, prevalence, risk factors, and outcomes (*Class I; Level of Evidence C*).
2. Additional data should be collected to determine the use of decompressive craniectomy in current clinical practice, including whether there is variation by physician, hospital, health system, or patient characteristics and preferences (*Class I; Level of Evidence C*).

## Definition and Clinical Presentation

The target population is defined as patients who are at high risk for or who ultimately suffer neurological deterioration attributable to cerebral swelling after ischemia.

## Hemispheric Stroke

Patients with significant swelling typically have occlusions of the internal carotid artery, MCA, or both. The natural history

of a large infarction after internal carotid artery versus MCA infarction is not clear, especially when independent of anterior cerebral artery territory infarction. Infarctions from MCA branch occlusions typically do not result in swelling with clinically significant mass effect.<sup>4</sup> Additional vascular territories, incomplete circle of Willis, and marginal leptomeningeal collateral supply are also risk factors for the development of cerebral edema after ischemia.<sup>28</sup>

Although baseline follow-up neuroimaging parameters have been described that identify stroke patients who experience swelling with high specificity,<sup>16,29,30</sup> a number of clinical features are commonly seen in this syndrome. The most common findings are hemiplegia, global or expressive aphasia, severe dysarthria, neglect, gaze preference, and a visual field defect.<sup>4</sup> Pupillary abnormalities are a reflection of significant brainstem shift, typically not expected on initial presentation, and develop within the first 3 to 5 days. An early Horner syndrome may point to an acute carotid artery occlusion or dissection.<sup>4</sup> The initial National Institutes of Health Stroke Scale score is often >20 with dominant hemispheric infarction and >15 with nondominant hemispheric infarction, although this clinical predictor has not undergone rigorous prospective validation.<sup>31–33</sup> The initial score is a reflection of stroke severity and infarct volume, not a marker of tissue swelling, and although sensitive, it is not highly specific.

The most specific sign of significant cerebral swelling after stroke is a decline in the level of consciousness attributable to brain edema shifting the thalamus and brainstem, where major components of the ascending arousal system are situated.<sup>34</sup> Although right hemisphere infarction may result in a flattened affect, complete infarction of either hemisphere itself is rarely associated with diminished arousal.<sup>35</sup> Responsiveness, however, is diminished early in combined MCA and anterior cerebral artery infarctions. Cerebral ptosis (apraxia of eyelid opening) may be present and falsely suggest a decreased level of consciousness. It may appear de novo in deteriorating patients.<sup>36–38</sup>

Despite several attempts to date,<sup>39,40</sup> no clinical feature has been validated to reliably measure level of consciousness in this setting, nor has there been a good way of documenting the early changes in level of consciousness. (In several recent studies evaluating decompressive craniectomy, only item 1a of the National Institutes of Health Stroke Scale has been used to link decreased level of consciousness to brain swelling.) A single study suggested that diffuse slowing and increased delta activity on an electroencephalogram in the first 24 hours may document early global dysfunction in patients who are likely to swell.<sup>41</sup> The development of frequent or continuous, accurate methods to identify depression in level of arousal attributable to swelling is an important unmet need.

Neurological deterioration usually occurs in most patients within 72 to 96 hours.<sup>17</sup> Some patients may experience deterioration at 4 to 10 days, when previously at-risk penumbral tissue progresses to infarction, followed by delayed swelling and in some cases hemorrhagic transformation,<sup>42</sup> although the exact mechanism of this clinical course remains to be clarified. If patients are intubated for mechanical ventilation, brain death is a possible outcome if no aggressive measures to relieve swelling are undertaken.<sup>43</sup>

Although the data on the association between age and outcome in patients with severe stroke are inconsistent, in the absence of significant comorbidities and withdrawal of care, older patients may be less likely to suffer the consequences of cerebral edema because of increased intracranial compliance secondary to relative atrophy.<sup>4,44</sup> Conversely, younger patients with decreased compliance may be at increased risk for brain tissue shift.<sup>13,45,46</sup> Other clinical factors that are associated with edema after large stroke include early nausea and vomiting, female sex, congestive heart failure, and leukocytosis.<sup>22</sup> One series reported altered baroreceptor sensitivity as an early predictor of life-threatening edema; however, this observation has not been prospectively confirmed.<sup>47</sup>

### Cerebellar Stroke

Cerebellar infarction can be difficult to diagnose, especially when the chief complaints are dizziness, vertigo, and vomiting. Careful attention to speech, gait, coordination, and eye movements is required to make the diagnosis. It is a common pitfall to miss truncal ataxia in a patient during a bedside examination.<sup>48</sup> Few, if any, reliable clinical signs and symptoms can serve to stratify cerebellar stroke patients across a continuum of clinical severity. Swelling after cerebellar infarction may result in pontine compression, acute hydrocephalus secondary to obstruction of the fourth ventricle, and often both.

Similar to hemispheric infarction, the most reliable clinical symptom of tissue swelling is decreased level of consciousness and thus arousal.<sup>26,49</sup> In addition, pontine compression may lead to ophthalmoparesis, breathing irregularities, and cardiac dysrhythmias. Hearing loss is common with anterior inferior cerebellar infarction, and intractable hiccups may be seen in posterior inferior cerebellar infarction.<sup>50</sup> Deterioration, however, is more dependent on initial infarct volume rather than any specific vascular territory.<sup>25</sup> Peak swelling occurs several days after the onset of ischemia.<sup>25</sup> The initial CT can be normal in as many as 25% of patients.<sup>25,51</sup>

### Hemorrhagic Transformation of Strokes

Hemorrhagic transformation is a common complication of severe stroke and is a manifestation of damage to the BBB, loss of microvascular integrity, and disruption of the neurovascular unit.<sup>52</sup> It may be a consequence of recanalization and reperfusion of an infarcted area. The pathophysiology is incompletely understood but involves matrix metalloproteinases (MMPs; eg, MMP-9), inflammatory mediators, reactive oxygen species, and sequelae from thrombolytic agents or other anticoagulants such as low-molecular-weight heparin injections or intravenous heparin.<sup>1</sup> In fact, large infarcts that present acutely may be more likely to undergo thrombolysis, which itself can lead to upregulation of MMP-3 or MMP-9.<sup>53</sup> Reperfusion and BBB disruption may synergistically increase the risk of hemorrhagic transformation.<sup>54</sup> Clinically, hemorrhagic transformation may be associated with little change in neurological findings, worsening of existing deficits, or sudden rapid decline as a result of new mass effect. This major complication is seen more commonly in patients with severe stroke at high risk for swelling.<sup>54</sup> This increased risk of hemorrhage may be attributable to primary injury or a higher

incidence of thrombolytic therapy in this population, regardless of whether there is successful reperfusion. Advanced age and hyperglycemia have also been associated with this complication, which results in increased mortality, especially in patients with cerebellar infarction.<sup>25,54</sup>

