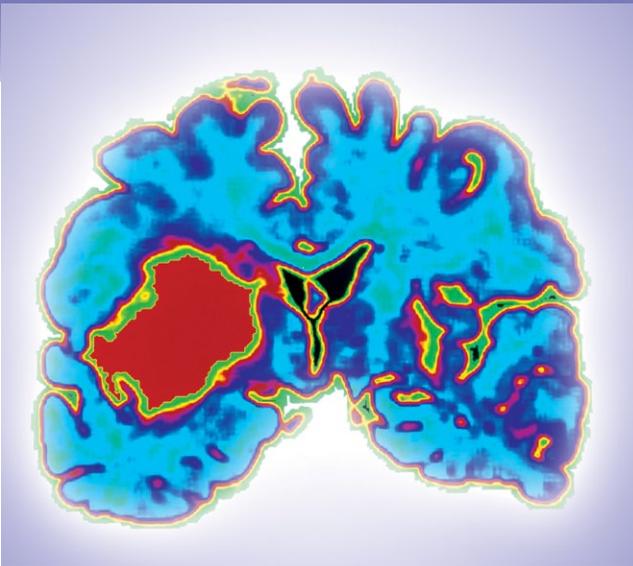


Management of Hemorrhagic Stroke

A Focused Review of Current Guidelines

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Stroke is a leading cause of death and disability, and its diagnosis can be challenging. This article reviews the presentation, diagnosis, and management of intracerebral hemorrhage and subarachnoid hemorrhage, the two main categories of stroke. Recommendations based on current consensus guidelines are also provided.

Stroke is the rapid loss of brain function due to disturbance in the blood supply to the brain. Each year, about 795,000 people in the United States suffer a stroke.¹ The treatment of stroke poses a major economic burden to the health care system, with an estimated cost per patient for the first year of approximately \$28,525.²

Stroke can result either from ischemia (in which occlusion of a blood vessel and the resulting lack of blood flow causes insult) or from a hemorrhage within the brain. The two main categories of hemorrhagic stroke are intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). ICH occurs when there is bleeding directly into the brain tissue, usually due to rupture of small arteries or arterioles. SAH occurs when there is bleeding in the subarachnoid space surrounding the brain parenchyma. This blood can leak into the cerebrospinal fluid (CSF) within the ventricles and cause irritation, vasospasm, and hydrocephalus. Limited evidence exists regarding the treatment and management of ICH

and SAH, and consensus guidelines are the primary resource. In this article, we will discuss the etiology, diagnosis, and management of both ICH and SAH.

INTRACEREBRAL HEMORRHAGE

Presentation

The annual incidence rate of ICH is 12 to 15 per 100,000 in the United States.³ ICH accounts for 10% to 15% of all strokes on an annual basis.⁴ The mortality rates for ICH at 7 days, 30 days, and 1 year are 34.6%, 50.3%, and 59%, respectively, with an overall 10-year survival rate of approximately 24.1%. The demographics of those affected by ICH are variable. According to one study, the average age of a patient presenting with ICH is 73 years, with an equal distribution between males and females.³ Altered mental status and decreased Glasgow Coma Scale (GCS) score are common in patients with ICH. Between the time of initial prehospital emergency medical services and examination in the ED, more than 20% of patients with ICH will have a decline of at least 2 points in their GCS score.⁵ In the typical presentation of ICH, there is a sudden onset of focal neurologic deficit that progresses during a period of minutes to hours. Headache occurs more often with ICH than with ischemic stroke but is less likely in ICH than in SAH. Vomiting is seen more often with ICH than with either ischemic stroke or SAH. However, it is not pos-

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sible to differentiate among ischemic stroke, SAH, or ICH based on clinical grounds alone.⁴

Diagnosis

While CT and MRI are equally sensitive for identifying acute hemorrhage, MRI is more sensitive in identifying prior hemorrhages.⁵ However, given the time involved to obtain an MRI and the limited availability of MRI, CT is the first-line test in the ED (Figure 1). ICH expansion is associated with lower GCS score and elevated NIH Stroke Scale score and worsening outcomes.⁶ In addition, CT angiography (CTA), contrast-enhanced CT, CT venography, contrast-enhanced MRI, MR angiography (MRA), or MR venography are useful for identifying structural lesions that may be the underlying cause of an ICH.⁵ The suggestion of an underlying structural cause may be seen on the initial CT, and the decision to pursue additional studies can be made at that time.

