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Critical Care Management of Acute Intracerebral Hemorrhage

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Opinion statement

Intracerebral hemorrhage is a medical emergency. It is the most deadly and disabling form of stroke, and no individual therapy has been demonstrated to improve outcome. However, it appears that aggressive medical care in general, and management by neuroscience specialists in particular, offers substantial benefit. Therefore, providing the best supportive care based on currently available evidence may well improve outcomes. Airway management and management of blood pressure aimed at maximizing cerebral perfusion while minimizing ongoing bleeding, as well as rapid reversal of anticoagulation, are likely to be important in the early phase. Additionally, efforts should be undertaken to provide careful glucose management and temperature management and to maximize cerebral perfusion pressure. Selected patients are likely to benefit from external ventricular drainage or even hematoma evacuation. Except in rare circumstances, most patients should be managed in a neuroscience intensive care unit during the acute phase. Some patients appear to have no reasonable likelihood of recovery and can be considered for limitations of care such as Do Not Resuscitate orders or Comfort Measures Only orders. However, it can be difficult to accurately predict long-term outcome in the acute phase; formal prognostic tools should be used to offer information to patients and their families. After the hemorrhage has stabilized, efforts to minimize complications include thromboembolism prophylaxis, physical therapy, and acute rehabilitation.

Introduction

Primary intracerebral hemorrhage (ICH), or spontaneous nontraumatic bleeding into the brain parenchyma, constitutes 10% to 15% of strokes in the United States, affecting approximately 65,000 people each year. Furthermore, ICH causes substantial disability in survivors, with only 20% of patients expected to be functionally independent at 6 months [1]. ICH also places a large financial burden on families and the US health care system, with the average hospitalization cost of nonsurvivors estimated to be $16,466 and the hospitalization cost of

survivors to be $28,360 (with an additional post-discharge cost of $16,035 during the first year) [2].

Risk factors for ICH include genetics, medical conditions, and lifestyle. Genetic risk factors include the presence of an apolipoprotein E2 or E4 allele and a first-degree relative with ICH [3]. Other known risks for ICH include increasing age, race, history of hypertension, smoking, and frequent alcohol use [3–6]. Though some risk factors clearly cannot be modified, some can, and there is evidence that doing so can actually decrease an individual's risk of ICH. The PROGRESS trial showed that blood pressure lowering treatment reduced the risk of ICH in patients with cerebral amyloid angiopathy and may be protective against ICH from other causes [7•, Class I]. Additionally, a large observational study found that less exercise, heavy alcohol use, and smoking predicted increased risk of ICH [8, Class II].

Most cases of primary ICH are the manifestation of one of two forms of chronic small vessel disease: hypertensive vasculopathy and cerebral amyloid angiopathy (CAA) [9, 10, 11]. Hypertensive vasculopathy is usually the result of longstanding hypertension resulting in lipohyalinosis of small, deep penetrating arteries [12]. CAA, or amyloid deposition in cerebral vessel walls, affects capillaries, arterioles, and small to medium-sized arteries [13, 14]. Acute vessel rupture, potentially due to small arteries with aneurysmal dilatation [15] or dissection [16], then causes injury by several mechanisms. First, there is mass effect from the hematoma itself [9, 17, 18]. Next, there is activation of the coagulation cascade, chemotaxis of leukocytes, expression of adhesion molecules, release of inflammatory cytokines, and disruption of the blood-brain barrier [17, 19, 20]. Finally, continued bleeding, or hematoma expansion, occurs in many patients. Proposed explanations include continued bleeding from the primary source, secondary bleeding at the periphery of the hemorrhage [12, 21], and potentiation of hemorrhage by acute hypertension or a locally coagulopathic environment [9, 17, 22, 23].

Rarer hemorrhages arise in the setting of vascular malformations, saccular aneurysms, cocaine intoxication, malignant hypertension, blood dyscrasias, and other less common processes. The location of the hemorrhage often provides clues to the underlying cause. Chronic hypertension is more often associated with ICH in the basal ganglia, thalamus, brainstem, and cerebellum, whereas CAA is typically associated with lobar and rarely cerebellar bleeds. There can be overlap between the various locations and etiologies.

