423 Nonlesional Spontaneous Intracerebral Hemorrhage

Sean P. Polster, Julián Carrión-Penagos, and Issam A. Awad

This chapter includes an accompanying lecture presentation that has been prepared by the authors: Video 423.1.

KEY CONCEPTS

- Hematoma volume, intraventricular extension, age, presenting Glasgow Coma Scale score, and medical comorbidities all contribute to the prognosis of intracerebral hemorrhage (ICH).
- Rapid implementation of critical care measures with a focus on correction of coagulopathies and blood pressure control can reduce hematoma expansion (see American Heart Association [AHA] Guidelines for the Management of Spontaneous Intracerebral Hemorrhage).
- Emergent hematoma evacuation is a lifesaving intervention in younger patients with large ICH volumes who are deteriorating clinically, and in patients with cerebellar ICH (resulting in brainstem compression and/or hydrocephalus). These patients have generally been excluded from clinical trials.
- Minimally invasive stereotactically placed catheters and thrombolytic hemorrhage evacuation can be done in a safe manner and may lead to reduced morbidity in patients with ICH without impending herniation. Results of the phase 3 MISTIE (Minimally Invasive Surgery Plus rt-PA for ICH Evacuation) trial showed that hematoma evacuation to ≤15 mL residual clot or ≥70% ICH volume reduction was associated with greater probability of achieving good functional outcomes.
- Thrombolytic clearance of intraventricular blood has been extensively evaluated, including in the phase 3 CLEAR trial (Clot Lysis: Evaluation of Accelerated Resolution of Intraventricular Hemorrhage [IVH]). Cases with IVH volume >20 mL and those achieving ≥80% IVH reduction had a greater probability of achieving a good functional outcome.
- Before performing any minimally invasive therapy, vascular imaging is required to rule out structural vascular lesions (aneurysm, arteriovenous malformation, moyamoya, arterial dissection), tumor, or hemorrhagic infarct. These etiologic studies are mandatory if the intent is to instrument a hematoma or deploy thrombolysis.

EPIDEMIOLOGY AND PROGNOSIS

The incidence of spontaneous intracerebral hemorrhage (ICH) is 24.6 cases per 100,000 people per year and is expected to double by the year 2050 with the increasing use of anticoagulation and antiplatelet medications and an aging population.[2] Although it represents only about 15% of all strokes, primary spontaneous ICH is associated with a higher rate of mortality, with surviving patients having significant functional deficits.[1,3-6] Contributing epidemiologic factors include age, ethnicity, and sex. Advancing age is clearly linked to an increased incidence of ICH, with individuals older than 80 years being affected at an incidence 25 times greater than in the general population.[7] Within this population, hypertension is the most common causative factor; cerebral amyloid angiopathy (CAA) occurs in a second substantial subset of patients. African-American, Japanese, and Chinese populations have a higher prevalence of ICH, with approximately 90,000 people in Japan dying each year from ICH.[8-10] Smoking, drug abuse, and heavy alcohol intake are also associated with a higher incidence of ICH.[11]

Hematoma volume at admission is a critical factor in determining mortality and functional outcome.[12,13] With CT, exact hematoma dimensions can be measured and evaluated in the context of the clinical examination. Volume of ICH can be quickly calculated by using the ABC/2 (a modification of the volume of an elliptical sphere) method (Fig. 423.1).[14] ICH volume is the strongest predictor of 30-day mortality regardless of hematoma location.[12] Lower GCS and medical comorbidities also portend a poorer prognosis. Patients with hematomas larger than 60 mL combined with a Glasgow Coma Scale (GCS) score below 8 have a predicted mortality rate of 91% within 30 days. Rebleeding or expansion of hemorrhage after the primary bleeding also portend poor prognosis and are the aims of acute blood pressure control and hemostatic pharmacotherapies.[1,12,15,16]

PATHOETIOLOGY

Primary ICH occurs after a parenchymal arteriole in the brain ruptures. The processes that lead to arteriole pathology include hypertension and CAA. Coagulopathy and drug abuse can contribute to ICH or its severity. Tumors, hemorrhagic transformation of an ischemic stroke, venous thrombosis, vasculitis, and vascular malformations (including cavernous angiomas, arteriovenous malformations (AVMs), aneurysms, or moyamoya vessels) are considered lesional causes. Lesional and traumatic ICH etiologies are not the primary focus of this chapter. Primary ICH is essentially a diagnosis of exclusion, and an underlying vascular or tumor etiology must remain in the differential diagnosis, to be excluded by appropriate diagnostic imaging (see later), regardless of patient's age, coagulopathy, or history of hypertension.

Hypertension

Chronic arterial hypertension is the most common cause of primary spontaneous ICH. Elevated arterial pressures lead to vascular remodeling with neointimal hypertrophy, damage to the endothelial lining, and lipohyalinosis. Histologically, these changes manifest as Charcot-Bouchard aneurysms, which are truly arteriolar dissections.[17-21] It is believed that rupture of these weakened blood vessels leads to the vast majority of hypertensive hemorrhages. As a result, hypertensive ICH occurs in deep

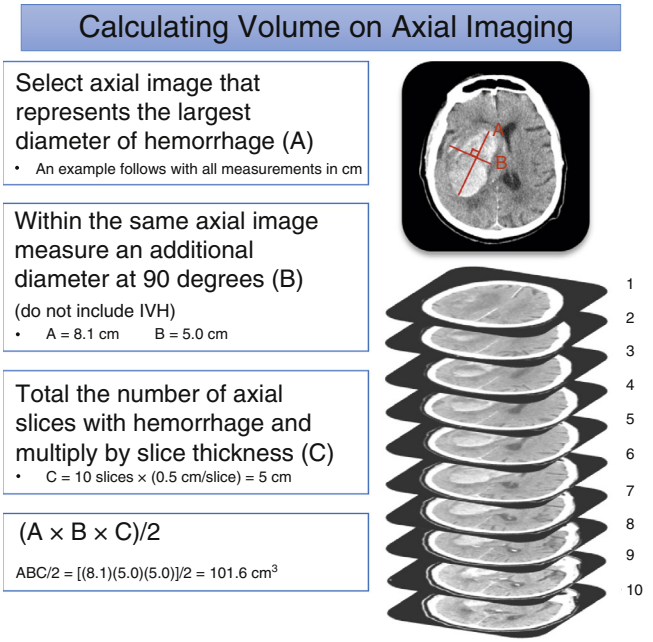

Figure 423.1. Calculating the volume of intracerebral hemorrhage from axial CT scan images.[14]

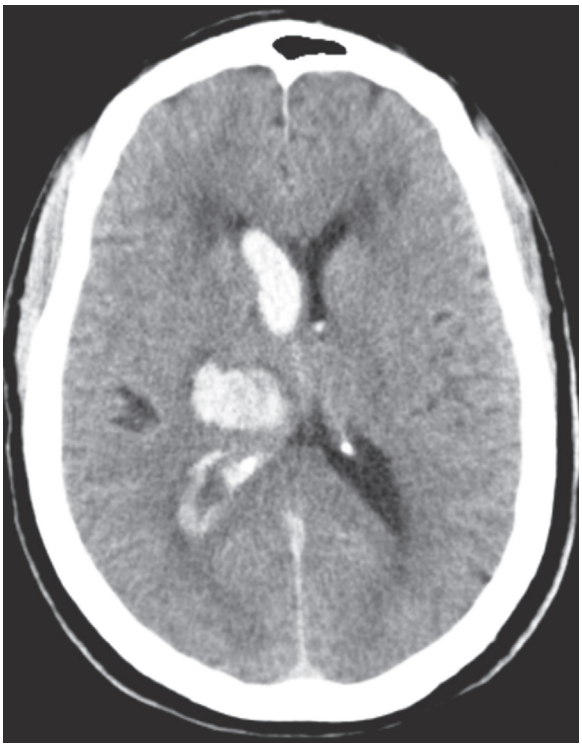

Figure 423.2. Hypertensive intracerebral hemorrhage and intraventricular hemorrhage extension. A 58-year-old man with known hypertension and a history of noncompliance with antihypertensive medications was seen after the acute onset of left-sided hemiplegia and hemisensory loss. Head CT (axial image shown) demonstrated a right thalamic hemorrhage with extension to the internal capsule and spillage into the lateral ventricle. Blood pressure on admission was 180/100 mm Hg. Neurological examination revealed lethargy and strength score of 0 of 5 on the left hemibody. A left frontal external ventricular drain was placed for relief of hydrocephalus that developed, and the patient was managed medically. The patient was discharged to a rehabilitation facility after placement of a ventriculoperitoneal shunt with improved cognition but no significant recovery of motor function.

locations that are supplied by these small vessels, such as the putamen, caudate, thalamus, brainstem, and deep cerebellar nuclei (Fig. 423.2).

Cerebral Amyloid Angiopathy

CAA is a disease primarily found in the elderly population, typically considered those older than 70 years.[22,23] Bleeding that occurs in this elderly age group is typically in lobar locations. Although the vast majority of cases are sporadic, familial forms of the disease have been identified. Early manifestation of the disease can be identified on MR susceptibility-weighted sequences in which small microhemorrhages are identified in lobar locations. Also of importance is the emerging link between CAA, Alzheimer disease, and cognitive decline.[24] The apolipoprotein E alleles ε2 and ε4 have been associated with CAA (Figs. 423.3 and 423.4).[25] The process of CAA is thought to occur because of amyloid deposition within the intracranial vessels, including cortical and leptomeningeal arterioles, capillaries, and veins. Histologic examination reveals that amyloid β is progressively accumulated within the tunica media and adventitia. The gradual loss of smooth muscle cells results in fibrinoid necrosis and microaneurysm formation. This process of progressive weakening leads to eventual vessel rupture.[26] The presence of amyloid protein can be confirmed on histologic sections by birefringence under polarized light with Congo red staining.[27]

Systemic Anticoagulation and Antiplatelet Therapy

Systemic anticoagulation is a known risk factor for spontaneous ICH, with an 8- to 19-fold increased risk of ICH with the use of warfarin or other therapeutic anticoagulants.[28,29] Fang and colleagues found that among anticoagulated patients with atrial fibrillation, ICH caused approximately 90% of the deaths from warfarin-associated hemorrhage.[28] Previous studies had demonstrated a 1% incidence of ICH in patients taking warfarin after myocardial infarction.[30] Investigators have reported higher frequencies of cerebellar and lobar hemorrhages in patients on systemic anticoagulation.[31,32] In addition to a higher incidence of ICH, anticoagulated patients also have larger hematomas on presentation and have a higher mortality rate.[30] Newer anticoagulant agents, the direct thrombin antagonists, and factor Xa inhibitors may be associated with a lower incidence of ICH when compared with warfarin therapy.[33-38] However, these newer agents require special reversal antidotes that are only starting to become available, thereby complicating the medical and surgical management of ICH.[33,34]

Antiplatelet therapy also contributes to the risk of ICH, albeit to a lesser extent than therapeutic anticoagulation.[39-41] Several reports describe increased hematoma sizes and expansion, as well as worse outcomes with antiplatelet therapies, but this has been called into questions with more recent studies showing clinical outcomes in ICH to be independent of antiplatelet therapy.[42,43] The PATCH (Platelet Transfusion Versus Standard Care After Acute Stroke Due to Spontaneous Cerebral Haemorrhage Associated With Antiplatelet Therapy) trial did not confirm clinical benefit and raised the possibility of additional harm from platelet transfusion.[44] However, this trial mostly included patients taking aspirin, and did not specifically address clopidogrel or stronger antiplatelet therapies, nor cases requiring surgical interventions.

