Current Updates in Perioperative Management of Intracerebral Hemorrhage

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KEYWORDS

• Cerebral hemorrhage • Stroke

Spontaneous intracerebral hemorrhages (ICH) account for 10% to 30% all strokes[1] and are a result of acute bleeding into the brain by rupturing of small penetrating arteries. Despite major advancements in the management of ischemic strokes and other causes of hemorrhagic strokes, such as ruptured aneurysm, arteriovenous malformations (AVMs), or cavernous angioma, during the past several decades, limited progress has been made in the treatment of ICH, and the prognosis for patients who suffer them remains poor. The societal impact of these hemorrhagic strokes is magnified by the fact that affected patients typically are a decade younger than those afflicted with ischemic strokes.

Since an early prospective randomized trial by McKissock and colleagues in 1961, controversy has persisted regarding medical therapy versus surgical interventions for the treatment of ICH.[2] Nevertheless, regardless of medical or surgical interventions, ICH continue to kill or disable most of their victims. Studies show that those who suffer ICH have a 30-day mortality rate of 35% to 44% and a 6-month mortality rate approaching 50%.[3–5] In addition, even in patients who survive ICH, only 20% of them are independent at 6 months.[6] As a result, approximately $125,000 is spent per patient per year for ICH, leading to an overall annual cost of $6 billion for ICH in the United States.[7,8] Therefore, it has been estimated that this small fraction of strokes accounts for half of stroke-related deaths, disability, and costs.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Approximately 700,000 new strokes occur in the United States annually and approximately 15% are hemorrhagic strokes related to ICH.[1,9,10] About 20 in 100,000 people every year are afflicted with ICH. Despite the small numbers relative to ischemic strokes, patients who have hemorrhagic stroke have some of the bleakest outcomes. ICH can be categorized as either primary or secondary. Primary ICHs account for 70% to 88% of the cases and are caused by either chronic hypertension or amyloid angiopathy.[1,11] Secondary ICH are associated with vascular malformations, tumors,

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substance abuse, coagulopathy, and the use of anticoagulation or thrombolytic agents. The mortality rate approaches 50% in patients who develop ICH, and only a limited number of survivors can achieve independent status.[3–6]

Primary ICH are seen most commonly in elderly men and in African Americans as well as Asians.[12,13] Most patients who have ICH present with acute symptoms of mass effects from hematoma. Patients who have smaller bleeds can have only headaches, nausea, or vomiting as their presenting symptoms. Those who have larger hematomas have depressed mental status, poor Glasgow Coma Scores (GCS), and focal neurologic deficits related to the site of hemorrhage.

Primary ICH typically occurs in the deep subcortical area, and more than 50% of all spontaneous ICH occur in the basal ganglia (**Fig. 1**). Most commonly, primary ICH are found in the putamen, thalamus, cerebellum, and pons (**Fig. 2**). Other locations include lobar areas of the cerebral hemispheres and infratentorial structures, such as the cerebellum or the pons.

The morbidity and mortality rates of patients who have ICH are associated closely with the age, size of hemorrhage, location of clot, and neurologic status at presentation (ie, GCS).[4,14,15] Patients who have supratentorial hemorrhages greater than 60 mL have a morality rate up to 93%, and patients with cerebellar hemorrhages between 30 to 60 mL have a 75% mortality rate.[10,11] In addition, nearly all pontine ICH greater than 5 mL are lethal bleeds. Intraventricular hemorrhage (IVH) can be associated with ICH in 40% of cases (see **Fig. 1**B). IVH can cause hydrocephalus and increased intracranial pressure (ICP). IVH is an additional negative predictor of clinical outcomes, especially when associated with ventricular obstruction.[16]

The poor outcome associated with ICH is related to the extent of brain destruction. The hemorrhage volume is the most important predictor of clinical outcome after ICH.[4,10,11] Large clots exert mass effect and elevate ICP. They also produce direct destruction and compression of surrounding brain tissue. The direct compressive force causes poor brain perfusion and venous drainage in the surrounding penumbra at risk, resulting in ischemia to the tissues that need perfusion the most. Furthermore, the extravasated blood and ischemic brain release vasoactive and toxic chemicals that compound cerebral insult and contribute to the morbidity and mortality of ICH.[17–23]

RISK FACTORS AND PATHOETIOLOGY

The most important risk factors that predispose to ICH are age and hypertension.[24,25] Aging leads to increased degenerative changes of cerebral vessels placing them at risk for rupturing. The increasing life span of the general population is one of the factors leading to predictions that the incidence of ICH may double over the next 50 years. Hypertension is the most common diagnosis in the adult population and easily is modifiable with the large armamentarium of antihypertensive treatments currently available.[26] Yet, many individuals suffer from chronic hypertension because of failure to treat or poor compliance with medications. Chronic hypertension leads to lipohyalinosis, which includes degradation, fragmentation, and necrosis of small penetrating arteries (**Fig. 3**). Arteriolar microaneurysms, known as Charcot-Bouchard aneurysms, can develop as a result of chronic hypertension. Rupturing of these microaneurysms or fragile vessel walls of small and medium-sized arteries during pressure spikes result in extravasation of blood into the brain parenchyma. Hypertensive bleeds are associated

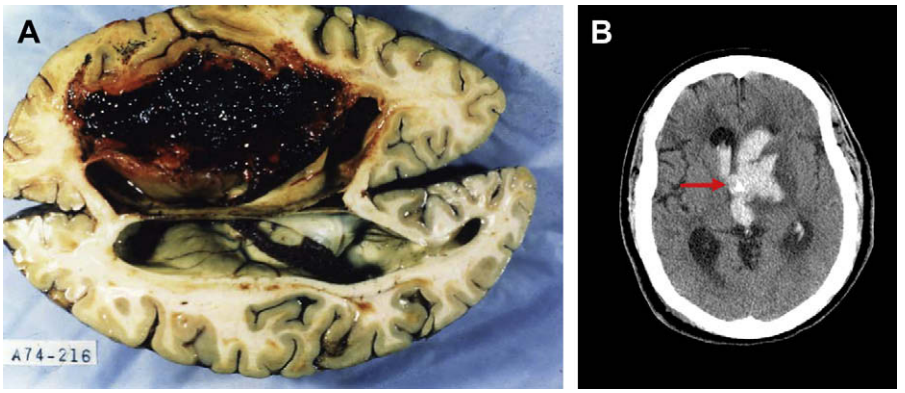

Fig. 1. ICH. (*A*) Gross specimen of basal ganglia ICH. (*B*) CT scan of left thalamic ICH with ventricular extension. Arrow demonstrates the tip of EVD within IVH.