Diagnosis

Early and accurate diagnosis of ICH is critical. Initial presenting symptoms can include abrupt onset of headache, vomiting, seizure, and any focal or generalized neurologic symptoms. The differentiation of ischemic from hemorrhagic stroke cannot be made in the absence of neuroimaging [24]. The initial test of choice in most centers for patients with an acute neurologic complaint is a CT scan of the brain. CT scanners are widely and rapidly available in the United States and are highly sensitive for ICH [25, 26].

Though most patients have primary ICH, many have what is termed secondary ICH, or ICH that is due to a cause other than small arteriolar disease. Causes of secondary ICH can include aneurysm, arteriovenous malformation, Moyamoya disease, tumor, cerebral venous sinus thrombosis, or hemorrhagic transformation of ischemic stroke. Features suggesting high risk for secondary ICH include lobar ICH, intraventricular blood, and younger age [27, Class IV]. Younger patients with lobar ICH are at higher risk for underlying vascular malformation, but this risk is present even for deep hemorrhages. A scoring system has been suggested to risk-stratify patients for risk of secondary ICH [28, Class IV]. Those who have aneurysms or arteriovenous malformations may be candidates for surgical or endovascular interventions.

Besides CT scanning, other modalities can provide value in diagnosing acute ICH:

CT angiography CT angiography (CTA) produces high-quality images of the larger arterial vessels and can be rapidly available in the emergency setting, as multislice CT scanners are available in most emergency departments [25]. CTA can help to exclude secondary causes such as aneurysm, arteriovenous malformation, or fistula. In addition, use of a venous phase (CTV) can evaluate for venous sinus thrombosis. Finally, some patients demonstrate evidence of contrast extravasation on CTA, which helps predict which patients will suffer ongoing bleeding and hematoma expansion [29, 30, 31, Class IV]. The risk of contrast-induced nephropathy is probably lower than traditionally thought [32, Class IV].

Magnetic resonance imaging MRI can help detect underlying lesions such as tumor, and may offer better resolution for evaluating perihematomal edema. Use of gradient-echo imaging (GRE) provides the ability to detect white-matter hyperintensities and previous small ICHs (microbleeds). Such findings not only can guide the clinician as to the underlying cause of ICH but also can predict risk of future hemorrhage [33].

MR angiography As above, MR angiography (MRA) can detect vascular abnormalities such as aneurysm and arteriovenous malformation. Use of a venous phase (MRV) can detect venous sinus thrombosis.

Digital subtraction angiography In many centers, digital subtraction angiography (DSA) remains the standard to rule out an underlying vascular abnormality.

Treatment

- Overall, no specific therapy has been demonstrated to improve outcomes in a phase III clinical trial. However, many lines of indirect evidence support the value of current medical care. First, there appears to be a benefit to admission to a specialized stroke unit [34, Class IV]. Second, among critically ill stroke patients, including those with ICH, long lengths of stay in the emergency department prior to ICU transfer independently predict worse outcomes [35, Class IV]. Third, an increased risk of in-hospital death has been demonstrated for ICH admissions over the weekend, as a surrogate measure of differences in hospital staffing, compared with patients admitted on weekdays [36, Class IV]. Finally, the use of Do Not Resuscitate orders independently predicts worse outcomes (after adjusting for disease severity), even in patients who do not require cardiopulmonary resuscitation or defibrillation, suggesting that more aggressive care in general improves outcome even if the specific intervention that benefits patients is unclear [37, 38, Class IV]. These and similar studies suggest that even in the absence of therapies specifically proven in phase III trial, multidisciplinary care by neurointensivists may well provide benefit.

