Subarachnoid Hemorrhage

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Opinion statement

All patients who present with subarachnoid hemorrhage should be admitted to the intensive care unit for close neurologic and cardiorespiratory monitoring. Neurosurgical consultation should be obtained if external ventricular drain placement, arteriography, or surgical planning are considered. Seizure prophylaxis, antihypertensive treatment for mean arterial blood pressure greater than 130 mm Hg, pain control, and bed rest are important measures for the prevention of rebleeding, which is associated with a high mortality rate. Standard deep venous thrombosis and gastrointestinal prophylaxis are recommended to prevent medical complications associated with critical illness. In patients with good-grade subarachnoid hemorrhage, early arteriography and definitive aneurysm management are recommended. The location and neck size of the aneurysm and the medical condition of the patient are factors in the decision to proceed with surgical rather than interventional aneurysm management. Postoperatively, clinical examination and transcranial Doppler ultrasonography are recommended for surveillance of vasospasm. If clinical or arteriographic evidence of vasospasm is present, *hemodilution, hypertension,* and *hypervolemia* (triple H) therapy should be instituted. If vasospasm is resistant to conservative measures, balloon angioplasty or intra-arterial papaverine therapy should also be considered.

Introduction

Nontraumatic subarachnoid hemorrhage is a potentially devastating disorder that occurs in approximately 30,000 patients per year in the United States. Up to 30% of patients die within the first 2 weeks after hemorrhage, and survivors have a high incidence of long-term morbidity. Aneurysmal rupture is the most common cause of nontraumatic subarachnoid hemorrhage, greatly surpassing arteriovenous malformation rupture, vasculitis, and hematologic diathesis as causes.

Clinically, subarachnoid hemorrhage presents as a severe headache of abrupt onset, often accompanied by nausea, vomiting, and meningismus. Patients may also have a transient alteration in consciousness or focal neurologic deficits. The initial assessment of patients in whom subarachnoid hemorrhage is suspected should include stabilization of cardiorespiratory status. Once cardiorespiratory status is secure, it is important to obtain a brief history and determine the level of consciousness and the presence of focal deficits by examination. Several clinical scales have been developed for the assessment of subarachnoid hemorrhage, including the World Federation of Neurological Surgeons Scale (Table 1) [1] and the Hunt Hess Scale (Table 2) [2]. These scales provide quick, prognostically useful measures that can guide further triage and management.

In patients in whom subarachnoid hemorrhage is suspected, computed tomographic scan without contrast should be obtained emergently. If the scan is obtained within 24 hours of the initial onset of neurologic symptoms, 92% of patients with subarachnoid hemorrhage will have areas of high attenuation in the subarachnoid space. If clinical suspicion is high and the initial CT scan result is negative, a lumbar puncture should be performed at least 6 hours after onset of neurologic symptoms. An increased erythrocyte count that does not clear over four tubes, elevated protein levels, and evidence of xanthochromia are typical findings.

Once the diagnosis of subarachnoid hemorrhage has been made, the patient should be admitted to an intensive care unit for close monitoring of the cardiorespiratory and neurologic status. Treatment is aimed at prevention and expeditious detection of neurologic

Table 1. World Federation of Neurological Surgeons grading scale

Grade	Focal deficit	Glasgow Coma Score
1	Absent	15
2	Absent	13–14
3	Present	13–14
4	May or may not be present	7–12
5	May or may not be present	3–6

Table 2. Hunt-Hess grading scale*

Grade	Description
0	Unruptured aneurysm
1	No symptoms or mild headache and slight nuchal rigidity
2	Cranial nerve palsy, moderate to severe headache, and nuchal rigidity
3	Mild focal deficit, lethargy, or confusion
4	Stupor, moderate to severe hemiparesis, and early decerebrate rigidity
5	Deep coma, decerebrate rigidity, and moribund appearance

*Add one grade for serious systemic illness (hypertension, diabetes, severe atherosclerosis, chronic obstructive pulmonary disease) or severe vasospasm on arteriography.

causes of deterioration—such as rebleeding, cerebral vasospasm with delayed cerebral ischemia, and hydrocephalus—as well as medical complications associated with subarachnoid hemorrhage and critical illness.

Rebleeding may be an early cause of deterioration in patients with acute subarachnoid hemorrhage. The risk of rebleeding is about 4% within the first 24 hours and 1% per day thereafter for the first 2 weeks after hemorrhage. Mortality rates after rebleeding approach 50% to 70%; medical intervention and early surgery are therefore important initial goals in prevention of rebleeding. Simple preventive measures include bed rest, pain and agitation control, seizure prophylaxis, and stool softener. Antihypertensive agents are indicated for mean arterial pressures greater than 130 mm Hg. Antifibrinolytic medications used in the past reduced the rate of rebleeding but increased the risk of delayed cerebral ischemia; therefore, they are used only in rare cases in which the patient is unable to undergo early surgery and has a low risk for the development of vasospasm. The most definitive means of preventing rebleeding is clipping or coiling the aneurysm.

