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**Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A  
Guideline for Healthcare Professionals From the American Heart  
Association/American Stroke Association**

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## Guidelines for the Management of Spontaneous Intracerebral Hemorrhage

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

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

*The American Association of Neurological Surgeons and the Congress of Neurological Surgeons have reviewed this document and affirm its educational content.*

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**Purpose**—The aim of this guideline is to present current and comprehensive recommendations for the diagnosis and treatment of acute spontaneous intracerebral hemorrhage.

**Methods**—A formal literature search of MEDLINE was performed. Data were synthesized with the use of evidence tables. Writing committee members met by teleconference to discuss data-derived recommendations. The American Heart Association Stroke Council's Levels of Evidence grading algorithm was used to grade each recommendation. Prerelease review of the draft guideline was performed by 6 expert peer reviewers and by the members of the Stroke Council Scientific Statements Oversight Committee and Stroke Council Leadership Committee. It is intended that this guideline be fully updated in 3 years' time.

**Results**—Evidence-based guidelines are presented for the care of patients presenting with intracerebral hemorrhage. The focus was subdivided into diagnosis, hemostasis, blood pressure management, inpatient and nursing management, preventing medical comorbidities, surgical treatment, outcome prediction, rehabilitation, prevention of recurrence, and future considerations.

**Conclusions**—Intracerebral hemorrhage is a serious medical condition for which outcome can be impacted by early, aggressive care. The guidelines offer a framework for goal-directed treatment of the patient with intracerebral hemorrhage. (*Stroke*. 2010;41:2108-2129.)

**Key Words:** AHA Scientific Statements ■ intracerebral hemorrhage ■ treatment ■ diagnosis  
■ intracranial pressure ■ hydrocephalus ■ surgery

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Spontaneous, nontraumatic intracerebral hemorrhage (ICH) is a significant cause of morbidity and mortality throughout the world. Although much has been made of the lack of a specific targeted therapy, much less is written about the success and goals of aggressive medical and surgical care for this disease. Recent population-based studies suggest that most patients present with small ICHs that are readily survivable with good medical care.<sup>1</sup> This suggests that excellent medical care likely has a potent, direct impact on ICH morbidity and mortality now, even before a specific therapy is found. Indeed, as discussed later, the overall aggressiveness of ICH care is directly related to mortality from this disease.<sup>2</sup> One of the purposes of this guideline, therefore, is to remind clinicians of the importance of their care in determining ICH outcome and to provide an evidence-based framework for that care.

In order to make this review brief and readily useful to practicing clinicians, the reader is referred elsewhere for the details of ICH epidemiology.<sup>1,3,4</sup> Similarly, there are many ongoing clinical studies throughout the world related to this disease. The reader is encouraged to consider referring patients to these important efforts, which can be found at <http://www.strokecenter.org/trials/>. We will not discuss ongoing studies because we cannot cover them all; the focus of this statement is on currently available therapies. Finally, a recent guideline on pediatric stroke was published<sup>5</sup> that obviates the need to repeat the issues of pediatric ICH here.

The last ICH Guidelines were published in 2007,<sup>6</sup> and this current article serves to update those guidelines. As such, differences from former recommendations are specified in the current work. The writing group met by phone to determine subcategories to evaluate. These included emergency diagnosis and assessment of ICH and its causes; hemostasis, blood pressure (BP); intracranial pressure (ICP)/fever/glucose/seizures/hydrocephalus; iron; ICP monitors/tissue oxygenation; clot removal; intraventricular hemorrhage (IVH); withdrawal of technological support; prevention of recurrent ICH; nursing care; rehab/recovery; future considerations. Each subcategory was led by an author with 1 or 2 additional authors making contributions. Full MEDLINE searches were done of all English-language articles regarding relevant human disease treatment. Drafts of summaries and recommendations were circulated to the whole writing group for feedback. A conference call was held to discuss controversial issues. Sections were revised and merged by the Chair. The resulting draft was sent to the whole writing group for comment. Comments were incorporated by the Vice Chair and Chair, and the entire committee was asked to approve the final draft. Changes to the document were made by the Chair and Vice Chair in response to peer review, and the document was again sent to the entire writing group for suggested changes and approval. Recommendations follow the American Heart Association Stroke Council's methods of classifying the level of certainty of the treatment effect and the class of evidence (Tables 1 and 2). All Class I recommendations are listed in Table 3.

### Emergency Diagnosis and Assessment of ICH and Its Causes

ICH is a medical emergency. Rapid diagnosis and attentive management of patients with ICH is crucial because early

deterioration is common in the first few hours after ICH onset. More than 20% of patients will experience a decrease in the Glasgow Coma Scale (GCS) score of  $\geq 2$  points between the prehospital emergency medical services assessment and the initial evaluation in the emergency department (ED).<sup>7</sup> Among those patients with prehospital neurological decline, the GCS score decreases by an average of 6 points and the mortality rate is  $>75\%$ . Further, within the first hour of presentation to a hospital, 15% of patients demonstrate a decrease in the GCS score of  $\geq 2$  points.<sup>8</sup> The risk for early neurological deterioration and the high rate of poor long-term outcomes underscores the need for aggressive early management.

### Prehospital Management

The primary objective in the prehospital setting is to provide ventilatory and cardiovascular support and to transport the patient to the closest facility prepared to care for patients with acute stroke (see ED Management section that follows). Secondary priorities for emergency medical services providers include obtaining a focused history regarding the timing of symptom onset (or the time the patient was last normal) and information about medical history, medication, and drug use. Finally, emergency medical services providers should provide advance notice to the ED of the impending arrival of a potential stroke patient so that critical pathways can be initiated and consulting services can be alerted. Advance notice by emergency medical services has been demonstrated to significantly shorten time to computed tomography (CT) scanning in the ED.<sup>9</sup>

### ED Management

It is of the utmost importance that every ED be prepared to treat patients with ICH or have a plan for rapid transfer to a tertiary care center. The crucial resources necessary to manage patients with ICH include neurology, neuroradiology, neurosurgery, and critical care facilities including adequately trained nurses and physicians. In the ED, appropriate consultative services should be contacted as quickly as possible and the clinical evaluation should be performed efficiently, with physicians and nurses working in parallel. Table 4 describes the integral components of the history, physical examination, and diagnostic studies that should be obtained in the ED.

For patients with ICH, emergency management may include neurosurgical interventions for hematoma evacuation, external ventricular drainage or invasive monitoring and treatment of ICP, BP management, intubation, and reversal of coagulopathy. Although many centers have critical pathways developed for the treatment of acute ischemic stroke, few have protocols for the management of ICH.<sup>18</sup> Such pathways may allow for more efficient, standardized, and integrated management of critically ill patients with ICH.

### Neuroimaging

The abrupt onset of focal neurological symptoms is presumed to be vascular in origin until proven otherwise. However, it is impossible to know whether symptoms are due to ischemia or hemorrhage based on clinical characteristics alone. Vomiting, systolic BP  $>220$  mm Hg, severe headache, coma or decreased level of consciousness, and progression over minutes or hours all suggest ICH, although none of these findings are specific;

Table 1. Applying Classification of Recommendations and Level of Evidence

		SIZE OF TREATMENT EFFECT <span style="float: right;">→</span>			
		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> <i>Additional studies with focused objectives needed</i> <b>IT IS REASONABLE</b> to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>Risk ≥ Benefit</i> Procedure/Treatment should <b>NOT</b> be performed/administered <b>SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL</b>
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>	<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>
	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	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

\*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. 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. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACCF/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

neuroimaging is thus mandatory.<sup>19</sup> CT and magnetic resonance imaging (MRI) are both reasonable for initial evaluation. CT is very sensitive for identifying acute hemorrhage and is considered the gold standard; gradient echo and T2\*-susceptibility-weighted MRI are as sensitive as CT for detection of acute blood and are more sensitive for identification of prior hemorrhage.<sup>20,21</sup> Time, cost, proximity to the ED, patient tolerance, clinical status, and MRI availability may, however, preclude emergent MRI in a sizeable proportion of cases.<sup>22</sup>