Airway management

- Emergency airway management requires balancing the risk of airway compromise against the loss of the neurologic examination. For patients who cannot support their airway, those in the emergency setting are typically candidates for rapid sequence endotracheal intubation, whereas patients undergoing urgent intubation who have been in the hospital for some time may be candidates for the use of induction agents such as etomidate or propofol.

Rapid-sequence intubation

Pretreatment medications: Consider lidocaine, 1.5 mg/kg (may blunt a rise in intracranial pressure [ICP] associated with intubation).

Induction: Consider etomidate, 0.3 mg/kg (may preserve cerebral perfusion pressure).
Paralysis: Consider succinylcholine (1.5 mg/kg), rocuronium (1 mg/kg), or vecuronium (0.15 mg/kg).

Postintubation sedation

Consider propofol (5–80 mcg/kg/min) as a continuous drip for sedation. The goal is to provide effective sedation while retaining the ability to follow a neurologic examination in the acute phase.

Ventilation

Mechanical ventilation should minimize positive end-expiratory pressure (PEEP) and high peak inspiratory pressure (PIP) to avoid increasing venous congestion in the brain. Typical initial settings are 100% FiO_2, a ventilatory rate of 10 to 12 breaths per minute, and a tidal volume of approximately 5 to 8 cc/kg. Hyperventilation can reduce ICP for the short term only, and should be reserved for patients with impending or active herniation who require operative management.

Pharmacologic therapy

Blood pressure control

- Elevated blood pressure (BP) at admission predicts worse outcome, raising the question of whether reducing blood pressure is beneficial. The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) found that early intensive BP management reduced the risk of hematoma expansion but had no effect on outcomes [39, Class I]. As a result, it is unclear whether BP should be lowered, and if so, what the goal of treatment should be.
- American Heart Association (AHA) treatment recommendations [40••, Class IV]:
  - If systolic BP is >200 mm Hg or mean arterial pressure (MAP) is >150 mm Hg, consider aggressive reduction of blood pressure with continuous intravenous (IV) infusion, with BP monitoring every 5 min.
  - If systolic BP is >180 mm Hg or MAP is >130 mm Hg and there is the possibility of elevated ICP, consider monitoring ICP and reducing BP using intermittent or continuous IV medications to keep cerebral perfusion pressure less than 60 mm Hg.
  - If SBP is >180 mm Hg or MAP is >130 mm Hg and there is no evidence or suspicion of elevated ICP, consider a modest BP reduction (eg, MAP of 110 mm Hg or target BP of 160/90 mm Hg) using intermittent or continuous IV medications to control BP; clinically reexamine the patient every 15 min.
- European Union Stroke Initiative (EUSI) recommendations [59••]:
  - If there is a history of hypertension, and BP is >180/105, then consider lowering below 170/100.
  - If there is no history of hypertension, and BP is >160/95, then consider lowering below 150/90.

  - Do not lower MAP by more than 20% in the acute phase.
- AHA medication recommendations for BP control [1]:
  - Labetalol: intermittent boluses of 5–20 mg every 15 min or continuous drip (2 mg/min).
  - Nicardipine: 5–15 mg/hour.
  - Esmolol: 250 mcg/kg load, then 25–300 mcg/kg per minute maintenance.
  - Hydralazine: 5–20 mg intermittent boluses.