### Definition and Clinical Presentation: Recommendations

- 1. Patients with or at high risk for infarction and swelling should be identified through the use of clinical data, including vessel occlusion status (Class I; Level of Evidence B).**

### Neuroimaging

Cerebral infarction is characterized by progressive cerebral edema and mass effect, with ipsilateral sulcal effacement, compression of the ipsilateral ventricular system, and then a shift of the midline structures such as the septum pellucidum and the pineal gland. The foramen of Monro or the third ventricle might be blocked, leading to entrapment and dilatation of the contralateral lateral ventricle and obstructive hydrocephalus, which might contribute to increased intracranial pressure (ICP). Brainstem displacement may lead to widening of the ipsilateral ambient cistern. These cisterns become effaced when swollen tissue eventually fills the cisterns. Compression and compromise of the anterior or posterior cerebral arteries may be seen in some patients, along with infarctions in the corresponding vascular territories.<sup>55</sup>

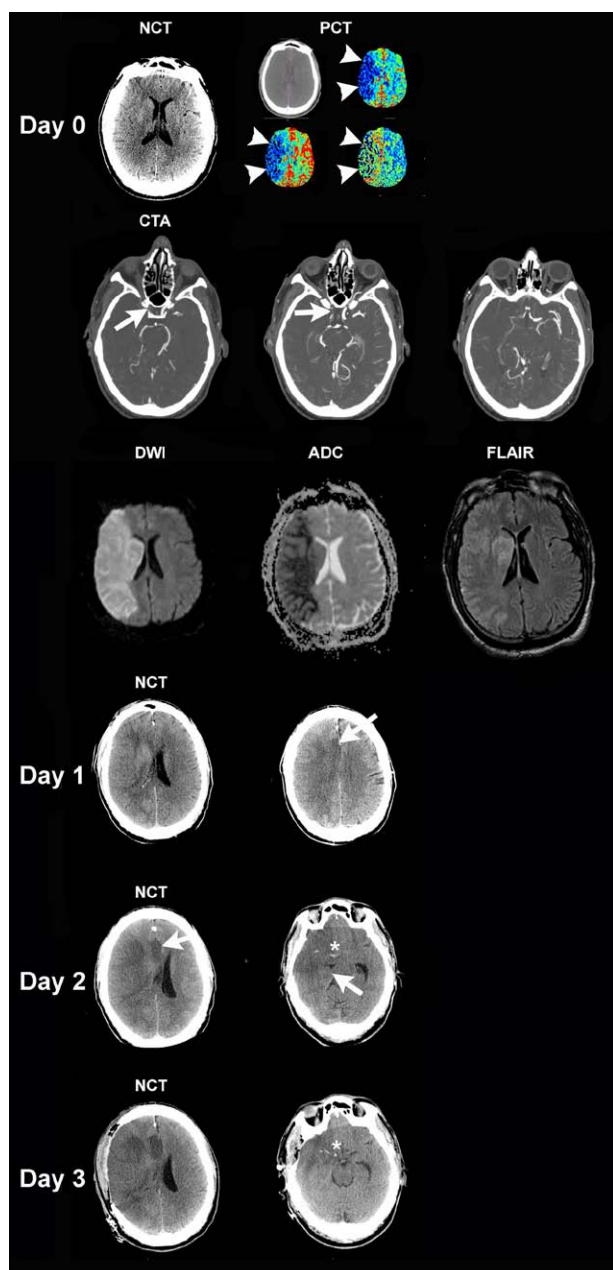
In the setting of cerebellar infarction with swelling, effacement of the fourth ventricle is a key radiologic marker, followed by basal cistern compression, followed by brainstem deformity, hydrocephalus, downward tonsillar herniation, and upward transtentorial herniation.<sup>25</sup>

### CT Imaging

A noncontrast CT scan of the brain is the first-line diagnostic test to exclude nonvascular, structural, intracranial lesions as the cause of the focal neurological symptoms; to differentiate between brain ischemia and hemorrhage; to ascertain the cause and prognosis; and to guide immediate intervention. CT is also the modality of choice to follow up patients with cerebral or cerebellar infarcts with swelling. CT findings that predict malignant edema and poor prognosis include frank hypodensity on head CT within the first 6 hours and involvement of one third or more of the MCA territory (Figure 1).<sup>22,56–58</sup> The presence of a dense MCA sign<sup>58</sup> or midline shift  $\geq 5$  mm within the first 2 days<sup>59</sup> is also associated with neurological deterioration and early mortality (Figure 1).

Several angiographic findings on CT angiography or digital subtraction angiography are predictive of deterioration caused by swelling. A “T occlusion” of the distal internal carotid artery<sup>45,57</sup> is frequently associated with malignant edema. An incomplete circle of Willis,<sup>45</sup> which leads to involvement of multiple vascular territories (eg, the MCA and either the anterior cerebral artery or posterior cerebral artery),<sup>22,60</sup> is predictive of worse outcome. A host of radiographic findings have been used to describe deterioration after MCA infarction.





**Figure 1.** A 56-year-old male patient was admitted 5 hours after onset of right hemiplegia. Initial noncontrast computed tomography (NCT) showed slight effacement of the right lentiform nucleus but no hypodensity. A perfusion computed tomography (PCT) study obtained immediately after the NCT demonstrated a large area of hypoperfusion (prolonged mean transit time, decreased cerebral blood flow, and cerebral blood volume; arrowheads) in the right middle cerebral artery (MCA) territory, consistent with a large infarct core. The computed tomographic angiogram (CTA) revealed an occlusion of the right internal carotid artery (ICA) extending to the right MCA (arrows). A magnetic resonance image obtained shortly after the computed tomographic workup confirmed the PCT findings, namely a large infarct in the right MCA territory with restricted diffusion (bright signal on diffusion-weighted images [DWIs] and dark signal on average diffusion coefficient [ADC] maps). Fluid-attenuated inversion recovery (FLAIR) images showed early abnormalities in the same distribution. Endovascular revascularization was not attempted because of the size of the infarct core on DWI. At day 1, follow-up NCT shows a frank hypodensity in the right MCA territory, with a suggestion of hemorrhagic transformation in the right basal ganglia.