The high rate of early neurological deterioration after ICH is in part related to active bleeding that may proceed for hours after symptom onset. The earlier time from symptom onset to first neuroimage, the more likely subsequent neuroimages will demonstrate hematoma expansion.<sup>15,23,24</sup> Among patients undergoing head CT within 3 hours of ICH onset, 28% to 38% have hematoma expansion of greater than one third on

follow-up CT.<sup>8,25</sup> Hematoma expansion is predictive of clinical deterioration and increased morbidity and mortality.<sup>8,10,15,25</sup> As such, identifying patients at risk for hematoma expansion is an active area of research. CT angiography and contrast-enhanced CT may identify patients at high risk of ICH expansion based on the presence of contrast extravasation within the hematoma.<sup>26–30</sup> MRI/angiogram/venogram and CT angiogram/venogram are reasonably sensitive at identifying secondary causes of hemorrhage, including arteriovenous malformations, tumors, moyamoya, and cerebral vein thrombosis.<sup>31–33</sup> A catheter angiogram may be considered if clinical suspicion is high or noninvasive studies are suggestive of an underlying vascular cause. Clinical suspicion of a secondary cause of ICH may include a prodrome of headache, neurological, or constitutional symptoms. Radiological suspicions of secondary causes of ICH should be

**Table 2. Definition of Classes and Levels of Evidence Used in American Heart Association Stroke Council 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

invoked by the presence of subarachnoid hemorrhage, unusual (noncircular) hematoma shape, the presence of edema out of proportion to the early time an ICH is first imaged, an unusual location for hemorrhage, and the presence of other abnormal structures in the brain like a mass. An MR or CT venogram should be performed if hemorrhage location, relative edema volume, or abnormal signal in the cerebral sinuses on routine neuroimaging suggest cerebral vein thrombosis.

In summary, ICH is a medical emergency, characterized by high morbidity and mortality, which should be promptly diagnosed and aggressively managed. Hematoma expansion and early deterioration are common within the first few hours after onset.

## Recommendations

- 1. Rapid neuroimaging with CT or MRI is recommended to distinguish ischemic stroke from ICH (Class I; Level of Evidence: A).** (Unchanged from the previous guideline)
- 2. CT angiography and contrast-enhanced CT may be considered to help identify patients at risk for hematoma expansion (Class IIb; Level of Evidence: B), and CT angiography, CT venography, contrast-enhanced CT, contrast-enhanced MRI, magnetic resonance angiography, and magnetic resonance venography can be**

**useful to evaluate for underlying structural lesions, including vascular malformations and tumors when there is clinical or radiological suspicion (Class IIa; Level of Evidence: B).** (New recommendation)

## Medical Treatment for ICH

### Hemostasis/Antiplatelets/Deep Vein Thrombosis Prophylaxis

Underlying hemostatic abnormalities can contribute to ICH. Patients at risk include those on oral anticoagulants (OACs), those with acquired or congenital coagulation factor deficiencies, and those with qualitative or quantitative platelet abnormalities. Patients undergoing treatment with OACs constitute 12% to 14% of patients with ICH,<sup>34,35</sup> and with increased use of warfarin, the proportion appears to be increasing.<sup>36</sup> Recognition of an underlying coagulopathy thus provides an opportunity to target correction in the treatment strategy. For patients with a coagulation factor deficiency and thrombocytopenia, replacement of the appropriate factor or platelets is indicated.

For patients being treated with OACs who have life-threatening bleeding, such as intracranial hemorrhage, the general recommendation is to correct the international normalized ratio (INR) as rapidly as possible.<sup>37,38</sup> Infusions of vitamin K and fresh-frozen plasma (FFP) have historically been recommended, but more recently, prothrombin complex concentrates (PCCs) and recombinant factor VIIa (rFVIIa) have emerged as potential therapies. Vitamin K remains an adjunct to more rapidly acting initial therapy for life-threatening OAC-associated hemorrhage because even when given intravenously, it requires hours to correct the INR.<sup>39–41</sup> The efficacy of FFP is limited by risk of allergic and infectious transfusion reactions, processing time, and the volume required for correction. Likelihood of INR correction at 24 hours was linked to time to FFP administration in 1 study, although 17% of patients still did not have an INR  $\leq 1.4$  at this time, suggesting that FFP administered in this manner may be insufficient for rapid correction of coagulopathy.<sup>42</sup>

PCCs are plasma-derived factor concentrates primarily used to treat factor IX deficiency. Because PCCs also contain factors II, VII, and X in addition to IX, they are increasingly recommended for warfarin reversal. PCCs have the advantages of rapid reconstitution and administration, having high concentrations of coagulation factors in small volumes, and processing to inactivate infectious agents. Though different PCC preparations differ in relative amounts of factors (with VII the most likely to be low), several studies have shown that PCCs can rapidly normalize INR (within minutes) in patients taking OACs (reviewed in<sup>43–45</sup>). Nonrandomized retrospective reviews and a small case-control study have shown more rapid correction of INR with vitamin K and PCC than vitamin K and FFP, but have not revealed a difference in clinical outcome.<sup>46–48</sup> One randomized trial compared the use of a PCC (Konyne) to supplement FFP versus FFP alone in patients with OAC-related ICH, finding that those who received PCC had significantly shorter time to INR correction and received less volume of FFP. Although there was no difference in outcome, those who received FFP also had more adverse events, primarily attributable to fluid overload.<sup>49</sup> Although PCCs may theoretically increase the risk of thrombotic complications, this risk appears relatively low.<sup>43</sup> De-

**Table 3. Class I Recommendations**

	Recommendations	Class/Level of Evidence
Emergency diagnosis and assessment of ICH and its causes	Rapid neuroimaging with CT or MRI is recommended to distinguish ischemic stroke from ICH. ( <i>Unchanged from the previous guideline</i> )	Class I, Level A
Medical treatment for ICH	Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively. ( <i>New recommendation</i> )	Class I, Level C
Hemostasis/antiplatelets/DVT prophylaxis	Patients with ICH whose INR is elevated due to OAC should have their warfarin withheld, receive therapy to replace vitamin K–dependent factors and correct the INR, and receive intravenous vitamin K. ( <i>Revised from the previous guideline</i> )	Class I, Level C
	Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism in addition to elastic stockings. ( <i>Unchanged from the previous guideline</i> )	Class I, Level B
Inpatient management and prevention of secondary brain injury		
General monitoring	Initial monitoring and management of ICH patients should take place in an intensive care unit, preferably one with physician and nursing neuroscience intensive care expertise. ( <i>Unchanged from the previous guideline</i> )	Class I, Level B
Management of glucose	Glucose should be monitored and normoglycemia is recommended	Class I, Level C
Seizures and antiepileptic drugs	Patients with clinical seizures should be treated with antiepileptic drugs. ( <i>Revised from previous guideline</i> )	Class I, Level A
	Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with antiepileptic drugs	Class I, Level C
Procedures/surgery—clot removal	Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible. ( <i>Revised from the previous guideline</i> )	Class I, Level B
Prevention of recurrent ICH	After the acute ICH, absent medical contraindications, BP should be well controlled, particularly for patients with ICH location typical of hypertensive vasculopathy. ( <i>New recommendation</i> )	Class I, Level A

CT indicates computed tomography; MRI, magnetic resonance imaging; DVT, deep vein thrombosis; INR, international normalized ratio; OAC, oral anticoagulants; and EEG, electroencephalogram.

spite the lack of large, well-controlled, randomized trials, PCCs are being increasingly recommended as an option in guidelines promulgated for warfarin reversal in the setting of OAC-associated life-threatening or intracranial hemorrhages.<sup>37,38,50–52</sup> Table 5 provides a list of several products for factor replacement in warfarin reversal that are commercially available in the United States at the present time.

rFVIIa, licensed to treat hemophilia patients with high titer inhibitors or congenital factor VII deficiency, has garnered attention as a potential treatment for spontaneous and OAC-associated ICH. Although rFVIIa can rapidly normalize INR in the setting of OAC-associated ICH,<sup>53–57</sup> it does not replenish all of the vitamin K–dependent factors and therefore may not restore thrombin generation as well as PCCs.<sup>58</sup> In light of the limited data, a recent American Society of Hematology evidence-based review recommended against routine use of rFVIIa for warfarin reversal.<sup>59</sup>

rFVIIa has also been tested in patients with non-OAC ICH. A phase 2 randomized trial showed that treatment with rFVIIa within 4 hours after ICH onset limited hematoma growth and improved clinical outcomes relative to placebo, though with increased frequency of thromboembolic events

(7% versus 2%).<sup>60</sup> A subsequent phase 3 study comparing placebo with 20  $\mu\text{g}/\text{kg}$  and 80  $\mu\text{g}/\text{kg}$  of rFVIIa failed to show differences in clinical outcome, despite confirming the ability of both doses to diminish hematoma enlargement.<sup>61</sup> Although overall serious thromboembolic adverse events were similar, the higher rFVIIa (80  $\mu\text{g}/\text{kg}$ ) group had significantly more arterial events than the placebo group. The authors noted imbalances in the treatment groups, particularly the greater number of patients with IVH in the higher-dose rFVIIa group.<sup>60</sup> It remains to be determined whether rFVIIa will benefit a particular subset of patients with ICH, but currently its benefits in ICH patients, whether or not they are undergoing treatment with OACs, remain unproven.