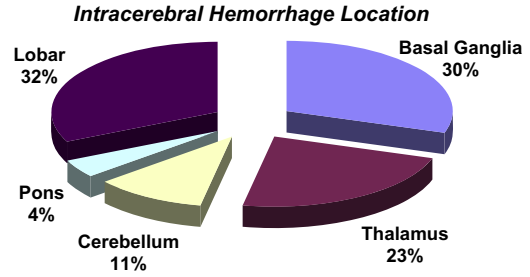

Fig. 2. Distribution of ICH locations.

mostly with deep or brainstem hemorrhages, but hypertension can contribute to risk of stroke in all brain locations. Indeed, lipohyalinosis leads to occlusive changes and microaneurysms formation on the same vessels. These changes explain the presence of lacunes adjacent to ICH.

Cerebral amyloid angiopathy is the culprit for ICH in approximately 15% of cases and is the second most common cause of ICH.[11,27–29] It occurs most commonly in elderly patients and the hemorrhage pattern is most commonly in lobar distribution (**Fig. 4**). Cerebral amyloid angiopathy is not associated with systemic amyloidosis. Histologically, the small to medium vessels of the brain and leptomeninges are deposited with amyloid β-peptide.[29,30] Deposition of the amyloid peptides leads to fragility of the vessel and results in lobar hemorrhages. Recurrent hemorrhages can occur in 5% to 15% of patients who have lobar hemorrhage, probable amyloid angiopathy, and chronic hemorrhages on gradient-echo MRI (**Fig. 5**).[31,32] The E2 and E4 alleles of apoprotein E gene are reported to be associated with increased risk of recurrent hemorrhages in those patients with angiopathy.[31–33] Cerebral parenchyma in the brain of older patients also manifests progressive dilation of Virchow-Robin perivascular spaces (etat criblé), general rarefaction, and demyelination of brain parenchyma in association with chronic ischemia (leukoaraiosis). These changes are believed to predispose to hemorrhagic fragility in the aged brain, and to hemorrhagic expansion in the more compliant brain.

Other secondary causes related to spontaneous ICH include alcohol, cocaine, amphetamine, antiplatelet therapy, coumadin, other anticoagulation medications, and systemic or intra-arterial recombinant tissue plasminogen activator (r-tPA) therapy. Heavy alcohol consumption, particularly during a binge, can induce hypertension and inhibit platelet function.[34–36] Cocaine, when snorted or smoked as crack, is known to be associated with ICH.[37] In addition, cocaine may induce cerebral vasculopathy that predisposes to ICH.[38] Amphetamine also is associated with ICH. Similar to cocaine, it causes transient hypertension and sympathetic surge by blockade of noradrenaline uptake. Finally, therapeutic agents, such as aspirin, coumadin, and r-tPA, all increase risks for ICH.[39–43] However, these medications are commonly used and are effective in the treatment of serious medical conditions, such as coronary artery disease, peripheral vascular disease, and ischemic cerebrovascular disease. All these diseases also can result in severe morbidity or mortality without appropriate treatment. The risk-to-benefit ratio must be considered carefully for individual patients by medical providers.

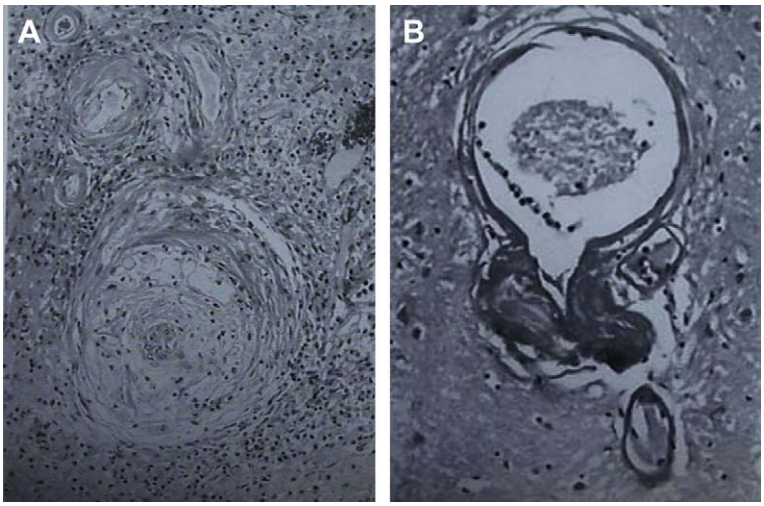

Fig. 3. Vasculopathy changes associated with chronic hypertension. (*A*) Lipohyalinosis. (*B*) Microaneurysm.

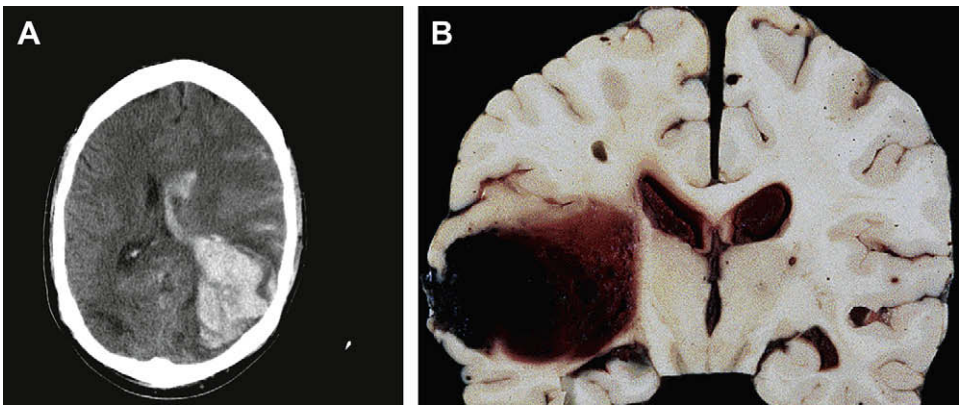

Fig. 4. Lobar ICH. (*A*) CT scan demonstrating left parietal-occipital lobar ICH. (*B*) Gross specimens demonstrating lobar ICH.