Some simply use the term *transtentorial herniation* without being more specific.<sup>29,61,62</sup> Other descriptions include effacement of the ipsilateral sulci and lateral ventricle<sup>63</sup> and CT signs of elevated ICP.<sup>64</sup> Most commonly, the degree of midline shift is used as the benchmark for radiographic deterioration, either undefined<sup>16,60,65</sup> or specified as  $>5$  mm at the level of septum pellucidum,<sup>19,41,47,66–68</sup>  $>2$  mm at the level of septum pellucidum or pineal gland,<sup>69,70</sup> or  $>10$  mm.<sup>71</sup> Although all these arbitrary parameters are indicative of tissue shift, further development and validation of serial CT measures that identify patients at highest risk of clinical deterioration are required. Other predictors are hypodensity  $>50\%$  of the MCA territory and basal ganglia involvement in infarction territory.<sup>56,72</sup>

### Magnetic Resonance Imaging

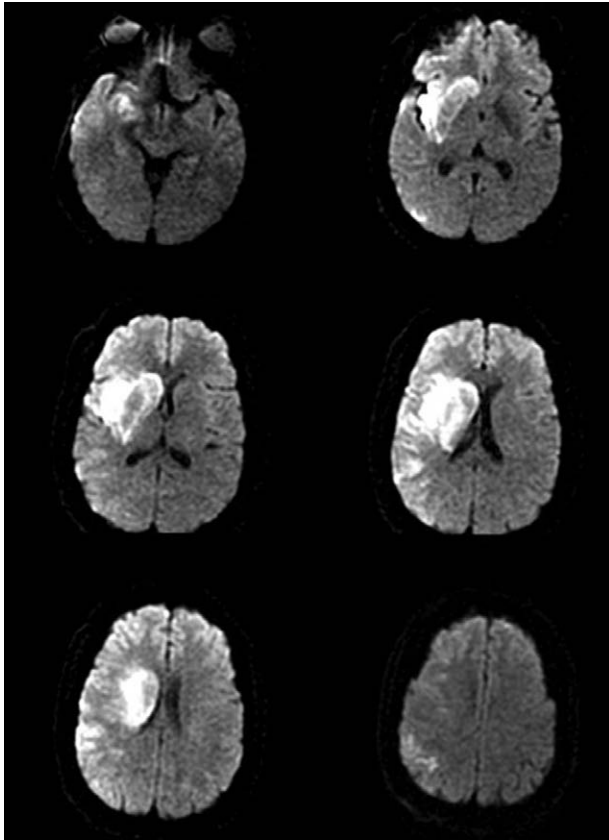
MRI can be substituted for CT, but it is less widely available and there are more contraindications for use (including metal implants, cardiac pacemakers, and unstable patients). Four studies have evaluated the ability of acute DWI volume to predict neurological deterioration from cerebral edema. Three studies have evaluated patients with MRI obtained within  $\approx 6$  hours of stroke onset, and the optimal DWI cutoff was largely in agreement, with values of  $>80$ ,<sup>54</sup>  $>82$ ,<sup>16</sup> or  $>89$  mL<sup>29</sup> predicting a rapid fulminant course (Figures 1 and 2). When MRI was obtained 14 hours after stroke onset, a DWI volume of  $>145$  mL was predictive of clinical deterioration.<sup>73</sup> Predictive MRI-based infarct volumes have not been robustly identified for cerebellar stroke, and this is an important area of inquiry.

The utility of perfusion-weighted imaging has been evaluated, but perfusion-weighted imaging less consistently showed predictive ability, with some studies demonstrating its value<sup>54</sup> and others not. The utility of MRI imaging in predicting swelling, assessing of brainstem shift, and evaluating secondary damage to critical structures has not sufficiently been examined.

### Other Neuroimaging

Transcranial Doppler sonography has been suggested as a non-invasive method of monitoring elevated ICP in patients with large infarctions. An increase in pulsatility indexes has been shown to correlate with midline shift and outcome. Transcranial Doppler sonography provides information for detecting cerebral herniation and deciding on the medical or surgical therapy.<sup>74,75</sup> At this time, near-infrared spectroscopy remains an investigational modality to noninvasively provide information on intracranial oxygenation in patients with infarctions and swelling.<sup>76</sup> Additional modalities that have been explored and require further study include perfusion CT imaging (Figure 1),<sup>18,20</sup> stable

**Figure 1. (Continued)** In addition, there is a new hypodensity in the right anterior cerebral artery territory (arrow), suggesting extension of the infarct to this distribution. In terms of mass effect, there is compression of the right lateral ventricle and minimal right-to-left midline shift, but there is no herniation. At day 2, subfalcine and right uncus herniation (arrows) have developed, along with entrapment of the left lateral ventricle. A dense clot is seen in the terminal right ICA and the MCA (asterisk), indicating persistent occlusion. The patient's condition, related to the mass effect and herniation, prompted a surgical craniectomy, and a postsurgery NCT obtained at day 3 showed relief of the mass effect. The patient survived but was left with significant handicap.



**Figure 2.** Acute diffusion-weighted images in a 59-year-old female patient admitted 4 hours after symptom onset showing an infarct of ~90 mL.

xenon CT,<sup>77</sup> single-photon emission CT,<sup>30,78</sup> positron emission tomography,<sup>69</sup> and BBB permeability imaging.<sup>79–81</sup>

### Neuroimaging: Recommendations

1. Frank hypodensity on head CT within the first 6 hours, involvement of one third or more of the MCA territory, and early midline shift are CT findings that are useful in predicting cerebral edema (*Class I; Level of Evidence B*).
2. The measurement of MRI DWI volume within 6 hours is useful, and volumes ( $\geq 80$  mL) predict rapid fulminant course (*Class I; Level of Evidence B*).
3. A noncontrast CT scan of the brain is a useful first-line diagnostic test and modality of choice to monitor patients with hemispheric cerebral or cerebellar infarcts with swelling. Serial CT findings in the first 2 days are useful to identify patients at high risk for developing symptomatic swelling (*Class I; Level of Evidence C*).

### Basics of Support

The management of ischemic stroke has been summarized in 2 major guidelines from the Stroke Council of the American Stroke Association and the European Stroke Organization.<sup>82,83</sup> Their recommendations similarly apply to patients with a large ischemic stroke, but there are several specific and pertinent issues to consider in the management of patients with

a large hemispheric or cerebellar stroke and early edema. The writing group recommendations discussed here relate specifically to medical management of patients who are at high risk for or are developing tissue swelling.