Treatment

Patients with ICH and a known factor deficiency should undergo transfusion with appropriate factor replacement. This information may not always be available from the patient, and a search through the medical records of family should be performed. Patients with thrombocytopenia (generally defined as $\leq 50,000$ platelets/ μL) and evidence of ICH should undergo platelet transfusion.⁵

Patients taking oral anticoagulants who are diagnosed with ICH should stop taking the anticoagulant for the short term. Warfarin causes depletion of vitamin K-dependent factors II, VII, IX, and X as well as proteins C and S. These factors should be replaced and the international normalized ratio (INR) should be corrected. Vitamin K should be given intravenously, but because this takes hours to correct the INR, it is not suitable as a sole agent. INR can be corrected with fresh frozen plasma (FFP) or with prothrombin complex concentrates (PCC). FFP contains all clotting factors contained within the blood and several proteins, including proteins C and S. PCC contains factors II, VII, IX, and X. In PCC, factor VII is of variable concentration and may need to be supplemented with FFP.⁵ PCC has several advantages over FFP, one being that it is more concentrated and



FIGURE 1. CT image of head showing intracranial hemorrhage.

requires less volume when transfused.⁷ PCC can also be constituted in a shorter period of time than FFP, does not need a type and screen, and can reverse an elevated INR faster than FFP. In one recent study, 93% of patients with an INR exceeding 2.0 had successful reversal to an INR of 1.3 or less within 30 minutes of PCC administration.⁷ Forty-eight hours after initial transfusion of PCC, INR remained at 1.3 or less, suggesting a sustained effect. New oral anticoagulants have been approved and are currently or will soon be available. Among them are apixaban, dabigatran, and rivaroxaban. There is no reversal strategy available for a patient with ICH who is receiving these new oral anticoagulants.⁸

Recombinant factor VIIa (rFVIIa) is the activated form of factor VII in the clotting cascade and interacts with tissue factor and can also activate factor IX and factor X to promote clot formation. rFVIIa has been used extensively in uncontrolled bleeding in hemophilia patients and recently has been studied in ICH without use of oral anticoagulants.⁹ While this phase III trial showed a significant reduction in growth of volume of ICH in patients given rFVIIa, no change in clinical outcome was observed in these patients compared with those given placebo. Because of the increase in thromboembolic risk associated with rFVIIa and lack of clinical benefit, its use in unselected patients is not

currently recommended.⁵ No studies have evaluated the efficacy of rFVIIa in the setting of oral anticoagulants.

Hypertension is seen in all forms of stroke. Systolic blood pressure (SBP) of 140 mm Hg or higher is seen in 67% of ischemic stroke cases, 75% of ICH cases, and 100% of SAH cases.¹⁰ The recommendations for blood pressure management have not changed significantly from those in previously established guidelines. Current recommendations state that if SBP is greater than 200 mm Hg or mean arterial pressure (MAP) is greater than 150 mm Hg, aggressive management is warranted.⁵ At these elevated pressures, reduction with an IV antihypertensive infusion is necessary, with blood pressure checks every 5 minutes and infusion rates titrated as needed. If SBP is greater than 180 mm Hg or MAP is greater than 130 mm Hg and there is evidence of elevated intracranial pressure (ICP), invasive monitoring of ICP should be considered.⁵ Once an ICP monitor has been placed, cerebral perfusion pressures should be maintained at 60 mm Hg or higher with IV infusions or intermittent medications. If SBP is greater than 180 mm Hg or MAP is greater than 130 mm Hg and there is no evidence of elevated ICP, then reduction of MAP to 110 mm Hg using infusion or intermittent IV medications with reexamination every 15 minutes is needed and considered safe.⁵

Previously, it was thought that rapid lowering of SBP was not safe. However, the INTERACT study challenged that theory. In INTERACT, two groups of patients with newly diagnosed ICH were randomly assigned to rapid SBP reduction to either 140 or 180 mm Hg using IV medications.¹¹ More stringent SBP control resulted in a hematoma growth rate of 13.7% in the first 24 hours, while standard SBP control resulted in a higher rate of 36.3%. While this trial illustrated that rapid lowering of SBP to 140 mm Hg is safe, no changes in 90-day morbidity or mortality were found.¹¹ Currently a new study, INTERACT2, is under way in several countries, with a larger population and the same investigative model, to determine if improvement in morbidity and mortality can be demonstrated.