Studies of the effect of prior antiplatelet agent use or platelet dysfunction on ICH hematoma growth and outcome have found conflicting results. Reported antiplatelet agent use was not associated with hematoma expansion or clinical outcome in the placebo group of an ICH neuroprotective study.<sup>62</sup> However, others have suggested that platelet dysfunction as measured by platelet function assays may be associated with hematoma expansion and clinical outcome.<sup>63,64</sup> The utility and safety of platelet transfusion or

**Table 4. Integral Components of the History, Physical Examination, and Work-Up of the Patient With ICH in the ED**

	Comments
History	
Time of symptom onset (or time the patient was last normal)	
Initial symptoms and progression of symptoms	
Vascular risk factors	Hypertension, diabetes, hypercholesterolemia, and smoking
Medications	Anticoagulants, antiplatelet agents, decongestants, antihypertensive medications, stimulants (including diet pills), sympathomimetics
Recent trauma or surgery	Carotid endarterectomy or carotid stenting in particular, as ICH may be related to hyperperfusion after such procedures
Dementia	Associated with amyloid angiopathy
Alcohol or illicit drug use	Cocaine and other sympathomimetic drugs are associated with ICH, stimulants
Seizures	
Liver disease	May be associated with coagulopathy
Cancer and hematologic disorders	May be associated with coagulopathy
Physical examination	
Vital signs	Fever is associated with early neurologic deterioration <sup>10</sup> Higher initial blood pressure is associated with early neurologic deterioration and increased mortality <sup>11</sup>
A general physical examination focusing on the head, heart, lungs, abdomen, and extremities	
A thorough but time-urgent neurologic examination	A structured examination such as the National Institutes of Health Stroke Scale can be completed in minutes and provides a quantification that allows easy communication of the severity of the event to other caregivers. GCS score is similarly well known and easily computed, and the initial GCS score is a strong predictor of long-term outcome. <sup>12,13</sup> These can be supplemented as needed
Serum and urine tests	
Complete blood count, electrolytes, blood urea nitrogen and creatinine, and glucose	Higher creatinine is associated with hematoma expansion. Higher serum glucose is associated with hematoma expansion and worse outcome (although there are no data to suggest that normalization improves outcome) <sup>11,14</sup>
Prothrombin time or INR and an activated partial thromboplastin time	Warfarin-related hemorrhages are associated with an increased hematoma volume, greater risk of expansion, and increased morbidity and mortality <sup>15–17</sup>

(Continued)

**Table 4. Continued**

	Comments
Toxicology screen in young or middle-aged patients to detect cocaine and other sympathomimetic drugs of abuse	Cocaine and other sympathomimetic drugs are associated with ICH
Urinalysis and urine culture and a pregnancy test in a woman of childbearing age	
Other routine tests	
ECG	To assess for active coronary ischemia or prior cardiac injury that may indicate poor cardiac function and to obtain a baseline in the event of cardiopulmonary issues during hospitalization
Chest radiograph	
Neuroimaging	As described in the text
GCS indicates Glasgow Coma Scale; ECG, electrocardiogram.	

other agents in patients with a normal platelet count, but use of antiplatelet agents or platelet dysfunction, is not known.

Patients with ICH have a high risk of thromboembolic disease.<sup>65</sup> Women and African Americans appear to be at greater risk.<sup>65–67</sup> Intermittent pneumatic compression combined with elastic stockings has been shown by a randomized trial to be superior to elastic stockings alone in reducing occurrence of asymptomatic deep vein thrombosis after ICH (4.7% versus 15.9%).<sup>68</sup> Graduated compression stockings alone are ineffective in preventing deep vein thrombosis.<sup>69</sup> Less clear, however, is the role of adding anticoagulation to pneumatic compression. Two small randomized studies found no difference in deep vein thrombosis incidence, and no increase in bleeding, in patients given low-dose subcutaneous heparin initiated at day 4 or at day 10 after ICH.<sup>70,71</sup> An uncontrolled study of treatment initiated on day 2 found a reduction in thromboembolic disease without increased rebleeding.<sup>70</sup>

## Recommendations

- 1. Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively (Class I; Level of Evidence: C).** (New recommendation)
- 2. Patients with ICH whose INR is elevated due to OACs should have their warfarin withheld, receive therapy to replace vitamin K–dependent factors and correct the INR, and receive intravenous vitamin K (Class I; Level of Evidence: C). PCCs have not shown improved outcome compared with FFP but may have fewer complications compared with FFP and are reasonable to consider as an alternative to FFP (Class IIa; Level of Evidence: B). rFVIIa does not replace all clotting factors, and although the INR may be lowered, clotting may not be restored in vivo; therefore, rFVIIa is not routinely recommended as a sole agent for OAC reversal in ICH (Class III; Level of Evidence: C).** (Revised from the previous guideline).
- 3. Although rFVIIa can limit the extent of hematoma expansion in noncoagulopathic ICH patients, there**

**Table 5. Products Commercially Available in the United States for Coagulation Factor Replacement**

Product	Factor(s)	Dose (Consultation With a Hematologist Is Recommended for Specific Dosing)	Uses
Fresh-frozen plasma	I (fibrinogen), II, V, VII, IX, X, XI, XIII, antithrombin	10–15 mL/kg with ideal recovery would raise factor levels 15%–20%	OAC reversal Consumptive coagulopathy Hepatic dysfunction
Cryoprecipitate	I, VIII, XIII, vWF	1–2 U/10 kg	Hypo/a-fibrinogenemia Lack of factor-specific products for factor VIII deficiency or vWD Factor XIII deficiency
Prothrombin complex concentrates Bebulin VH (Baxter), Profilnine SD (Grifols)	II, IX, X (small amounts of VII)	Assayed in factor IX activity  Both Bebulin and Profilnine are 3-factor PCCs that have approximately 1/10th the factor VII activity relative to factor IX activity. The amounts of factor II and X relative to IX is variable, but for Bebulin X>II>IX and for Profilnine II>X~IX  Dosing for factor IX deficiency—1 U/kg raises activity by 1% Dosing for OAC reversal has not been well established	Factor IX deficiency (hemophilia B)  OAC reversal (not FDA-approved)
NovoSeven RT (Novo Nordisk)	Recombinant activated VII	Higher risk of thromboembolic complications with higher doses For hemophilia A or B patients with inhibitors, 90 µg/kg every 2 h For factor VII-deficient patients, 15–30 µg/kg every 4–6 h	Factor VIII or IX deficiency with inhibitors to factor VIII or IX Congenital factor VII deficiency Not recommended for spontaneous ICH or OAC reversal
Factor VIII concentrates Plasma-derived Alphanate (Grifols)*† Humate-P (CSL-Behring)*† Koate-DVI (Bayer)* Wilate (Octapharma)*† Immunoaffinity purified Hemofil-M (Baxter) Monarc-M (Baxter) Monoclote-P (CSL-Behring) Recombinant Advate (Baxter) Helixate FS (CSL-Behring) Kogenate FS (Bayer) Recombinate (Baxter) Xyntha (Wyeth)	VIII	Each factor VIII unit/kg raises the serum factor VIII level by 2% (typically, a 50-U/kg dose is used to raise the factor VIII level to 100%)	Factor VIII deficiency (hemophilia A)  Wilate is not indicated for hemophilia A.
Factor IX concentrates Plasma-derived AlphaNine SD (Grifols) Mononine (Baxter) Recombinant BeneFix (Wyeth)	IX	Each Factor IX unit/kg raises the serum level by 1% (typically, a 100-U/kg dose is used to raise the level to 100%)	Factor IX deficiency (hemophilia B)  One unit of BeneFix raises the serum level by ≈0.83%, so 120 U/kg raises the activity to 100%.

vWD indicates von Willebrand disease; FDA, US Food and Drug Administration; and PCCs, prothrombin complex concentrates.