### Triage

Before any intervention is undertaken, an appropriate triage should be established. If a full resuscitative status and comprehensive medical care are warranted in a patient with a large territorial stroke, admission to a unit with neuromonitoring capabilities is needed. Once the diagnosis is established, these patients are best admitted to intensive care or stroke units attended by skilled physicians. Neurosurgical consultation should be sought early to facilitate planning of decompressive surgery or ventriculostomy with decompressive surgery (in the case of cerebellar infarction) if the patient deteriorates. Early identification of patients who may experience swelling and consequent transfer to a center with a higher level of care should be initiated urgently if comprehensive care is agreed on and cannot be provided. The level of expertise to manage these patients must be high and requires a multidisciplinary approach that could include neurointensivists, vascular neurologists, and neurosurgeons.

### Triage: Recommendations

1. Transfer to an intensive care or stroke unit is recommended for patients with a large territorial stroke to plan close monitoring and comprehensive treatment (*Class I; Level of Evidence C*).
2. Triage to a higher level center is reasonable if comprehensive care and timely neurosurgical intervention are not available locally (*Class IIa; Level of Evidence C*).

### Airway and Mechanical Ventilation

The most common reason for endotracheal intubation and mechanical ventilation is a decline in consciousness and an inability to maintain a patent airway, leading to inadequate ventilation.<sup>43,65</sup> Indications for endotracheal intubation are persistent or transient hypoxemia, an obstructing upper airway with pooling secretions, apneic episodes, and the development of hypoxemic or hypercarbic respiratory failure as measured by noninvasive means or an arterial blood gas. Other clinical situations that may lead to a need for mechanical ventilation are generalized tonic-clonic seizures and recent aspiration.<sup>84,85</sup> The mortality of mechanically ventilated patients after hemispheric ischemic stroke is increased, but most studies were performed before decompressive craniectomy.

Rapid sequence intubation is preferred.<sup>86</sup> There is no evidence that depolarizing agents or fentanyl, lidocaine, and propofol are deleterious to the patient. After intubation, the  $Paco_2$  should be corrected to normocapnia. Both  $Pao_2$  and  $Paco_2$ <sup>87,88</sup> goals have been stipulated, but there is marked variation in the published literature. Many investigators have advocated for normocapnia.<sup>76,87,89</sup> There is no evidence of benefit with prophylactic hyperventilation, and there is no published evidence of harm with hyperventilation in this population.

In patients who are sufficiently alert to experience discomfort from the endotracheal tube, low doses of short-acting anesthetics such as propofol or dexmedetomidine can be



used to avoid marked hypertension, anxiety, or dyssynchrony with the ventilator. An adequate mean arterial blood pressure should be maintained at all times, although an evidence-based target level is not established.

Mechanical ventilation may be needed after decompressive surgery. The incidence of tracheostomy in patients with hemispheric stroke with or without decompressive craniectomy is not known, but neurological improvement is anticipated, and in the absence of an intercurrent infection, liberation from the ventilator may be expected in the first postoperative days. A subset of patients with significant swelling may exist in whom it is futile to attempt extubation; however, these parameters have not been defined. Weaning is dependent on the alertness of the patient, among other respiratory physiological parameters, but early extubation in patients with a decompressive craniectomy for cerebellar infarcts can be problematic because of abnormal oropharyngeal function, lack of strong cough, and copious thick secretions.<sup>90</sup> The presence of a cough and gag reflex and normal eye movements may predict successful extubation.<sup>91</sup>

### Airway and Mechanical Ventilation: Recommendations

1. Maintaining normocarbida is reasonable (*Class IIa; Level of Evidence C*).
2. Intubation may be considered for patients with decreased levels of consciousness resulting in poor oxygenation or impaired control of secretions (*Class IIb; Level of Evidence C*).
3. Prophylactic hyperventilation is not recommended (*Class III; Level of Evidence C*).

### Hemodynamic Support

Maintenance fluid management in patients with acute hemispheric or cerebellar strokes includes the use of isotonic saline and the avoidance of hypo-osmolar fluids. Fluids without dextrose are preferred. Some groups have suggested using crystalloids and colloids to ensure adequate cerebral perfusion pressure<sup>63</sup> and normovolemia.<sup>5,31,65,92</sup>

There are insufficient data to recommend mannitol or hypertonic saline as a preemptive measure in patients with early CT swelling, but practices could vary. Some practices may switch to mildly hypertonic solutions as maintenance fluids (eg, 1.5% saline). Other practices may use an incidental bolus of mannitol or hypertonic saline as a bridge to decompressive craniectomy. Even if osmotic agents are used, a predefined hyperosmolar or hypernatremic target is not established.

Cardiac arrhythmias or worsening of preexisting cardiac arrhythmias is common after a large ischemic stroke, particularly in patients with a cerebellar infarct compressing the brainstem or with infarcts involving the insular region.<sup>93</sup> Most such cardiac arrhythmias are self-limited and do not require any intervention. Atrial fibrillation with rapid ventricular response often requires pharmaceutical control.

### Blood Pressure Management

Acute hypertension is a frequent accompanying clinical sign in any stroke. Hypotension is far less common and points to an associated medical or surgical problem. Hemispheric

stroke with marked blood pressure changes may be attributable to unusual circumstances such as an aortic dissection or myocardial infarction, and further diagnostic tests might be necessary. There is marked variation in set blood pressure goals in published studies<sup>31,61</sup> or avoidance of antihypertensive agents in the first days.<sup>5</sup> However, hypertension, defined as systolic blood pressure >220 mmHg or diastolic pressure >105 mmHg, increases the risk of hemorrhagic transformation.<sup>94</sup> Because of the large variation in practice and the lack of data from randomized, controlled trials, specific blood pressure recommendations cannot be made.

### Hemodynamic Support and Blood Pressure Management: Recommendations

1. Aggressive treatment of worsening cardiac arrhythmias with appropriate medications and continued cardiac monitoring is recommended (*Class I; Level of Evidence C*).
2. There are insufficient data to recommend a specific systolic or mean arterial blood pressure target. Blood pressure-lowering drugs may be considered for the treatment of extreme hypertension. Specific blood pressure targets are not established (*Class IIb; Level of Evidence C*).
3. Use of adequate fluid administration with isotonic fluids might be considered (*Class IIb; Level of Evidence C*).
4. Hypotonic or hypo-osmolar fluids are not recommended (*Class III; Level of Evidence C*).
5. Use of prophylactic osmotic diuretics before apparent swelling is not recommended (*Class III; Level of Evidence C*).