Anticoagulation reversal

- Anticoagulation with warfarin increases the risk of ICH and worsens the severity of disease, approximately doubling its mortality [41, Class III]. This excess mortality is likely related to prolonged bleeding, which is commonly observed in patients with anticoagulation-related ICH. Therefore, early reversal of coagulopathy is likely to be critical, and all anticoagulation-related hemorrhages should be treated as neurologic emergencies [42, Class IV].
- Treatment with IV vitamin K (5–10 mg) allows the patient to begin producing coagulation factors in as little as 4 to 6 h [40••]. Avoid subcutaneous or intramuscular forms, which are minimally effective.
- Provide factor repletion, which may improve hemostasis in the acute phase while awaiting an effect of vitamin K:
  - Prothrombin complex concentrate (PCC), depending on the agent, can provide most or all of the missing factors, and can reverse the INR in minutes. Dosing depends on the agent available.
  - Fresh frozen plasma (FFP) can require 30 min to several hours to obtain and deliver, but it is widely available in most hospitals [43, Class IV]. Dosing can begin at 15 mL/kg; up to 2 L may be required in practice.
  - Recombinant factor VIIa can be infused in minutes and reverses the INR, but it is unclear whether clinical hemostasis is restored. The AHA guidelines recommend not using this agent as monotherapy [40••].
  - Check the INR immediately after factor repletion, then every 6 h for 24 h. When using activated factor VII or a PCC that does not contain all four vitamin K–dependent coagulation factors (II, VII, IX, and X), it may be important to coadminister FFP.
- **Heparin use**: Some patients suffer ICH while using heparin or a heparinoid agent. Consider protamine (10–50 mg IV) for such patients.

Platelet disorders

- The most common source of platelet dysfunction is the use of antiplatelet agents. Studies have produced conflicting evidence regarding whether antiplatelet use independently predicts worse outcomes [44, Class III].

- **Recent use of antiplatelet agents such as aspirin or clopidogrel**: This area is controversial. Some centers recommend 1 dose (6 unit equivalent) of platelets. The AHA states that "the usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is unclear and is considered investigational" [40••].
- **Thrombocytopenia** (platelet count <100,000/μL): Platelet transfusion can be considered.
- **Von Willebrand syndromes**: Administer 0.3 mcg/kg DDAVP (desmopressin) IV over 30 min, and consider von Willebrand factor (vWF) concentrate.

Management of elevated intracranial pressure

- Patients with clinical or radiographic evidence of elevated ICP should be considered for therapies aimed at lowering ICP. ICP monitoring should be considered for patients with clinical or radiographic evidence of hydrocephalus, or for patients in whom therapies aimed at decreasing ICP will be used. Consider placement of an external ventricular drain (EVD) for patients with intraventricular blood who show signs of hydrocephalus or are at risk of developing it.
  - Mannitol 20%, 0.25–1.0 g/kg.
  - Hypertonic saline: The optimal dosing is not clear. Consider 3% NaCl as a bolus of 250 cc over 20 min, or 30 mL of 23.4% NaCl (4 mEq/mL) delivered intravenously over 20 min.
  - Barbiturates: Consider pentobarbital (10 mg/kg) or thiopental (1.5–3.5 mg/kg).
  - Paralysis: Consider vecuronium (0.1 mg/kg) or pancuronium (0.1 mg/kg).
  - Hyperventilation (temporary measure only): Raise the ventilation rate with a constant tidal volume, for a goal pCO_2 of 30 to 35 mm Hg.

Glucose control

- Admission hyperglycemia predicts worse outcomes after ICH. In addition, hyperglycemia is likely to be neurotoxic. As a result, clinical practice typically involves strict glucose control with insulin in patients with hyperglycemia, although one study demonstrated that very early insulin therapy does not appear to improve outcomes in patients with spontaneous ICH [45, Class II].
- Consider intensive insulin therapy versus a sliding scale to maintain blood glucose of 80 to 140 mg/dL.

Temperature control

- Fever following ICH is relatively common and has been shown to be independently associated with poor outcome. Treatment with antipyretics (eg, acetaminophen) and the use of cooling blankets are

recommended, though new adhesive surface-cooling systems and endovascular heat-exchange catheters may prove more effective [22].

Seizure prophylaxis

- Though antiepileptic drugs (AEDs) are often provided, it is not clear that their routine use is beneficial. Current AHA guidelines recommend that AEDs not be used routinely in patients with ICH without a specific indication. They note that continuous EEG monitoring is probably indicated in ICH patients with depressed mental status out of proportion to the degree of brain injury [40••, Class IV].
- Indications for AED therapy include a seizure or altered mental status and EEG evidence of seizure activity. If AED therapy is to be used, agents to consider include:
  - Phenytoin, 20 mg/kg IV.
  - Fosphenytoin, 20 mg phenytoin equivalents/kg IV.
  - Valproate, 10–15 mg/kg IV.
  - Levetiracetam, 500–1500 mg IV.
  - Phenobarbital, 20 mg/kg IV.