Vasospasm is the narrowing of capacitance vessels at the base of the brain associated with arteriographic evidence of narrowing. Approximately half the patients with arteriographic arterial narrowing have clinical symptoms (focal or global neurologic deficit); of these patients, 15% to 20% will suffer ischemic stroke or death. Delayed cerebral ischemia is most common 4 to 14 days after acute subarachnoid hemorrhage and is an independent predictor of poor outcome. Risk factors for the development of vasospasm include hyponatremia, hypovolemia, antihypertensive treatment, antifibrinolytic treatment, and, most important, the amount and location of the blood on CT scan. The Fisher Grading Scale correlates the severity of vasospasm with CT findings of blood volume and location (Table 3) [3]. Transcranial Doppler ultrasonography is normally performed on day 3 after subarachnoid hemorrhage and every other day postoperatively for vasospasm surveillance. Standard preventive measures include nimodipine therapy and triple H therapy (hypertension, hypervolemia, and hemodilution). Because of the risk for rebleeding, definitive aneurysm treatment before the initiation of triple H therapy is preferred. Hypervolemia and hypertension can be achieved with a combination of intravenous fluids, albumin, and pressors. Viscosity can be reduced without compromising oxygen-carrying capacity by using hemodilution to a hematocrit of 33%. Triple H therapy should be discontinued if clinical or CT evidence of a large infarction or cerebral edema is present. When conservative medical management fails, intra-arterial papaverine therapy or angioplasty may be beneficial.

Hydrocephalus may be present on admission or may be the cause of acute, early deterioration, which is often heralded by a decreased level of consciousness. Risk factors for hydrocephalus include increasing age, hypertension, posterior circulation aneurysm, or CT evidence of intraventricular blood or diffuse subarachnoid blood. When patients have dilated ventricles on admission but are alert, intervention should be delayed because only one third of these patients become symptomatic. Any deterioration in the level of consciousness warrants immediate intervention.

Table 3. Fisher grading scale

Grade	Blood on computed tomography	Patients, *n*	Angiographic vasospasm, %	Symptomatic vasospasm, %
1	None	14	29	0
2	Diffuse subarachnoid blood	21	52	10
3	Clot more than 1 mm thick	46	96	91
4	Intracerebral or intraventricular hemorrhage with or without diffuse subarachnoid blood	7	43	0

Treatment

Pharmacologic treatment

Initial management of subarachnoid hemorrhage

Fluids

Fluid depletion or restriction carries an increased risk for development of delayed cerebral ischemia.

In one study, administration of 3 L of normal saline per day was associated with reductions in the total case-fatality rate and in the incidence of ischemia when rates of rebleeding and hydrocephalus were equal [4, Class III].

Standard procedure Intravenous administration of 2.5 to 3.5 L of normal saline, 0.9%, each day.

Contraindications Cardiogenic shock.

Main drug interactions None.

Main side effects Pulmonary edema, electrolyte disturbances, and cardiac ischemia.

Special points It is important to maintain accurate intake and output measurements. Fluids should be increased for insensible losses (*eg*, fever). Initial goals for hemodynamic variables are central venous pressure greater than 8 and pulmonary artery wedge pressure greater than 6 to 10.

Cost effectiveness The average wholesale price of 1 L of normal saline is $0.58.

Initial management of blood pressure

- Management of acute blood pressure is controversial. Impaired autoregulation results in pressure-dependent cerebral blood flow. Therefore, decreasing the blood pressure may decrease the cerebral blood flow and increase the risk of delayed cerebral ischemia. On the other hand, increased blood pressure may pose a risk of rebleeding. Studies on the safe threshold of blood pressure management are inconclusive with a wide variety of practices.
- In general, treating mean arterial blood pressures greater than 130 mm Hg is recommended. To calculate the mean arterial blood pressure, use the following formula: **2(diastolic blood pressure) + systolic blood pressure/3**.

Labetalol

Standard dosage Intravenous administration of 10 to 80 mg every 10 minutes or an intravenous infusion of 2 mg/min (up to 300 mg total).

Contraindications Heart failure, bronchospasm, severe bradycardia, and second- or third-degree atrioventricular block.

Main drug interactions May potentiate other antihypertensive agents.

Main side effects Hypotension, bradycardia, rash, and nausea.

Special points The short half-life of labetalol makes it easy to titrate the dose in patients with labile hypertension.

Cost effectiveness The average wholesale price is $18.73 per 20-mg intravenous dose.

Hydralazine

Standard dosage	Intravenous administration of 10 to 20 mg every 4 to 6 hours.
Contraindications	Allergy, mitral valve rheumatic disease, or coronary artery disease.
Main drug interactions	May potentiate other antihypertensive agents, especially diazoxide. It may also reduce the pressor response to epinephrine.
Main side effects	Hypotension, systemic lupus erythematosus, rash, tachycardia, and diarrhea.
Special points	May theoretically increase intracranial pressure as a result of vasodilation. The long half-life of hydralazine makes it difficult to titrate the dose in patients with labile hypertension.
Cost effectiveness	The average wholesale price is $157.50 for a 20-mg intravenous dose.

