

## REVIEW ARTICLE

## CURRENT CONCEPTS

## Aneurysmal Subarachnoid Hemorrhage

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**N**ONTRAUMATIC SUBARACHNOID HEMORRHAGE IS A NEUROLOGIC EMERGENCY characterized by the extravasation of blood into the spaces covering the central nervous system that are filled with cerebrospinal fluid. The leading cause of nontraumatic subarachnoid hemorrhage is rupture of an intracranial aneurysm, which accounts for about 80 percent of cases and has a high rate of death and complications.<sup>1</sup> Nonaneurysmal subarachnoid hemorrhage, including isolated perimesencephalic subarachnoid hemorrhage, occurs in about 20 percent of cases and carries a good prognosis with uncommon neurologic complications.<sup>2</sup> This review focuses on aneurysmal subarachnoid hemorrhage.

As many as 46 percent of survivors of subarachnoid hemorrhage may have long-term cognitive impairment, with an effect on functional status and quality of life.<sup>3,4</sup> The disorder is also associated with a substantial burden on health care resources, most of which are related to hospitalization.<sup>5</sup> Subarachnoid hemorrhage has distinct demographic characteristics, risk factors, and treatments. It accounts for 2 to 5 percent of all new strokes and affects 21,000 to 33,000 people each year in the United States.<sup>6-8</sup> The incidence of the disorder has remained stable over the past 30 years,<sup>1</sup> and although it varies from region to region, the aggregate worldwide incidence is about 10.5 cases per 100,000 person-years.<sup>9</sup> The incidence increases with age, with a mean age at presentation of 55 years.<sup>7</sup> The risk for women is 1.6 times that of men,<sup>10</sup> and the risk for blacks is 2.1 times that of whites.<sup>11</sup> The average case fatality rate for subarachnoid hemorrhage is 51 percent, with approximately one third of survivors needing lifelong care.<sup>12</sup> Most deaths occur within two weeks after the ictus, with 10 percent occurring before the patient receives medical attention and 25 percent within 24 hours after the event.<sup>13</sup> Overall, subarachnoid hemorrhage accounts for 5 percent of deaths from stroke but for 27 percent of all stroke-related years of potential life lost before the age of 65.<sup>14</sup>

The major factors associated with poor outcome are the patient's level of consciousness on admission, age, and the amount of blood shown by initial computed tomography (CT) of the head.<sup>15</sup> Several grading systems are used to assess the initial clinical and radiologic features of subarachnoid hemorrhage<sup>16-19</sup> (Table 1). The two most widely used clinical scales are those of Hunt and Hess<sup>16</sup> and the World Federation of Neurological Surgeons.<sup>17</sup> The latter is currently preferred since it is based on the sum score of the Glasgow Coma Scale (a very reliable method for evaluating the level of consciousness) and the presence of focal neurologic signs. The higher the score, the worse the prognosis. The amount of blood seen on initial head CT scanning can be easily evaluated.<sup>18,19</sup> A thick subarachnoid clot and bilateral ventricular hemorrhage are both predictive of poor outcome and can be reliably graded on head CT.<sup>19</sup>

The major identified modifiable risk factors include cigarette smoking, hypertension, cocaine use, and heavy alcohol use.<sup>20-22</sup> Patients with a family history of first-degree relatives with subarachnoid hemorrhage are also at a higher risk.<sup>21,23</sup> Heritable connective-tissue disorders associated with the presence of intracranial

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**Table 1. Clinical and Radiologic Grading Scales for Subarachnoid Hemorrhage.**

Clinical Grading Scale of the World Federation of Neurological Surgeons*			Head CT Grading Scale†		
Grade	Score on Glasgow Coma Scale‡	Clinical Appearance	Grade	Subarachnoid Hemorrhage	Intraventricular Hemorrhage
1	15	No motor deficit	0	Absent	Absent
2	13–14	No motor deficit	1	Minimal	Absent in both lateral ventricles
3	13–14	Motor deficit	2	Minimal	Present in both lateral ventricles
4	7–12	With or without motor deficit	3	Thick§	Absent in both lateral ventricles
5	3–6	With or without motor deficit	4	Thick§	Present in both lateral ventricles

\* Data are from the Report of the World Federation of Neurological Surgeons.<sup>17</sup>

† Data are from Claassen et al.<sup>19</sup>

‡ The overall score on the Glasgow Coma Scale is the sum of points for eye opening (4 points), best motor response (6 points), and best verbal response (5 points).