ESTABLISHING DIAGNOSIS AND INTRACEREBRAL HEMORRHAGES ETIOLOGY

Diagnosis of ICH is based largely on clinical history and corroborative CT scanning of the brain. A clinical history of acute onset of focal neurologic deficit associated with elevated intracranial hypertension is highly suspicious for ICH. Therefore, patients who have acute onset of severe headache, nausea, vomiting, or depressed mental status should be evaluated promptly for ICH or other hemorrhagic stroke, including subarachnoid hemorrhage.

Patients suspicious for suffering from ICH should have a noncontrast CT immediately (see **Figs. 1**B and **4**A). CT scan of the head has a sensitivity and specificity that approach 100% for acute ICH. In addition, the pattern of hemorrhage can be helpful in determining the likelihood of various causes of hemorrhage. The localization of the hemorrhage combined with the characteristics of presenting symptoms and the patient's risk factors can allow medical providers to help determine a possible cause and the need for further diagnostic studies. Elderly patients who have a history of chronic hypertension with ICH found in the putamen, the thalamus, the cerebellum, or the pons most likely have spontaneous primary ICH resulting from hypertension. Alternatively, patients who have a temporal lobe ICH associated with sylvian fissure subarachnoid blood (**Fig. 6**A) or a frontal hemorrhage associated with interhemispheric fissure blood (**Fig. 6**B) are highly suggestive of ruptured aneurysm causing a combination of parenchymal hemorrhage and SAH. ICH associated with intralesional or perilesional large vessels are suspicious for AVM (**Fig. 6**C). Calcification within an ICH is suspicious for either tumor or cavernous angioma as the cause of ICH.

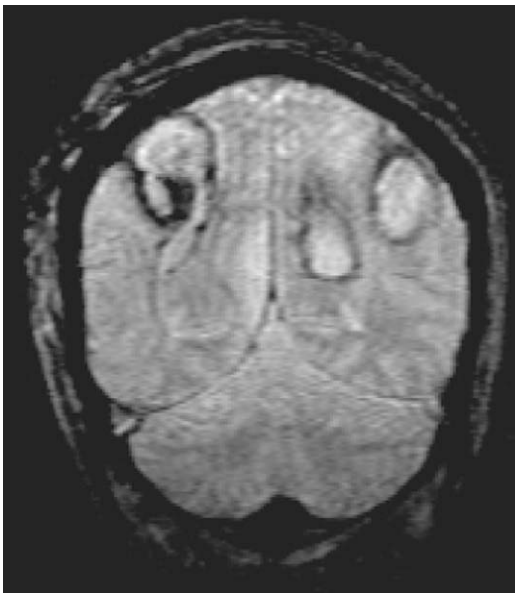

Fig. 5. T2 Gradient-echo MRI image demonstrating multiple ICHS.

The volume of ICH can be approximated rapidly with a head CT. It is an important prognostic indicator and criterion for therapeutic intervention, and its expansion is associated with neurologic deterioration. The estimated volume in cubic centimeters is calculated easily based on the formula, $(A \times B \times C)/2$, where *A* is the largest diameter of the hematoma on axial CT scan slice in centimeters; *B* is the diameter perpendicular to *A* on the same slice; and *C* is the thickness of the hematoma on CT in centimeters, also counted as the number of axial cuts on CT multiplied by the slice thickness in centimeters (excluding the highest and lowest cuts visualizing ICH) (**Fig. 7**). This is based on approximation of the geometric volume of an ellipse of the same dimensions and correlates with true volumetric measurements and excellent interobserver agreement.[4,44]