Esmolol

Standard dosage	Intravenous administration of a loading dose of 500 μg/kg and maintenance with an intravenous infusion of 50 to 200 μg/kg per minute.
Contraindications	Cardiogenic shock, congestive heart failure, second- and third-degree atrioventricular block, sinus bradycardia, and asthma or bronchospastic disease.
Main drug interactions	Can potentiate nondepolarizing neuromuscular blocking agents and other antihypertensive agents. Should not be taken concurrently with a monoamine oxidase inhibitor. Concurrent use with intravenous phenytoin can produce an additive cardiac depressant effect. Morphine can increase the esmolol steady-state level by 46%. Esmolol can increase the digoxin level by 10%.
Main side effects	Bradycardia, hypotension, nausea, and bronchospasm.
Special points	The half-life is 4.5 minutes.
Cost effectiveness	The average wholesale price is $160.12 per 5-g dose.

Enalaprilat

Standard dosage	Intravenous administration of 0.625 to 1.25 mg every 6 hours.
Contraindications	Hypersensitivity and history of angioedema due to use of angiotensin-converting enzyme inhibitors.
Main drug interactions	Can potentiate other antihypertensive agents. Aspirin and nonsteroidal anti-inflammatory drugs can impair the antihypertensive effect of enalaprilat. Hyperkalemia or renal dysfunction can result when enalaprilat is used in combination with trimethoprim or cyclosporine.
Main side effects	Hypotension, renal impairment in patients with renal artery stenosis, and diarrhea.
Special points	The long half-life of enalaprilat (1.3 hours) makes labile hypertension more difficult to control.
Cost effectiveness	The average wholesale price is $14.75 per 1.25-mg dose.

Diazoxide

Standard dosage	Intravenous administration of 50 to 150 mg every 5 to 10 minutes or an intravenous infusion of 15 to 30 mg/min (up to 600 mg total).
Contraindications	Allergy, hypotension, and coarctation of the aorta or atrioventricular shunt.
Main drug interactions	May potentiate other antihypertensive agents. Can displace protein-bound substrates, alter requirements for insulin or hypoglycemic agents, increase metabolism, and decrease protein binding of phenytoin.
Main side effects	Hypotension, sodium and water retention, hyperglycemia, and sweating and flushing.
Cost effectiveness	The average wholesale price is $3.70 per 50-mg intravenous dose.

Nicardipine

Standard dosage	Intravenous administration of 2 to 10 mg/h.
Contraindications	Hypersensitivity to calcium channel blockers. Use with precaution in patients with liver or renal disease or with severe aortic stenosis.

Main drug interactions Can potentiate the effects of other antihypertensives.
Main side effects Flushing, tachycardia, hypotension, pedal edema, angina, dizziness, nausea, constipation, myalgia, and cramps.
Special points The half-life of nicardipine is 1 to 4 hours.

Prevention of seizures

- Approximately 10% to 20% of patients who present with subarachnoid hemorrhage have seizures, most often within the first 24 hours after hemorrhage.
- Risk factors for seizures include middle cerebral artery aneurysm, intracerebral hemorrhage, infarction, or history of hypertension.
- Seizures can cause respiratory compromise and increase cerebral blood flow and blood pressure, posing a potential threat for rebleeding.
- Antiepileptic prophylaxis should be considered for most patients with subarachnoid hemorrhage. The antiepileptic drug dose should be tapered over 1 to 3 months after subarachnoid hemorrhage unless a history of seizures, hematoma, or infarction is present.
- Phenytoin or fosphenytoin is the drug of choice. Alternatives, in the case of drug sensitivity, are carbamazepine in patients taking oral medications or phenobarbitol in patients who require an intravenous route of administration.

Phenytoin

Standard dosage An intravenous loading dose of 10 to 20 mg/kg and a maintenance dosage of 5 mg/kg per day, intravenously or orally.
Contraindications Allergy, sinus bradycardia, or atrioventricular block. Should be used with caution in patients with renal or hepatic disease.
Main drug interactions Phenytoin can reduce the efficacy of some calcium-channel blockers, including nimodipine, theophylline, furosemide, digoxin, midazolam, acetaminophen, Demerol (Abbott Hospital Products, Abbott Park, IL), corticosteroids, and quinidine. Concurrent use of phenytoin with amiodarone, cimetidine, ranitidine, diltiazem, or omeprazole may increase the toxicity of phenytoin. Concurrent use of phenytoin with diazoxide may reduce the efficacy of phenytoin and produce hypoglycemia. Lidocaine may have an additive cardiac depressant effect when used in conjunction with dilantin because both drugs are Class Ia antiarrhythmic agents.
Main side effects Rash, purple glove syndrome, confusion, ataxia, nystagmus, and hypotension and bradycardia during infusion.
Special points The therapeutic level is 10 to 20 μg/mL.
Cost effectiveness The average wholesale price is $5.97 per 300-mg intravenous dose.