§ This designation denotes a hemorrhage filling one or more cisterns or fissures. The 10 cisterns or fissures evaluated include the frontal interhemispheric fissure, the quadrigeminal cistern, both suprasellar cisterns, both ambient cisterns, both basal sylvian fissures, and both lateral sylvian fissures.

aneurysm and subarachnoid hemorrhage include polycystic kidney disease, the Ehlers–Danlos syndrome (type IV), pseudoxanthoma elasticum, and fibromuscular dysplasia.<sup>24</sup> The risk of rupture depends on the size and location of the aneurysm.<sup>25,26</sup> According to an international study of unruptured intracranial aneurysms,<sup>25</sup> in patients with no history of subarachnoid hemorrhage, the five-year cumulative rate of rupture of aneurysms located in the internal carotid artery, anterior communicating artery, anterior cerebral artery, or middle cerebral artery is zero for aneurysms under 7 mm, 2.6 percent for 7 to 12 mm, 14.5 percent for 13 to 24 mm, and 40 percent for 25 mm or more. This rate is in contrast to rupture rates of 2.5 percent, 14.5 percent, 18.4 percent, and 50 percent, respectively, for the same sizes of aneurysms in the posterior circulating and posterior communicating artery.

#### DIAGNOSIS

Subarachnoid hemorrhage should always be suspected in patients with a typical presentation (Fig. 1),<sup>27</sup> which includes a sudden onset of severe headache (frequently described as the “worst ever”), with nausea, vomiting, neck pain, photophobia, and loss of consciousness. Physical examination may reveal retinal hemorrhages, meningismus, a diminished level of consciousness, and localizing neurologic signs. The latter finding

usually includes third-nerve palsy (posterior communicating aneurysm), sixth-nerve palsy (increased intracranial pressure), bilateral lower-extremity weakness or abulia (anterior communicating aneurysm), and the combination of hemiparesis and aphasia or visuospatial neglect (middle cerebral artery aneurysm). Retinal hemorrhages should be differentiated from the preretinal hemorrhages of Terson’s syndrome,<sup>28</sup> which indicates a more abrupt increase in intracranial pressure and increased mortality.

In the absence of the classic signs and symptoms, subarachnoid hemorrhage may be misdiagnosed.<sup>27,29</sup> The frequency of misdiagnosis may be up to 50 percent in patients presenting for their first visit to a physician. The common incorrect diagnoses are migraine and tension-type headaches. Failure to obtain the appropriate imaging study accounts for 73 percent of cases of misdiagnosis, and failure to perform or correctly interpret the results of a lumbar puncture accounts for 23 percent. Misdiagnosed patients tend to be less ill and have a normal neurologic examination. However, in such cases, neurologic complications occur later in as many as 50 percent of patients, and these patients have an associated higher risk of death and disability. Headache may be the only presenting symptom in up to 40 percent of patients and may abate completely within minutes or hours<sup>30</sup>; these are called sentinel or thunderclap headaches or “warning leaks.”