\*Also contains von Willebrand factor.

†Indicated for von Willebrand disease (dose by ristocetin cofactor units; ratio of fVIII to ristocetin cofactor unit varies by product).

**is an increase in thromboembolic risk with rFVIIa and no clear clinical benefit in unselected patients. Thus rFVIIa is not recommended in unselected patients. (Class III; Level of Evidence: A).** (New recommendation) *Further research to determine whether any selected group of patients may benefit*

*from this therapy is needed before any recommendation for its use can be made.*  
**4. The usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is unclear and is considered investigational (Class IIb; Level of Evidence: B).** (New recommendation)



5. Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism in addition to elastic stockings (*Class I; Level of Evidence: B*). (Unchanged from the previous guideline)
6. After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered for prevention of venous thromboembolism in patients with lack of mobility after 1 to 4 days from onset (*Class IIb; Level of Evidence: B*). (Revised from the previous guideline)

## Blood Pressure

### Blood Pressure and Outcome in ICH

Blood pressure (BP) is frequently, and often markedly, elevated in patients with acute ICH; these elevations in BP are greater than that seen in patients with ischemic stroke.<sup>72,73</sup> Although BP generally falls spontaneously within several days after ICH, high BP persists in a substantial proportion of patients.<sup>72,73</sup> Potential pathophysiologic mechanisms include stress activation of the neuroendocrine system (sympathetic nervous system, renin-angiotensin axis, or glucocorticoid system) and increased intracranial pressure. Hypertension theoretically could contribute to hydrostatic expansion of the hematoma, peri-hematoma edema, and rebleeding, all of which may contribute to adverse outcomes in ICH, although a clear association between hypertension within the first few hours after ICH and the risk of hematoma expansion (or eventual hematoma volume) has not been clearly demonstrated.<sup>25,74</sup>

A systematic review<sup>75</sup> and a recent large multisite study in China<sup>73</sup> show that a measurement of systolic BP above 140 to 150 mm Hg within 12 hours of ICH is associated with more than double the risk of subsequent death or dependency. Compared with ischemic stroke, where consistent U- or J-shaped associations between BP levels and poor outcome have been shown,<sup>76</sup> only 1 study of ICH has shown a poor outcome at very low systolic BP levels (<140 mm Hg).<sup>77</sup> For both ischemic stroke and possibly ICH, a likely explanation for such association is reverse causation, whereby very low BP levels occur disproportionately in more severe cases, so that although low BP levels may be associated with a high case fatality, it may not in itself be causal.

### Effects of BP-Lowering Treatments

The strong observational data cited previously and sophisticated neuroimaging studies that fail to identify an ischemic penumbra in ICH<sup>78</sup> formed the basis for the INTensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) pilot study, published in 2008.<sup>79</sup> INTERACT was an open-label, randomized, controlled trial undertaken in 404 mainly Chinese patients who could be assessed, treated, and monitored within 6 hours of the onset of ICH; 203 were randomized to a treatment with locally available intravenous BP-lowering agents to target a low systolic BP goal of 140 mm Hg within 1 hour and maintained for at least the next 24 hours, and 201 were randomized to a more modest systolic BP target of 180 mm Hg, as recommended in an earlier AHA guideline.<sup>80</sup> The study showed a trend toward lower relative

**Table 6. Suggested Recommended Guidelines for Treating Elevated BP in Spontaneous ICH**

1. If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of BP with continuous intravenous infusion, with frequent BP monitoring every 5 min.
2. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is the possibility of elevated ICP, then consider monitoring ICP and reducing BP using intermittent or continuous intravenous medications while maintaining a cerebral perfusion pressure  $\geq$ 60 mm Hg.
3. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is not evidence of elevated ICP, then consider a modest reduction of BP (eg, MAP of 110 mm Hg or target BP of 160/90 mm Hg) using intermittent or continuous intravenous medications to control BP and clinically reexamine the patient every 15 min.

Note that these recommendations are Class C. SBP indicates systolic blood pressure; MAP, mean arterial pressure.

and absolute growth in hematoma volumes from baseline to 24 hours in the intensive treatment group compared with the control group. In addition, there was no excess of neurological deterioration or other adverse events related to intensive BP lowering, nor were there any differences across several measures of clinical outcome, including disability and quality of life between groups, although the trial was not powered to detect such outcomes. The study provides an important proof of concept for early BP lowering in patients with ICH, but the data are insufficient to recommend a definitive policy. Another study, the Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) trial,<sup>81</sup> also confirms the feasibility and safety of early rapid BP lowering in ICH.<sup>82</sup> This study used a 4-tier, dose escalation of intravenous nicardipine-based BP lowering in 80 patients with ICH.

Thus, advances have been made in our knowledge of the mechanisms of ICH and the safety of early BP lowering since the publication of the 2007 American Heart Association ICH guidelines. INTERACT and ATACH now represent the best available evidence to help guide decisions about BP lowering in ICH. Although these studies have shown that intensive BP lowering is clinically feasible and potentially safe, the BP pressure target, duration of therapy, and whether such treatment improves clinical outcomes remain unclear.

### Recommendations

1. Until ongoing clinical trials of BP intervention for ICH are completed, physicians must manage BP on the basis of the present incomplete efficacy evidence. Current suggested recommendations for target BP in various situations are listed in Table 6 and may be considered (*Class IIb; Level of Evidence: C*). (Unchanged from the previous guideline)
2. In patients presenting with a systolic BP of 150 to 220 mm Hg, acute lowering of systolic BP to 140 mm Hg is probably safe (*Class IIa; Level of Evidence: B*). (New recommendation)

## Inpatient Management and Prevention of Secondary Brain Injury

### General Monitoring

Patients with ICH are frequently medically and neurologically unstable, particularly within the first few days after

onset. Care of ICH patients in a dedicated neuroscience intensive care unit is associated with a lower mortality rate.<sup>83</sup> Frequent vital sign checks, neurological assessments, and continuous cardiopulmonary monitoring including a cycled automated BP cuff, electrocardiographic telemetry, and O<sub>2</sub> saturation probe should be standard. Continuous intra-arterial BP monitoring should be considered in patients receiving intravenous vasoactive medications.

### **Nursing Care**

The specific nursing care required for ICH patients in intensive care units may include (1) surveillance and monitoring of ICP, cerebral perfusion pressure and hemodynamic function; (2) titration and implementation of protocols for management of ICP, BP, mechanical ventilation, fever, and serum glucose; and (3) prevention of complications of immobility through positioning, airway maintenance, and mobilization within physiological tolerance. The consensus document from the Brain Attack Coalition on comprehensive stroke centers delineates these as specific areas of monitoring and complication prevention in which nurses should be trained. This document also recommends that nurses be trained in detailed assessment of neurological function including standardized scales such as the National Institutes of Health Stroke Scale, GCS, and the Glasgow Outcome Scale.

In a Canadian study of 49 hospitals that included ICH patients, a higher proportion of registered nurses and better nurse–physician communications were independently associated with lower 30-day mortality even after adjusting for disease severity, comorbidities, and hospital characteristics.<sup>84</sup>

### **Recommendation**

- 1. Initial monitoring and management of ICH patients should take place in an intensive care unit with physician and nursing neuroscience intensive care expertise (Class I; Level of Evidence: B).** (Unchanged from the previous guideline)

### **Management of Glucose**

High blood glucose on admission predicts an increased risk of mortality and poor outcome in patients with and without diabetes and ICH.<sup>85–87</sup> A randomized trial showing improved outcomes with tight glucose control (range 80 to 110 mg/dL) using insulin infusions in mainly surgical critical care patients<sup>88</sup> has increased the use of this therapy. However, more recent studies have demonstrated increased incidence of systemic and cerebral hypoglycemic events and possibly even increased risk of mortality in patients treated with this regimen.<sup>89–92</sup> At present the optimal management of hyperglycemia in ICH and the target glucose remains to be clarified. Hypoglycemia should be avoided.