Strict glucose control, with target glucose levels near 100 mg/dL, may cause adverse hypoglycemic events and be detrimental. It has been suggested previously that suitable glucose levels may be 140 to 185 mg/dL.⁴ Patients with glucose levels greater than 185 mg/dL may

benefit from insulin.⁴ However, more research is needed before specific glucose parameters are determined.

Previous recommendations suggested that prophylactic antiepileptic therapy may be beneficial.⁴ A 2009 study showing that indiscriminate prophylactic antiepileptic therapy in ICH was associated with increased fever and worse clinical outcome at 14 days upon hospital discharge¹² has prompted changes to the guidelines.⁵ Specifically, the antiepileptic medication phenytoin was shown in this study to be associated with worse outcomes. Currently, only ICH patients who have seizures documented either by electroencephalography (EEG) or clinical observation should be treated with antiepileptics. Patients with a change in mental status should be placed on EEG monitoring to detect subclinical seizures. Prophylactic anticonvulsant medications should not be initially given upon diagnosis of ICH.⁵

The role of surgical treatment in the majority of ICH cases is unclear. One subset of ICH, cerebellar ICH, has shown significant benefit from surgical treatment.¹³⁻¹⁸ Currently, surgical treatment in the form of craniotomy and evacuation is recommended for cerebellar ICH larger than 3 cm in diameter and for patients with brain stem compression or hydrocephalus.⁵ These recommendations are based on nonrandomized studies,¹³⁻¹⁸ but patients treated surgically in this defined population had markedly better outcomes.

SUBARACHNOID HEMORRHAGE

Every year 2% of all patients who visit the ED have a chief complaint of headache, and approximately 1 of every 100 of these patients has an SAH.¹⁹ SAH occurs in approximately 30,000 persons each year in North America,¹⁹ and 85% of SAHs are caused by a ruptured cerebral aneurysm.²⁰ Other etiologies include inflammatory lesions of the cerebral arteries, arterial dissection, vascular lesions of the spinal cord, coagulopathies, tumors, or illicit drug use.

Cerebral aneurysms are found in approximately 2% of the population. Most aneurysms do not cause any problems and are recognized only incidentally on autopsy.²⁰ However, the presence of aneurysm does increase the likelihood of rupture leading to SAH. The risk of aneurysm rupture increases proportionally with the size of the aneurysm. A recent large study deter-

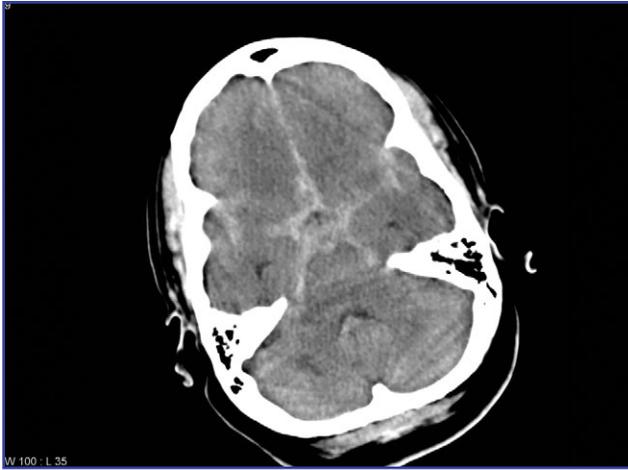


FIGURE 2. CT image of head showing subarachnoid hemorrhage.

mined that the annual incidence of rupture of cerebral aneurysms 7 mm in diameter or smaller is 0.1% and that the incidence of rupture increases as the aneurysm diameter increases.²¹

Determining which patients need a workup for SAH can be a daunting task. A “sentinel bleed” can present with a mild headache and be nondescript. This initial minor hemorrhage can occur several weeks to several days prior to a large SAH. Diagnosing SAH during this early stage may prevent a larger bleed, lead to appropriate treatment, and prevent significant morbidity and mortality.