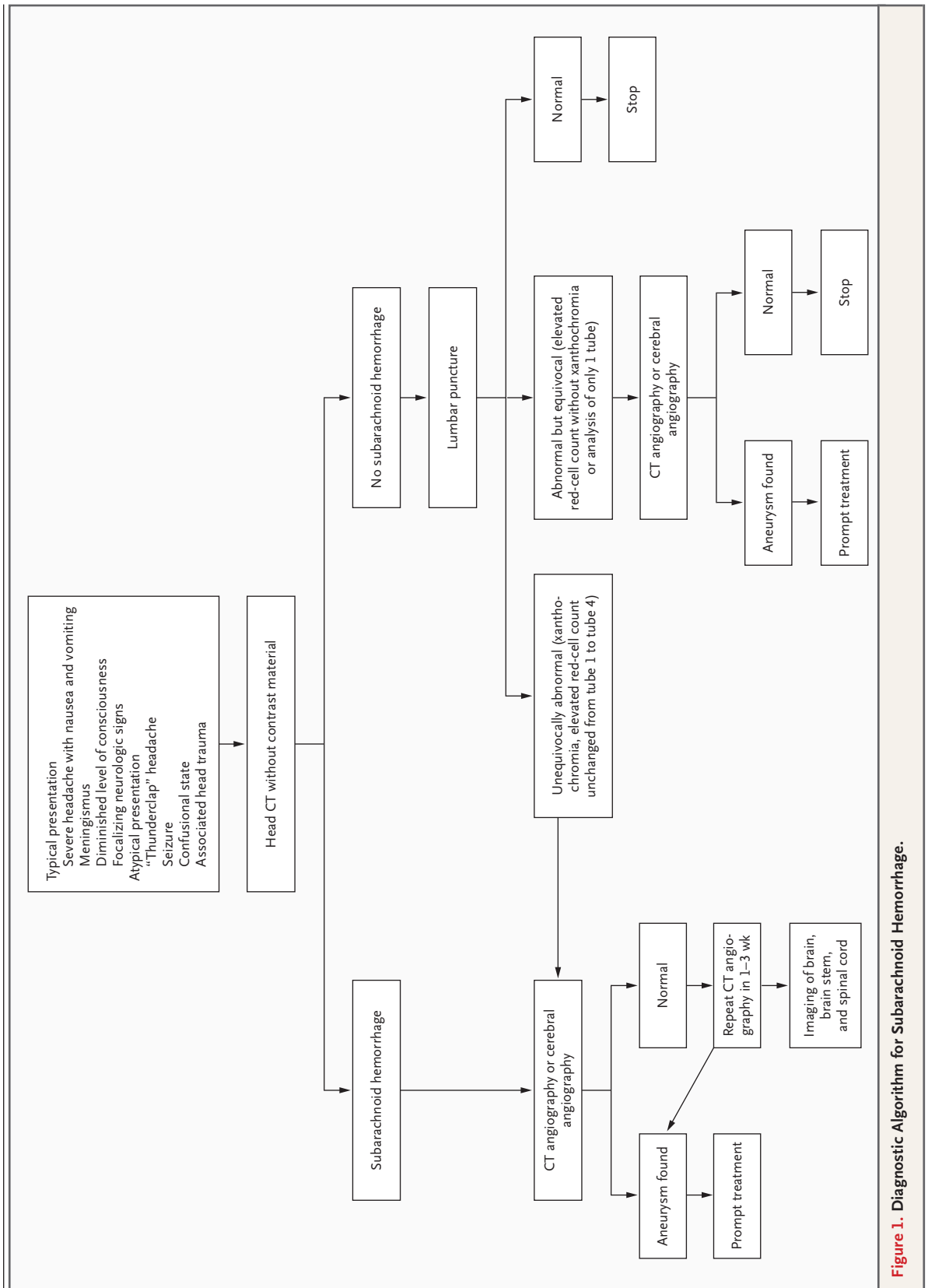
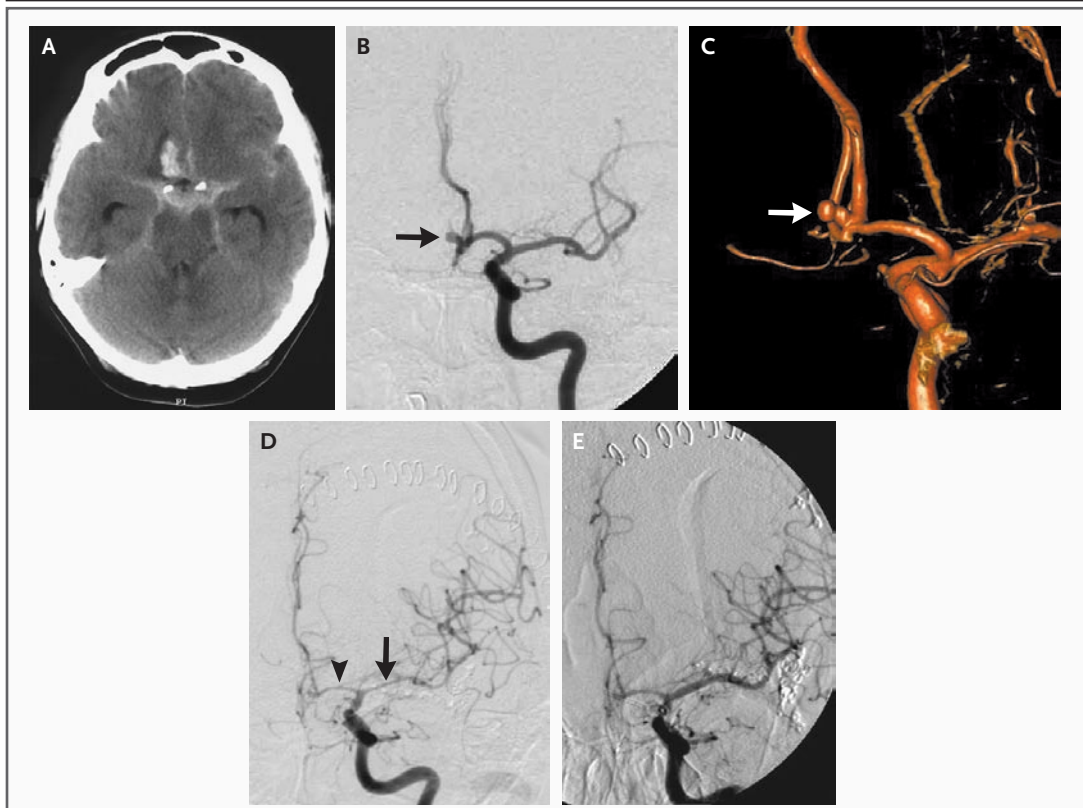