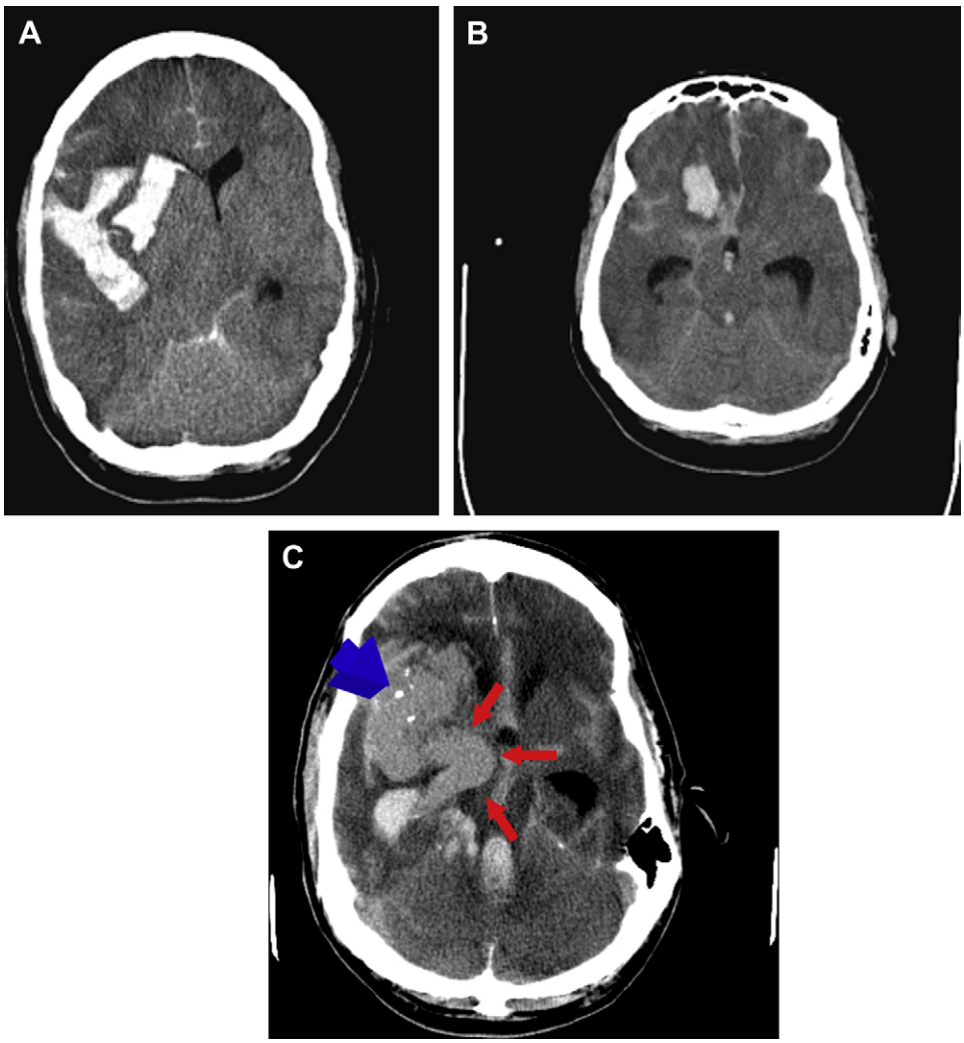

Fig. 6. ICH with associated with ruptured aneurysms or AVM. (*A*) Right ICH associated with sylvian fissure hematoma. (*B*) Right frontal ICH associated with interhemispheric fissure and sylvian fissure subarachnoid hemorrhage. (*C*) ICH resulting from AVM hemorrhage. Arrows indicate the large draining varix and large arrowhead points to the intranidal calcification.

Contrast-enhanced CT scan and newer CT angiographic (CTA) acquisitions now can be obtained quickly on the latest-generation scanners. These images can exclude most gross vascular and tumor causes of hemorrhage rapidly, and they can have an impact on the therapeutic plan. Cases of occult aneurysm or AVM may be invisible on the noncontrast-enhanced study but are easily detectable on CTA (**Fig. 8**). Findings on CTA may affect a surgical plan in the those case that require emergent ICH evacuation. Such studies should be performed emergently and certainly before evacuation of ICH if possible.

MRI rarely is used in the acute setting for diagnosis of ICH. Although MRI is highly sensitive for ICH, it is used most often as a supplementary test to CT scans for ICH. When the cause of ICH is unclear, MRI is used to detect other potential cause of ICH. MRI is highly sensitive to detect flow voids and gliosis associated with AVM or the various heme degradation products associated with cavernous angioma. An underlying enhancing mass associated with ICH on contrast MRI is suggestive of a hemorrhagic tumor (**Fig. 9**). MRI sequences should include FLAIR, T2 images, gradient-echo (T2*) images, diffusion images, and T1-weighted images before and after contrast enhancement. Diffusion abnormalities are suggestive of hemorrhage into an acute infarction, and multiple chronic hemorrhages on

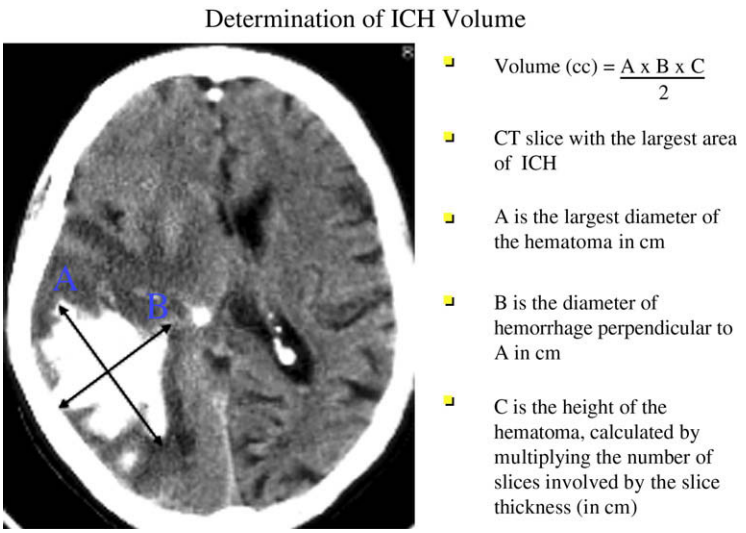

Fig. 7. The ABC method for determining ICH volume.

gradient-echo MRI are indicative of amyloid angiopathy (see **Fig. 5**). It must be remembered, however, that acute and subacute paramagnetic effects of hemorrhage on all sequences may obscure subtle underlying pathologies. Delayed magnetic resonance scanning after resolution of ICH is important to exclude such etiologies and should not be postponed too long in case there is a malignant etiology (such as primary or metastatic tumor) with rapid growth potential. Follow-up MRI scans at 6 to 8 weeks and at 3 to 4 months are recommended if underlying neoplasia is suspected, or at the later interval to rule out occult vascular anomalies. Magnetic resonance angiography sequences are not likely to add much information to contrast-enhanced MRI or to CTA in cases of ICH but may reveal aneurysms, large vessel occlusive disease, and larger AVMs (that also can also be seen on CTA).

Catheter cerebral angiogram with digital subtraction views remains the study of choice for demonstrating (or excluding with certainty) small AVMs (dural or parenchymal), demonstrating smaller aneurysms and outlining their precise anatomy, and revealing unsuspected arteriopathies, including vasculitis. An angiogram is necessary in younger patients and in cases where such pathology or an aneurysm is suspected on CT, CTA, or MRI.