Unfortunately, the frequency of misdiagnosis of SAH on initial presentation ranges from 5% to 37%.²²⁻²⁴ Correct diagnosis is important because without appropriate treatment, 26% to 73% of patients with SAH due to aneurysm experience rebleeding within days to weeks of the initial hemorrhage. Patients with smaller hemorrhage and normal mental status are more likely to be misdiagnosed initially. This delay in diagnosis is associated with significantly poorer quality of life scores both at discharge from the hospital and 3 months after discharge.²³

Presentation

Patients with SAH are typically awake and neurologically intact on presentation. Headache is much more common in patients with SAH than in those with ICH, and it is more often the main complaint in SAH than in ICH; however, it can be difficult to differentiate between SAH and ICH based on clinical presentation alone.²⁵

The classic presentation of SAH is a headache that is rapid in onset, like a “thunder clap.” Patients often describe this headache as the “worst headache of my life.” However, in a Dutch study involving 102 adult patients who presented to the ED with acute severe headache, only 50% of patients with SAH reported instantaneous onset of headache.²⁶ Nevertheless, certain characteristics of the patient’s headache may raise clinical suspicion for SAH and prompt further investigation. These characteristics include but are not limited to sudden onset of headache, large qualitative difference in headache compared with previous headaches, and nausea, vomiting, or neck pain.²⁷ When these features are present, a high level of clinical suspicion for SAH is warranted, even with seemingly benign presentations.

Diagnosis

Non-contrast-enhanced head CT is the first appropriate test to order when a diagnosis of SAH is possible (Figure 2). MRI can also be used, but due to time constraints and limited availability, it is not considered a first-line test. Sensitivity of CT for SAH depends largely on how soon it is performed after onset of SAH; initial sensitivity is greater but diminishes as time passes. Sensitivity is 98% to 100% in the first 12 hours after onset of symptoms, 93% at 24 hours after onset, and 57% to 85% at 6 days after onset.²⁵

After a negative head CT, the next diagnostic step is lumbar puncture (LP). Sentinel bleeds are smaller events that may occur prior to a large SAH. Even small amounts of blood within the CSF can be detected by LP. While no defined CSF red blood cell (RBC) count value has been determined as specific for SAH, an elevated RBC count that remains elevated in consecutive studies can be indicative of SAH. While an RBC count that decreases in subsequent tubes may be suggestive of a traumatic LP, this cannot be relied upon to rule out SAH.²² The strategy of negative head CT with subsequent LP for diagnosis of SAH has recently been validated. In a 3-year, large prospective cohort study conducted at two EDs, the sensitivity of CT and subsequent LP for diagnosis of SAH was 100%.²⁸

As CT scanners continue to improve, the question has been raised whether a negative head CT alone may be sufficient. A 2011 prospective multicenter study in-

volving approximately 3,100 patients examined the sensitivity of third-generation CT scanners when scanning was performed within 6 hours of onset of headache.²⁹ The sensitivity and specificity of CT alone were 100% and 100%, respectively, with a negative predictive value of 99.5% to 100%. One limitation of the 2011 study is that the scans must be read by a neuroradiologist or a radiologist experienced in reading head CT. In addition, it should be noted that patients do not always present to the ED within 6 hours of a sentinel bleed. Nevertheless, this study can be a helpful adjunct to the discussion with patients regarding LP after a negative head CT.

Xanthochromia is a pink to yellow coloring of the CSF that is caused by degradation products of lysed RBCs. Xanthochromic CSF can be highly suggestive of SAH.³⁰ However, other causes of xanthochromia do exist and may lead to false-positive results in the evaluation of CSF for SAH. These causes include systemic jaundice, elevated CSF protein concentration, rifampin therapy, and dietary hypercarotenemia.³¹ The presence of xanthochromia can be determined by either visual inspection or spectrophotometry. The majority of hospitals in the United States use visual inspection, while many hospitals in Europe use spectrophotometry. Spectrophotometry has been shown to be more sensitive than visual inspection,³² but it has poor specificity.³³ Xanthochromia may not be present if symptoms have not been present for at least 12 hours, as the RBCs have not had time to lyse and release the pigments that cause xanthochromia. Therefore, the absence of xanthochromia on inspection of CSF gathered less than 12 hours after onset of symptoms is not a reliable finding in ruling out SAH. Research has evaluated bilirubin levels within CSF. While bilirubin levels are very sensitive, they are not specific for SAH and cannot be reliably used as a marker.¹⁹