Figure 1. Diagnostic Algorithm for Subarachnoid Hemorrhage.

Emergency evaluation of sentinel headaches is required since patients may have a serious subarachnoid hemorrhage within three weeks.<sup>31</sup> In many instances, no reliable clinical features distinguish a sentinel headache from a benign headache. Some patients may not have a severe headache, or other symptoms, such as seizures or a confusional state, may be more prominent. Any patient's first or worst headache should suggest subarachnoid hemorrhage and prompt the ordering of a CT scan of the head (Fig. 1).

## DIAGNOSTIC STUDIES

Head CT scanning should be the first study performed in any patient with suspected subarachnoid hemorrhage (Fig. 1). The characteristic appearance of extravasated blood is hyperdense (Fig. 2). Since small amounts of blood can be missed, all scans should be performed with thin cuts through the base of the brain.<sup>32</sup> A good-quality head CT scan will reveal subarachnoid hemorrhage in 100 percent of cases within 12



**Figure 2.** Subarachnoid Hemorrhage in a 69-Year-Old Woman.

This patient, who had a long-standing history of smoking and hypertension, presented to the emergency room with severe headache with nausea and vomiting for four hours and had meningismus on physical examination. Initial computed tomography (CT) of the head revealed a subarachnoid hemorrhage, a right frontal hematoma suggestive of an anterior communicating artery aneurysm, and hydrocephalus (Panel A). An external ventricular drain was inserted on arrival. Digital-subtraction cerebral angiography (oblique view) showed an aneurysm stemming from the anterior communicating artery (Panel B, arrow). Three-dimensional digital-subtraction angiography clearly showed the bilobed, irregular nature of the aneurysm (Panel C, arrow). The patient underwent craniotomy and surgical clipping of the aneurysm, with good postoperative recovery. Six days after admission, the patient had rapid onset of global aphasia and right hemiparesis. Transcranial Doppler ultrasonography demonstrated a severe elevation in blood-flow velocities ( $>200$  cm per second) in the left middle and anterior cerebral arteries. Angiography showed considerable vasospasm (Panel D) in the proximal segments of the left anterior arteries (arrowhead) and middle cerebral arteries (arrow). The patient underwent transluminal balloon angioplasty of the left middle cerebral artery, and direct vasodilators (papaverine and verapamil) were infused into the left anterior cerebral artery with good resolution of the vasospasm (Panel E). The patient's clinical course evolved favorably, and she was independent three months after presentation.