### Glucose Management

Hyperglycemia is associated with increased edema in patients with cerebral ischemia and with an increased risk of hemorrhagic transformation.<sup>95-97</sup> The ideal glucose target after a large hemispheric stroke is unknown. The European Stroke Initiative<sup>29</sup> suggested avoiding hyperglycemia defined as exceeding a glucose of 180 mg/dL<sup>3,4,98</sup> or aiming for glucose within normal ranges.<sup>31,76,99</sup> A recent randomized study in ischemic stroke found an increase in infarct size with aggressive control (aiming at glucose <126 mg/dL or <7 mmol/L).<sup>100</sup>

### Glucose Management: Recommendations

1. Hyperglycemia should be avoided, and glucose levels between 140 and 180 mg/dL are recommended (*Class I; Level of Evidence C*).
2. Tight glycemic control (glucose <110 mg/dL) is not indicated, but an insulin infusion may be used to avoid significant hyperglycemia (*Class IIb; Level of Evidence C*).
3. Hypoglycemia should be avoided at all times (*Class III; Level of Evidence C*).

### Temperature Management

Fever is uncommon after ischemic stroke and may more often indicate early infection rather than a stress response.<sup>101,102</sup> Normothermia is preferred, but therapeutic hypothermia has

not been sufficiently studied prospectively. The European Stroke Initiative<sup>29</sup> has recommended treating temperatures  $>37.5^{\circ}\text{C}$ .<sup>43,87,103–105</sup> Others have stipulated simply avoiding hyperthermia (not defined)<sup>3,4,98</sup> or aiming for normothermia (not defined).<sup>31,75</sup> There is insufficient research to recommend early hypothermia for the treatment of ischemic stroke.<sup>88,106</sup> Temperature management has evolved, and the use of cooling devices has increased. The development of early fever after a hemispheric or cerebellar stroke warrants complete assessment for an infectious or a drug-induced cause.

### Temperature Management: Recommendations

1. Temperature management is part of basic support, and a normal temperature is reasonable (*Class IIa; Level of Evidence C*).
2. The effectiveness of the use of therapeutic hypothermia before brain swelling is not known (*Class IIb; Level of Evidence C*).

### ICP Management

Clinical deterioration is more often the result of displacement of midline structures such as the thalamus and the brainstem than of a mechanism of globally increased ICP. There is sufficient evidence that ICP is not increased in the early days after presentation with a hemispheric infarct.<sup>33,107</sup> There does not appear to be any value of ICP monitoring or placement of a ventriculostomy in a patient presenting early with a large supratentorial swollen hemispheric stroke.<sup>107</sup> Even in patients with deterioration from cerebral edema, ICP values may remain  $<20$  mmHg, suggesting that displacement from mass effect is the likely mechanism. In patients with a cerebellar stroke with early swelling, acute hydrocephalus may occur. Placement of a ventriculostomy for the treatment of acute hydrocephalus in most cases is accompanied by suboccipital decompressed craniectomy.<sup>108</sup>

### ICP Management: Recommendations

1. Routine ICP monitoring is not indicated in hemispheric ischemic stroke (*Class III; Level of Evidence C*).
2. Ventriculostomy is recommended in obstructive hydrocephalus after a cerebellar infarct but should be followed or accompanied by decompressive craniectomy (*Class I; Level of Evidence C*).

### Miscellaneous Medical Measures

As a result of the substantial risk of hemorrhagic conversion or development of an expanding hematoma, it is common practice to reverse an increased international normalized ratio in a patient on warfarin, but only after carefully judging the risks of not anticoagulating the patient. There are no data indicating whether slow reversal of warfarin, for example, discontinuation of warfarin versus use of vitamin K and fresh-frozen plasma or other hemostatic agents, decreases the risk of hemorrhagic conversion.

Because of the risk of hemorrhagic transformation, the combination of aspirin and clopidogrel is typically discontinued.<sup>109</sup> Aspirin may be continued. Intravenous heparin is

avoided, but subcutaneous heparin or low-molecular-weight heparin is necessary to prevent deep venous thrombosis, even if there is some hemorrhagic conversion or early edema on CT scan.

Seizures are uncommon after a hemispheric infarct, but any patient with a fluctuating level of consciousness may require more prolonged electroencephalography monitoring to exclude that possibility. There is no evidence of benefit in using seizure prophylaxis.<sup>110,111</sup>

### Miscellaneous Medical Measures: Recommendations

1. Deep venous thrombosis prophylaxis with subcutaneous or low-molecular-weight heparin should be used (*Class I; Level of Evidence C*).
2. Intravenous heparin or combination antiplatelet agents are not recommended in patients with swollen strokes (*Class III; Level of Evidence C*).
3. Seizure prophylaxis in patients without seizures at presentation is not indicated (*Class III; Level of Evidence C*).

### Recognition of Deterioration

The most commonly described signs in deterioration from hemispheric supratentorial infarction are ipsilateral pupillary dysfunction, varying degrees of mydriasis, and adduction paralysis.<sup>2,7,58</sup> Worsening limb power can be seen,<sup>29</sup> progressive to extensor posturing of the extremity.<sup>4,58,77,103,112,113</sup> A Babinski sign contralateral to the hemiparesis as a result of brainstem notching against the tentorium can occur.<sup>2</sup> Abnormal respiratory patterns, signaling lower brainstem dysfunction, typically occur late in the course; these include central neurogenic hyperventilation or ataxic respiratory patterns<sup>58</sup> and periodic breathing.<sup>2</sup>

Generally, deterioration in a supratentorial hemispheric infarct may present in 2 ways. Clinically, it may present with a gradual progressive rostrocaudal deterioration (development of midposition pupils, worsening of motor responses, and progression to irregular breathing and death)<sup>5,114</sup> or more suddenly present with a unilaterally dilated pupil progressing to bilateral pupils followed by decreasing motor response from localization to flexion rigidity.<sup>114</sup>

Deterioration in cerebellar infarcts with swelling has been defined as clinical signs of brainstem compression with neurological deterioration,<sup>25,115</sup> brainstem compression and obstructive hydrocephalus,<sup>26</sup> depression in level of consciousness,<sup>26,116</sup> Glasgow Coma Scale score  $<12$  on admission,<sup>25</sup> acute hydrocephalus, rapid deterioration to coma,<sup>117</sup> and Glasgow Coma Scale score decline of  $\geq 2$  points.<sup>108</sup> Radiographic deterioration was defined in 1 study as fourth ventricular compression and evidence of hydrocephalus.<sup>116</sup> Cerebellar infarcts worsen from brainstem compression, and obstructive hydrocephalus is a secondary manifestation in most instances. Deterioration from swelling or extension of the infarct into the brainstem cannot be clinically distinguished, but many patients develop pupillary anisocoria, pinpoint pupils, and loss of oculocephalic responses.

Further brainstem compression may lead to bradycardia, irregular breathing patterns, and sudden apnea.