Drug Abuse

Primary spontaneous ICH in young individuals is rare, and an underlying vascular etiology must be ruled out. There is a clear

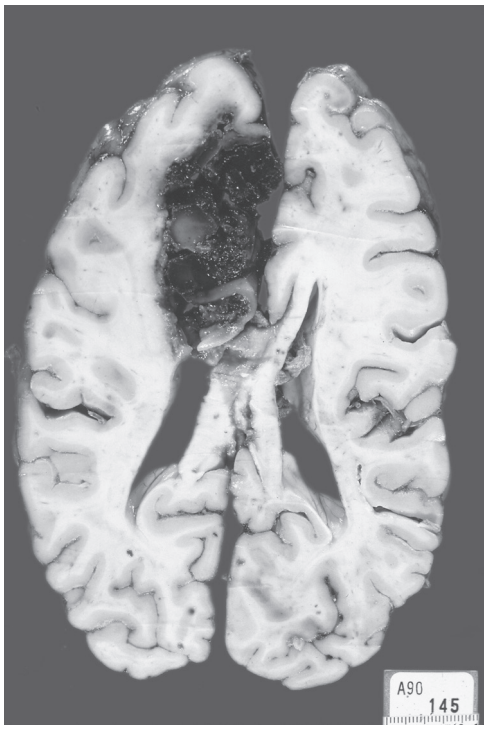

Figure 423.3. Autopsy image of axial brain section with an extensive medial frontal intracerebral hemorrhage secondary to amyloid angiopathy.

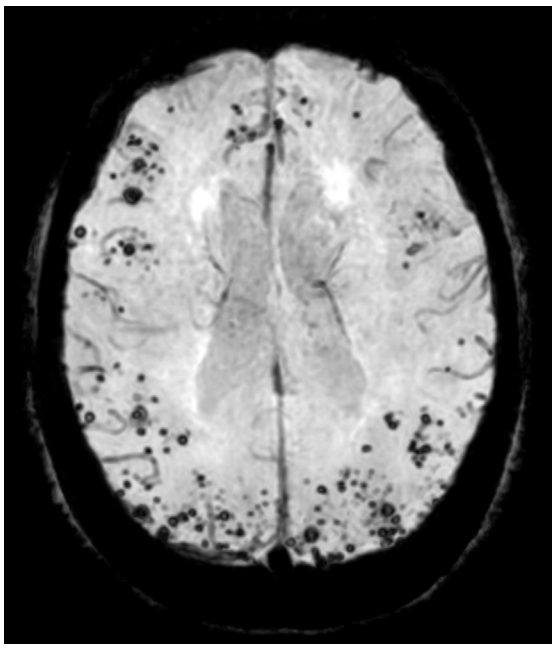

Figure 423.4. A 79-year-old woman underwent high-field MRI with susceptibility-weighted sequence, which revealed multiple microhemorrhages secondary to amyloid angiopathy. This can lead to lobar intracerebral hemorrhage in elderly patients.

association between ICH and illicit drug abuse, particularly among those using sympathomimetic agents, such as amphetamines and cocaine.[45,46] Because hemorrhages most commonly occur within hours of use, it is believed that a sudden and transient increase in blood pressure leads to vessel rupture. Chronic abuse of intravenous drugs, including heroin, may also result in

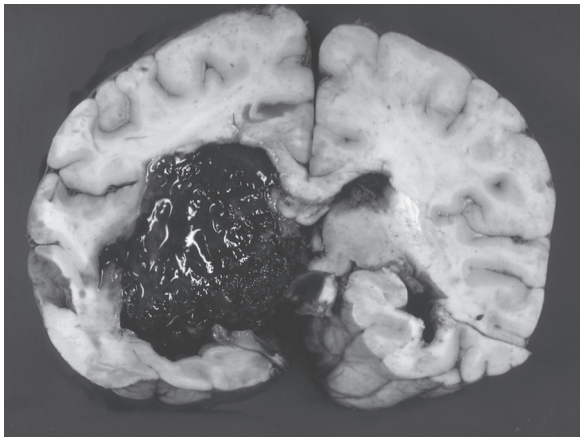

Figure 423.5. Extension of a primary putaminal hemorrhage into the head of the caudate, internal capsule, thalamus, and ventricle, as evident at autopsy (coronal brain slice shown).

vasculitis changes, vessel wall weakening, and rupture. Drug-related hemorrhages may occur in the deep locations associated with hypertensive ICH, but also may be lobar, subarachnoid, or intraventricular.[47-50] We advocate for urine drug screens in all patients with ICH, especially those of younger age without clear risk factors. Little is known about the impact of cannabis use on ICH.[51]

HEMATOMA LOCATION AND CLINICAL PRESENTATION

Deep Hemispheric Hemorrhages (Putaminal, Capsular, Thalamic, and Caudate)

The putamen is the most common location for spontaneous ICH. Putaminal hemorrhage is nearly always associated with hypertension. As with nearly all ICH, the abrupt onset of a severe headache is the first symptom and may or may not be associated with nausea and vomiting. Neurological deficits develop over time as the hematoma expands, typically in the first 3 to 6 hours after symptom onset. Later hematoma expansion occurs less frequently, and rarely after 24 hours. Additional presenting symptoms are variable and dependent primarily on the volume of the hemorrhage. Patients with small hemorrhages may have only minor deficits and remain fairly asymptomatic (Fig. 423.5). Putaminal hemorrhages extending to other deep structures result in contralateral progressive hemiparesis, hemisensory loss, and homonymous hemianopsia.[52-54]

About 15% of all primary spontaneous ICH arises from the thalamus, also a result of chronic hypertension.[53,55,56] Lateral extension into the internal capsule or superior dissection into the white matter tracts results in contralateral hemiparesis. Inferior extension into the midbrain may result in coma. Midbrain involvement is often associated with characteristic ocular findings of upward gaze palsy; miotic, unreactive pupils; retraction nystagmus; and skew gaze deviation (Fig. 423.6).[57]

ICHs located in the caudate are relatively less common (<7% of all ICHs).[58] The ruptured vessels are the perforating lenticulostriate arteries arising from the anterior and middle cerebral arteries. Dissection of the hematoma into the thalamus results in transient short-term memory deficits.[59] Most patients recover fully without permanent neurological deficits if the ICH remains restricted to the caudate.[58]

Large hemorrhages result in an alteration of consciousness ranging from lethargy to coma, and a dense neurological deficit. Comatose patients have a poor prognosis, and recovery of

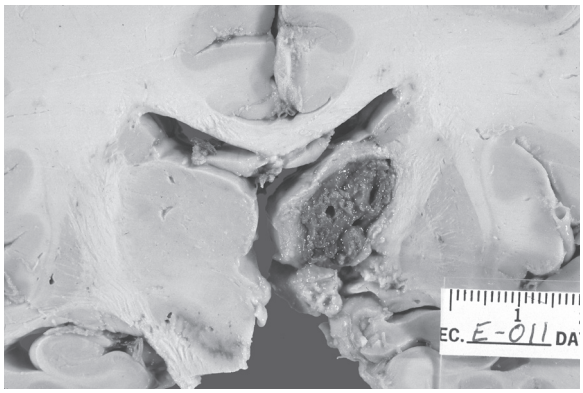

Figure 423.6. Medium-sized hypertensive thalamic hemorrhage, which was well confined and spared the capsular fibers laterally. The patient died from secondary medical complications (coronal brain slice shown at autopsy).

neurological function is unlikely owing to dissection of the deep white matter tracts.[58,59] Intraventricular extension from a deep ICH can also occur, resulting in obstruction of the cerebrospinal fluid (CSF) circulation, and is associated with worse outcome.

Lobar Hemorrhage

Lobar ICH can present with a variety of clinical findings depending on the size and location of the hematoma. These hemorrhages are most frequently found in the subcortical white matter of the parietal, temporal, and occipital lobes, which accounts for the lower incidence of coma and fixed neurological deficits.[60,61] Patients have headache and vomiting, and because of the superficial location of the hematoma, seizures are more frequently observed in this population.[60,62,63] Compared with deeper lesions, lobar hemorrhage is associated with relatively mild hemiparesis.[64] In the elderly population, the majority of these hemorrhages are likely a result of CAA, and these patients may have multiple hemorrhages over time. Nonlesional lobar ICH may also be the result of coagulopathy, including therapeutic anticoagulation and, to a lesser extent, antiplatelet therapy. In younger patients, lobar hemorrhages almost always indicate an underlying vascular anomaly, which should be pursued with aggressive diagnostic screening.

Cerebellar Hemorrhage

Nonlesional cerebellar ICH accounts for 5% to 10% of ICH and represents a unique clinical entity. Even comatose patients with cerebellar hemorrhage may improve significantly if emergent evacuation occurs before irreversible brainstem injury.[53,65-71] The perforating vessels supplying the dentate nucleus are the most common source of hemorrhage, particularly with hypertension. Extension of the hematoma into the surrounding white matter may dissect into the fourth ventricle and result in obstructive hydrocephalus. As is true in all locations, coagulopathy and platelet dysfunction result in larger hemorrhages, more rapid deterioration, and poorer overall neurological outcome (Fig. 423.7).[70,71]

Symptom onset follows a progressive course starting with headache, dizziness, neck stiffness, nausea and vomiting, and dysarthria. Further deterioration consists of appendicular and truncal ataxia, peripheral facial palsy, ipsilateral sixth nerve palsy, and nystagmus. If no surgical intervention occurs, patients with sizable cerebellar hematomas will become increasingly less responsive. At the time of presentation to a hospital, approximately one-third of patients are comatose.[70]

Prognosis is largely determined by clinical examination findings on presentation.[72] However, it must be remembered

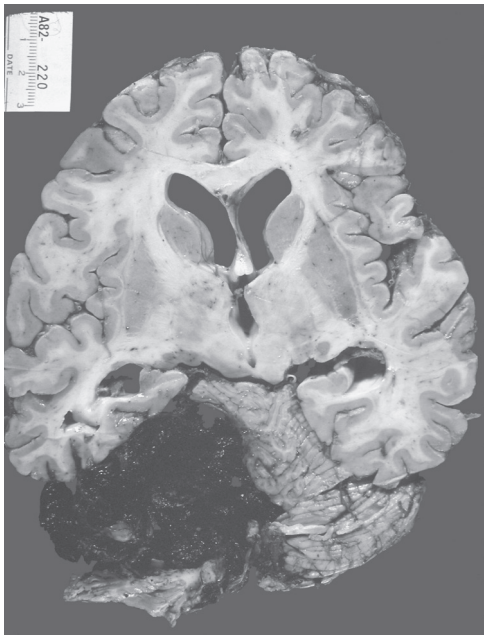

Figure 423.7. The extensive hypertensive cerebellar hematoma started in the deep nuclei of the cerebellum and expanded throughout the cerebellum, causing brainstem compression, hydrocephalus, and the patient's death (axial brain slice shown at autopsy).

that even comatose patients with cerebellar ICH may achieve a favorable recovery with timely surgical decompression. The time course over which symptoms manifest is variable, and rapid deterioration into coma or even death can occur without warning (Fig. 423.8).[70,71] In general, patients with cerebellar hematomas greater than 3 cm in diameter (15-mL volume) are more likely to rapidly deteriorate, develop obstructive hydrocephalus, and require emergent surgical evacuation. Patients alert at presentation most commonly have hematomas smaller than 3 cm in diameter (15-mL volume) and can be treated medically.[73-75] Surgical management should focus on relieving brainstem compression as well as hydrocephalus. External ventricular drainage (EVD) alone cannot accomplish this and may cause upward transtentorial herniation and worsened brainstem compression from cerebellar ICH; hence it not a substitute for emergent posterior fossa decompression.