hours after the onset of symptoms and in more than 93 percent of cases within 24 hours.<sup>33</sup> Head CT scanning can also demonstrate intraparenchymal hematomas, hydrocephalus, and cerebral edema and can help predict the site of aneurysm rupture, particularly in patients with aneurysms in the anterior cerebral or anterior communicating arteries (Fig. 2).<sup>34</sup> Head CT scanning is also the most reliable test for predicting cerebral vasospasm and poor outcome.<sup>35</sup> Because of rapid clearance of blood, delayed head CT scanning may be normal despite a suggestive history, and sensitivity drops to 50 percent at seven days.<sup>23</sup>

Lumbar puncture should be performed in any patient with suspected subarachnoid hemorrhage and negative or equivocal results on head CT scanning (Fig. 1). Cerebrospinal fluid should be collected in four consecutive tubes, with the red-cell count determined in tubes 1 and 4. Findings consistent with subarachnoid hemorrhage include an elevated opening pressure, an elevated red-cell count that does not diminish from tube 1 to tube 4, and xanthochromia (owing to red-cell breakdown detected by spectrophotometry), which may require more than 12 hours to develop. In patients with either equivocal or diagnostic lumbar puncture, an imaging study, such as CT angiography of the head or cerebral angiography, should be the next step (Fig. 1 and 2). Digital-subtraction cerebral angiography has been the gold standard for the detection of cerebral aneurysm, but CT angiography has gained popularity and is frequently used owing to its noninvasiveness and a sensitivity and specificity comparable to that of cerebral angiography.<sup>36</sup>

In all instances, a careful evaluation of all cerebral vessels should be undertaken, since about 15 percent of patients will have multiple aneurysms. Patients with a negative imaging study should have a repeated study 7 to 14 days after the initial presentation. If the second evaluation does not reveal an aneurysm, magnetic resonance imaging (MRI) should be performed to uncover a possible vascular malformation of the brain, brain stem, or spinal cord. Other imaging techniques that may be used include MRI of the head to determine the size of the aneurysm (particularly in cases of partial thrombosis of the aneurysm) and three-dimensional digital-subtraction cerebral angiography (which helps delineate the morphology of the aneurysm) (Fig. 2C). Also, recent advances in three-dimensional CT angiog-

raphy may obviate the need for invasive cerebral angiography and its inherent risks.

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## TREATMENT

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All patients with subarachnoid hemorrhage should be evaluated and treated on an emergency basis with maintenance of airway and cardiovascular function (Table 2). After initial stabilization, patients should be transferred to centers with neurovascular expertise and preferably with a dedicated neurologic critical care unit to optimize care.<sup>37,38</sup> Once in the critical care setting, the main goals of treatment are the prevention of rebleeding, the prevention and management of vasospasm, and the treatment of other medical and neurologic complications.

### GENERAL THERAPY

Blood pressure should be maintained within normal limits, and if necessary, intravenous antihypertensive agents such as labetalol and nicardipine can be used.<sup>23</sup> Once the aneurysm is secured, hypertension is allowed, but there is no agreement on the range. Analgesia is often required, and reversible agents such as narcotics are indicated. Two important factors that are associated with poor outcome are hyperglycemia and hyperthermia, and both should be corrected.<sup>39,40</sup> Prophylaxis of deep venous thrombosis should be instituted early with sequential compressive devices, and subcutaneous heparin should be added after the aneurysm is treated. Calcium antagonists reduce the risk of poor outcome from ischemic complications, and oral nimodipine is currently recommended.<sup>41</sup> Prolonged administration of antifibrinolytic agents reduces rebleeding but is associated with an increased risk of cerebral ischemia and systemic thrombotic events.<sup>42</sup> Early treatment of aneurysms has become the mainstay of rebleeding prevention, but antifibrinolytic therapy may be used in the short term before aneurysm treatment.