### Recognition of Deterioration: Recommendations

1. Clinicians should frequently monitor level of arousal and ipsilateral pupillary dilation in patients with supratentorial ischemic stroke at high risk for deterioration. Gradual development of midposition pupils and worsening of motor response may also indicate deterioration (*Class I; Level of Evidence C*).
2. Clinicians should frequently monitor for level of arousal or new brainstem signs in patients with cerebellar stroke at high risk for deterioration (*Class I; Level of Evidence C*).

### Medical Options in a Deteriorated Patient

Several immediate measures are needed to treat a deteriorating patient. The initial management should focus on reducing the space-occupying effects of brain swelling. In the absence of increased ICP in patients deteriorating from swelling of supratentorial hemispheric infarcts, measures to reduce ICP may not be beneficial. Nonetheless, most studies recommend elevation of the head of the bed to 30°.<sup>10,33,65,107,118</sup> Osmotic therapy works mostly through an osmotic gradient and draws water out of neurons into arteries, leading to vasoconstriction and reduced cerebrovascular volume. Osmotic therapy has consisted primarily of mannitol and hypertonic saline with varying osmolar loads. Mannitol has been used both as a single dose and in recurrent bolus form such as mannitol 15 g once<sup>119</sup>; 0.5 to 1 g/kg<sup>76,120</sup>; mannitol 1.0 g/kg<sup>70</sup>; and 0.5 g/kg every 4 to 6 hours. Hypertonic saline has been used at a variety of doses and concentrations (3%, 7.5%, 23%).

Other agents that have been used include tromethamine buffer at 3 mmol/h<sup>3,4,89,121</sup> or 1 mmol/kg body weight bolus.<sup>122</sup> "Hyper HES," or hypertonic saline and hydroxyethyl starch, has been used in multiple forms.<sup>87</sup>

Only small limited studies have studied the effect of different osmotic agents in a randomized fashion. One study<sup>70</sup> compared the effects of mannitol (1 g/kg of 20%) and hypertonic saline (0.686 mL/kg of 23.4% saline, equiosmolar to mannitol) using positron emission tomography to evaluate cerebral hemodynamics. Neither agent led to a decrease in cerebral blood volume, nor did the degree of increase in cerebral blood flow with either agent appear to be mediated by blood pressure. One prospective study<sup>123</sup> reported 30 episodes of ICP crisis in 9 patients, randomizing them to 100 mL of hypertonic saline–hydroxyethyl starch (75 g/L NaCl and 60 g/L HES) or mannitol 40 g over 15 minutes. Treatment was effective in all 16 hypertonic saline–hydroxyethyl starch episodes and in 10 of 14 mannitol episodes. Hypertonic saline–hydroxyethyl starch did not raise the cerebral perfusion pressure to the same degree as mannitol.

Hypothermia has been used to various degrees and for multiple durations such as 34°C to 36°C,<sup>76</sup> 35°C for 48 hours,<sup>124</sup> 33°C,<sup>125</sup> and 33°C with an endovascular cooling device for 12 to 24 hours.<sup>126</sup> Prospective randomized studies are currently underway to further evaluate therapeutic hypothermia in patients with cerebral infarcts. Barbiturates have

been used in a paucity of studies, again with various agents and varying doses/durations.<sup>89,107</sup> Similarly, neither the dose of corticosteroids nor its efficacy has been studied systematically, and the dose used in studies varied greatly.<sup>127–129</sup> Corticosteroids have been administered to reduce brain swelling, but a recent Cochrane review concluded after review of 8 clinical trials that there was no benefit on mortality or functional outcome.<sup>130</sup>

### Medical Options: Recommendations

1. Osmotic therapy for patients with clinical deterioration from cerebral swelling associated with cerebral infarction is reasonable (*Class IIa; Level of Evidence C*).
2. There are insufficient data on the effect of hypothermia, barbiturates, and corticosteroids in the setting of ischemic cerebral or cerebellar swelling, and they are not recommended (*Class III; Level of Evidence C*).

### Neurosurgical Options in a Deteriorated Patient

Surgical treatment of the swelling associated with cerebellar or cerebral infarctions is performed by removal of the skull and expansion of the dura to alleviate the volume constraints of the cranial vault during the acute swelling phase of the infarction. Since the earliest reports of surgical intervention for cerebellar infarction in 1956,<sup>131,132</sup> it has been repeatedly shown that patients who deteriorate neurologically after cerebellar infarction benefit from suboccipital craniectomy (unilateral or bilateral) with dural expansion. The procedure may include resection of infarcted tissue.<sup>133</sup> Because the benefits of surgical intervention have repeatedly been apparent, no prospective, randomized trials have been pursued. In a large series of 84 patients with massive cerebellar infarction,<sup>26</sup> 40% required surgical craniotomies, and 17% were managed with ventricular drainage. In this series, 74% of patients had very good outcomes (modified Rankin Scale [mRS] score, 0 or 1).

Three prospective, randomized trials (ie, Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery [DESTINY], Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarction [DECIMAL], and Hemicraniectomy After Middle Cerebral Artery Infarction With Life-threatening Edema Trial [HAMLET])<sup>31,87,98,134</sup> and 14 case series<sup>135</sup> have studied patients with supratentorial infarctions treated with decompressive craniectomy, usually within 48 hours of stroke onset. Three prospective trials showed reduced mortality with hemicraniectomy compared with medical management (22% versus 71% mortality, pooled analysis) in patients <60 years of age, but no individual study showed an improvement in the percentage of survivors with good outcomes (mRS score, 0–3), although this improvement (43% versus 21%) was noted in a pooled analysis.<sup>31,134</sup> There were no survivors in either group who were asymptomatic (mRS score, 0) or had no significant disability (mRS score, 1). Only 14% of surgical survivors could look after their own affairs without assistance (mRS score, 2).<sup>134</sup> In all clinical trials, it is difficult to assess whether the nonsurgical group was treated identically



or whether equally aggressive medical measures were initiated. Three prospective, randomized studies have compared decompressive craniectomy with conservative therapy. The DESTINY study<sup>87</sup> used osmotic therapy, including mannitol, glycerol, and hypertonic saline–hydroxyethyl starch, as well as other standard conservative measures, including blood pressure management, blood glucose control, and progressive hyperventilation, to decrease Pco<sub>2</sub> goals, depending on ICP control. The DECIMAL trial<sup>98</sup> incorporated elevation of the head of the bed, fluid restriction, blood pressure control, and glucose control and used mannitol or furosemide in patients with clinical worsening. HAMLET may have had far more aggressive management in the surgically treated patients because the medically treated patients were admitted to a stroke unit. This trial protocol also included recommendations on osmotherapy, intubation and mechanical ventilation, monitoring of ICP, jugular bulb oximetry, and blood pressure control with suggested target values. Use of these parameters was left to the physicians' discretion, but use remained largely unreported. Osmotic therapy was more commonly used in medically treated patients than in patients who underwent decompressive craniotomy.<sup>31</sup> Technical and patient-specific features associated with outcomes of the surgical procedure have been reported.<sup>136</sup>

Decompressive craniectomy for supratentorial infarction with swelling thus results in a reproducible large reduction in mortality, but nearly all survivors suffer residual permanent disabilities. All prior clinical trials involved patients <60 years of age (mean age, 45 years), but it remains unclear whether older patients would experience a similar effect. One randomized study of 47 patients included patients 18 to 80 years of age, with 18 patients 61 to 70 years and 11 patients 71 to 80 years of age. A significant benefit of surgery was found in this small subset of patients >60 years of age (1-year mortality reduced from 69.6% to 16.7%) and on poor outcome (1-year mRS score >4 reduced from 100% to 37.5%).<sup>105</sup> Further data will be forthcoming after publication of DESTINY 2, which included patients 62 to 82 years of age.