### **Temperature Management**

Fever worsens outcome in experimental models of brain injury.<sup>93,94</sup> The incidence of fever after basal ganglionic and lobar ICH is high, especially in patients with IVH. In patients surviving the first 72 hours after hospital admission, the duration of fever is related to outcome and appears to be an independent prognostic factor in these patients.<sup>95</sup> These data provide a rationale for aggressive treatment to maintain normothermia in patients with ICH; however, there are no data linking fever

treatment with outcome. Similarly, therapeutic cooling has not been systematically investigated in ICH patients.

### **Seizures and Antiepileptic Drugs**

The incidence of clinical seizures within the first 2 weeks after ICH has been reported to range from 2.7% to 17%, with the majority occurring at or near onset.<sup>96–100</sup> Studies of continuous electroencephalography (EEG) have reported electrographic seizures in 28% to 31% of select cohorts of ICH patients, despite most having received prophylactic anticonvulsants.<sup>101,102</sup> In a large, single-center study, prophylactic antiepileptic drugs did significantly reduce the number of clinical seizures after lobar ICH.<sup>98</sup> However, in prospective and population-based studies, clinical seizures have not been associated with worsened neurological outcome or mortality.<sup>97,103,104</sup> The clinical impact of subclinical seizures detected on EEG is also not clear. A recent analysis from the placebo arm of an ICH neuroprotectant study found that patients who received antiepileptic drugs (primarily phenytoin) without a documented seizure were significantly more likely to be dead or disabled at 90 days, after adjusting for other established predictors of ICH outcome.<sup>105</sup> Another recent single-center observational study had similar findings, specifically for phenytoin.<sup>106</sup> Thus only clinical seizures or electrographic seizures in patients with a change in mental status should be treated with antiepileptic drugs. Continuous EEG monitoring should be considered in ICH patients with depressed mental status out of proportion to the degree of brain injury. The utility of prophylactic anticonvulsant medication remains uncertain.

### **Recommendations**

#### **Management of Glucose**

- 1. Glucose should be monitored and normoglycemia is recommended (Class I; Level of Evidence: C).** (New recommendation)

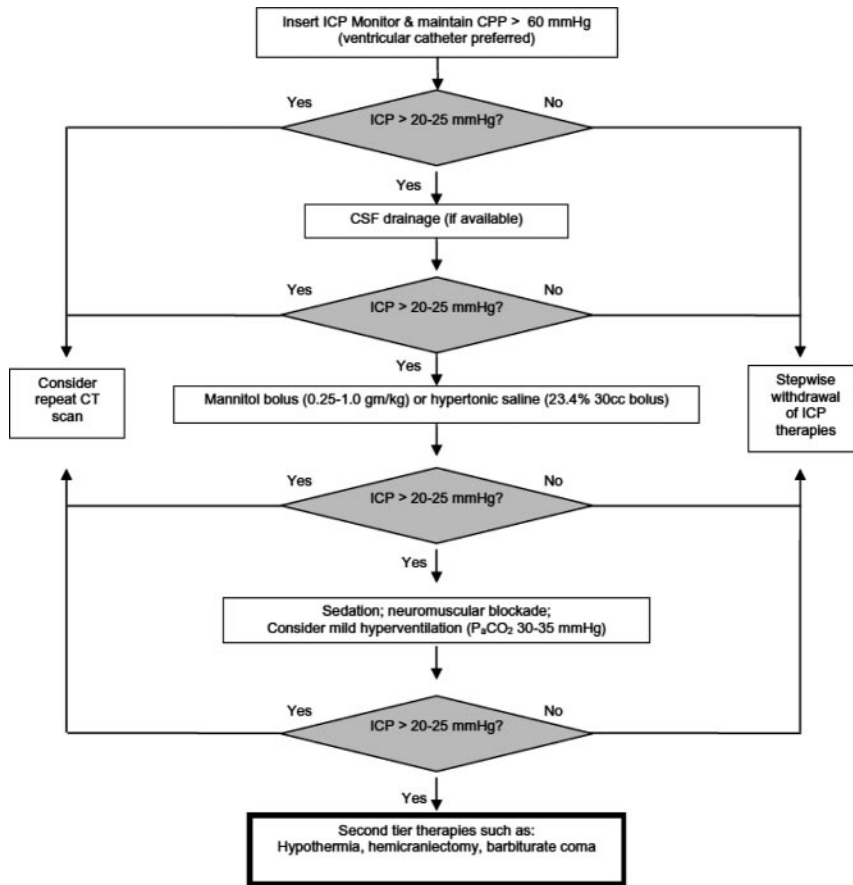
#### **Seizures and Antiepileptic Drugs**

- 1. Clinical seizures should be treated with antiepileptic drugs (Class I; Level of Evidence: A).** (Revised from the previous guideline) **Continuous EEG monitoring is probably indicated in ICH patients with depressed mental status out of proportion to the degree of brain injury (Class IIa; Level of Evidence: B). Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with antiepileptic drugs (Class I; Level of Evidence: C). Prophylactic anticonvulsant medication should not be used (Class III; Level of Evidence: B).** (New recommendation)

### **Iron**

Systemic treatment with the iron chelator deferoxamine ameliorates ICH-induced changes in markers of DNA damage, attenuates brain edema, and improves functional recovery in rat models of ICH.<sup>107–111</sup> A few studies have examined the role of iron in ICH patients and reported that high serum ferritin levels are associated with poor outcome after ICH<sup>112</sup> and correlate with the perihematoma edema volume.<sup>113,114</sup>

Limiting iron-mediated toxicity is a promising therapeutic target in ICH. Besides chelating iron, deferoxamine exhibits other neuroprotective properties.<sup>115</sup> It induces transcription of



**Figure.** Intracranial pressure treatment algorithm. CPP indicates cerebral perfusion pressure; CSF, cerebrospinal fluid. Adapted from Brain Trauma Foundation Head Injury Guidelines.<sup>126</sup> Copyright 2000, Brain Trauma Foundation.

heme oxygenase-1 and inhibits hemoglobin-mediated glutamate excitotoxicity and hypoxia inducible factor prolyl hydroxylases.<sup>116–119</sup> Further studies in this area are warranted, but no current therapeutic recommendation can be made at present.

## Procedures/Surgery

### ICP Monitoring and Treatment

ICP monitoring is often performed in patients with ICH. However, only very limited published data exist regarding the frequency of elevated ICP and its management in patients with ICH.<sup>120,121</sup> There is evidence for differential pressure gradients in at least some cases so that ICP may be elevated in and around the hematoma but not distant from it.<sup>122</sup> Because the usual causes of elevated ICP are hydrocephalus from IVH or mass effect from the hematoma (or surrounding edema), patients with small hematomas and limited IVH usually will not require treatment to lower ICP.

ICP is measured using devices inserted into the brain parenchyma, typically at the bedside. Fiberoptic technology can be used in both types of devices. A ventricular catheter (VC) inserted into the lateral ventricle allows for drainage of cerebrospinal fluid, which can help reduce ICP in patients with hydrocephalus. A parenchymal catheter ICP device is inserted into the brain parenchyma and allows for monitoring of ICP, but not cerebrospinal fluid drainage. The absence of published studies showing that management of elevated ICP impacts on ICH outcome makes the decision whether to monitor and treat elevated ICP unclear. Risks associated with

ICP monitor insertion and use include infection and intracranial hemorrhage. In general, the risk of hemorrhage or infection is thought to be higher with VC than with parenchymal catheters, although data on these rates are not derived from patients with ICH, but rather principally from those with traumatic brain injury or aneurysmal subarachnoid hemorrhage. In a 1997 series of 108 intraparenchymal devices, the rate of infection was 2.9% and the rate of intracranial hemorrhage was 2.1% (15.3% in patients with coagulopathies).<sup>123</sup> A direct comparison of the complications associated with each type of monitoring device was reported in a 1993 to 1997 series of 536 intracerebral monitoring devices (274 VCs, 229 intraparenchymal parenchymal catheters, and 33 other types of devices) in which the overall rate of infection was 4% and the overall rate of intracranial hemorrhage was 3%.<sup>124</sup> Before insertion of a monitoring device, the patient's coagulation status should be evaluated. Prior use of antiplatelet agents may justify platelet transfusion before the procedure, and the use of warfarin may require reversal of coagulopathy before placement. The decision to use a VC or a parenchymal catheter device should be based on the specific need to drain cerebrospinal fluid in patients with hydrocephalus or trapped ventricle and the balance of monitoring risks with the unknown utility of ICP management in patients with ICH.