Preventing complications

- Thromboembolic complications are relatively common following ICH [46, Class IV]. Both mechanical and pharmacologic interventions can be used:
  - Intermittent pneumatic compression (in addition to elastic stockings) can reduce the risk of deep vein thrombosis and typically should be used [40••, Class II].
  - Low-dose subcutaneous heparin or enoxaparin can probably be safely instituted within 1 to 4 days after ICH [40••, Class IV].

Interventional procedures

Intracranial pressure monitoring

- Placement of an ICP monitor provides the clinician with the ability to dynamically monitor cerebral perfusion pressure. The AHA recommends considering ICP monitoring for patients who have a Glasgow Coma Score less than 8, clinical evidence of transtentorial herniation, or significant intraventricular hemorrhage or hydrocephalus.
- In treating changing ICP, it may be reasonable to maintain a cerebral perfusion pressure of 50 to 70 mm Hg, depending upon the status of cerebral autoregulation.

Hydrocephalus management

- Placement of an EVD not only allows for ICP monitoring, but also provides the ability to relieve elevated ICP. The AHA recommenda-

tions say that "Ventricular drainage as treatment for hydrocephalus is reasonable in patients with decreased level of consciousness" [40••].

Surgery

- Surgical interventions in ICH are typically reserved for selected candidates. The STICH trial was a large, randomized controlled clinical trial of hematoma evacuation that found no clear benefit to early surgical intervention [47, Class I]. However, some patients underwent evacuation up to 36 h after ICH, and it may be that more emergent evacuation would demonstrate a benefit. In addition, subgroup analysis suggested that those patients with more easily accessible lobar hemorrhages may benefit. A followup study, STICH II, is ongoing.
- Surgical evacuation is typically considered for two groups of patients, those with cerebellar hematomas and those with lobar hematomas.
    - **Cerebellar hematomas**: These patients were not enrolled in the STICH trial. Surgical evacuation of cerebellar hemorrhages can be lifesaving and deficit-sparing. Although patients with hemorrhages less than 3 cm in diameter may recover well without surgery, it is reasonable for all patients with cerebellar ICH to receive emergent neurosurgical consultation. The AHA recommends that 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.
    - **Lobar hematomas**: Patients with lobar hemorrhages that are easily accessible may selectively benefit from hematoma evacuation. The AHA recommends that evacuation may be considered for patients presenting with lobar clots larger than 30 mL and within 1 cm of the surface.
- In contrast to open craniotomy, a promising line of therapy involves the use of minimally invasive stereotactic hematoma evacuation [48]. It may be that such procedures, by reducing trauma to nearby brain tissue, can shift the risk/benefit ratio in favor of benefit for removing hematoma burden. Use of a minimally invasive technique can at least reduce operative time and the length of hospital stay [49, Class III]. One randomized trial comparing this technique with medical management suggested improved outcomes for noncomatose patients with subcortical rather than deep hematomas [50, Class II]. This finding is consistent with the subgroup analysis of the STICH trial: the more easily the hematoma can be surgically accessed, the more likely it is that a benefit can be demonstrated. In contrast, however, a recent randomized controlled trial of basal ganglia hemorrhages (a location potentially less accessible) showed improved outcomes in those undergoing minimally invasive evacuation compared with medical management [51, Class II]. A follow-up trial suggested that adding urokinase infusion (to help dissolve clotted blood) improved outcomes compared with craniotomy [52, Class II]. Finally, a large clinical trial of stereotactic catheter placement followed by injection of a thrombolytic agent and clot aspiration is ongoing [53].