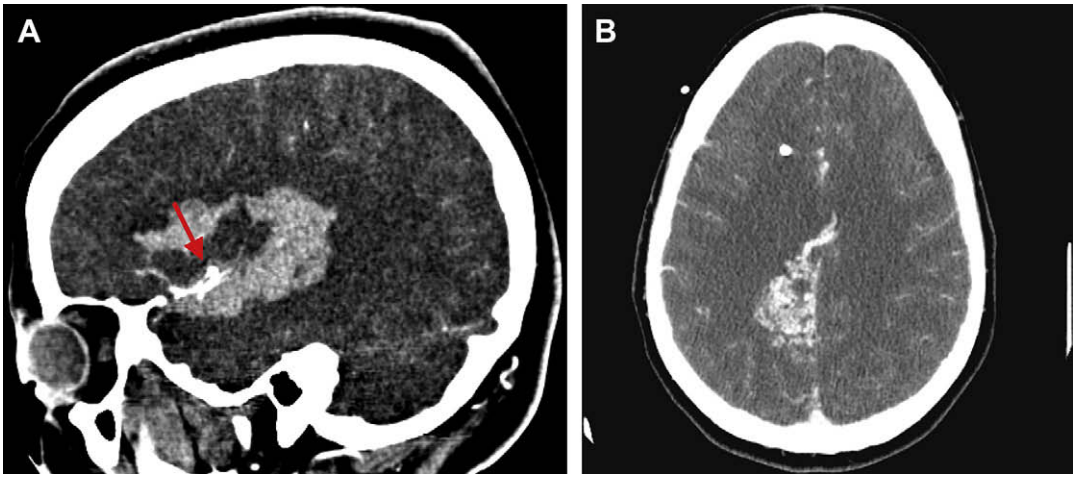

Fig. 8. CTA demonstrating aneurysms and AVM. (*A*) Sagittal CTA image demonstrating a right MCA aneurysm (*arrow*) within the hematoma. (*B*) Axial CTA image demonstrating right frontal-parietal AVM with a draining vein anteriorly.

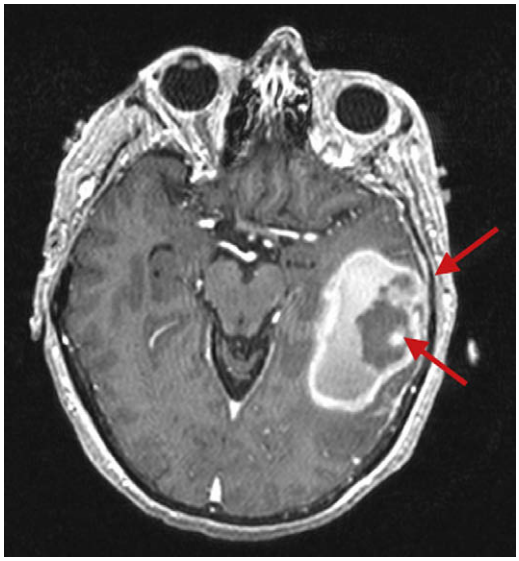

Fig. 9. Contrast-enhanced T1-weighted MRI image demonstrating an enhancing nodule (*arrows*) associated with an intracerebral hematoma.

The majority of spontaneous ICH without underlying vascular malformation or aneurysm is found in the elderly population that has a history of chronic hypertension. In young and nonhypertensive patients and in patients whose ICH are in atypical locations, cerebral angiography should be performed even if MRI and CTA are negative. Zhu and coworkers found in their study that 48% of their patients under 45 years old, who did not have preexisting hypertension that had either putaminal, thalamic, or posterior fossa ICH, had positive angiographic findings. Moreover, in those young and nonhypertensive patients who suffered lobar hemorrhages, the angiographic yield was 65%.[45] Also, an underlying etiology is often uncovered in patients suffering ICH in association with cocaine use.[46,47]

RESUSCITATION AND ACUTE MANAGEMENT

Similar to acute resuscitation for trauma or other illnesses, adhering to the ABC guides of securing the airway, maintaining normal blood pressures, and ensuring circulation, helps to prevent secondary injuries. Decreased level of consciousness is found in approximately 30% of patients who have supratentorial ICH and almost all patients who have brainstem ICH.[48] All patients who have GCS 8 or less and are unable to protect their airway should be intubated to avoid aspiration, hypoxemia, and hypercapnia. Hypoxemia and hypercapnia in this setting lead to further cerebral ischemia and worsen intracranial hypertension. More than 90% of patients who have ICH also have acute hypertension, typically greater than 160/90 mm Hg.[27] Elevated blood pressure is associated with expansion of hematoma and poor outcomes.[49–52] Blood pressure should be reduced aggressively in a controlled fashion to achieve a reduction of blood pressure without compromise of cerebral perfusion (**Table 1**). Studies show that controlled reduction of blood pressure by approximately 20% has no adverse side effects.[53,54] The American Heart Association recommends that blood pressure be maintained below a mean arterial pressure (MAP) of 130 mm Hg in patients who have a history of hypertension.[53] A central line and arterial line should be considered strongly in patients who have ICH, particularly those who require continuous intravenous antihypertensive infusions.

In patients who have GCS 8 or less whose neurologic examination cannot be followed reliably, a monitoring device to measure ICP should be placed. Fiber-optic intraparenchymal monitor and intraventricular catheter monitor with external ventricular drain (EVD) are used commonly. The intraparenchymal ICP bolt is more accurate and less vulnerable to obstruction. Alternatively, the EVD catheter allows simultaneous drainage of cerebrospinal fluid to treat elevated ICP, if needed, and is required in cases of demonstrated or imminent ventricular obstruction from associated IVH (see **Fig. 1**B). Elevated ICP is defined as ICP exceeding 20 mm Hg for more than 5 minutes. The goal of treatment is to keep ICP less than 20 mm Hg and cerebral perfusion pressure (CPP) greater than 60 to 70 mm Hg. The CPP is defined as MAP minus ICP and is the pressure gradient responsible for cerebral perfusion. Compromise of CPP results in cerebral ischemia.