ICP treatment should be directed at the underlying cause, especially if due to hydrocephalus or mass effect from the hematoma. Because of limited data regarding ICP in ICH, management principles for elevated ICP are borrowed from

traumatic brain injury guidelines, which emphasize maintaining a cerebral perfusion pressure of 50 to 70 mm Hg, depending on the status of cerebral autoregulation<sup>125,126</sup> (see Figure). ICH patients with a GCS score of  $\leq 8$ , those with clinical evidence of transtentorial herniation, or those with significant IVH or hydrocephalus may be considered for ICP monitoring and treatment.

Numerous studies have assessed ventricular size and effects of enlargement on ICH outcome.<sup>127–130</sup> Among 902 patients with follow-up data randomized into the international Surgical Trial of Intracerebral Hemorrhage (STICH) trial of early hematoma evacuation, 377 had IVH and 208 of these had hydrocephalus (23% of all patients, 55% of those with IVH).<sup>131</sup> Hydrocephalus predicted poor outcome in this study, as well as other previous studies.<sup>127</sup> Thus, hydrocephalus is an important cause of ICH-related morbidity and mortality,<sup>1</sup> and treatment should be considered in patients with decreased level of consciousness.

Small case series have described the use of brain tissue oxygen and cerebral microdialysis monitoring in patients with ICH.<sup>132,133</sup> Because of the small numbers of patients and limited data, no recommendation can be made regarding the use of these technologies at this time.

## Recommendations

1. **Patients with a GCS score of  $\leq 8$ , those with clinical evidence of transtentorial herniation, or those with significant IVH or hydrocephalus might be considered for ICP monitoring and treatment. A cerebral perfusion pressure of 50 to 70 mm Hg may be reasonable to maintain depending on the status of cerebral autoregulation (Class IIb; Level of Evidence: C).** (New recommendation)
2. **Ventricular drainage as treatment for hydrocephalus is reasonable in patients with decreased level of consciousness (Class IIa; Level of Evidence: B).** (New recommendation)

## Intraventricular Hemorrhage

IVH occurs in 45% of patients with spontaneous ICH.<sup>134</sup> IVH can be primary (confined to the ventricles) or secondary (originating as an extension of an ICH). Most IVHs are secondary and are related to hypertensive hemorrhages involving the basal ganglia and the thalamus.<sup>134,135</sup>

Although inserting a VC should theoretically aid in drainage of blood and cerebrospinal fluid from the ventricles, VC use alone may be ineffective because of difficulty maintaining catheter patency and the slow removal of intraventricular blood.<sup>136</sup> Thus there has been recent interest in the use of thrombolytic agents as adjuncts to VC use in the setting of IVH.

Animal studies and clinical series reported that intraventricular administration of fibrinolytic agents, including urokinase, streptokinase, and recombinant tissue-type plasminogen activator, in IVH may reduce morbidity and mortality by accelerating blood clearance and clot lysis.<sup>137–142</sup> Recently the Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR-IVH) Trial prospectively evaluated the safety of open-label doses of intraventricular recombinant tissue-type plasminogen activator in 52 IVH patients. Symptomatic bleeding occurred in 4% and bacterial ventriculitis in 2%, and the 30-day mortality rate was 17%.<sup>143</sup> The efficacy of this treatment requires confirmation before its use can be recommended outside of a clinical trial.

Some reports suggest alternative procedures for IVH such as endoscopic surgical evacuation and ventriculostomy,<sup>144–146</sup> ventriculoperitoneal shunting,<sup>147</sup> or lumbar drainage for hydrocephalus.<sup>148</sup> Few data exist to support these strategies.

## Recommendation

1. **Although intraventricular administration of recombinant tissue-type plasminogen activator in IVH appears to have a fairly low complication rate, efficacy and safety of this treatment is uncertain and is considered investigational (Class IIb; Level of Evidence: B).** (New recommendation)

## Clot Removal

### Surgical Treatment of ICH

The decision about whether and when to surgically remove ICH remains controversial. The pathophysiology of brain injury surrounding the hematoma is due to the mechanical effects of the growing mass of blood as well as the subsequent toxic effects of blood in the surrounding brain tissue. Early surgery to limit the mechanical compression of brain and the toxic effects of blood may limit injury, but the surgical risks in a patient with ongoing bleeding may be greater. In addition, operative removal of hemorrhage by craniotomy in all but the most superficial hemorrhages involves cutting through uninjured brain. Among the limitations of ICH surgical trials is that young and middle-aged patients at risk of herniation from large ICHs were unlikely to be randomized for treatment. Recommendations for these patients are uncertain.

### Craniotomy by Location of ICH

Most but not all<sup>149</sup> of the randomized trials of surgery for ICH excluded patients with cerebellar ICH, which comprises 10% to 15% of cases. Previous versions of these guidelines<sup>6</sup> cited nonrandomized studies showing that patients with cerebellar ICH larger than 3 cm in diameter or those with brainstem compression or hydrocephalus had good outcomes with surgery to remove the hematoma, whereas similar patients managed medically did poorly.<sup>150–155</sup> If the hemorrhage is  $< 3$  cm in diameter and there is no brainstem compression or hydrocephalus, reasonable outcomes may be achieved without surgery. Even though randomized trials of cerebellar hematoma evacuation have not been undertaken, the differences in outcome in the earlier studies are such that clinical equipoise does not exist for a trial. Furthermore, the use of a VC alone instead of immediate cerebellar hematoma evacuation is generally considered insufficient and is not recommended, especially in patients with compressed cisterns.<sup>155</sup>

The STICH trial found that patients with hematomas extending to within 1 cm of the cortical surface had a trend toward more favorable outcome with surgery within 96 hours, although this finding did not reach statistical significance (odds ratio, 0.69; 95% confidence interval, 0.47 to 1.01).<sup>156</sup> Patients with lobar hemorrhages and a GCS score of 9 to 12 also had a trend toward better outcome. Because the benefit of surgery for patients with superficial ICH was not statistically significant after adjusting for multiple testing, the authors recommended additional clinical trials to confirm this benefit.<sup>157</sup>

By contrast, patients in the STICH study with an ICH >1 cm from the cortical surface or with a GCS score of  $\leq 8$  tended to do worse with surgical removal as compared with medical management. Another study randomized 108 patients with supratentorial subcortical or putaminal ICH >30 mL in volume to craniotomy or medical management within 8 hours of onset.<sup>158</sup> Good outcome (good recovery or moderate disability on the Glasgow Outcome Scale at 1 year) was significantly better in those treated with surgery, but there was no difference in overall survival. Other randomized trials have had too few patients to determine outcomes in subgroups by location, randomized only patients with deep ICH, or did not report these results.<sup>159–161</sup> Enthusiasm for surgical evacuation of thalamic and pontine ICH has been limited.<sup>154,162,163</sup>

### Minimally Invasive Surgical Removal of ICH

If the indications for surgical evacuation of intracerebral hematomas are controversial, the means by which to achieve this evacuation are even less well established. Several groups have developed minimally invasive clot removal techniques. These techniques tend to make use of stereotactic guidance combined with either thrombolytic-enhanced or endoscopic-enhanced aspiration. Both randomized trials of thrombolytic-enhanced aspiration for subcortical ICH<sup>149,161,164</sup> and endoscopic-enhanced aspiration<sup>165–167</sup> with or without stereotaxis have reported increased clot removal and decreased mortality in those subjects treated surgically within 12 to 72 hours, but improved functional outcome has not been consistently demonstrated.