Fosphenytoin

Standard dosage A loading dose of 10 to 20 mg of phenytoin equivalents per kg, intravenously or intramuscularly, administered at up to 100 to 150 mg of phenytoin equivalents per minute, and maintenance therapy with 5 mg of phenytoin equivalents per kg per day, intravenously or intramuscularly.
Contraindications Allergy, sinus bradycardia, or atrioventricular block. Should be used with caution in patients with renal or hepatic disease.
Main drug interactions Fosphenytoin can reduce the efficacy of some calcium-channel blockers, including nimodipine, theophylline, furosemide, digoxin, midazolam, acetaminophen, Demerol (Abbott Hospital Products, Abbott Park, IL), corticosteroids, and quinidine. Concurrent use with amiodarone, cimetidine, ranitidine, diltiazem, or omeprazole may increase the toxicity of fosphenytoin. Concurrent use with diazoxide may

	reduce the efficacy of fosphenytoin and produce hypoglycemia. Lidocaine may have an additive cardiac depressant effect when used in conjunction with dilantin because both drugs are Class Ia antiarrhythmic agents.
Main side effects	Somnolence, ataxia, nystagmus, paresthesias, pruritus, and hypotension with infusion.
Special points	Fosphenytoin is superior to phenytoin in that it produces less hypotension with infusion, has a faster infusion rate, and carries a reduced risk of development of phlebitis.
Cost effectiveness	The average wholesale price is $54.00 per 300-mg intravenous dose.

Carbamazepine

Standard dosage	Administration of 5 to 8 mg/kg/day PO or NG divided in three doses.
Contraindications	Hypersensitivity, history of bone marrow depression, or concomitant use of monoamine oxidase inhibitors. Use with precaution in liver or kidney failure.
Main drug interactions	Carbamazepine decreases the effectiveness of benzodiazepines, including midazolam, corticosteroids, tricyclic antidepressants, lamotrigine, topiramate, tiagabine, and nimodipine. Cimetidine, clarithromycin, erythromycin, diltiazem, verapamil, and valproic acid may cause carbamazepine toxicity. Addition of carbamazepine to phenytoin may increase or decrease levels of phenytoin. Phenytoin decreases the levels of carbamazepine.
Main side effects	Rash, nausea, dizziness, unsteadiness, diplopia, and syndrome of inappropriate antidiuretic hormone secretion. Rarely causes aplastic anemia, pancytopenia, or agranulocytosis.
Cost effectiveness	The average wholesale price of a 10-day supply of carbamazepine (200 mg tid) is $8.70.

Phenobarbital

Standard dosage	Intravenous administration of a loading dose of 10 to 20 mg/kg, then 2 to 3 mg/kg/day.
Contraindications	Hypersensitivity, porphyria, and severe liver dysfunction. Use with precaution in renal dysfunction.
Main drug interactions	Phenobarbital decreases the effectiveness of benzodiazepines, corticosteroids, and calcium channel blockers, including nimodipine, carbamazepine, lamotrigine, valproic acid, and tiagabine. Phenobarbital may cause an increase, decrease, or no change in the levels of phenytoin. Valproic acid may cause phenobarbital toxicity.
Main side effects	Hypotension, lethargy/sedation, respiratory depression, nausea, vomiting, and rash. Rarely causes agranulocytosis or thrombotic thrombocytopenic purpura.
Special points	The half-life of phenobarbital is 1.5 to 4.9 days.
Cost effectiveness	The average wholesale price of an intravenous loading dose of phenobarbital in a 70-kg person is $4.76.

Pain control and sedation

- Pain, ventilator-related agitation, and suctioning can increase blood pressure and intracranial pressure and therefore must be controlled to prevent rebleeding.
- Pain control can be achieved with simple analgesics or narcotics if necessary.
- Midazolam or propofol is ideal for sedation because their short half-lives allow for close monitoring of neurologic status.

Codeine

Standard dosage	Administration of 30 to 60 mg (orally, intramuscularly, or intravenously) every 4 hours as needed.

Contraindications	Allergy.
Main drug interactions	May potentiate other narcotics.
Main side effects	Constipation.
Special points	Codeine is generally well tolerated and, in low doses, is not too sedating. It is important to add a stool softener to prevent sudden increases in intracranial pressure associated with Valsalva's maneuver.
Cost effectiveness	The average wholesale price is $0.36 per 30-mg tablet.

Midazolam

Standard dosage	Administration of 0.02 to 0.1 mg/kg per hour (1 to 7 mg/h). Dose should be titrated to sedation.
Contraindications	Hypotension and respiratory depression. Midazolam should be used with caution in patients with hepatic or renal failure.
Main drug interactions	Concurrent use of cimetidine, ranitidine, famotidine, omeprazole, macrolide antibiotics, diltiazem, or verapamil may increase the concentration of midazolam. Carbamazepine may induce metabolism of midazolam and reduce its efficacy. Larger doses may also be needed with concurrent use of theophylline or phenytoin. Fentanyl can increase the risk of respiratory depression.
Main side effects	Respiratory depression, hypotension, amnesia, and euphoria.
Special points	The half-life of midazolam is 1.8 to 6.4 hours.
Cost effectiveness	Approximately $130 per day in a 70-kg person.