Brainstem Hemorrhage

Nonlesional brainstem ICH is most commonly the result of chronic hypertension resulting in rupture of small perforating branches arising from the basilar or long circumferential arteries.[20,21,64,65,76] Pontine hemorrhages are the most frequent, with midbrain and medullary hematomas being relatively rare.[64] Pontine ICH is among the most devastating of all ICHs, with a large number of patients comatose at presentation. In cases of hematoma extension into the midbrain and fourth ventricle, the vast majority of patients die within 48 hours, and the prognosis for survivors is extremely poor (Fig. 423.9).[76]

At presentation, awake patients complain of headache, nausea, and vomiting. Neurological examination reveals focal pontine signs, such as diplopia, hemiparesis or quadriparesis, sensory deficits, and possibly deafness. Large hematomas result in coma with decorticate or decerebrate posturing, abnormal breathing patterns, pinpoint pupils, and ocular bobbing.[66,77,78] The larger hematomas are almost all ultimately fatal.[64,78]

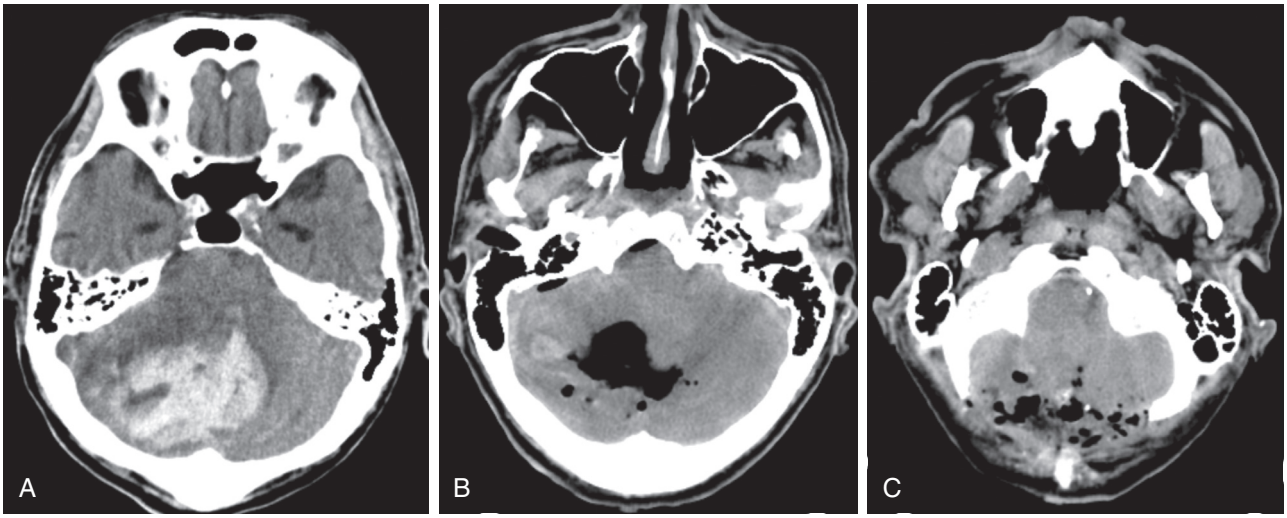

Figure 423.8. Cerebellar hemorrhage with surgical evacuation. (A) This 58-year-old man on warfarin (with admission international normalized ratio of 3.5) for a prosthetic mitral valve replacement had an acute onset of severe headache, nausea, and vomiting. While en route to the hospital, he became progressively more lethargic and was not arousable at admission. The CT scan demonstrated a 45-mL right-sided cerebellar hematoma with compression of the fourth ventricle. The patient coagulation profile was corrected and a right frontal external ventricular drain was placed. (B and C) An emergent suboccipital craniectomy and hematoma evacuation were performed. The patient was discharged to a rehabilitation facility, ambulating with assistance.

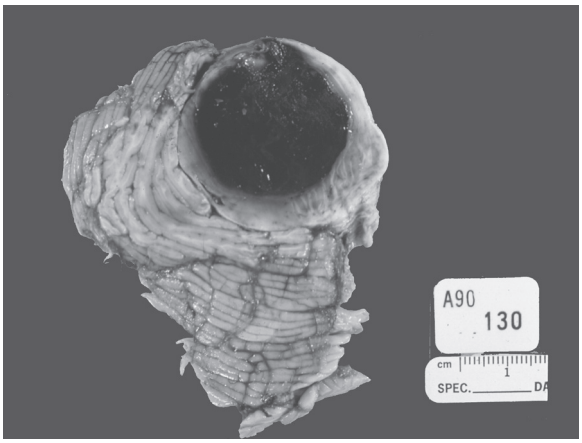

Figure 423.9. Brainstem hemorrhage. Large hypertensive pontine hematoma expanding and distorting the pons, resulting in death (axial brain slice shown at autopsy).

Intraventricular Hemorrhage

Intraventricular hemorrhage (IVH) is most commonly the result of intraparenchymal hematomas extending into the ventricular system.[79] IVH related to spontaneous parenchymal ICH is associated with an 86% incidence of a poor prognosis and a 72% mortality rate.[80] The clinical course is often complicated by the toxicity of blood breakdown products and acute obstructive and, later, communicating hydrocephalus.[80,81] IVH is also commonly observed after aneurysmal subarachnoid hemorrhage, not addressed in this chapter.

EVD is a standard of care for acute obstructive hydrocephalus and can prevent mortality after IVH.[82] IVH that "casts" the ventricles is difficult to treat, because the EVD will often clog with blood products, requiring catheter changes or additional catheters. Chronic communicating hydrocephalus requires ventriculoperitoneal shunting after the clot resolves. Current American Heart Association (AHA)/American Stroke Association (ASA) guidelines state that EVD is reasonable in the management of ICH and IVH, especially in patients with decreased level of consciousness and obstructive hydrocephalus (class IIa; level of evidence B). The use of a thrombolytic, typically recombinant tissue plasminogen activator (r-tPA), to maintain EVD patency has a low complication rate (class IIb; level of evidence B) but has not been shown to lower the rate of ventriculoperitoneal shunting. In the Clot Lysis: Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR) trial, further detailed later, patients with initial IVH volumes >20 mL and those with >80% IVH removal during the active treatment phase of EVD with r-tPA demonstrated significant better functional outcome (modified Rankin Scale [mRS] scores of 0–3) at 180 days after adjustment for ICH/IVH severity confounders.[83]

A normal inflammatory process of IVH has been characterized wherein aseptic CSF inflammation after IVH is primarily dependent on the volume of initial bleeding. This may mask underlying EVD bacterial infections, which are very infrequent, but can best be detected with frequent screening cultures of the CSF while the EVD is in place. In the CLEAR trial, thrombolysis was observed to intensify this aseptic inflammatory response, with no apparent detrimental effect on clinical outcome.[84]

MEDICAL MANAGEMENT

Current management of the critically ill neurosurgical patient is largely performed in a multidisciplinary setting by a team including critical care specialists, neurologists, and neurosurgeons. Beyond the neurological consequences of ICH, patients are susceptible to systemic complications, such as deep venous thrombosis (DVT), pulmonary embolism (PE), pneumonia, cardiac pathology, urinary tract infections, and skin breakdown. As result, a comprehensive approach must be taken to the care of this complicated patient population, and hence the AHA recommends that initial monitoring and management of patients with ICH should take place in an intensive care unit or dedicated stroke unit with physician and nursing neuroscience acute care expertise (class I; level of evidence B).[1,85]

Initial medical management after the standard principles of critical care have been implemented (i.e., airway, breathing, circulation) are to control systemic hypertension and correct

TABLE 423.1 Trials Investigating the Medical Treatment of Intracerebral Hemorrhage (ICH) and Intraventricular Hemorrhage (IVH)[a]

Trial and Year Enrollment Ended	Enrolled Patients or Groups	Intervention	Hematoma	Primary End Point	Time From Symptom Onset	Outcome (30–360 Days)	Comments
INTERACT[87] 2007	Assigned to early intensive lowering of BP (203 patients) or standard guideline-based management of BP (201) patients	SBP to 140 mm Hg	Reduced	Proportional change in hematoma at 24 h	6 h	Not different	Preliminary pilot for INTERACT 2
INTERACT 2[171] 2012	Intensive treatment, 719 of 1382 participants Guideline-recommended treatment, 785 of 1412 participants	SBP to 140 mm Hg	No change	mRS score 0–3 vs 4–6	6 h	Improved mRS score and HRQOL	Ordinal mRS and QOL outcomes better in intensive treatment group Hematoma growth: no difference
ATACH-2[89] 2015	1000 underwent randomization; 500 patients were assigned to intensive treatment and 500 to standard treatment	SBP to 140 mm Hg	No change	mRS score 0–3 vs 4–6	4.5 h	Not different	Higher proportion of renal adverse events within 7 days after randomization among participants randomly assigned to intensive treatment
FAST phase 3[172] 2007	Randomized 841 Placebo (268 patients) 20 μg of rFVIIa/kg (276 patients) 80 μg of rFVIIa/kg (297 patients)	Factor rVIIa In noncoagulopathic patients with ICH	Reduced	mRS score 0–4 vs 5–6	4 h	No effect on mortality or mRS score	Hematoma growth reduced in high-dose group, with increased incidence of arterial thromboembolism
PATCH[173] 2015	97 participants were randomly assigned to platelet transfusion and 93 to standard care	Platelet transfusion	No change	Difference in functional outcome	1.5 h (from diagnostic imaging)	Worse	Does not address patients undergoing cranial procedures
i-DEF[174] 2017	144 patients assigned to the deferoxamine mesylate group and 147 assigned to the placebo group	Deferoxamine	Not measured	mRS score 0–2 vs 3–6	24 h	No effect on mRS score	Novel mechanism
TICH-2[175] 2017	1161 patients received tranexamic acid and 1164 received placebo	Tranexamic acid	Reduced	mRS score	8 h	No effect on mRS score	Fewer early deaths in the tranexamic group; same at 90 days

[a]Selected list, intended to highlight trials with the greatest impact on the field.
ATACH, Antihypertensive Treatment of Acute Cerebral Hemorrhage trial; *BP,* blood pressure; *EVD,* external ventricular drainage; *FAST,* Factor Seven for Acute Hemorrhagic Stroke Treatment trial; *HRQOL,* health-related quality of life; *i-DEF,* Deferoxamine Mesylate in Patients With Intracerebral Haemorrhage trial; *INTERACT,* Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage trial; *mRS,* Modified Rankin Scale; *PATCH,* Platelet Transfusion Versus Standard Care After Acute Stroke Due to Spontaneous Cerebral Haemorrhage Associated With Antiplatelet Therapy trial; *QOL,* quality of life; *rFVIIa,* recombinant activated factor VII; *SBP,* systolic blood pressure; *TICH,* Tranexamic Acid for Hyperacute Primary Intracerebral Haemorrhage trial.

any coagulopathy. Controlling intracranial pressure (ICP) and preventing hematoma expansion follow.