### Timing of Surgery

One key issue has been the lack of consensus on the time frame of what constitutes early surgery. Clinical studies have reported a wide variability in the timing of surgery, ranging from within 4 hours up to 96 hours from the onset of symptoms to time of operation.<sup>156,158,161,168</sup> Such time variance among the studies has made direct comparison and analysis of the impact of surgical timing difficult. A retrospective Japanese series of surgical removal of 100 putaminal ICHs within 7 hours of onset (60 within 3 hours) reported better than expected outcomes.<sup>169</sup> However, subsequent randomized trials that treated subjects within 12 hours of onset reported mixed results.<sup>158,161,168</sup> An increased risk of rebleeding was noted in the small trial of subjects randomized within 4 hours of onset.<sup>170</sup>

Trials that randomized patients within 24 hours,<sup>171</sup> 48 hours,<sup>159,165</sup> 72 hours,<sup>149,160</sup> and 96 hours<sup>156</sup> have also demonstrated no clear benefit for surgery as compared with initial medical management except for improved outcome in the subgroup of patients in the STICH trial with superficial ICH and decreased mortality in those patients with subcortical hemorrhages treated with minimally invasive methods within 12 to 72 hours, as noted above.

### Recommendations

1. **For most patients with ICH, the usefulness of surgery is uncertain (Class IIb; Level of Evidence: C).** (New recommendation) **Specific exceptions to this recommendation follow**
2. **Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression**

**and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible (Class I; Level of Evidence: B).** (Revised from the previous guideline) **Initial treatment of these patients with ventricular drainage alone rather than surgical evacuation is not recommended (Class III; Level of Evidence: C).** (New recommendation)

3. **For patients presenting with lobar clots >30 mL and within 1 cm of the surface, evacuation of supratentorial ICH by standard craniotomy might be considered (Class IIb; Level of Evidence: B).** (Revised from the previous guideline)
4. **The effectiveness of minimally invasive clot evacuation utilizing either stereotactic or endoscopic aspiration with or without thrombolytic usage is uncertain and is considered investigational (Class IIb; Level of Evidence: B).** (New recommendation)
5. **Although theoretically attractive, no clear evidence at present indicates that ultra-early removal of supratentorial ICH improves functional outcome or mortality rate. Very early craniotomy may be harmful due to increased risk of recurrent bleeding (Class III; Level of Evidence: B).** (Revised from the previous guideline)

### Outcome Prediction and Withdrawal of Technological Support

Many observational and epidemiological studies have identified a wide range of factors that are predictive of outcome after acute ICH. From these studies numerous outcome prediction models have been developed for mortality and functional outcome. Features found in most of these prediction models include individual patient characteristics such as the score on the GCS or National Institutes of Health Stroke Scale, age, hematoma volume and location, and the presence and amount of IVH.<sup>12,172–180</sup> No outcome prediction model for ICH, however, has considered the impact of care limitations such as do not resuscitate (DNR) orders or withdrawal of technological support.

Most patients that die from ICH do so during the initial acute hospitalization, and these deaths usually occur in the setting of withdrawal of support due to presumed poor prognosis.<sup>181,182</sup> Several studies, however, have now identified withdrawal of medical support and other early care limitations, such as DNR orders within the first day of hospitalization, as independent outcome predictors.<sup>2,183,184</sup> It is likely that current outcome prediction models as well as more informal methods of early prognostication after ICH are biased by the failure to account for these care limitations. Concern has been raised that decisions by physicians to limit care early after ICH are resulting in self-fulfilling prophecies of poor outcome due to inaccurately pessimistic prognostication and failure to provide initial aggressive therapy in severely ill ICH patients who nonetheless still have the possibility of favorable outcome.

Although a DNR order by definition means that no attempt at resuscitation should be made in the event that a cardiopulmonary arrest occurs, in practical use, when administered early after ICH, it is a proxy for overall lack of aggressiveness of care.<sup>2</sup> This implies that the overall aggressiveness of ICH care at a hospital may be critically important in determining patients' outcome, irrespective of specific individual characteristics.<sup>2,83,185</sup>

Although prognostication early after ICH may be desired by physicians, patients, and families, it is currently based on uncertain ground. Given this uncertainty and the potential for self-fulfilling prophecies of poor outcome, great caution should be undertaken in attempting precise prognostication early after ICH, especially if the purpose is to consider withdrawal of support or DNR orders.<sup>186</sup> Thus, aggressive guideline-concordant therapy is recommended for all ICH patients who do not have advanced directives specifying that this should not be undertaken. Care limitations such as DNR orders or withdrawal of support should not be recommended by treating physicians during the first few days after ICH.

## Recommendation

- 1. Aggressive full care early after ICH onset and postponement of new DNR orders until at least the second full day of hospitalization is probably recommended (Class IIa; Level of Evidence: B). Patients with preexisting DNR orders are not included in this recommendation. Current methods of prognostication in individual patients early after ICH are likely biased by failure to account for the influence of withdrawal of support and early DNR orders. Patients who are given DNR status at any point should receive all other appropriate medical and surgical interventions unless otherwise explicitly indicated.** (Revised from the previous guideline)

## Prevention of Recurrent ICH

Population-based studies of survivors of a first hemorrhagic stroke have identified rates of recurrent ICH of 2.1% to 3.7% per patient-year,<sup>187,188</sup> substantially higher than these individuals' rate of subsequent ischemic stroke.

The most consistently identified risk factor for recurrent ICH is lobar location of the initial ICH.<sup>187,189</sup> This finding likely represents the association of cerebral amyloid angiopathy with lobar location and increased recurrence.<sup>190,191</sup> Hemorrhage in locations characteristic of hypertensive vasculopathy, such as basal ganglia, thalamus, or brainstem,<sup>192</sup> also recur, but less frequently. Other factors linked to ICH recurrence in some studies include older age,<sup>188</sup> post-ICH anticoagulation,<sup>188</sup> previous hemorrhage before the presenting ICH,<sup>191</sup> carriership of the apolipoprotein E  $\epsilon$ 2 or  $\epsilon$ 4 alleles,<sup>191,193</sup> and greater number of microbleeds on T2\*-weighted gradient-echo MRI.<sup>194</sup>

Hypertension is the most important currently modifiable risk factor for prevention of ICH recurrence.<sup>195,196</sup> The importance of BP control was supported by data from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showing that subjects with cerebrovascular disease randomized to perindopril plus optional indapamide had significantly lower risk of first ICH (adjusted hazard ratio, 0.44; 95% confidence interval, 0.28 to 0.69) and a similar, though statistically insignificant, reduction in recurrent ICH (adjusted hazard ratio, 0.37; 95% confidence interval, 0.10 to 1.38).<sup>193</sup> Notably, this reduction appeared to apply to lobar as well as deep hemispheric ICH. Although specific data on the optimal BP for reducing ICH recurrence are not available, a reasonable target is a BP <140/90 (or <130/80 in the presence of diabetes or chronic kidney disease) as suggested by the most recent report from the Joint National

Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.<sup>197</sup>

Oral anticoagulation is associated with worse ICH outcome<sup>198,199</sup> and increased risk of recurrence,<sup>188</sup> raising the question of whether the benefits of anticoagulation for preventing thromboembolism outweigh its risks after initial ICH. For a hypothetical 69-year-old man with nonvalvular atrial fibrillation and prior lobar ICH, Markov modeling predicted that long-term anticoagulation would shorten quality-adjusted survival because of the high risk of recurrence after lobar ICH.<sup>200</sup> The results for anticoagulation after deep hemispheric ICH were less clear-cut and varied depending on assumptions about risk of future thromboembolism or ICH. The effects of antiplatelet agents on ICH recurrence and severity appear to be substantially smaller than for anticoagulation,<sup>16,62,189,201</sup> suggesting that antiplatelet treatment may be a safer alternative to anticoagulation after ICH. Recently, the ACTIVE A (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events—Aspirin) study reported on a randomized, double-blind study of the safety and efficacy of adding clopidogrel 75 mg daily to aspirin 75 to 100 mg daily in patients with high-risk atrial fibrillation and a contraindication to warfarin. Although previous ICH was listed as one of the many reasons for study entry, the authors did not report the proportion of subjects with previous ICH, and therefore the study results may not directly apply to those with previous ICH. Subjects who received clopidogrel added to aspirin had a 0.8% per year absolute risk reduction of major vascular events at the cost of 0.7% per year increase in major bleeding events.<sup>202</sup>

The recent Stroke Prevention with Aggressive Reductions in Cholesterol Levels (SPARCL) study found increased risk of subsequent ICH (unadjusted hazard ratio, 1.68; 95% confidence interval, 1.09 to 2.59) among subjects with prior stroke randomized to high-dose atorvastatin.<sup>203</sup> It remains unclear whether this effect outweighs the benefits of statin treatment in reducing ischemic cardiac and cerebral events in ICH survivors. Frequent alcohol use (defined in the Greater Cincinnati/Northern Kentucky study as >2 drinks per day) has been linked to increased ICH risk<sup>204</sup> and is therefore reasonable to avoid after ICH. Other behaviors, such as physical exertion, sexual activity, or stress, have not been linked to ICH,<sup>205</sup> though little systematic data have been reported.