One prospective, randomized study compared 25 patients who underwent decompressive craniectomy with hypothermia with those who underwent decompressive craniectomy alone. Hypothermia to 35°C was initiated immediately after the operation for a duration of 48 hours. There was no difference in mortality, and a trend toward better clinical outcome was seen in patients who underwent combination therapy. Timing of decompressive craniectomy remains unresolved, but it is generally agreed that the surgery is best undertaken before clinical signs of brainstem compression, and all the randomized studies were associated with a bony window of ≥12 cm in diameter. Technical factors associated with outcome after decompressive craniectomy have been studied. It appears to be important for ICP reduction to accomplish dural relaxation with a large dural augmentation graft. One large series found that young patients with very large infarcts (>400 cm<sup>3</sup>) may benefit from temporal lobectomy and even reoperation if brainstem decompression is not adequately relieved by bony and dural decompression alone.<sup>136</sup>

Postoperative concerns include wound dehiscence, typically near the posterior aspect of the large craniectomy flap. A

substantial proportion of patients may also require tracheostomy and gastrostomy for management in the initial postoperative phase.<sup>136</sup> The timing of cranioplasty after decompressive craniectomy remains unknown, but the complication rate (eg, hydrocephalus, infection) was slightly higher in early cranioplasty (within 10 weeks of craniectomy), particularly in patients with a ventriculoperitoneal shunt at the time of cranioplasty.<sup>137</sup> Finally, if bone flap replacement is delayed, a communicating hydrocephalus may develop, requiring ventriculoperitoneal shunt placement.<sup>138</sup> However, wide variations in practice remain as to the specific timing of the procedure, the neurological deficits required to prompt the intervention, and the technical aspects of the dural modification.

There are similar considerations with decompressive surgery (bioccipital craniectomy) in cerebellar swelling. Most clinical series have used a combination of clinical and radiologic worsening when deciding on surgery. The time interval to surgery does not seem to affect outcome. The value of preemptive surgery (ie, when swelling and hydrocephalus progress on CT scan in a clinically stable patient) and the best neurosurgical approach (ie, removal of necrotic tissue versus decompression alone versus decompression and ventriculostomy) are not known.<sup>139,140</sup>

## Neurosurgical Options: Recommendations

- 1. In patients <60 years of age with unilateral MCA infarctions that deteriorate neurologically within 48 hours despite medical therapy, decompressive craniectomy with dural expansion is effective. The effect of later decompression is not known, but it should be strongly considered (Class I; Level of Evidence B).**
- 2. Although the optimal trigger for decompressive craniectomy is unknown, it is reasonable to use a decrease in level of consciousness and its attribution to brain swelling as selection criteria (Class IIa; Level of Evidence A).**
- 3. The efficacy of decompressive craniectomy in patients >60 years of age and the optimal timing of surgery are uncertain (Class IIb; Level of Evidence C).**
- 4. Suboccipital craniectomy with dural expansion should be performed in patients with cerebellar infarctions who deteriorate neurologically despite maximal medical therapy (Class I; Level of Evidence B).**

## Biomarkers

Biomarkers are typically used as determinants of prognosis or in the assessment of the risk of developing disease.<sup>141</sup> Whereas many candidate biomarkers have been evaluated for ischemic stroke,<sup>142</sup> a smaller subset have potential application in large infarctions and swelling.<sup>143</sup> Biomarkers for cerebral swelling can be broadly categorized into neuroimaging modalities, serum markers, or continuous neuromonitoring techniques. The radiologic features that serve as surrogates for edema are described in detail above. Blood-based biomarkers and continuous neuromonitoring technologies, if translated into routine clinical practice, are generally envisioned as an adjunct to the overall clinical assessment.

## Serum Biomarkers

Circulating markers that relate to the BBB have been studied most extensively, reflecting the central role that the integrity of the BBB may play in the development of cerebral edema. Edema and hemorrhagic conversion can be viewed as existing on a spectrum of BBB injury. A key BBB-degrading enzyme, MMP-9, has been associated with edema,<sup>12</sup> with 1 study reporting that a concentration of  $\geq 140$  ng/mL has a 64% sensitivity and 88% specificity for predicting infarction. Elevated MMP-9 is also associated with an increased risk of hemorrhagic conversion,<sup>144–146</sup> in accord with the high rates of hemorrhagic conversion found in this population.<sup>54</sup>

Other reports using biomarkers to predict edema include cellular fibronectin, a constituent of the basal lamina. Cellular fibronectin elevations of  $>16.6$   $\mu\text{g/mL}$  predict edema with 90% sensitivity and 100% specificity.<sup>12</sup> The glial marker S100B is released into the bloodstream after ischemic stroke, with increasing amounts correlating with infarct size.<sup>147,148</sup> Serum levels  $>1.03$   $\mu\text{g/L}$  at 24 hours are also associated with large infarction.<sup>9</sup>

## Other Biomarkers

In addition to circulating proteins, other investigational biomarkers include invasive intracranial monitoring with microdialysis, flumazenil imaging with positron emission tomography, and continuous electroencephalography. Microdialysis probe placements adjacent to hemispheric infarcts have revealed decreases in extracellular amino acids in infarction compared with nonmalignant edema.<sup>61</sup> Similarly, positron emission tomography imaging with [<sup>11</sup>C] flumazenil has shown a larger volume of irreversible neuronal damage in patients with edema.<sup>69</sup> Finally, continuous electroencephalography monitoring in the first 24 hours that exhibits a pattern of slow delta activity is associated with deterioration.<sup>41</sup> Although none of these biomarkers have reached usefulness in clinical practice, they may offer insights into the pathophysiology of brain edema and warrant further investigation. The difficulty of translating biomarkers into clinical practice is not unique to large infarction,<sup>149,150</sup> with substantial attrition being a common finding.<sup>149</sup> Future work in biomarkers for edema and stroke needs to focus on prospective validation in independent cohorts and the development of rapid and reliable testing methodologies.