Propofol

Standard dosage	Administration of 5 to 50 μg/kg per minute. Dose should be titrated to sedation.
Contraindications	Hypersensitivity.
Main drug interactions	Can extend the sedative effects of benzodiazepines. Theophylline may reduce the effectiveness of propofol.
Main side effects	Hypotension, nausea, sedation, respiratory depression, and hepatotoxicity.
Special points	The half-life of propofol is 1.5 to 12.4 hours.
Cost effectiveness	Approximately $360 to $1000 per day in a 70-kg person.

Morphine

Standard dosage	Intramuscular or intravenous administration of 2.5 to 10 mg every 4 to 6 hours as needed.
Contraindications	Hypersensitivity, respiratory depression, and paralytic ileus. Use with precaution in patients with liver or kidney failure, seizures, or hypotension.
Main drug interactions	Morphine can potentiate the respiratory depressant effect of other medications. It may also reduce the efficacy of trovafloxacin.
Main side effects	Hypotension, respiratory depression, hallucinations, nausea, constipation, and rash.
Cost effectiveness	The average wholesale price for a 2-mg intravenous dose is $0.83.

Gastrointestinal prophylaxis

- Patients in the intensive care unit have a high incidence of gastritis, although significant gastrointestinal bleeding is uncommon.
- The incidence of gastrointestinal bleeding in patients with subarachnoid hemorrhage is approximately 4%.
- Gastrointestinal prophylaxis is recommended in patients with subarachnoid hemorrhage who are mechanically ventilated or have a history of peptic ulcer disease. This prophylaxis may be discontinued once enteral feedings begin.

- In a recent study [5, Class I], intravenous ranitidine was found to be superior to sucralfate in preventing serious gastrointestinal bleeding. The rate of ventilator-associated pneumonia was higher with ranitidine than with sucralfate, however, although the difference was not significant.

Sucralfate

Standard dosage	Oral or nasogastric administration of 1 g four times per day.
Contraindications	Allergy.
Main drug interactions	Reduces absorption of phenytoin, digoxin, ranitidine, and fat-soluble vitamins. Antacids may impair the effectiveness of sucralfate.
Main side effects	Nausea and gastric discomfort.
Cost effectiveness	The average wholesale price is $2.73 per day.

Ranitidine

Standard dosage	Intravenous administration of 50 mg every 8 hours or an intravenous infusion of 6.25 mg/h.
Contraindications	Hypersensitivity.
Main drug interactions	Antacids may reduce absorption of ranitidine. Ranitidine may increase concentrations of phenytoin, calcium-channel blockers, and midazolam. The hypoglycemic effect of glipizide is augmented by concurrent use. Ranitidine may reduce theophylline metabolism, resulting in toxicity.
Main side effects	Confusion, thrombocytopenia, rash, and nausea.
Special points	Increasing the gastric pH may predispose patients to nosocomial pneumonia.
Cost effectiveness	The average wholesale price is $11.97 per day.

Prevention of delayed cerebral ischemia

Nimodipine

Standard dosage	Oral or nasogastric administration of 60 mg every 4 hours for 21 days.
Contraindications	Hypotension.
Main drug interactions	May potentiate the hypotensive effects of other antihypertensive agents.
Main side effects	Hypotension.
Special points	Oral nimodipine has been shown to reduce the rate of cerebral infarction due to vasospasm by 34% [6, Class I] and to improve outcome [6, Class I; 7, Class I]. On angiographic study, it has not been shown to change blood vessel caliber.
Cost effectiveness	The average wholesale price is $75.04 per day.

Triple H therapy

- Triple H therapy is used prophylactically after aneurysm treatment in patients at risk for vasospasm (according to the Fisher scale). Hemodynamic goals are modified when a patient becomes symptomatic.
- In low- or moderate-risk patients (Fisher grades 1 or 2), hypervolemia is maintained with crystalloid and colloid as needed to maintain the following hemodynamic parameters: systolic blood pressure greater than 160 mm Hg, central venous pressure (CVP) greater than 8, and pulmonary capillary wedge pressure (PCWP) greater than 10 to 14.
- In high-risk patients (patients with Fisher grade 3 or with increased velocities according to transcranial Doppler examination), hypervolemia and hypertension are induced with crystalloids, colloids, and pressors to achieve systolic blood pressure greater than 180 mm Hg, CVP greater than 10, and PCWP greater than 12 to 14.

- When a patient becomes symptomatic, the systolic blood pressure should be increased to 20 to 40 mm Hg above baseline (up to 210 mm Hg), the CVP should be increased to 8 to 12, and the PCWP should be elevated to 14 to 18 with a combination of crystalloid, colloid, and pressors. If these measures fail, emergent angioplasty or intra-arterial papaverine therapy should be considered.
- We do not recommend the routine use of dextran or hetastarch as a volume expander because of the potential for associated coagulopathies and thrombocytopenia.