After SAH is diagnosed, it is appropriate to further search for the etiology of the hemorrhage. The current gold standard for this purpose is cerebral angiography, which provides the best information for documenting the presence and features of aneurysms that may be corrected with surgical intervention.²⁵ However, angiography may not be appropriate for an unstable patient because it is relatively time-consuming and its availability is limited. CTA has become the first-line imaging study for evaluation of SAH (Figure 3). CTA is 95% to

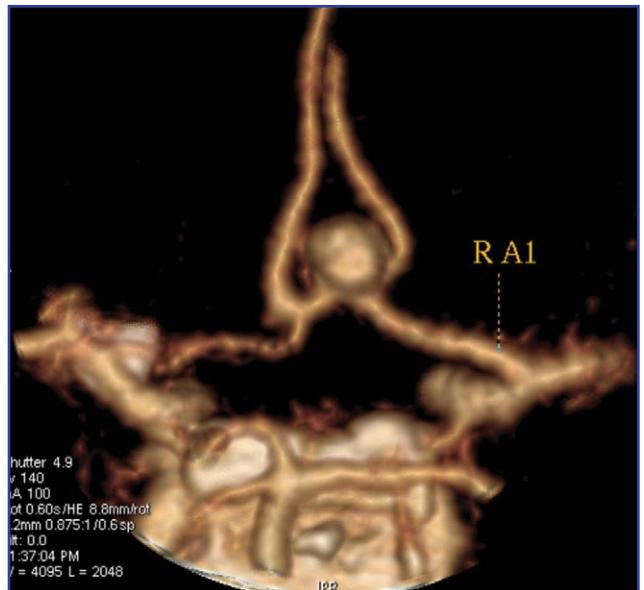


FIGURE 3. CTA image showing aneurysm.

100% sensitive for detecting aneurysms 5 mm or larger in diameter and 64% to 83% sensitive for aneurysms with a diameter less than 5 mm.^{25,34-40} The information provided by CTA may be sufficient to proceed directly to intervention. With selected patients, a decision for intervention can be made on the results of CTA alone. MRA can also be used in evaluation. However, the availability of MRA may be limited in many areas. MRA is 85% to 100% sensitive for detecting aneurysms 5 mm or greater in diameter, and approximately 56% sensitive for aneurysms with a diameter less than 5 mm.^{25,41-44} MRA does not require iodinated contrast or ionizing radiation and may be useful in patients with renal insufficiency or in pregnant women. If CTA or MRA is negative, the next step is cerebral angiography, neurosurgical consultation, or both. Depending on the clinical condition of the patient, the consultant may choose either to proceed with cerebral angiography immediately or to observe for 24 to 48 hours before reimaging. After negative CTA, no new findings were revealed in 74% of cases in which cerebral angiography was subsequently performed.^{25,37}

Treatment

The ABCs (airway, breathing, and circulation) are obvious concerns for any patient with hemorrhagic stroke. Neurologic decline and depressed level of consciousness may result in inability to maintain an airway. Failure

Table. Hunt and Hess Grading Scale for Subarachnoid Hemorrhage

Grade	Clinical Description
1	Asymptomatic or low-grade headache and minimal nuchal rigidity
2	Moderate/severe headache, nuchal rigidity, possible cranial nerve palsy, but no other focal neurologic deficit
3	Somnolence, mildly altered mental status, mild focal neurologic deficit
4	Stupor, moderate/severe hemiparesis, decerebrate rigidity, vegetative disturbances
5	Profound coma, decerebrate rigidity, death-like appearance

Adapted from Brisman et al⁴⁷; Hunt and Hess.⁴⁸

to appropriately manage the airway with endotracheal intubation may lead to aspiration, hypoxemia, or hypercapnea.⁴⁵ Using medications that do not raise ICP in patients with hemorrhagic stroke may prevent further neurologic damage and yield maximum benefit. These medications include sedatives such as propofol or etomidate and nondepolarizing neuromuscular paralytic drugs such as atracurium or vecuronium.⁴⁵

In the setting of SAH, blood pressure parameters are based on consensus agreement. Increased episodes of rebleeding were found to occur with elevated SBP, especially with SBP greater than 150 mm Hg.²⁵ It is reasonable to attempt blood pressure control in this setting, using short-acting IV infusion medications such as nicardipine, labetalol, or esmolol.

Management of SAH patients taking oral anticoagulants is similar to that described for ICH patients.