## Biomarkers: Recommendations

1. The usefulness of serum biomarkers as predictors of ischemic brain swelling is not well established (*Class IIb; Level of Evidence C*).
2. The usefulness of electrophysiological studies as predictors of deterioration after a hemispheric stroke is not well established (*Class IIb; Level of Evidence C*).

## Outcome and Family Discussion

Mortality after large ischemic strokes with cerebral edema has remained between 20% and 30% despite medical and surgical interventions. The vast majority of patients with a hemispheric ischemic stroke are markedly disabled. Approximately one third of the patients are unable to walk without assistance and need continuous nursing care. The initial experience with

outcome assessment does not identify a major difference in outcome between a dominant or nondominant hemispheric stroke.<sup>151–157</sup> Outcome assessed years after hemispheric stroke is not available, but continuously improving quality of life has been described.<sup>158</sup> There is a discrepancy between physical disability and quality of life, with many patients and families rating a good quality of life despite severe functional handicap.

Decision making is shared between physicians and families, and discussion is of paramount importance. Families have the burden of predicting what the patient would want in this situation, but that usually is the best guide for decision making. In discussion with family members, it is important to discuss the possibility of depression, lack of initiative, irritability, disinhibition, and being wheelchair-bound. Simple designations such as “survived but handicapped,” “survived but walks with a cane,” or “cannot tell” are ambiguous and not helpful in decision making. Families could be told that when their loved one is  $<60$  years old and decompressive craniectomy is performed within 2 days after a supratentorial ischemic stroke, nearly 3 of 4 patients survive, but nearly half will be severely disabled and nearly half will also be suffering from depression.<sup>159</sup> If their loved one is  $>60$  years old, good information is lacking, and our expectations may not be as high as for younger patients.

The outcome after a cerebellar hemispheric stroke is often good if there has been no evidence of brainstem infarction,<sup>139,140</sup> and the decisions in this situation are much less problematic. Prior severe comorbidity or advanced age may factor into the decision to proceed with surgery.

## Outcome and Family Discussion: Recommendations

1. Clinicians may discuss with family members that half of the surviving patients with massive hemispheric infarctions, even after decompressive craniectomy, are severely disabled and a third are fully dependent on care (*Class IIb; Level of Evidence C*).
2. Clinicians may discuss with family members that the outcome after cerebellar infarct can be good after suboccipital craniectomy (*Class IIb; Level of Evidence C*).

## Summary

Strokes that swell require immediate close attention, and medical and surgical options have been proposed. The main principles have been well defined and involve avoidance of permanent brainstem injury from brain tissue shift. Therefore, any measure that relieves compression is warranted. Medical options have not been validated well, but neurosurgical management of hemispheric supratentorial strokes has been tested prospectively in clinical trials. Decompressive craniectomy reduces mortality by reducing progression to brain death and reduces the probability of permanent coma that eventually may lead to de-escalation of care and death. In surviving patients, morbidity can be substantial in a third of the patients, but the remaining patients have good potential for recovery after rehabilitation.

## Future Directions

There are many gaps in our knowledge of the recognition, management, and prognostication of patients with a swollen

stroke, and an urgent agenda is suggested for research in this area. Brain swelling is the cause of significant neurological morbidity and mortality in acute brain injury, yet fundamental, basic research in this area with immediate clinical relevance has been lacking.

The mechanistic basis of edema formation after ischemia remains to be clarified. Future work should identify other biological mediators, the role of intracellular and vascular sources of swelling, and the time course of relative contributions. In this population, the role of recombinant tissue-type plasminogen activator in swelling is also not known and is of direct clinical relevance.

Clinical areas of uncertainty, including the incidence of significant swelling after ischemia and the assessment of ongoing swelling, need clarification. In addition, a major priority for research should be an improved understanding of the relationship between edema and outcome, if any, independently of and in conjunction with infarction. The roles of

vessel occlusion, collateral circulation, and perfusion status in edema formation are also unknown, especially in patients who receive intravenous or endovascular reperfusion therapy. There is a tremendous gap in clinically available neuroimaging that quantitatively identifies, in a manner similar to DWI infarct volumes, brain swelling after ischemia and other surrogates for swelling. Early, sensitive, and specific neuroimaging markers of cerebellar swelling are also needed.

Clarification of critical care neurology practice, including the effects of endotracheal intubation, sodium, glucose, and fluid management strategies, and temperature modulation is also needed. Patient factors, including age and timing, must be identified for optimal decompressive craniectomy selection, as well as the optimal trigger (neurological deterioration versus prophylaxis). Finally, to advance novel therapeutic and management strategies, the development and validation of patient-centered outcome measures that incorporate the severity of illness are urgently needed.

## Disclosures

### Writing Group Disclosures

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Eelco F.M. Wijdicks	Mayo Clinic	None	None	None	None	None	None	None
Kevin N. Sheth	Yale University School of Medicine	NIH†; Remedy†	None	None	None	None	None	None
Bob S. Carter	University of California, San Diego	None	None	None	None	None	None	None
David M. Greer	Yale University School of Medicine	None	None	None	None	None	None	None
Scott E. Kasner	University of Pennsylvania	Gore Associates†	None	None	None	None	Astra-Zeneca*; Brainsgate (DSMB)*; Cardionet*; Medtronic (DSMB)*; Novartis*; Parexel*; Pfizer*	None
W. Taylor Kimberly	Massachusetts General Hospital	NIH/NINDS†; Remedy Pharmaceuticals†	None	None	None	None	None	None
Stefan Schwab	University Hospital Erlangen	None	None	None	None	None	None	None
Eric E. Smith	University of Calgary	None	None	None	None	None	None	None
Rafael J. Tamargo	Johns Hopkins University School of Medicine	None	None	None	None	None	None	None
Max Wintermark	University of Virginia	GE Healthcare†; Philips Healthcare†	None	None	None	None	Bayer*; Biogen idec*; St. Jude Medical*	None

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\*Modest.

†Significant.



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Opeolu Adeoye	University of Cincinnati	None	None	Genentech*	None	None	None	None
Kyra Becker	University of Washington	None	None	None	None	None	None	None
Jonathan Friedman	Texas A&M Health Science Center	None	None	None	None	None	None	None
Alejandro Rabinstein	Mayo Clinic	None	None	None	None	None	None	None
Babu Welch	UT Southwestern Medical Center	None	None	None	None	None	None	None

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\*Modest.

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