Crystalloid

Standard dosage	Administration of 3 L of normal saline, 0.9%, per day.
Contraindications	Cardiogenic shock.
Main drug interactions	None.
Main side effects	Pulmonary edema, cardiac ischemia, electrolyte disturbances, coagulopathy, complications of invasive monitoring, and hemorrhagic infarction.
Cost effectiveness	The average wholesale price of 1 L of normal saline is $0.58.

Colloid

Standard dosage	Administration of 250 to 500 mL of 5% albumin every 6 to 8 hours.
Contraindications	Cardiogenic shock.
Main drug interactions	None.
Main side effects	Same as for fluid, plus urticaria and dilutional hyponatremia.
Cost effectiveness	The average wholesale price of 250 mL of 5% albumin is $55.60.

Dopamine

Standard dosage	Intravenous infusion of 2 to 20 μg/kg per minute.
Contraindications	Allergy or hypersensitivity, concurrent use of monoamine oxidase inhibitor, peripheral necrosis, or gangrene.
Main drug interactions	Other sympathomimetics may exacerbate adverse cardiovascular effects.
Main side effects	Tachycardia and other arrhythmias, cardiac ischemia, and peripheral ischemia.
Special points	Dopamine has a dose-dependent effect. At low dosages (1 to 3 μg/kg per minute), it primarily affects dopaminergic receptors. At intermediate dosages (3 to 10 μg/kg per minute), it affects β receptors. At high dosages (10 to 20 μg/kg per minute), it affects α and β receptors.
Cost effectiveness	The average wholesale price is $72 for 200 mg/250 mL.

Phenylephrine

Standard dosage	Intravenous infusion of 2 to 10 μg/kg per minute.
Contraindications	Hypersensitivity, hypertension, and tachycardia.
Main drug interactions	Monoamine oxidase inhibitors and other sympathomimetic drugs.
Main side effects	Arrhythmia, tachycardia, cardiac and peripheral ischemia, and hypertension.
Special points	Phenylephrine is an α1-agonist.
Cost effectiveness	The average wholesale price is $67 for 10 mg/250 mL.

Surgery

- The goals of surgical intervention are to isolate the aneurysm from the arterial circulation and to preserve flow in the parent vessel with minimal trauma to the brain, cranial nerves, and blood vessels.
- Surgery is influenced by the complexity of the aneurysm, the difficulty of the surgical approach, and the clinical grade of the patient.
- The International Cooperative Study on the Timing of Aneurysm Surgery and other studies revealed a reduction in the rate of rebleeding when surgery was done within 0 to 3 days after subarachnoid hemorrhage [8]. Early surgery or interventional procedures are standard for those with moderate- or good-grade subarachnoid hemorrhage.
- In patients with poor-grade subarachnoid hemorrhage (World Federation of Neurological Surgeons Scale grade 4 or 5 or Hunt Hess Scale grade 4 or 5), surgical management and timing are more controversial. Patients with poor-grade subarachnoid hemorrhage have an increased risk of medical complications, rebleeding, and delayed ischemia associated with vasospasm. The mortality rates associated with grade 4 and grade 5 hemorrhages are 34% and 71%, respectively. Immediate surgical intervention is indicated in patients with poor-grade subarachnoid hemorrhage and large intracerebral hemorrhage or hydrocephalus because the intracerebral hemorrhage or hydrocephalus may be the reason for the poor condition. In cases of poor-grade subarachnoid hemorrhage without evidence of hydrocephalus or intracerebral hemorrhage, no difference in mortality rate or outcome is seen between patients receiving early surgery and those receiving late surgery.

Surgical clipping

Standard procedure	A craniotomy is performed, and the aneurysm is isolated. Proximal and distal control of the parent blood vessel is then achieved. A surgical clip is placed at the neck of the aneurysm, leaving flow in the parent blood vessel. Barbiturates and hypothermia are used to reduce ischemic injury when cross-clamping of arteries is necessary.
Contraindications	Tenuous cardiorespiratory status.
Complications	Cerebral infarction, intracerebral hemorrhage, aneurysmal rebleeding, and infection.
Cost effectiveness	Variable.

External ventricular drain placement

Hydrocephalus occurs in 20% to 25% of patients with acute subarachnoid hemorrhage. It is a common cause of deterioration, which is often heralded by a decreasing level of consciousness. Early hydrocephalus is usually secondary to obstruction, whereas late hydrocephalus is due to reduced absorption of cerebrospinal fluid in the arachnoid granules.

When ventricles are dilated on admission but the patient is alert, intervention should be delayed because only one third of these patients become symptomatic. Any deterioration in the level of consciousness warrants immediate intervention.