### TREATMENT OPTIONS FOR ANEURYSMS

Currently, the two main therapeutic options for securing a ruptured aneurysm are microvascular neurosurgical clipping and endovascular coiling. Historically, microsurgical clipping has been the preferred method of treatment. Although the timing of surgery has been debated, most neurovascular surgeons recommend early operation. Evi-

**Table 2. Treatment Guidelines for Subarachnoid Hemorrhage.\***

Management of Condition	Recommendations
<b>General measures</b>	
Airway and cardiovascular system	Monitor closely in intensive care unit or preferably in neurologic critical care unit
Environment	Maintain reduced noise level and limit visitors until aneurysm is treated
Pain	Administer morphine sulfate (2–4 mg IV every 2–4 hr) or codeine (30–60 mg IM every 4 hr)
Gastrointestinal prophylaxis	Administer ranitidine (150 mg PO twice daily or 50 mg IV every 8–12 hr) or lansoprazole (30 mg PO daily)
Deep venous thrombosis prophylaxis	Use thigh-high stockings and sequential compression pneumatic devices; administer heparin (5000 U SC three times daily) after treatment of aneurysm
Blood pressure	Keep systolic blood pressure at 90–140 mm Hg before aneurysm treatment, then allow hypertension to keep systolic blood pressure <200 mm Hg
Serum glucose	Maintain level at 80–120 mg/dl; use sliding scale or continuous infusion of insulin if necessary
Core body temperature	Keep at $\leq 37.2^{\circ}\text{C}$ ; administer acetaminophen (325–650 mg PO every 4–6 hr) and use cooling devices if necessary
Calcium antagonist	Administer nimodipine (60 mg PO every 4 hr for 21 days)
Antifibrinolytic therapy (optional)	Administer aminocaproic acid (first 24–48 hr, 5 g IV, followed by infusion at 1.5 g/hr)
Anticonvulsants	Administer phenytoin (3–5 mg/kg/day PO or IV) or valproic acid (15–45 mg/kg/day PO or IV)
Fluids and hydration	Maintain euvolemia (CVP, 5–8 mm Hg); if cerebral vasospasm is present, maintain hypervolemia (CVP, 8–12 mm Hg, or PCWP, 12–16 mm Hg)
Nutrition	Try oral intake (after evaluation of swallowing); for alternative routes, enteral feeding preferred
<b>Other treatment</b>	
Surgical clipping	Perform procedure within first 72 hr
Endovascular coiling	Perform procedure within first 72 hr
<b>Common complications</b>	
Hydrocephalus	Insert external ventricular or lumbar drain
Rebleeding	Provide supportive care and emergency treatment of aneurysm
Cerebral vasospasm	Maintain hypervolemia or induced hypertension with phenylephrine, norepinephrine, or dopamine; provide endovascular treatment (transluminal angioplasty or direct vasodilators)
Seizures	Administer lorazepam (0.1 mg/kg, at a rate of 2 mg/min), followed by phenytoin (20 mg/kg IV bolus at <50 mg/min, up to 30 mg/kg)
Hyponatremia	With SIADH, restrict fluids; with cerebral salt-wasting syndrome, aggressively replace fluids with 0.9% saline or hypertonic saline solution
Myocardial injury and arrhythmias	Administer metoprolol (12.5–100 mg PO twice daily); evaluate ventricular function; treat arrhythmia
Pulmonary edema	Provide supplemental oxygen or mechanical ventilation if necessary; monitor PCWP and ventricular function; distinguish cardiogenic vs. neurogenic pulmonary edema
<b>Long-term care</b>	
Rehabilitation	Provide physical, occupational, and speech therapies
Neuropsychological evaluation	Perform global and domain-specific testing; provide cognitive rehabilitation
Depression	Administer antidepressant medications and provide psychotherapy
Chronic headaches	Administer NSAIDs, tricyclic antidepressants, or SSRIs; gabapentin