AHA guidelines include consideration of early CT angiography (CTA) to assess for a "spot sign" (active extravasation of contrast agent within the hematoma), as this increases the probability of expansion of bleeding, although the usefulness of this information is debatable. A spot sign is of limited relevance after the bleeding has stabilized on repeated CT scan. Neuroimaging to prove stability (6-hour interval) and identify potential causes should be completed. Characteristics that increase the likelihood of finding a vascular cause include (1) female sex, (2) lobar ICH in a patient younger than 65 years, (3) primary IVH without ICH, and (4) no history of hypertension, smoking, or coagulopathy. Yet there is no sex, age, or history alone that will exclude a vascular or tumor-related cause without proper vascular imaging. In younger patients, and whenever invasive interventions may be planned, it is prudent to always perform vascular imaging with at least CTA. MR angiography (MRA) alone may be less sensitive to vascular causes in the setting of ICH, but MRI may reveal tumors or infarcts as the cause of ICH and is useful in late follow-up after the blood has cleared, identifying underlying cavernous angioma. Catheter cerebral angiography should be undertaken in cases in which clinical suspicion is high (young nonhypertensive patient, associated subarachnoid hemorrhage, suspicious finding on CTA or MR). Venous thrombosis should also be considered as a potential cause of ICH, particularly in cases of patchy lobar ICH and those associated with potential venous infarct, and can be evaluated with CT or MR venography (MRV).

Table 423.1 highlights some of the most important medical-based interventions that aim to improve functional outcomes in ICH.

Hypertension

Hypertension at admission is associated with worse outcome, and a systolic blood pressure (SBP) above 140 to 150 mm Hg after ICH has been shown to double the risk of subsequent death or dependency.[86] Although the need to manage hypertension in the

period immediately after the bleeding episode is well established, the target blood pressure remains controversial.

The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) randomized 203 patients to a low-target SBP of 140 mm Hg to be achieved within 1 hour and maintained for at least 24 hours after hemorrhage, versus 201 patients randomized to an SBP target of 180 mm Hg.[87] Patients treated with aggressive lowering of blood pressure did not have a higher mortality, rate of dependency, or cardiovascular morbidity. There was also a trend toward reduced hematoma expansion within the first 6 hours after ICH. INTERACT-2 was a larger study that also did not find a difference with aggressive control for death or major disability, the primary outcomes. Ordinal analysis showed improved outcomes in the treatment group and superior quality of life; there were no differences when assessing hematoma growth or in the adverse events resulting from aggressive control.

The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) and ATACH-2 trials evaluated the use of nicardipine to lower blood pressure in hypertensive ICH.[88] In the ATACH-2 trial, a phase 3 study, patients were randomized to intensive treatment (SBP target of 110–139 mm Hg) or standard treatment (SBP target of 140–179 mm Hg). The trial was stopped early owing to a significantly increased rate of renal adverse events within 7 days of randomization in patients in the intensive treatment group. Also, lowering SBP from 110 to 139 mm Hg did not improve mortality or disability rates at 3 months compared with the standard treatment.[89] A subanalysis of the group of patients who achieved an SBP <140 mm Hg within 24 hours showed a higher rate of neurological deterioration and cardiac adverse effects.[90]

AHA/ASA guidelines recommend that for patients with ICH with SBP between 150 and 220 mm Hg and without contraindication to acute blood pressure treatment, acute lowering of SBP to 140 mm Hg is safe (class I; level of evidence A) and may improve functional outcome (class IIa; level of evidence B). For patients with ICH with SBP >220 mm Hg, it may be reasonable to consider aggressive reduction of blood pressure with a continuous intravenous infusion and frequent blood pressure monitoring (class IIb; level of evidence C).[1]

ICH occurs in a background of medical comorbidities (renal, cardiac) and underlying cerebrovascular occlusive disease. Blood pressure should be managed with these variables in mind.

Blood Glucose Control

Although there are limited data pertaining to the optimal blood glucose level for patients with ICH, it is known that hyperglycemia is detrimental in this patient population.[91] Hyperglycemia in animal models of ICH results in more profound cerebral edema and increased perihematomal cell death.[92] Clinical studies appear to confirm the deleterious effects of hyperglycemia in patients with a previous diagnosis of diabetes mellitus and those with acute hyperglycemia. AHA/ASA guidelines state that glucose should be monitored. Both hyperglycemia and hypoglycemia should be avoided (class I; level of evidence C).[1]

Kimura and colleagues prospectively studied the admission blood glucose in 100 patients with spontaneous supratentorial ICH.[93] Patients were evaluated over the course of 2 weeks and divided into patients who died within 14 days and those who survived. The median admission glucose in the death group was 205 mg/dL versus 131 mg/dL in the survivors. Further statistical analysis found an admission blood glucose level of 150 mg/dL to be the cutoff value for predicting early death.

Kazui and colleagues found a fasting plasma glucose level of 141 mg/dL or higher combined with SBP of 200 mm Hg or higher to independently increase the risk of hematoma expansion.[94] Passero and colleagues evaluated the effect of diabetes and admission hyperglycemia on outcomes and neurological and systemic complications in patients with ICH.[95] In the case of comatose patients, diabetes and hyperglycemia did not play a significant role in determining outcomes, because the majority of patients died. However, diabetes was an independent predictor of 30-day and 3-month mortality in noncomatose patients. Patients with diabetes also had a greater incidence of infectious and cerebral complications. Patients without diabetes with hyperglycemia also had poorer outcomes and a greater incidence of cerebral complications.

Data also suggest that aggressive glucose management with an insulin infusion can lead to a low cerebral extracellular glucose concentration.[96] Prakash and Matta concluded that systemic glucose levels should not be treated acutely in the setting of ICH unless exceeding 180 mg/dL.[97]

Temperature Management

Fever occurs commonly after ICH and IVH. The duration of fever is related to outcome and appears to be an independent prognostic factor in patients with ICH.[98] Maintenance of normothermia has not been clearly demonstrated as beneficial to outcome. AHA/ASA guidelines were updated in 2015 to include that treatment of fever after ICH may be reasonable (class IIb; level of evidence C). However, treatment with hypothermia should be considered investigational in ICH.[99]

Systemic Anticoagulation

The prevention of hematoma expansion and the urgent need to minimize the size of the clot are primary goals of emergent ICH management. Once the diagnosis of ICH is confirmed, blood pressure control and normalization of the coagulation profile should be aggressively initiated (including stopping administration of anticoagulant medications). These goals hold true even in patients on systemic anticoagulation for thrombotic conditions with a risk of ischemic complications. Vitamin K antagonists, warfarin being the most common, are associated with approximately 20% of spontaneous ICHs, with a reported mortality rate as high as 67%.[28,29] An international normalized ratio (INR) higher than 3 is associated with larger hematoma volumes, a greater incidence of hematoma expansion, and poorer neurological outcomes.

Multiple agents are currently used in the reversal of warfarin-induced coagulopathy. Fresh frozen plasma (FFP) and vitamin K historically had the most widespread use. FFP effectiveness is limited by the fact that it must be thawed and requires blood typing (except for type AB, which is the universal donor) before use, thus causing critical delays in the early period of hematoma expansion. It has been shown that for every 30-minute delay in FFP transfusion, there is a 20% reduction in the probability of a successful correction of the INR at 24 hours.[100] In addition, large volumes may be required to achieve a clinically significant effect, thereby leading to volume overload, heart failure, and transfusion-related acute lung injury. Intravenous vitamin K has a slow onset, taking approximately 6 hours to achieve therapeutic effect.[101-104]

Current guidelines on the management of ICH from the AHA/ASA recommend replacement of vitamin K–dependent factors along with IV vitamin K (class I; level of evidence C). Furthermore, the recommendations support the use of prothrombin complex concentrates (PCCs) as an option for rapidly reversing warfarin-induced coagulopathy (class IIb; level of evidence B).[1] These commercially available products are concentrated mixtures of nonactivated, vitamin K–dependent clotting factors.[105] Four-factor PCCs contain high concentrations of factors II, VII, IX, and X, whereas three-factor PCCs lack factor VII.[105,106] Several studies have shown that PCC normalizes the INR within minutes in patients taking warfarin; however, the use and advantages of PCC

over FFP and vitamin K have not resulted in a clear improvement in patient outcomes. A large phase 3 randomized controlled trial demonstrated noninferiority of PCC to FFP for reversal of INR to <1.3 within 30 minutes (62.2% achieved this with use of PCC, and 9.6% with FFP). The rates of thromboembolic events were similar (7.8% with PCC and 6.4% with FFP).[107]

The direct thrombin antagonists and factor Xa inhibitors are being used increasingly as an alternative to warfarin for specific conditions. These medications do not require routine monitoring with laboratory tests and have fewer interactions with drugs and food. However, they unfortunately have limited pharmacologic means of reversal. Early studies, including RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy With Dabigatran Etexilate; dabigatran), ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; rivaroxaban), and ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; apixaban), found these agents to be associated with a lower incidence of intracranial hemorrhage when compared with warfarin.[35-38] However, when bleeding does occur, particularly in emergent situations, no clear consensus approach to management has been reached. AHA/ASA guidelines recommend that PCC or rFVIIa might be considered on an individual basis. Activated charcoal might be used if the most recent oral dose was taken <2 hours beforehand, to bind and prevent absorption (class IIb; level of evidence C).[1]

More recently, reversal agents for the novel oral anticoagulants (NOACs) have been developed. Factor Xa inhibitors can be reversed with the use of a recombinant modified version of factor X that acts as decoy receptors, freeing the endogenous factor Xa to activate clotting. Andexanet alfa (Andexxa) was approved in the United Stated in 2018 as an antidote to rivaroxaban and apixaban. The reversal of dabigatran, a reversible inhibitor of factor IIa (thrombin), can be achieved with idarucizumab, a monoclonal antibody that binds dabigatran and its metabolites. These reversal agents have been tested for reversal efficacy in the ANNEXA-A and ANNEXA-R and RE-VERSE AD phase 3 studies, respectively. The use in ICH specifically and its effects on clinical outcomes will require further study and wider availability of these medicines.[108,109]

Adequate reversal of novel anticoagulant effects can be reliably achieved with hemodialysis, but this is often impractical in the most emergent settings, causing potentially life-threatening delays.[33,34]

Antiplatelet Agents

Aspirin is associated with an absolute risk increase of ICH of 12 events per 10,000 persons—a risk that grows even higher in the elderly population. With the evolution of endovascular technology and techniques, a growing number of patients are maintained on long-term dual-antiplatelet therapy, primarily aspirin and clopidogrel, for coronary and carotid stents, intracranial stents, and flow-diverting stents. Preclinical and clinical trials have shown dual aspirin and clopidogrel therapy to exhibit significant synergistic effects, resulting in increased platelet inhibition and bleeding risk.[39,41,69] As a result, these agents have also been found to be an independent predictor of hematoma expansion.[110]

Both aspirin and clopidogrel irreversibly inhibit platelet aggregation. Aspirin inhibits platelet function for the 7- to 10-day lifespan of the platelet.[111] With the discontinuation of clopidogrel, platelet function begins to recover after 3 to 5 days, and complete restoration of function is achieved at 7 or 8 days.[112,113] Obviously, in the setting of acute ICH, discontinuation of antiplatelet therapy alone may not affect hematoma expansion. The PATCH trial (Platelet Transfusion Versus Standard Care After Acute Stroke Due to Spontaneous Cerebral Haemorrhage Associated With Antiplatelet Therapy), a randomized, open-label, phase 3 trial, investigated functional outcome or death at 3 months and found no benefit and a possible signal of harm by attempting to reverse antiplatelets.[44]