Intracranial hypertension can be treated by draining cerebrospinal fluid, decreasing brain tissue bulk, or decreasing cerebral blood volume. In addition, sedation and pharmacologic paralysis can decrease brain metabolic demands to lower ICP. EVD allows diversion of cerebrospinal fluid in cases of hydrocephalus or whenever ICP exceeds a certain level. This may be performed continuously (by titrating the level of the drip chamber) or intermittently, depending on ICP. EVD is ineffective if the ventricles are slit as a result of brain edema or overdrainage. It is also ineffective if the catheter is obstructed by clotted blood. It may be possible to restore EVD patency and enhance ventricular clearance of IVH effectively using intraventricular r-tPA administered through the EVD in doses of 0.3 to 2 mg every 8 to 12 hours (**Fig. 10**).[55–57] This application currently is being investigated in clinical trials and otherwise is

Table 1
Blood pressure management in hemorrhagic stroke

Elevated Blood Pressure (Some Suggested Medications)	
Labetalol	5–100 mg/h by intermittent bolus doses of 10–40 mg or continuous drip (2–8mg/min)
Esmolol	500 μg/kg as a load; maintenance use, 50–200 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Nitroprusside	0.5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Hydralazine	10–20 mg Q 4–6 h
Enalapril	0.625–1.2 mg Q 6 h as needed
Nicardipine	5–15 mg/h infusion
The following algorithm, adapted from guidelines for antihypertensive therapy in patients with acute stroke, may be used in the first few hours of ICH (level of evidence V, grade C recommendation)	
1. If systolic BP is >230 mm Hg or diastolic BP >140 mm Hg on 2 readings 5 minutes apart, institute nitroprusside.	
2. If systolic BP is 180 to 230 mm Hg, diastolic BP 105 to 140 mm Hg, or mean arterial BP $\geq$130 mm Hg on 2 readings 20 minutes apart, institute intravenous labetalol, esmolol, enalapril, or other smaller doses of easily titratable intravenous medications, such as diltiazem, lisinopril, or verapamil.	
3. If systolic BP is <180 mm Hg and diastolic BP <105 mm Hg, defer antihypertensive therapy. Choice of medication depends on other medical contraindications (eg, avoid labetalol in patients who have asthma).	
4. If ICP monitoring is available, CPP should be kept at >70 mm Hg.	
Low blood pressure	
Volume replenishment is the first line of approach. Isotonic saline or colloids can be used and monitored with central venous pressure or pulmonary artery wedge pressure. If hypotension persists after correction of volume deficit, continuous infusions of pressors should be considered, particularly for low systolic blood pressure, such as <90 mm Hg.	
Phenylephrine	2–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Dopamine	2–20 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Norepinephrine	Titrate from 0.05–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$

Adapted from Jabbour PM, Awad IA, Huddle D. Hemmorrhagic cerebrovascular disease. In: Layon AJ, Gabrielli A, Friedman WA, editors. Textbook of Neurointensive Care. Philadelphia: Saunders; 2003. Section 1.

reserved for compassionate off-label use in cases where patients are deteriorating from obstructed EVD and where AVM or aneurysm have been excluded.

Brain bulk may be deceased to lower ICP with osmotherapy using mannitol (0.25–0.5 g/kg every 4 hours) and furosemide (10 mg every 2–8 hours). Alternating administering of these agents is routine, and they are administered as needed for ICP spikes. Serum osmolarity and sodium concentrations should be measured typically every 6 hours to target an osmolarity less than 310 mOsm/L. Fluid management should aim to maintain euvolemia and normonatremia. Osmotherapy cannot be used to treat ICP if extremes of hypovolemia and hypernatremia are allowed to develop. Corticosteroids should not be used in treatment of ICH. Randomized trials show no efficacy in the treatment of ICH with corticosteroids.[58–60]

Hypocarbia (25–35 mm Hg) decreases the ICP by causing a cerebral vasoconstriction, and this is very effective in acute crises with waves of elevated ICP. However, extreme hyperventilation (P_{CO_2} < 20 mm Hg) can exacerbate brain ischemia by decreasing cerebral blood flow. Hyperventilation also should not be used for a prolonged period of time, because it becomes ineffective with metabolic adjustment to respiratory alkalosis. Further response to life-threatening ICP waves becomes ineffective after chronic hyperventilation. In addition, patients become vulnerable to rebound increased ICP when restoring normocapnia.

Sedation with neuromuscular paralysis can reduce elevated ICP by preventing agitation and straining. It also decreases brain metabolic demands. If the ICP remains high despite maximizing medical management (discussed previously), induced barbiturate coma may be instituted with continuous EEG monitoring. A central line and arterial line are used. Swan-Ganz catheter and pressors may be needed to maintain hemodynamic support during barbiturate-induced coma. Barbiturates can decrease ICP in

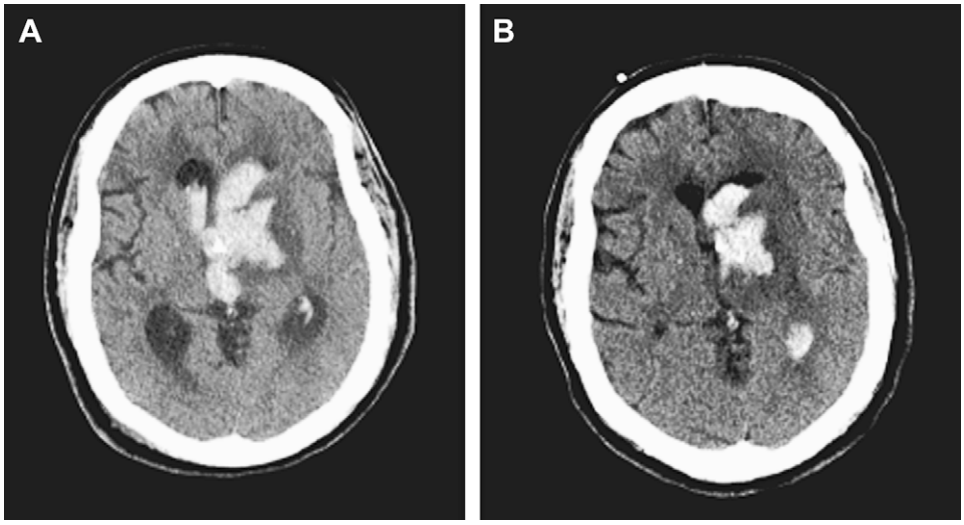

Fig. 10. CT axial images demonstrating decreased IVH and improved EVD with intrathecal r-tPA without any evidence of re-hemorrhage. (*A*) Preintrathecal r-tPA infusion with dense IVH in bilateral frontal horns and third ventricle. (*B*) Postintrathecal r-tPA infusion with decreased IVH with complete resolution of right frontal horn and third ventricular IVH.

proportion to the level of sedation, down to EEG burst suppression. Further administration of barbiturates beyond effective EEG burst suppression does not offer additional benefits of ICP control, and it will increase risk of toxic complications.