\* Recommendations are based on generally accepted practices and may not be based on controlled trials. IV denotes intravenously, IM intramuscularly, PO orally, SC subcutaneously, CVP central venous pressure, PCWP pulmonary-capillary wedge pressure, SIADH syndrome of inappropriate secretion of antidiuretic hormone, NSAIDs nonsteroidal antiinflammatory drugs, and SSRIs selective serotonin-reuptake inhibitors.

dence from clinical trials suggests that patients undergoing early surgery have a lower rate of rebleeding and tend to fare better than those treated later.<sup>43</sup> Securing the ruptured aneurysm will also facilitate the treatment of complications such as cerebral vasospasm.<sup>7</sup> Although many neurovascular surgeons use mild hypothermia during microsurgical clipping of aneurysms, it has not proved to be beneficial in patients with lower grades of subarachnoid hemorrhages.<sup>44</sup>

Endovascular treatment of aneurysms has been available as an alternative to surgical therapy for the past 15 years.<sup>45</sup> Coils are made of platinum and are attached to a delivery wire. Once proper position within the aneurysm is achieved, coils are detached from the wire. Multiple coils of various length and diameter are often packed into the aneurysm to exclude it from the circulation (Fig. 3).

The International Subarachnoid Aneurysm Trial (ISAT) prospectively examined patients with ruptured aneurysms who were considered equally suitable for either endovascular coiling or microsurgical clipping.<sup>46,47</sup> The authors found that for this particular subgroup of patients, a favorable outcome, which was defined as survival free of disability at one year, occurred significantly more often in patients treated with endovascular coiling than with surgical placement of clips. The risk of epilepsy was substantially lower in patients who underwent endovascular coiling, but the risk of rebleeding was higher. Also, in patients who underwent follow-up cerebral angiography, the rate of complete occlusion of the aneurysm was greater with surgical clipping.

ISAT was a landmark study that validated the technique of endovascular coiling. However, many aneurysms are not equally suitable for either microsurgical clipping or endovascular coiling. In individual cases, several factors — such as the patient's age and overall medical condition and the aneurysm's location, morphology, and relationship to adjacent vessels — need to be analyzed to decide on the most appropriate treatment.<sup>48-50</sup> In general, elderly patients or patients in poor medical condition are often better suited for endovascular coiling. Aneurysms of the vertebrobasilar circulation or aneurysms deep in the skull base, such as paraophthalmic aneurysms, may be more easily accessed by an endovascular approach. Wide-neck aneurysms (in which the ratio of the

neck diameter to that of the largest dome is more than 0.5) tend to be less suitable for endovascular coiling. Aneurysms associated with large parenchymal hematomas and those that have normal branches arising from the base or dome are often more suitable for microsurgical clipping. In addition, for aneurysms causing a local mass effect, surgical therapy may be more efficacious. Owing to the complex analysis of specific variables among patients and types of aneurysms that is needed to determine the most appropriate treatment for individual patients, we recommend evaluation by practitioners who have detailed knowledge of neurovascular surgery, endovascular techniques, and neurologic critical care.