Standard procedure	A burr hole is placed in the right frontal region, 3 cm lateral to the midline, just anterior to the coronal suture. The ventricular catheter is passed into the lateral ventricle. The external tubing is tunneled under the scalp and connected to the outflow bag. The bag is set 10 to 20 cm above the external auditory meatus (level of the foramen of Monro).
Contraindications	Ipsilateral intraparenchymal hemorrhage and scalp infection.
Complications	Risk for rebleeding, intraparenchymal hemorrhage, and infection.

Special points The external ventricular drain catheter should be changed every 5 to 7 days. Prophylactic daily intravenous administration of antibiotics (cefazolin or vancomycin) is warranted until the catheter is withdrawn.

Cost effectiveness Variable.

Interventional procedures

Initial management

- Arteriography is the most accurate method with which to characterize the size and location of an aneurysm, its relationship to other vessels, and the presence of intraluminal thrombus.
- Additional information obtained from arteriography includes evidence of multiple aneurysms (in up to 20% of patients), associated arteriovenous malformation, and vasospasm.
- Four-vessel arteriography should generally be performed in any patient in whom a subarachnoid hemorrhage is suspected. A posterior inferior cerebellar artery aneurysm may be missed if only a three-vessel study is done.

Arteriography

Standard procedure A microcatheter is guided to the origin of each artery using a transfemoral approach, and radiopaque dye is injected.

Contraindications Renal insufficiency and allergy to dye.

Complications Nonneurologic complications include risk of acute renal failure; hypersensitivity or allergic reaction; and development of an infection, a hematoma, or a pseudoaneurysm at the site of arterial entry. The risk of development of a transient neurologic deficit is approximately 0.5%. The risk of development of a persistent neurologic deficit is approximately 0.1%. Aneurysmal rebleeding is a rare complication.

Special points Although angiography is the gold standard, 16% of angiographic results may be false negatives. False-negative results may be caused by vasospasm, thrombus, or an inadequate study. Repeated angiography is recommended in patients with subarachnoid hemorrhage whose initial angiogram is negative.

Cost effectiveness Variable.

Aneurysm management

Selective aneurysm occlusion

Selective occlusion of an aneurysm with detachable coils is an alternative to surgical clipping. The decision to proceed with endovascular treatment is influenced by the morphology and location of the aneurysm, the difficulty of the surgical approach, and the clinical grade of the patient.

The standard for selective endovascular occlusion of intracranial aneurysms is the GDC (Guglielmi detachable coils) system. Negatively charged blood elements migrate to the positively charged platinum electrode coil, promoting thrombosis.

The goal of treatment is to fill the lumen as completely as possible. This results in thrombosis of the aneurysm and disruption of flow within the aneurysm.

The main advantage of GDC coils over previous coils and endovascular polymers is the ability of the GDC coils to be repositioned or withdrawn before deployment. Other advantages include the ability to promote thrombus formation within the aneurysm, the number of coil sizes available, and the compliance of the coil (which allows it to adapt to the shape of the aneurysm).

Standard procedure A stainless-steel guidewire with attached platinum coils is guided into the aneurysm through a transfemoral approach. When the guidewire has been properly placed, an electric current is applied to the proximal end of the guidewire. The positive charge of the platinum coil attracts the negatively charged blood products, causing thrombus formation. The coil is detached. Multiple coils of various diame-

ters and sizes can be introduced into an aneurysm until complete packing is achieved. Most patients require only a single procedure, but up to 20% may require multiple or staged procedures.

Contraindications Same as for angiography.

Complications Procedure-related morbidity is dependent on the size and location of the aneurysm, the vascular anatomy, and the clinical grade of the patient. Risks include (in descending order) cerebral embolism, intracerebral hemorrhage, thrombosis, perforation of the aneurysm, and worsening symptoms.

Special points Success with the coiling procedure is increased when the aneurysm is small (less than 1 cm) and when the size of the aneurysm neck relative to the dome is small. In patients with a small-neck aneurysm, the occlusion rate is close to 90%, and the recanalization rate is 7% [9]. If the aneurysm is large and has a wide neck, the occlusion rate is 50%, and the recanalization rate is 30%. If coils are not tightly packed, recanalization may occur. In addition, if thrombus is present, remodeling of clot can cause migration of coils. Angiographic follow-up in 1 to 3 months and 6 to 12 months clarifies the degree of aneurysm obliteration.

Cost effectiveness Variable.

Large-vessel balloon occlusion

Indications for large-vessel occlusion include technically difficult surgery, such as that done for petrous or cavernous internal carotid artery aneurysms; presence of ectatic fusiform aneurysms without well-defined necks; and presence of aneurysms in which coiling or surgical clipping is not safe.

Although balloons can be used for direct aneurysm occlusion, other techniques have supplanted this method.

Standard procedure A test occlusion should first be performed with anticoagulation. In this procedure, the catheter is guided to the proximal parent artery through a transfemoral approach. The balloon is inflated until occlusion of the artery is complete with cessation of blood flow. For carotid balloon occlusion, test occlusion is done for 30 minutes alone or in conjunction with a Diamox (Storz/Lederle, St. Louis, MO) single photon emission computed tomography or xenon CT scan. If tolerated, a detachable balloon can be used to achieve permanent occlusion.