In the setting of operative intervention or EVD placement, the usefulness of a platelet transfusion is not well studied. One study showed that in aspirin-sensitive patients on aspirin with ICH who received a platelet transfusion had less frequent postoperative hemorrhages and improved outcomes.[114] Most surgeons will administer platelets before EVD placement or other operations, and in cases with demonstrated expanding hematomas in patients on clopidogrel. However, there is no consensus regarding the volume of platelets required to effectively reverse aspirin and clopidogrel. Studies have suggested that a transfusion of 10 to 12.5 units of platelets results in the restoration of platelet function after administration of aspirin or clopidogrel.[115,116]

Intracranial Pressure

Large hematomas, especially those associated with IVH and obstructive hydrocephalus, are frequently associated with elevated ICP. Medical management of ICP includes systemic cooling, sedation, diuretics, and the administration of paralytics. Hydrocephalus is treated with the insertion of an external ventricular drain (AHA/ASA guidelines class IIa; level of evidence B). Patients should have all coagulopathies corrected before insertion, to prevent hemorrhagic complications of the procedure. When ICP is refractory to medical therapy, surgical decompression is considered.[1,117-121] Corticosteroids should not be administered for treatment of elevated ICP in ICH, in view of a higher rate of complications (AHA/ASA guidelines class III; level of evidence B).[1]

Antiepileptic Medications

Seizures associated with ICH may be nonconvulsive; hence the true incidence is likely underreported[1] Passero and colleagues found seizures to be rarely associated with spontaneous ICH, occurring in approximately 4.2% of patients.[122] At 30 days of follow-up, 8.1% of patients had seizures. Lobar hemorrhage, most likely caused by the close proximity to the cortical surface, was significantly associated with the occurrence of early seizures. Vespa and colleagues, with the use of continuous electrophysiologic monitoring, recorded electrographic seizures in 28% of patients.[123] AHA/ASA guidelines state that seizures that are uncontrolled lead to elevated ICP and elevated blood pressure and require intravenous antiepileptic therapy. Clinical seizures should be treated with antiseizure drugs (AHA/ASA guideline class I; level of evidence A). Patients with a change in mental status who are found to have electrographic seizures on electroencephalography (EEG) should be treated with antiseizure drugs (class I; level of evidence C). Continuous EEG monitoring is probably indicated in patients with ICH with depressed mental status that is out of proportion to the degree of brain injury (class IIa; level of evidence C). Prophylactic antiseizure medication is not recommended (class III; level of evidence B).[1]

Systemic Complications

As with any neurological insult leading to immobility and prolonged hospitalization, patients with ICH are susceptible to multiple systemic complications. Preexisting cardiac disease, such as coronary artery disease and arrhythmias, may be exacerbated. DVT and PE are commonly encountered, with the incidence ranging from 1.3% to 15.9% depending on screening methods, coagulopathy reversal, prophylaxis regimen, and timing from admission.[124,125] Subcutaneous heparin and serial compression stockings, along with routine screening, are key components of DVT and PE prevention. In the CLEAR trials it was shown that

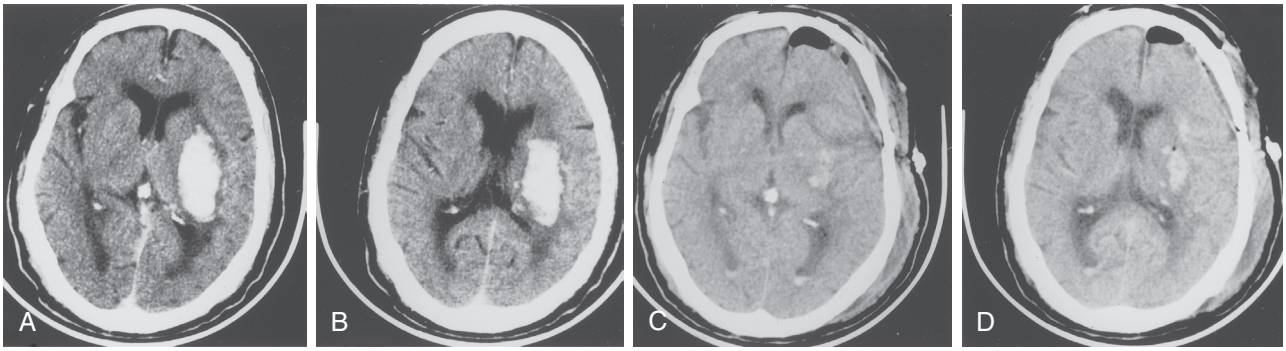

Figure 423.10. Surgical intervention for intracerebral hemorrhage (ICH). (A) Admission CT scan of a 54-year-old patient with an acute hypertensive putaminal hemorrhage, 42 mL in volume, causing hemiparesis and mild confusion. (B) CT scan of the same patient on day 1, with patient becoming more lethargic. (C and D) CT scans showing evacuation of the intracerebral hemorrhage (ICH) via open craniotomy, with mild residual ICH.

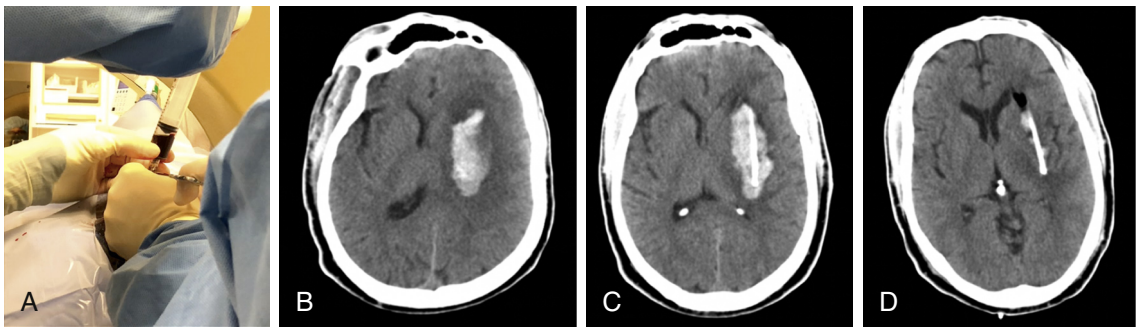

Figure 423.11. MISTIE catheter placement. (A) Hematoma aspiration during the MISTIE procedure with a Dandy needle under real-time imaging in CT procedure room, incrementally confirming placement and hematoma. (B) Axial CT scan showing a 37-mL intracerebral hemorrhage. (C) After aspiration and subsequent placement of the MISTIE catheter (good placement with all catheter perforations engaged within the clot). (D) Hematoma evacuation to final volume of 1 mL after three doses of recombinant tissue plasminogen activator. (*Reproduced with permission from Awad IA, Polster SP, Carrion-Penagos J, et al. Surgical performance determines functional outcome benefit in the Minimally Invasive Surgery Plus Recombinant Tissue Plasminogen Activator for Intracerebral Hemorrhage Evacuation (MISTIE) procedure. Neurosurgery. 2019;84(6):1157–1168.*)

DVT prophylaxis with subcutaneous heparin was safe 24 hours after stabilization of bleeding.[126] Additional studies in ICH have shown that this reduced the rate of PE without affecting hematoma size.[127] Pulmonary aspiration of gastrointestinal contents at the time of hemorrhage and prolonged intubation can result in the development of pneumonia. A formal screening procedure for dysphagia should be performed in all patients recovering from ICH (AHA/ASA recommendation class I; level of evidence B). Long-term Foley catheterization contributes to urinary tract infections. Infections often progress rapidly and result in sepsis; hence protocolized maintenance and assessment for duration of catheterization should be done frequently. The source of infection must be identified early, and antibiotic therapy must be tailored to the specific organism.

SURGICAL MANAGEMENT

Surgical hematoma evacuation remains an actively studied area given the successful results in protocoled case series. Identification of patients who will benefit from evacuation has been the subject of multiple investigations, and the recent results of the Minimally Invasive Surgery Plus rt-PA for ICH Evacuation (MISTIE) and CLEAR trials have identified a threshold of evacuation that may be vital to effect functional outcome in ICH. Hier and colleagues in 1977 evaluated 5000 putaminal hemorrhages by CT scan to correlate hematoma volume with clinical presentation and prognosis.[59] Patients were divided into groups based on hematoma volume, which correlated with GCS score and ultimately the possibility of a good outcome. Other studies have shown that regardless of location of bleeding, hematoma volume is the strongest predictor of outcome.[12] To date no robust study has shown benefit from surgical intervention; however, in properly selected patients who reach the defined threshold of hematoma evacuation, there is strong indication of improved functional outcome after ICH.[128]

Surgical hematoma evacuation has been associated with a decreased 30-day mortality rate, but any potential improvement in functional outcomes has not been convincingly demonstrated. This is in part due to the concurrent advancement in ICH medical management. In the evolution of the MISTIE trials, each iteration showed significant improvement in morbidity and mortality in the medical arms. Surgical intervention needs to keep pace, and a robust pragmatic trial will be required to show clear benefit on functional outcome. This goal is within reach and likely to be realized within the next 5 to 10 years. Emergent hematoma evacuation remains a lifesaving intervention in younger patients with large ICH volumes who are deteriorating clinically, and in patients with cerebellar ICH. These patients have generally been excluded from clinical trials. Historical trials such as the international Surgical Trial in Intracerebral Hemorrhage (STICH) have paved the way to minimally invasive approaches for ICH evacuation. (Figs. 423.10, 423.11, and 423.12).

International Surgical Trial in Intracerebral Hemorrhage (STICH)

The goal of the 2005 STICH study was to compare early surgery with initial conservative treatment in patients with spontaneous