#### MANAGEMENT OF COMPLICATIONS

Neurologic complications are common and include symptomatic vasospasm (46 percent of patients), hydrocephalus (20 percent), and rebleeding (7 percent).<sup>51,52</sup> Patients with rebleeding have a high risk of permanent neurologic disability and a mortality rate of about 50 percent.<sup>23</sup> Rebleeding can be prevented with early treatment, since the condition is more common in the initial few days (4 percent on the first day and 1.5 percent per day for the next two weeks).<sup>23</sup> Cerebral vasospasm is most likely an inflammatory reaction in the blood-vessel wall and develops between days 4 and 12 after subarachnoid hemorrhage. The best predictor of vasospasm is the amount of blood seen on the initial head CT scan.<sup>15,18,19</sup> Angiographic vasospasm is more common (occurring in about two thirds of patients) than is symptomatic vasospasm (with clinical evidence of cerebral ischemia). Transcranial Doppler ultrasonography is performed either daily or every other day to monitor for vasospasm, which is defined as a mean velocity of cerebral blood flow of more than 120 cm per second in a major vessel. Doppler ultrasonography has a sensitivity that is similar to that of cerebral angiography for the detection of narrowed vessels, particularly in the middle cerebral and internal cerebral arteries.<sup>53</sup> Once symptomatic vasospasm is evident (with focal neurologic signs), patients are treated with hypervolemia and induced hypertension (Table 2). Patients whose condition does not improve with medical therapy undergo emergency cerebral angiography and transluminal angioplasty or vasodilator infusion when focal vessel narrowing is

**Figure 3. Endovascular Coiling of Ruptured Intracranial Aneurysm.**

Panel A shows a drawing of a platinum coil after deployment. Panel B shows cerebral angiography of a ruptured aneurysm at the basilar tip before endovascular coiling (arrow) and immediately after endovascular coiling (Panel C).

detected (Fig. 2). Other radiologic evaluation, such as brain MRI, should also be selectively undertaken because brain infarctions do not always have gross clinical manifestations. Symptomatic hydrocephalus that is caused by diminished absorption of cerebrospinal fluid may require treatment with temporary external ventricular drainage or the placement of a permanent shunt. Seizures occur in up to a third of patients.<sup>7</sup> Although the effectiveness of prophylactic anticonvulsant agents has not been formally tested, the potentially devastating effects of seizures, which may lead to re-bleeding, suggest the use of anticonvulsants for at least one week after the initial bleed (Table 2). Patients who are in a coma should undergo monitoring with electroencephalography, since the frequency of nonconvulsive seizures can be as high as 20 percent.<sup>54</sup>

Potentially preventable medical complications after subarachnoid hemorrhage may increase morbidity, the length of the hospital stay, and mortality. The vast majority of patients experience a medical complication, which could be severe in 40 percent of cases.<sup>51</sup> The most common medical complications include pulmonary edema in 23 percent (either cardiogenic or neurogenic with the acute respiratory distress syndrome), cardiac arrhythmias in 35 percent, and electrolyte disturbances in 28 percent of patients. Hyponatremia can be caused by inappropriate secretion of antidiuretic hormone (normal or increased intravascular volume) or cerebral salt wasting (low intravascular volume).<sup>2,4</sup> Treatment of hyponatremia consists of fluid restriction for the former condition and aggressive fluid administration for the latter. In general, patients should be kept euvolemic at all times, since hypovolemia is associated with cerebral ischemia and a worse outcome (Table 2).<sup>2</sup>

**LONG-TERM CARE**

Many survivors of subarachnoid hemorrhage may have chronically disabling problems.<sup>3,4</sup> More than 50 percent of survivors report problems with mem-



ory, mood, or neuropsychological function. These deficits result in an impairment of social roles, even with an absence of apparent physical disability. Half to two thirds of survivors are able to return to work one year after a subarachnoid hemorrhage. Prompt physical and neuropsychological evaluation and treatment should be initiated (Table 2).

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#### FUTURE RESEARCH

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Further epidemiologic studies and new treatments are needed to improve the outcome of patients with subarachnoid hemorrhage. Determinants of the growth and rupture of aneurysms need to be studied. Improved prevention and diagnosis of cerebral vasospasm require more study. Promising areas of research that warrant further testing

in well-designed clinical trials include, among others, the use of human albumin for neuroprotection,<sup>55</sup> intracisternal application of thrombolytic therapy and washing to decrease the blood burden,<sup>56</sup> and new radiologic and endovascular techniques (e.g., biologically active coils and stents) to improve the treatment of aneurysm and vasospasm.<sup>57,58</sup> Other areas to be addressed are the need for prophylactic anticonvulsants and the implementation of aggressive preventive measures, such as hypertension control and smoking cessation.

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