The highest risk of neurologic deterioration and cardiovascular instability is within the first 24 hours after onset of hemorrhage. The authors advocate that patients who have ICH be admitted and monitored in an ICU, preferably an ICU that is dedicated to treatment of neurovascular diseases. Early neurologic deterioration within the first 24 hours after hemorrhage occurs in approximately one fourth of patients who have ICH.[15,61] The most common cause of early neurologic deterioration is expansion of the hematoma. This is most ominous in, but not limited to, cases of uncorrected coagulopathy (**Fig. 11**). Brott and colleagues, in a study of 103 patients, report that 26% of patients had expansion of hematoma within 1 hour after the initial CT scan and approximately 38% of these patients had increased in hematoma volume by more than 33% within 3 hours of onset.[62]

Many patients who have early hematoma expansion have no evidence of coagulopathy. The expansion is believed related to active bleeding from the primary culprit and to mechanical disruption and shearing of surrounding vessels. Additionally, breakdown of brain-blood barrier, reduction of venous outflow, and transient creation of local coagulopathy are other possible causes of the hematoma expansion. Recombinant activated factor VII (rVIIa) is a hemostatic agent that is approved for treatment of bleeding in patients who have hemophilia who are refractory to factor VIII replacement therapy. rVIIa initiates coagulation cascade and enhances thrombin generation on the surface of activated platelet, leading to the formation of stable lysis-resistance clot at the site of vascular injury. In a randomized, double-blinded, placebo-controlled trial of 399 patients, treatment of ICH patients with rVIIa within 4 hours of hemorrhage onset decreased

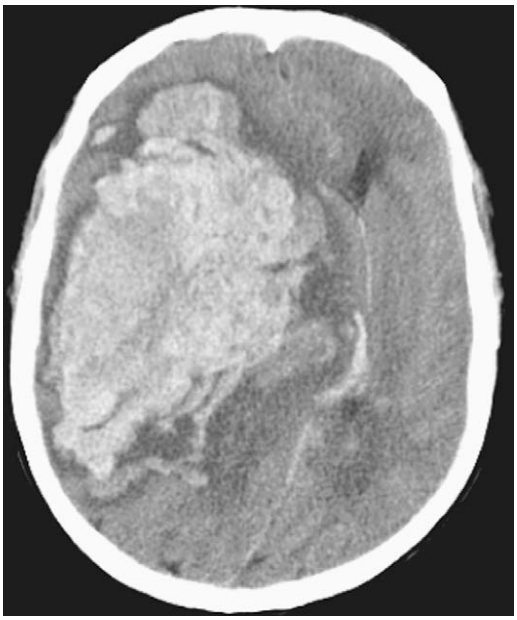

Fig. 11. Large ICH resulting from uncorrected coagulopathy from use of coumadin.

hematoma growth by approximately 50%.[63] Treatment with rVIIa at doses of 40 μg/kg, 80 μg/kg, and 160 μg/kg were given. There was a mean increase of hematoma by 29% in the placebo group. Alternatively, the mean increase of hematoma in the treatment groups of 40 μg/kg, 80 μg/kg, and 160 μg/kg were 16%, 14%, and 11%, respectively. The study found that treatment with rVIIa reduced mortality rate from 29% in the placebo group to 18% in the three treatment groups at 3 months. Additionally, significant improvements of functional outcomes at 90 days were observed in the treatment group. There was a 7% rate of thromboembolic adverse events in the treatment groups compared with a 2% rate in the placebo group, occurring primarily in higher dose strata, but these were outweighed vastly by primary benefit of the drug. The efficacy of rVIIa in the treatment of ICH was formally studies under the phase III FAST trial.

Anticoagulation with warfarin is found in approximately 15% of ICH cases, and warfarin increases risk of ICH five- to tenfold.[41] Anticoagulation is associated with progressive bleeding, clinical deterioration, and increased mortality.[40] Although all patients who have ICH and are on warfarin should be given vitamin K and fresh frozen plasma (FFP), vitamin K and FFP reversal typically is delayed and associated with significant fluid load. rVIIa is shown to expedite the reversal of warfarin anticoagulation without significant volume load. rVIIa given intravenously can normalize the prothrombin time and international normalized ratio within minutes. rVIIa is used to reverse the warfarin anticoagulation in acute ICH and to expedite the effect neurosurgical intervention with favorable clinical results.[64] Nevertheless, rVIIa should be given as an adjunct to treatment with vitamin K and FFP. Although larger rVIIa doses can produce longer duration of effect, the effect of rVIIa typically lasts for only several hours. The use of rVIIa must be weighed carefully in each patient against potential risks of thromboembolic complications. It likely is contraindicated in patients who have had severe arterial or venous occlusive disease, active thromboembolic sources, or metal prostheses, and its use should be reserved for patients in clinical trials or for compassionate use in instances where further clot expansion or delaying surgery likely would be fatal or severely disabling.

SURGICAL INTERVENTIONS

Annually, more than 7000 patients in the United States are estimated to receive surgical evacuation of hematoma after being diagnosed with ICH.[10] The goals of surgery are to reduce mass effect and to remove potential neurotoxic factors, prevent their interactions with surrounding normal tissue. Surgical removal of these typically deep hematomas, however, often requires traversing substantial amount of normal brain tissue, causing neural damage in the process.

McKissock and coworkers reported the first prospective, randomized, controlled trial on surgical evacuation of ICH in 1961.[2] They found that surgical intervention was associated with worse clinical outcomes and increased mortality rate compared with medical treatment. This study was completed, however, in an era before CT scan was available, and factors, such as undetermined hemorrhage volume and delayed treatment, may have interfered with the study results. Since their study, several trials have been conducted and reported during the past half of century and most found similar results to the McKissock study. Juvela and colleagues in 1989 reported a randomized study of 52 patients comparing craniotomy evacuation within 48 hours of symptom onset to medical treatment and found increased mortality in the surgical group.[65] In 1990, Batjer and colleagues reported a randomized trial comparing surgical evacuation versus medial treatment or medical management with ventriculostomy ICP monitoring. This trial was terminated prematurely, however, secondary to poor outcome in all treatment arms and poor recruitment.[66]

Only one randomized trial since the McKissock study has demonstrated improved neurologic and overall outcome and reduced mortality rate with stereotactic surgery.[67] Auer and coworkers evaluated ultrasonic-guided endoscopic hematoma evacuation versus medical therapy alone in a randomized trial of 100 patients. They report a mortality of 42% in the surgical group and a mortality rate of 70% in the medical group. Moreover, they found improved functional outcome in the surgical group compared with the medical group. The surgical patients in this study were younger, however, and subgroup analysis indicated that only younger patients appeared to benefit.