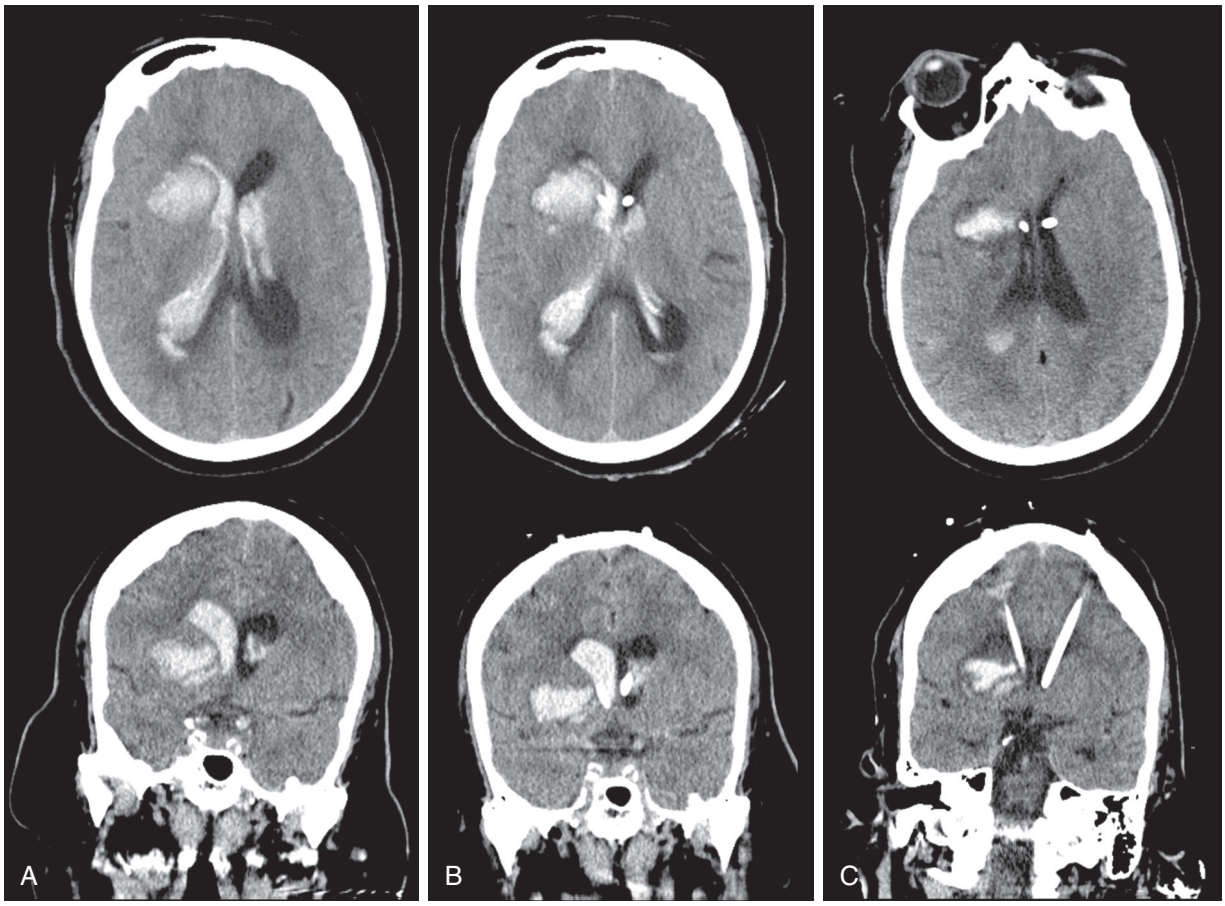

Figure 423.12. CLEAR intervention for intraventricular hemorrhage, axial (top) and coronal (bottom) non–contrast-enhanced CT scans. (A) Images in 69-year-old woman with a hypertensive right intracerebral hemorrhage with extension into the ventricular system resulting in casting of the right lateral ventricle as well as the third and fourth ventricles. The patient was increasingly somnolent. (B) Emergency placement of an external ventricular drain into the less casted ventricle to control intracranial pressure was completed, along with a second catheter placed into the right lateral ventricle, directly into the ventricular clot with all catheter perforation in contact with clot. (C) Three doses of recombinant tissue plasminogen activator were injected into the right lateral ventricle (every 8 hours, 1 mg/mL), resulting in resolution of ventricular clotted blood as well as clearance of the third and fourth ventricles. The patient did not require a shunt and achieved a modified Rankin Scale score of 2 after 3 months.

supratentorial intracerebral hematomas. The prospective randomized trial divided patients into either an early surgery group that combined hematoma evacuation within 24 hours of randomization and medical management or a group that received medical treatment only. Hematoma evacuation in the medical treatment group was performed outside of the 24-hour window if the patient developed neurological deterioration. Patients were required to have a minimum hematoma diameter of 2 cm and a GCS score of 5 or greater. The groups were further stratified, based on their neurological status at the time of randomization, into patients with a good prognosis versus those with a poor prognosis. The Glasgow Outcome Scale score at 6 months was the primary outcome measure. Using this scale, a good outcome in the good prognosis group was defined as good recovery or moderate disability, whereas a good outcome in the poor prognosis group also included the upper level of severe disability.

The study, which included data from over 1000 patients, consisted of two relatively well-matched groups randomized to surgery or initial conservative management. Of the 529 patients randomized to initial conservative management, 26% underwent eventual surgical evacuation. The authors found no significant difference in the percentage of patients achieving a favorable outcome at 6 months (26% early surgery, 24% initial conservative management). The mortality rates between both groups differed by only 1% (36% early surgery, 37% initial conservative management). Furthermore, for those patients who were comatose at the time of randomization, early surgery increased the relative risk of poor outcome by 8%. Patients with hematomas extending within 1 cm from the cortical surface were more likely to have a favorable outcome with early surgery than those with deeper hematomas. Of patients initially randomized to medical treatment, 26% eventually received surgical hematoma evacuation.[129] These crossovers may have masked potential benefits of the procedure in patients randomized to medical therapy, and trial results analyzed by intention to treat. There were no statistically significant data to show an overall benefit from early surgery when compared with initial conservative treatment in patients with spontaneous supratentorial ICH.

STICH II Trial for Lobar Intracerebral Hemorrhage Without Intraventricular Hemorrhage

Subgroup analysis in the STICH trial demonstrated a trend toward improved outcomes in patients with hematomas 1 cm or less from the cortical surface, and without concomitant IVH. Based on these findings, the STICH II trial randomized patients without IVH and hematomas 10 to 100 cm^3 either to surgical evacuation within 12 hours plus medical treatment or to

initial medical management alone.[130] The primary outcome was a dichotomized (favorable or unfavorable) outcome based on the Extended Glasgow Outcome Scale (EGOS) at 6 months. Using a predefined hematoma volume of 26.7 cm^3, patients were divided into a good prognosis group (<26.7 cm^3) and a poor prognosis group (>26.7 cm^3). Favorable outcomes in the good prognosis group were defined as good recovery or moderate disability. In the poor prognosis group, upper level of severe disability was included with the favorable outcomes. Craniotomy was the chosen surgical approach in 98% of cases. Based on the EGOS score, 123 (41%) of 297 patients in the early surgery group had a favorable outcome at 6 months compared with 108 (38%) of 286 patients in the medical treatment group. Fifty-nine percent of patients in the early surgery group had an unfavorable outcome versus 62% of patients in the initial medical treatment group. The 6-month mortality rates were 18% in the surgery group and 24% in the medical group. There was no significant difference in survival advantage between groups during the first 6 months.

Owing to a lack of statistically significant difference in the postulated primary outcome, the STICH II trial was interpreted as neutral. It is important to note that 21% of the medically treated group underwent surgery in a delayed fashion and that these patients had a much worse neurological condition at the time of surgery. Surgery may have prevented a fatal outcome, but because of the statistical analysis, these patients remained in the medical treatment arm. In conclusion, STICH II demonstrated that early surgery does not lead to increased rates of death and disability at 6 months and may confer a survival advantage. A retrospective review of STICH II has further confirmed that goal thresholds of hematoma evacuation may affect the probability of achieving a good functional outcome. Also, recent post hoc analyses have suggested potential benefit in STICH II patients who had GCS levels of 9 to 12—neither too poor nor too good to benefit from surgery.[131]

Endoscopic and Minimally Invasive Evacuations

One argument against conventional open surgical evacuation of spontaneous ICH is that the approach to the hematoma may result in additional damage to otherwise unaffected brain. Multiple studies have evaluated the usefulness of endoscopic evacuation as an option that achieves hematoma removal while limiting the tissue destruction associated with open surgical procedures.

In 1989 Auer and colleagues evaluated the efficacy of medical treatment versus endoscopic evacuation in 100 patients with spontaneous ICH.[132] Subgroup analysis divided the patients into groups based on state of consciousness, age, location, size, and side of the hematoma. At least 50% clot removal was achieved in all patients, with 15% of patients having over 90% of the hematoma evacuated. In the overall analysis, those patients treated with endoscopic evacuation achieved better outcome than those in the medically treated group. Within 1 week of treatment, there was a 14% mortality rate in the endoscopic group versus a 28% mortality rate in the medical treatment arm. At 6-month follow-up, the mortality rate in the surgical group was 42% versus 70% in the medical group. It is important to note that in the subgroup analysis, age, clinical presentation, and hematoma size were critical factors in determining outcomes. Surgical benefit was limited to patients younger than 60 years, and the mortality rate was nearly identical in this population regardless of the treatment chosen. In patients with hematomas larger than 50 cm^3, although the mortality rate was significantly lower in the operative group, the quality of life was not improved by surgery. Finally, stuporous and comatose patients in both groups achieved a good outcome in less than 10% of cases. The data show endoscopic evacuation of ICH to be a safe procedure that may lead to decreased mortality and improved functional recovery in carefully selected patients.

These data have been supported by multiple more recent studies. Miller and colleagues (2008) randomized patients to medical treatment or endoscopic evacuation.[133] The study was limited by a small sample size; however, mortality was significantly lower in the endoscopic group (20%) versus the medical group (50%). Furthermore, endoscopic intervention resulted in an 80% reduction in hematoma volume within 24 hours of the procedure, whereas medically managed patients experienced an overall expansion in hematoma size in the same time period. Unfortunately, the surgical arm did not demonstrate significant improvement in functional outcomes at 90 days. Kuo and colleagues (2011), in a retrospective analysis, reported a 93% overall clot evacuation rate, with a 1.5% rebleeding rate.[134] Once again, these data alluded to the efficacy and the relatively low procedural morbidity of endoscopic evacuation. Nagasaka and colleagues retrospectively compared clinical outcomes in patients undergoing hematoma evacuation performed endoscopically versus through craniotomy.[135] The endoscopy group demonstrated a significantly higher evacuation rate (99% versus 95.9%), higher GCS scores at 1 week, and a greater improvement in GCS score from admission. Studies to date have been encouraging, but have largely been limited by poor design and potential outcome ascertainment biases.

Other minimally invasive approaches have been proposed, using specialized tools for less traumatic access and evacuation of hematoma; Table 423.2 highlights the most robust and recently completed clinical trials. To date, the potential advantages vis-à-vis endoscopy, or stereotactic aspiration and thrombolysis, have not been established.

Stereotactic Aspiration and Thrombolysis

Multiple studies have explored image-guided stereotactic aspiration in attempt to further reduce the trauma of surgical hematoma evacuation. Minimally invasive procedures have been reported with effective volume reduction from the 1970s and 1980s, specifically with the goal to relieve pressure, even with a subtotal ICH evacuation. Urokinase for lysis and catheter evacuation of ICH was then subsequently explored, which led the way for many other groups to attempt to use urokinase, and subsequently r-tPA for the same purposes, with promising results.[136-141] Another study compared minimally invasive stereotactic clot removal and thrombolysis with open craniotomy and showed that those treated with minimally invasive surgery had a better GCS score compared with those who underwent open craniotomy.[142] These studies provided promising results, which led to investigation of a protocolized trial of minimally invasive surgery catheter-based hematoma evacuation with r-tPA. Combining lessons learned in the MISTIE and CLEAR trial series has most recently led to phase 3 trials of ICH and IVH that have provided invaluable insight into hematoma removal, which has translated to lifesaving end points with functional benefit in cases that reach thresholds of evacuation.