Vasospasm following SAH is a significant cause of morbidity and mortality. Vasospasm causes constriction of blood flow to the brain and can lead to cerebral infarction. Vasospasm typically occurs in the days following SAH and gradually resolves within 2 to 4 weeks. In SAH patients surviving to treatment, vasospasm accounts for approximately 50% of deaths, with rebleeding and complications from surgery making up the remaining 50%.²⁵ Oral nimodipine has been shown

to improve outcomes related to vasospasm, with only 1.8% of patients given nimodipine within 96 hours of SAH experiencing long-term neurologic sequelae, compared with 13.3% of patients given placebo.⁴⁶ While the mechanism of action is unclear, nimodipine does not appear angiographically to reduce vasospasm.²⁵

Some patients with SAH are candidates for surgical intervention. The Hunt and Hess grading scale (Table)^{47,48} is useful to determine the severity of SAH in the clinical setting and to determine if surgical intervention may be helpful. Patients with Hunt and Hess grades 1 to 4 are generally treated early with surgical intervention. In grade 5, the most severe grade, the benefit from surgical intervention is less clear. Prognosis with or without surgical intervention is grim in these patients. For this reason, early surgical intervention has typically been withheld. However, if clinical improvement occurs, delayed surgical intervention may be appropriate.⁴⁷

Two basic types of surgical intervention are available: craniotomy with microsurgical clipping and endovascular occlusion with detachable coils. Endovascular occlusion is a procedure performed with an interventionalist and does not involve an open cranial procedure. Availability of this procedure varies. Patients whose risk with open surgical repair is greater—ie, those with poor clinical grade, medically unstable condition, early vasospasm, poorly defined anatomy of the surgical neck, or multiple aneurysms—have more often been treated with endovascular repair.⁴⁷

Anatomic location of the aneurysm may preclude endovascular repair; this applies to aneurysms in the cavernous sinus, basilar tip, or posterior fossa. Craniotomy with microsurgical clipping remains the standard for these difficult anatomic locations. Nevertheless, when compared to craniotomy with microsurgical clipping, endovascular occlusion with coiling has been associated with a 7.4% absolute risk reduction in mortality or dependence at 1 year.⁴⁹ Ultimately, the decision to treat the aneurysm is best made in consultation with the specialist.

Hydrocephalus is reported to occur within 72 hours in 20% to 30% of patients with SAH.²⁵ While hydrocephalus is more commonly seen in patients with a poor clinical grade, many patients with hydrocephalus are asymptomatic and may not require any intervention. However,

when the patient has a change in level of consciousness or mental status or worsening findings on neurologic exam, ventriculostomy is recommended. Long-term or permanent shunting may also be required and has been reported in 18% to 26% of patients surviving SAH.²⁵

CONCLUSION

The presentation of ICH is variable. The initial diagnostic test of choice is non-contrast-enhanced head CT. Once diagnosis of ICH is made, further testing may be needed to identify structural lesions that may be the underlying cause of ICH. Medical treatment of ICH may include platelet transfusion in thrombocytopenic patients, withholding oral anticoagulants and reversing effects in patients with elevated INR, rapid and aggressive hypertension treatment, and invasive ICP monitoring in patients with elevated ICP. Antiepileptic medications should be used only in patients with documented seizure activity observed clinically or on EEG. Craniotomy with clot evacuation is indicated in cerebellar ICH larger than 3 cm in diameter and in those with brain stem compression or hydrocephalus.

Diagnosing SAH can be challenging because headache often is the only presenting complaint. Non-contrast-enhanced CT of the head is the first-line diagnostic tool for SAH. Sensitivity for detecting SAH drops in a time-dependent manner after onset of SAH. For this reason, LP should be performed if clinical suspicion is present for SAH after a negative head CT. Xanthochromia or persistent elevation in RBCs within CSF can suggest the presence of SAH. Once the diagnosis of SAH is made, the etiology of SAH should be investigated. This can be done with cerebral angiography, CTA, or MRA.

For airway management, sedatives and nondepolarizing paralytics that do not raise ICP in hemorrhagic stroke should be used when clinically indicated. Medical treatment of SAH includes blood pressure control with IV medications and treatment of vasospasm with oral nimodipine. Surgical intervention for SAH is largely dependent on the clinical picture, which can be assessed using the Hunt and Hess grading scale. Craniotomy with microsurgical clipping and endovascular occlusion with detachable coils are surgical treatment options for SAH, and treatment selection is determined in consultation with the specialist. **EM**

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