The most recent trial is the landmark International Surgical Trial in Intracerebral Haemorrhage of 1033 patients.[68] The study compared early surgical evaluation of hematoma to initial medical management. Patients enrolled in the study had spontaneous supratentorial ICH and presented within 72 hours of symptom onset. In addition, there had to be a clinical uncertainty of the need of surgical evacuation. The study demonstrated no difference in mortality between the two groups and a favorable outcome at 6 months was found in 26% of the surgical group compared with 24% in the medical group. The investigators conclude that there is no overall benefit from early surgery

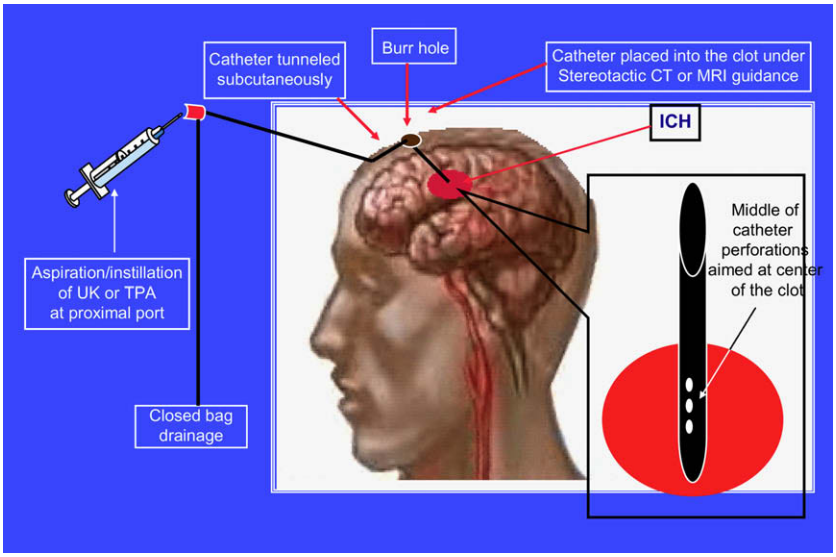

Fig. 12. Schematic diagram demonstrating the operative technique involved in the MISTIE trial.

compared with initial medical therapy in patients who have spontaneous supratentorial ICH. In this trial, however, all patients who the investigators believed would benefit from surgery were not enrolled. These included the majority of younger patients and those deteriorating from lobar hemorrhages (see **Fig. 4**). In more than two thirds of screened patients, the neurosurgeon expressed certainty about treatment, and surgery was performed in approximately one third of patients in this group. The patients in this subset group were younger patients who had lower GCS scores likely from rapid deterioration resulting from mass effect, who traditionally were considered good surgical candidates, and in whom the benefit of emergency surgery has been shown in a retrospective study. Furthermore, the median time between the ictus and surgery was 30 hours, so it remains unclear if earlier surgery performed within first 12 to 24 hours after symptom onset may in fact improve outcomes.

One current National Institutes of Health (NIH)–sponsored multicenter, prospective, randomized trial for surgical treatment of ICH is the Minimally Invasive Surgery Plus rt-PA for Intracerebral Hemorrhage Evacuation (MISTIE) trial. It is investigating the role of minimally invasive surgery plus r-tPA versus best medical therapy in treatment of ICH. The surgical procedure is performed with burr hole followed by stereotactic-guided (CT or MRI scan) catheter placement into the intracerebral hematoma with a one-time clot aspiration followed by administering r-tPA over the next 72 hours (**Fig. 12**). Patients in this study between ages 18 and 75 have GCS less than 13 or NIH stroke score greater than 6, and they must have supratentorial ICH greater than 25 cm^3. They have to present within 12 hours of symptoms and complete their initial diagnostic CT scan within that time period. A repeat CT scan at 6 hours subsequently is performed to ensure stabilization of ICH to within 5 cm^3 of initial ICH volume. Exclusion criteria for the study includes infratentorial hemorrhages, irreversible coagulopathy, thrombocytopenia less than 100 K, age greater than 75, pregnancy, IVHs, significant systemic disease or multiorgan failure, secondary ICH, and several others listed in the study website.[69] The primary outcome measurements for the study are the 30-day mortality rate of the two groups and procedure-related morbidities. Secondary outcome assessments include clot size reduction rate at days 4 to 5 and 90- and 180-day clinical outcomes measured by Glasgow Outcome Score, Rankin scale, and Stroke Impact Scale. It is hypothesized that this minimally invasive intervention would reduce hematoma size and facilitate more rapid recovery of neurologic function and decrease mortality from ICH compared with conventional medical management.

SUMMARY

Spontaneous ICH remains a formidable disease that continues to disable and kill the majority of its victims. Treatment of the disease continues to be controversial and without proven success, such as improvement in the overall disease mortality or functional disability in survivors. Primary prevention is the most effective medical intervention.

Nevertheless, as the population continues to age and patients remain undertreated for hypertension, the incidence of ICH likely will increase, resulting in significant socioeconomic impact on society in the coming years. It is imperative that more research be conducted to improve treatment outcomes of patients who have ICH. Unlike ischemic stokes or other causes of hemorrhagic stroke, such as SAH, where major advancement of treatment has led to improved outcomes, the increased incidence of ICH has not been matched with any considerable improvement in treatment. This burden to improve therapeutic interventions for patients who have ICH should be shared by all neurosurgeons, stroke neurologists, and critical care physicians who care for these patients on a routine basis. It is hoped that early diagnosis and resuscitation, prevention of hematoma growth, selective surgery or minimally invasive clot evacuation, judicious critical care, and functional rehabilitation will combine to lessen the burden of this disease.

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