Minimally Invasive Surgery Plus Recombinant Tissue Plasminogen Activator for Intracerebral Hemorrhage Evacuation (MISTIE) Trials

Building on a strong foundation of preliminary safety and efficacy studies, the MISTIE trials have further explored the safety, efficacy, technique, dose optimization, and outcome of image-guided cannula aspiration, followed by catheter placement for delivery of r-tPA and passive drainage of a hematoma in a recent phase 3 trial. Enrollment criteria consisted of supratentorial ICH volume ≥30 mL, clot stability for 6 hours, absence of obstructive IVH, no clinical herniation syndrome, and negative etiology screen for occult pathologies. Manual aspiration was accomplished through a cannula inserted in the ICH, followed by placement of a soft

TABLE 423.2 Completed and Ongoing Trials of Surgical Treatment for Intracerebral Hemorrhage (ICH)[a]

Trial and Year Enrollment Ended	Intervention and Groups	Hematoma	Primary End Point	Time From Symptom Onset	Outcome (30–360 Days)
COMPLETED (PAST) SURGICAL TRIALS					
McKissock et al.[176] 1961	Craniotomy (n = 89) vs medical treatment (n = 91)	Reduced	Assess prognosis	72 h	Not different
STICH[129] 2003	Craniotomy (n = 503) vs medical treatment only (n = 530)	Reduced	GOS score 5–8 (4 if poor initial prognosis) vs 1–4 (unfavorable)	72 h	Not different
STICH II[130] 2012	Lobar ICH Craniotomy (n = 307) vs medical treatment only (n = 294)	Reduced	GOS score 5–8 (4 if poor initial prognosis) vs 1–4 (unfavorable)	48 h	Possible small survival advantage
MISTIE II and III[144] 2017	MIS (n = 251) vs medical treatment only (n = 249)	Reduced	mRS score 0–3 vs 4–6	72 h	Improved mRS score
CLEAR II and III[143] 2015	MIS for IVH: rtPA (n = 249) vs placebo (n = 251)	Reduced	mRS score 0–3 vs 4–6	72 h	Not different. Lower mortality
ICES[177] 2012	MIS (n = 14) vs medical control group (n = 36)	Reduced	mRS score 0–3 vs 4–6	48 h	Improved mRS score
Newell et al.[178] 2009	Ultrasound-enhanced thrombolysis Single arm (N = 9)	Reduced	Hematoma volume reduction	72 h	Improved NIHSS score
EndoSurofICH/ INET[179] 2018	Endoscopic hematoma evacuation (n = 53) vs cranial puncture and drainage (n = 45)	Reduced	GOS score and mortality	72 h	Reduced mortality
SCUBA[180] 2017	Stereotactic underwater blood aspiration, single arm (N = 47)	Reduced	Evacuation efficiency	72 h	Volume analysis

ONGOING SURGICAL TRIALS

	Enrolled Patients	Intervention and Groups	Primary End Point	Time From Symptom Onset	Estimated Completion Date
ENRICH NCT02880878	Enrollment goal: 300	MIS (NICO BrainPath system)	mRS score at 180 days	24 h	December 2021
SWITCH NCT02258919	Enrollment goal: 300	Craniectomy	mRS score at 180 days	72 h	September 2021
MIND NCT03342664	Enrollment goal: 500	MIS (Artemis device)	mRS score and mortality at 180 days	72 h	July 2024
INVEST NCT02654015	Enrollment goal: 50	MIS (Apollo device)	Phase 1 (observational)	72 h	June 2021
DIST NCT03608423	Enrollment goal: 400	MIS (endoscopic guided surgery or hematoma aspiration)	Death within 24 h	8 h	February 2021
Risa-MIS-ICH NCT03862729	Enrollment goal: 300	MIS	Death (Barthel Index score) at 360 days	48 h	March 2022
MISICH NCT02811614	Enrolment goal: 900	Endoscopic surgery vs stereotactic catheter vs craniotomy	mRS score at 180 days	72 h	June 2021
Tao G et al. NCT04037267	Enrollment goal: 956	Endoscopic surgery vs EVD + urokinase	Death at 360 days	Not specified	September 2022
SOITBE NCT03957707	Enrollment goal: 360	Stereotactic surgery with or without thrombolysis	GOS score at 180 days	72 h	December 2021

[a]Selected list, intended to highlight the most robust trials, those with the greatest impact on the field, and future or ongoing trials referenced on ClinicalTrials.gov.

CLEAR, Clot Lysis: Evaluation of Accelerated Resolution of Intraventricular Hemorrhage trial; *DIST,* Dutch Intracerebral Hemorrhage Surgery trial; *EndoSurofICH,* Comparison Between Stereotactic Aspiration and Intra-endoscopic Surgery to Treat Intracerebral Hemorrhage trial; *ENRICH,* Early Minimally Invasive Removal of Intracerebral Hemorrhage trial; *EVD,* external ventricular drainage; *GOS,* Glasgow Outcome Scale; *ICES,* Intraoperative Stereotactic Computed Tomography–Guided Endoscopic Surgery trial; *INET,* intraneuroendoscopic technique; *INVEST,* Minimally Invasive Endoscopic Surgery With Apollo in Patients With Brain Hemorrhage trial; *IVH,* intraventricular hemorrhage; *MIND,* A Prospective Multicenter Study of Artemis, a Minimally Invasive Neuroevacuation Device, in the Removal of Intracerebral Hemorrhage; *MIS,* minimally invasive surgery; *MISICH,* Minimally Invasive Surgery Versus Craniotomy in Patients With Supratentorial Hypertensive Intracerebral Hemorrhage trial; *MISTIE,* Minimally Invasive Surgery Plus rt-PA for ICH Evacuation trial; *mRS,* modified Rankin scale; *NIHSS,* National Institutes of Health Stroke Scale; *Risa-MIS-ICH,* Risk Stratification and Minimally Invasive Surgery in Acute ICH Patients trial; *SCUBA,* Stereotactic Intracerebral Hemorrhage Underwater Blood Aspiration trial; *SOITBE,* Stereotactic Operation Integrating With Thrombolysis in Basal Ganglion Hemorrhage Evacuation trial; *STICH,* Surgical Trial in Intracerebral Hemorrhage; *SWITCH,* Swiss Trial of Decompressive Craniectomy Versus Best Medical Treatment of Spontaneous Supratentorial Intracerebral Hemorrhage.

catheter for thrombolytic administration and drainage, until a final hematoma volume of <15 mL was reached or nine doses of drug were administered. The dose 1.0 mg was tested in the phase 2 MISTIE study, with higher or more frequent doses tested in the CLEAR study causing greater symptomatic bleeding. An r-tPA dosage of 1.0 mg every 8 hours for up to nine doses (up to 72 hours) showed the best clearance rates without increasing hemorrhagic complications.[143]

In order to determine the possibility of achieving a good functional outcome at 1 year with a prespecified end-of-treatment (EOT) volume, a phase 3 trial was completed. The patients were randomly assigned to guideline-based medical management with

or without the MISTIE procedure.[144] The benefits of a catheter-based procedure were based on the theoretical drawbacks of the STICH trials by providing less operative trauma for the patient, less time in the operating room, shortened healing time, less pain and scarring, and shorter intensive care unit and hospital stays with lower associated costs.

Clot Stability and Etiology Screening

Clot stability is required for the safety of the procedure and is a cornerstone requirement prior to intervention. Patients were enrolled in the study after >6 hours of clot stability and an adequate correction of any coagulopathy, thrombocytopenia (<100,000) or platelet dysfunction other than aspirin exposure. Intervention on an expanding hematoma from a minimally invasive catheter could result in excess bleeding.[144] Cases whose ICH does not stabilize have very poor outcomes regardless of heroic interventions and were not candidates for this trial.

Prior to intervention, vascular imaging (typically CTA) was required to rule out underlying etiologic vascular pathology.[145] MRI is used if there is any suspicion of neoplasia or hemorrhagic infarct. The safety of MISTIE has not been examined in the setting of AVMs, arteriovenous fistulas, aneurysms, dissections, moyamoya, tumors, or infarcts. There is no contraindication to performing MISTIE in the setting of a remote unruptured aneurysm.

Catheter Trajectories

The surgical task of intervention in the MISTIE trial was the placement of a catheter directly into the intracerebral clot to facilitate aspiration and clearance. The phase 2 MISTIE trial showed that adequate catheter positioning is required for removal of the clot. Ideal positioning is to have all catheter perforations within the epicenter of the clot. The clot resolution rate, namely the technical success of the surgical task, is highly correlated with catheter placement accuracy.[145] Because of this, instructions to approach and target the clot were a key aspect of the MISTIE trial. The training of surgeons and the monitoring of their performance were focused on this very important surgical principle. The trajectories for catheter placement were standardized and overseen during the MISTIE III trial.[146] This was key in standardizing the procedure across centers and operators. Three trajectories (anterior, posterior, and lobar) were used based on the anatomic location of the bleeding.

To obtain adequate catheter placement, the MISTIE protocol required that the surgical procedure be done in the operating room with proper stereotactic navigation (frameless stereotaxis with CT or MRI guidance), using an image-guided stylet such as the Passive Catheter Introducer (PCI) or Navigus for Medtronic Stealth equipment, or equivalent stylet for Brainlab systems. The procedure may also be performed in a procedural CT or MRI scanner with real-time image guidance (see Fig. 423.11).

Cannula Aspiration and Catheter Placement for Thrombolysis

After the bur hole and dura are open, an introducer cannula (or Dandy needle) is placed stereotactically into the center of the hematoma. Aspiration is performed using a 10-mL syringe until there is fluid resistance. The rigid cannula is removed, leaving the soft catheter in place with the position optimized for proper engagement of thrombolytic. After catheter placement with CT confirmation, an additional 6-hour postsurgical stabilization is required prior to the first injection of r-tPA. If the ICH volume reaches ≤15 mL, r-tPA is withheld and the catheter is left in place for 24 to 48 hours of drainage prior to catheter removal. A catheter should not be manipulated or removed less than 24 hours after an r-tPA dose, nor should r-tPA be administered less than 6 hours after catheter placement, replacement, or repositioning, as these increase bleeding risk. Fig. 243.11 shows the resolution of a clot after an adequate catheter placement.

During the execution of the protocol, CT scans are performed daily, or more often if there is neurological worsening or concern about patency of the drainage system. The scans assess the volume of the remaining clot, and whether the catheter perforations continue to engage the residual ICH. If the catheter is no longer within the clot, thrombolytic should not be given and catheter repositioning should be considered (>24 hours after the last thrombolytic dose), if the residual clot is large (>15 mL) and targetable. Further details of the procedure, technical nuances, and other information can be found on the website of the trial (http://braininjuryoutcomes.com/).

Outcome

The use of the MISTIE protocol was optimized in the phase 2 trial, and has now been tested in a phase 3 trial and was shown to achieve safe hematoma volume reduction. The MISTIE III trial compared patients with an ICH of >30 mL undergoing the MISTIE surgical procedure against a control group that was given best medical treatment. In the overall trial cohort, surgically treated patients did not show a significantly better functional outcome, defined as an mRS of 0 to 3, at 1 year compared with the medically treated group (45% and 41%, respectively). However, the MISTIE procedure did achieve significantly lower mortality rates (6%–8% lower) than the medical arm at 1 year. Most important was the finding that higher extent of hematoma removal was associated with achieving better mRS scores (0–3, a good functional outcome—defined as only a moderate disability, able to walk unassisted or better).[144] Further analyses showed that EOT volumes of ≤15 mL or ≥70% of hematoma removal increased the likelihood of achieving a good functional outcome.[128] Higher probability of survival was achieved at ≤30 mL EOT volume, or after removal of >53% of the hematoma. Surgeon experience was also a factor, with those having performed more procedures producing better evacuations.

The MISTIE procedure will likely require an additional phase 3 trial with further optimization, given the now defined thresholds of evacuation. The key lessons learned thus far will be required to move forward and include the following: (1) clot stability and correction of coagulopathies are required for the safety of the procedure; (2) etiology screening using CTA, MRI/MRA, or catheter angiography is required to rule out other pathologies underlying the ICH; (3) clot evacuation is highly correlated with adequate catheter placement; (4) the use of r-tPA for ICH volume reduction is safe; (5) achieving EOT hematoma sizes of ≤15 mL or ≥70% of hematoma removal is associated with a significantly greater likelihood of mRS of 0 to 3 at 360 days, despite controlling for ICH severity confounders; and (6) lowering the hematoma volume to <30 mL (or about 53% evacuation) increases the probability of survival at 1 year. Future clinical trials might also address comparative effectiveness of MISTIE versus endoscopic and other approaches for ICH evacuation.