## Recommendations

- 1. In situations where stratifying a patient's risk of recurrent ICH may affect other management decisions, it is reasonable to consider the following risk factors for recurrence: lobar location of the initial ICH, older age, ongoing anticoagulation, presence of the apolipoprotein E  $\epsilon$ 2 or  $\epsilon$ 4 alleles, and greater number of microbleeds on MRI (Class IIa; Level of Evidence: B).** (New recommendation)
- 2. After the acute ICH period, absent medical contraindications, BP should be well controlled, particularly for patients with ICH location typical of hypertensive vasculopathy (Class I; Level of Evidence: A).** (New recommendation)
- 3. After the acute ICH period, a goal target of a normal BP of <140/90 (<130/80 if diabetes or chronic kidney disease) is reasonable (Class IIa; Level of Evidence: B).** (New recommendation)

4. **Avoidance of long-term anticoagulation as treatment for nonvalvular atrial fibrillation is probably recommended after spontaneous lobar ICH because of the relatively high risk of recurrence (Class IIa; Level of Evidence: B). Anticoagulation after nonlobar ICH and antiplatelet therapy after all ICH might be considered, particularly when there are definite indications for these agents (Class IIb; Level of Evidence: B).** (Unchanged from the previous guideline)
5. **Avoidance of heavy alcohol use can be beneficial (Class IIa; Level of Evidence: B). There is insufficient data to recommend restrictions on use of statin agents or physical or sexual activity (Class IIb; Level of Evidence: C).** (New recommendation)

### Rehabilitation and Recovery

Knowledge of differences in the natural history of recovery patterns and prognosis for residual disability and functioning between ICH and ischemic stroke is complicated by the disproportionately lower rate of ICH compared with ischemic stroke and the lumping of subarachnoid hemorrhage and ICH together in many studies. There are also problems associated with the insensitivity of many of the outcome measures used in rehabilitation to allow detection of clinically meaningful differences between groups. Even so, there is some evidence that patients with ICH make slightly greater and faster gains in recovery<sup>206–208</sup> compared with patients with ischemic stroke.

In general, recovery is more rapid in the first few weeks but may continue for many months after ICH,<sup>208,209</sup> with approximately half of all survivors remaining dependent on others for activities of daily living.<sup>176</sup> However, patients vary in their speed and degree of recovery, and there is no hard rule regarding when recovery is over. Cognition, mood, motivation, and social support all influence recovery, and it is difficult to separate intrinsic from adaptive recovery. A simple prognostic score utilizing age, ICH volume and location, level of consciousness at admission, and pre-ICH cognitive impairment has been shown to predict independence at 90 days.<sup>176</sup> Given that ICH is often located in lobar regions and complicated by intraventricular extension, some patients with specific cognitive deficits or delayed recovery that is disproportionate to the size of the lesion may require specialized therapy in rehabilitation.

The provision of stroke rehabilitation services has received considerable attention in recent years. In part this represents a need to tailor services to ensure optimal recovery for patients and in part is due to fiscal pressures on costly health services. Given strong evidence for the benefits of well-organized, multidisciplinary inpatient (stroke unit) care in terms of improved survival, recovery, and returning home compared with conventional nondedicated stroke wards,<sup>210</sup> efforts have been made to extend this service model of coordinated care into the community. Specifically, early supported hospital discharge and home-based rehabilitation programs have been shown to be cost-effective,<sup>210</sup> whereas home-based therapy in stable patients has been shown to produce comparable outcomes to conventional outpatient rehabilitation.<sup>211</sup> The success of these programs depends on caregiver training and support. However, the likely configuration of stroke rehabilitation services in any region will depend on available resources and funding options. A key portion of

rehabilitation should include education for the patient and caregiver regarding secondary stroke prevention and means to achieve rehabilitation goals. Rehabilitation programs should consider lifestyle changes, depression, and caregiver burden as important issues to work on with the patient and caregivers.

### Recommendations

1. **Given the potentially serious nature and complex pattern of evolving disability, it is reasonable that all patients with ICH have access to multidisciplinary rehabilitation (Class IIa; Level of Evidence: B). Where possible, rehabilitation can be beneficial when begun as early as possible and continued in the community as part of a well-coordinated (seamless) program of accelerated hospital discharge and home-based resettlement to promote ongoing recovery (Class IIa; Level of Evidence: B).** (New recommendation)

### Future Considerations

The future of ICH treatment centers on a cluster of targets. The first is clearly prevention. Community-based projects to reduce BP through healthy lifestyles and medication adherence are likely to be quite successful in reducing ICH incidence.<sup>212</sup> Animal studies aimed at preventing cerebral amyloid angiopathy show early promise.<sup>213,214</sup>

Once an ICH has occurred, efforts to mobilize communities to facilitate prompt treatment are similar to efforts aimed at acute ischemic stroke treatment.<sup>215</sup> Advanced imaging currently may identify patients with ongoing bleeding and provides a target for improved patient selection for testing of hemostatic agents.<sup>28</sup> Hemostatic agents' efficacy must be clearly weighed against potential arterial and venous thrombotic risk.

BP control theoretically may reduce hematoma growth and/or reduce cerebral edema. Early studies suggest that a randomized controlled BP-lowering study is feasible.<sup>79,81</sup> Safety and efficacy remain to be shown in larger studies.

There is active research on interfering with oxidative injury after ICH. Iron-chelating agents such as deferoxamine are being studied in early-phase trials.<sup>107,115</sup> Pathways that center around hypoxia-inducible factors and prolyl hydroxylases offer other potential targets for intervention centered around oxidative stress.<sup>216</sup> The role of microglia and macrophages in hematoma resolution is getting more attention.<sup>217</sup> Autophagy may be a cellular process that could be altered to prevent ICH-related cell death.<sup>218</sup>

There are probably many factors that contribute to injury after ICH, including mass effect, toxicity related to blood, and displacement of underlying tissue. Seemingly, a simple solution is hematoma removal. To date, however, surgery has not proved to be the panacea for this condition. New efforts utilizing minimally invasive surgical techniques that may remove blood's toxic and pressure effects while avoiding the damage caused by more invasive procedures, as well as new treatments to dissolve and drain intraventricular blood, are currently being studied.<sup>143,164</sup>

Priorities for ICH research have been published and reviewed extensively.<sup>13</sup> An aggressive, collaborative approach to both basic and clinical research in this field is likely to promote the highest yield. In the mean time, it is clear that our ability to prognosticate about ICH is limited,<sup>184</sup> and that aggressive care now, and hope for the future, are both clearly indicated.

## Disclosures

## Writing Group Disclosures

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Lewis B. Morgenstern	University of Michigan	NIH (R01 NS057127) Consultant—Safety and Tolerability of Deferoxamine in Acute Cerebral Hemorrhage (generic study drug)*; NINDS (U01 NS052510) Co-I (Deferoxamine therapy for intracerebral hemorrhage—animal translational grant examining generic deferoxamine in ICH)†; NIH (R01 NS38916) PI—Brain Attack Surveillance in Corpus Christi (observational study of stroke in a biethnic community)†	None	None	None	None	None	Medical adjudication board member Wyeth*
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E. Sander Connolly, Jr	Columbia University	None	None	None	None	None	None	None
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\*Modest.

†Significant.

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Karen C. Johnston	University of Virginia	NIH-NINDS R01 NS050192 - GRASP trial†	None	Multiple grand rounds, national talks on stroke*	None	None	Diffusion Pharmaceuticals, Inc.*; Remedy Pharmaceuticals, Inc.*	AAN as associate editor of neurology through July 2009†
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Greg Zipfel	Washington University	None	None	None	None	None	None	None

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\*Modest.

†Significant.

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