- For patients with intraventricular hemorrhage, a number of investigators have examined whether infusion of thrombolytic agents directly into the ventricles can provide benefit [54, Class IV]. By accelerating the time to breakup of the clot, the risk of obstructive hydrocephalus can be minimized, and perhaps intracranial pressure can be reduced. An EVD is placed, and thrombolytics are infused at specific time intervals. Animal studies initially demonstrated the value of this approach in minimizing the risk of hydrocephalus [55, Class IV]. In humans, some studies have suggested improved secondary outcomes, including an observational cohort study [56, Class IV] and a small randomized controlled trial [57, Class II] in which intraventricular infusion of thrombolytics led to more rapid resolution of intraventricular blood. More recently, a randomized trial using t-PA demonstrated safety, but not yet efficacy, though the trial is ongoing [58, Class III]. Some centers are currently using this approach off-label.

Emerging therapies

- STICH II—This randomized clinical trial is examining the efficacy of surgical evacuation of ICH. Patients with superficial lobar primary ICH will be randomized to craniotomy within 12 h of randomization versus best medical care with delayed evacuation only if necessary. The primary outcome will be the Glasgow Outcome Scale at 6 months.
- INTERACT2—This randomized clinical trial (ClinicalTrials.gov #NCT00716079) is testing the efficacy of acute BP lowering on hematoma expansion and outcome. Patients with spontaneous ICH within 6 h of onset and systolic BP over 150 mm Hg are eligible. Patients are randomized to use of IV BP-lowering agents to achieve a goal systolic BP less than 140 mm Hg, versus a goal systolic BP less than 180 mm Hg for the first 24 h. The primary outcome is death or dependency (on the modified Rankin score measured at 90 days).
- ATACH-II—This randomized clinical trial (ClinicalTrials.gov #NCT01176565) also will examine acute BP lowering. Patients with spontaneous ICH presenting within 2.5 h of symptom onset will be eligible. Patients will be randomized to IV BP-lowering therapy to achieve a goal systolic BP less than 140 mm Hg versus a goal systolic BP of less than 180 mm Hg for the first 24 h. The primary outcome will be modified Rankin score measured at 90 days.
- 4Balance—This randomized controlled trial (ClinicalTrials.gov #NCT00708435) is examining the use of PCCs for warfarin reversal. Patients with bleeding emergencies (including ICH) while taking an oral vitamin K antagonist, and with a presenting INR above 2.0, are randomized to receive a PCC (Beriplex) versus FFP for warfarin reversal. The primary outcome is hemostatic efficacy (for ICH patients, a reduced risk of hematoma expansion) at 24 h.
- CLEAR III—This randomized controlled trial (ClinicalTrials.gov #NCT00784134) will examine the efficacy of intraventricular injections of rt-PA. Patients with intraventricular hemorrhage will

be randomized to EVD plus intraventricular rt-PA, versus EVD plus placebo. The primary outcome is modified Rankin score at 180 days.

- MISTIE—This randomized controlled trial (ClinicalTrials.gov #NCT00224770) will examine the efficacy of minimally invasive surgery plus clot lysis. Patients with ICH will be randomized to medical management versus image-guided placement of a catheter and aspiration of the hemorrhage, followed by direct infusion of a thrombolytic. The primary outcome is mortality at 30 days.
- SPOTLIGHT and STOP-IT trials—These phase II clinical trials will test the use of the CTA spot sign in stratifying patients for treatment with recombinant Factor VIIa. Patients presenting with intracerebral hemorrhage will undergo emergent CTA, and those with signs of contrast extravasation (a "spot sign") will be randomized to receive recombinant Factor VIIa versus placebo. Primary outcomes will include hematoma expansion at 24 h and risk of thromboembolic events. Information on STOP-IT is found at ClinicalTrials.gov # NCT00810888; there is presently no number for SPOTLIGHT ("Spot Sign" Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy).

Disclosure

Conflicts of Interest: J. Goldstein: Consulting fees and travel expenses from CSL Behring; A. Gilson: None.

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- • Of importance
- •• Of major importance

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