Decompressive Hemicraniectomy With or Without Hematoma Evacuation

Decompressive hemicraniectomy is an effective and well-established procedure for the treatment of malignant intracranial hypertension and has been used largely in patients with severe traumatic brain injury and hemispheric infarcts. Bone removal allows the brain to swell outward, thereby preventing downward herniation and relieving pressure on still healthy tissue. Studies have also shown adequate decompression to result in improved tissue oxygenation, cerebral perfusion, and cerebral compliance.[147-149]

Intraparenchymal hemorrhage initiates a cascade of events leading to the loss of autoregulation and edema formation.[150,151] As a result, effective hematoma evacuation alone may not resolve the problem of elevated ICP.[152] Therefore hemicraniectomy has been explored, both in addition to and without hematoma evacuation, as a treatment option for spontaneous ICH. This has been examined in a meta-analysis regarding hemicraniectomy plus clot evacuation and hemicraniectomy alone.[152] Of 185 patients undergoing hemicraniectomy plus hematoma evacuation, 75 (41%) achieved a good outcome based on a multitude of outcome scales used across studies. Twenty-eight percent of patients had died during various follow-up periods. Three studies reported a significant improvement in functional outcome or mortality compared with control groups that underwent only hematoma evacuation, and one study reported no significant difference.[150,153-155] Common complications reported were hydrocephalus (19%), additional intracranial hemorrhage (3%), and infection (3%).[155-157]

Because of concerns regarding exacerbation of tissue damage during the removal of large hematomas, hemicraniectomy without clot evacuation has been explored as an alternate treatment. This option is of particular interest in the treatment of deep-seated lesions (e.g., basal ganglia and thalamus) and in large dominant hemisphere lesions. Ramnarayan and colleagues reported on 23 patients with large putaminal hemorrhages who were treated with hemicraniectomy alone.[158] Fifteen (65%) patients achieved a good clinical outcome of good recovery or moderate disability, and the 1-month mortality rate was 13%. Fung and colleagues treated 12 basal ganglia or lobar hemorrhages with an average volume of 61 mL with decompressive hemicraniectomy.[159] Patients had a median GCS score of 8 at presentation. Thirty-three percent of patients had a favorable outcome, and there was a 25% mortality rate at 6-month follow-up. Functional outcome was improved compared with the medical treatment control group. In all, studies examining hemicraniectomy are limited; however, there are data to indicate safety and potential benefit with this mode of treatment in selected patients.

MANAGEMENT OF CEREBELLAR HEMATOMAS

The vast majority of the literature discussed thus far has pertained to the management of supratentorial hematomas. Of all spontaneous ICHs, cerebellar hematomas are perhaps the most suited to surgical treatment. Evacuation is performed without entering eloquent tissue and with essentially no risk to motor and cognitive function. Poor neurological examination findings are secondary to mass effect on the brainstem and obstructive hydrocephalus and not a result of the destruction of critical structures. Surgical evacuation, along with ventriculostomy placement, immediately relieves both conditions. As a result, surgery is recommended for all hematomas greater than 3 cm in diameter (or 15 mL in volume).[52,70,160] Hematomas smaller than 3 cm in diameter in awake and alert patients may be medically managed in a neurological intensive care unit with close clinical observation. Any change in neurological examination status requires immediate reevaluation and follow-up imaging owing to the rapidity with these patients can deteriorate. Small hemorrhages adjacent to the fourth ventricle may cause obstructive hydrocephalus and are best treated with ventriculostomy.

Open Surgical Technique

Preoperatively, all patients are administered intravenous fluids and receive an arterial line for continuous blood pressure monitoring. Coagulation profiles are obtained and reviewed, and correction is initiated. Intravenous antihypertensive agents are administered to patients with an elevated blood pressure, and metabolic abnormalities are corrected. The importance of avoidance of hypertension during intubation must be discussed with the anesthesia/sedation team.

Putaminal hemorrhages are accessible via the transtemporal, transfrontal, and transsylvian approaches.[64,161,162] With the use of the microscope, a small corticectomy is made in the insular cortex, and the hematoma is evacuated with suction and bipolar cautery. Hematomas are sent for histologic analysis to ensure that small underlying lesions, such as tumors, AVMs, and cavernomas, are not overlooked. At the depths of the resection cavity, caution must be taken to avoid injuring traversing fibers of the internal capsule. Meticulous hemostasis is critical to prevent reaccumulation of blood. Extension of the hemorrhage into the temporal lobe requires the transtemporal approach. Large lobar hemorrhages or deep hemorrhages with significant extension of the clot require a transcortical approach.[163]

Cerebellar hematomas are evacuated with a standard suboccipital craniotomy with the patient in the prone or lateral position. Bone removal can be done with either a craniotomy or craniectomy.[64]

MANAGEMENT OF INTRAVENTRICULAR HEMORRHAGE

Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR) Trials

The use of intraventricular thrombolytic agents to prevent EVD obstruction and enhance the clearance of IVH has been widely reported.[145] A decreased fatality rate has been observed when EVD and thrombolytics are used in the setting of IVH as compared with conservative management with or without EVD.[164] A randomized, double-blind, multicenter trial assessed the safety and efficacy of intraventricular drainage using a thrombolytic (urokinase) for IVH compared with use of EVD alone and showed that thrombolytics improved the resolution of IVH.[165] These studies established the foundation for the CLEAR IVH trials, evaluating the safety and efficacy of r-tPA to accelerate the lysis and evacuation of IVH.[166]

The CLEAR IVH phase 2 trial randomly assigned patients to receive 0.3, 1.0, or 3.0 mg of r-tPA, every 8 or 12 hours, versus placebo, with a median duration of drainage of 7.5 days for the r-tPA group versus 12 days for the placebo group. Mortality and rate of ventriculitis were lower in the r-tPA group (18% and 8% r-tPA versus 23% and 9% placebo, respectively); symptomatic bleeding was present in 23% of patients treated with all dose ranges of r-tPA and in 5% of the placebo patients. The study found that low-dose r-tPA, 1.0 mg every 8 hours, has the best safety profile compared with placebo, with a significant beneficial effect on the rate of clot resolution. Doses of 0.3 mg did not provide an effective means of clot lysis, and 3.0 mg resulted in excess bleeding.[167]

The CLEAR IVH phase 2 trial assessed the effect of r-tPA on the resolution of IVH. This showed that r-tPA resolves IVH in a dose-dependent manner and that the resolution is greatest in the midline ventricles and least in the posterolateral ventricles.[168] Clearance of the third and fourth ventricles was unrelated to EVD laterality.[169] External ventricular drains contralateral to the dominantly casted ventricle allowed better ICP control but would not resolve the contralaterally casted ventricle.[170] The administration of intraventricular r-tPA had no impact on systemic coagulation, and prophylactic subcutaneous heparin to prevent DVTs and PE was safe.[126]

The CLEAR III study was a larger phase 3, prospectively randomized, double-blinded clinical trial to compare EVD plus r-tPA versus placebo in the management and treatment of 500 subjects with large IVHs resulting in obstruction of the third or fourth ventricles by intraventricular blood and associated ICHs <30 mL. All patients received EVD for obstructive IVH along

with best critical care management. More than one EVD was allowed and recommended for casted ventricles with mass effect and shift. The study did not show improved rates of functional recovery but did show a lifesaving benefit at 180 days. The extent of clot removal correlated with improved odds of having an mRS of 0 to 3, similar to the thresholds identified in the MISTIE trials.[143] In about half the patients with IVH volumes >20 mL (large obstructive IVH), there was a significantly better likelihood of an mRS of 0 to 3, and also if >70% of clot removal was achieved with r-tPA.[82]

Two or more catheters placed for IVH may improve management of this condition affecting ICP and cerebral perfusion pressure, which may not be controlled by a single catheter. Higher volume of clot removal should be aggressively pursued in order to achieve functional benefits of the procedure.[82,83] The 2015 AHA/ASA guidelines state that "Although intraventricular administration of r-tPA in IVH appears to have a fairly low complication rate, the efficacy and safety of this treatment are uncertain at this time" (class IIb; level of evidence B)[1] (Fig. 423.12).

Cerebrospinal Fluid Inflammation Versus Infection Following Intraventricular Hemorrhage

In the course of treating IVH with external ventricular drains throughout the CLEAR trial, infection rates were exceeding low with the use of antibiotic-impregnated catheters, intravenous antibiotics while drain(s) were in place, and daily CSF sampling. These studies, in addition to the clinical scenario, may confirm true infection (with positive cultures), which can prompt catheter exchange, administration of intrathecal vancomycin, catheter removal, and/or broadened systemic antibiotics. CSF white blood cell count peaks at days 1 to 3, and elevated white blood cell counts are associated with larger IVH volume. The use of intraventricular thrombolytics further increases the CSF white blood cell counts, with a return to baseline by day 7. These inflammatory variations do not appear detrimental to clinical outcomes.[84]

Clot Stability and Etiology Screening

Bleeding stability and etiology screening were important criteria for the safe deployment of the CLEAR procedure. The CLEAR study identified a rate of underlying lesion in 11% of screened patients, and hence we recommend that etiology screening occur in all patients being considered for surgical intervention.[85] Other safety precautions applied, such as not manipulating the external ventricular drain, or replacing it, or placing a second external ventricular drain within 24 hours of an r-tPA dose, and also not administering r-tPA without verifying stability of ICH and IVH and the absence of new or expanded catheter tract hemorrhages.[145]

Catheter Placement

Per results in the phase 2 trial, guidelines for the CLEAR III trial recommended placement of the initial external ventricular drain in the lateral ventricle with lesser blood (more CSF), for optimizing control of ICP. A second catheter was recommended to be placed in the lateral ventricle with greater IVH in cases with casting, trapping, mass effect, and/or shift due to dominant lateral ventricle IVH, for more efficient thrombolytic clearance.[145] In CLEAR III, there was again significantly greater IVH clearance with external ventricular drains ipsilateral to the dominant IVH, or with the use of bilateral catheters.[143]

Other Ongoing Studies

Multiple studies at various phases were on-going as of 2020 to assess interventions for ICH (see Table 423.2, which highlights selected trials currently listed on ClinialTrials.gov). These studies include technical adjuncts and innovations based on both clinical and preclinical data. More robust trials and comparative effectiveness studies are needed to better understand their potential role in ICH and IVH. Hypotheses must be clearly articulated, and trial design must be stringent. As surgical trials continue to strive for superiority over medical management, it is clear that both surgical and medical treatments have evolved and improved.

CONCLUSION

Spontaneous ICH and associated IVH remain a devastating disease despite decades of research, advances in medical treatment, and the evolution of surgical techniques. It appears that immediate and aggressive medical management, administered in the setting of a neurological intensive care unit, optimizes outcome regardless of surgical intervention. Hemorrhage size and presenting GCS score remain the best predictors of outcome. Inconsistent practice patterns with no clear standards or proven therapies, in the face of persistent poor outcomes, and the failure of early clinical trials contributed to early nihilism regarding aggressive interventions for ICH and IVH. Emergent surgical evacuation of large hemorrhages associated with mass effect and elevated ICP may be lifesaving; however, functional recovery is limited and often similar to that gained by medical therapy alone. More recent investigations have changed this outlook, optimizing case selection and deploying the surgical task with targeted thresholds of evacuation needed to achieve functional benefit.

SUGGESTED READINGS

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