Contraindications Failed test occlusion. If a test occlusion fails, some perform a bypass procedure and then proceed with balloon occlusion.

Complications There is approximately a 7% to 10% chance of a transient neurologic deficit during the balloon occlusion procedure and a 1.5% to 5% chance of a permanent deficit, usually related to thromboembolism [10••]. Even if the trial balloon occlusion is successful, the patient still has approximately a 1% risk of cerebral infarction with permanent occlusion.

Special points Balloon occlusion has several advantages over surgical ligation. It allows for the monitoring of neurologic status in an awake patient and for the convenient assessment of collateral and residual aneurysm flow by angiography.

Cost effectiveness Variable.

Vasospasm management

Angioplasty

Angioplasty is used to dilate narrowed large arterial segments mechanically. It is indicated in selected patients with severe symptomatic vasospasm that is not responsive to medical therapy.

Standard procedure A guidewire with a nondetachable silicone balloon is threaded through a transfemoral approach to the affected arteries. The balloon is inflated and then deflated to dilate the vasospastic vessel mechanically.

Contraindications Angioplasty is contraindicated if a hypodensity is seen on the CT scan.
In general, angioplasty is reserved for patients who have already undergone aneurysmal clipping.

Complications Complications include aneurysmal rebleeding, arterial rupture or occlusion, and hemorrhagic infarction. Angioplasty may also result in the displacement of clips. The risks associated with an angiographic procedure are also present.

Special points Of 173 patients undergoing dilation, 95% had angiographic improvement noted clinically and 63% had clinical improvement [11]. Bejjani *et al*. [12•, Class III] noted dramatic or moderate clinical improvement in most patients, especially if angioplasty was done within 24 hours of onset of the neurologic deficit.

Cost effectiveness Variable.

Papaverine injection

Papaverine is a nonspecific vasodilator useful in the treatment of vasospasm.

It may be used alone or in combination with angioplasty for medically refractory vasospasm.

Standard procedure The catheter is advanced through a transfemoral approach close to the involved vessel. Papaverine dissolved in normal saline is infused at a dose of 100 to 300 mg over 30 to 60 minutes. It may take as long as 90 minutes for the maximum effect to occur.

Contraindications Hypersensitivity. Papaverine should be used with caution in patients with glaucoma, liver disease, and Parkinson's disease.

Complications Possible side effects include rash, increased heart rate and blood pressure, headache, lactic acidosis, nausea, transient mydriasis, and seizures.

Special points In a series by Numaguchi and Zoarski [13, Class II], angiographic improvement was common after papaverine injection, but only 50% of patients showed clinical improvement after the first, second, or third injection. Recurrence of vasospasm is common; the rate of this recurrence may be as high as 50% after a single injection [13, Class II; 14]. Papaverine should be delivered in close proximity to the affected vessel because a steal phenomenon may occur with a more proximal injection.

Cost effectiveness Variable.

Other treatments

Hyponatremia

- Hyponatremia is the most common electrolyte disturbance after subarachnoid hemorrhage. It occurs in 10% to 30% of patients, typically 2 to 10 days after the initial appearance of neurologic symptoms.
- Clinical manifestations of hyponatremia may include change in level of consciousness, asterixis, hemiparesis, seizure, or coma.
- Contributions to hyponatremia include excessive administration of hypotonic saline, syndrome of inappropriate antidiuretic hormone secretion due to hydrocephalus or pituitary-hypothalamic injury, and cerebral salt-wasting syndrome.
- Sodium levels less than 125 mmol should be treated with isotonic saline. Sodium chloride tablets may be added, and furosemide may be used to decrease the amount of free water. Three percent saline may be used for acute, symptomatic hyponatremia. The maximal rate of correction should be no greater than 12 mmol/L per day.
- If hyponatremia is resistant to isotonic saline, fludrocortisone (400 μg/d in two doses) may be used.
- Fluid restriction should be avoided because it increases the risk of development of a delayed ischemic neurologic deficit.

Cardiac complications

- Electrocardiographic changes and cardiac arrhythmias are common after aneurysmal subarachnoid hemorrhage and may be due to sustained sympathetic stimulation.
- Electrocardiographic abnormalities include ST-segment and T-segment changes, prominent U waves, QT prolongation, and sinus arrhythmias.
- Prophylactic antiarrhythmia medications are not indicated, but arrhythmias must be treated aggressively.

Airway management

- Intubation is indicated in patients who are unable to protect their airways or in patients with impaired oxygenation or ventilation.
- Hypoxemia must be treated aggressively because it can increase cerebral blood flow and intracranial pressure.
- Worsening hypoxemia may result from aspiration pneumonitis, pulmonary edema secondary to hypervolemic therapy or neurogenic pulmonary edema, pulmonary embolus, mucus plugging, nosocomial pneumonia, or the adult respiratory distress syndrome.
- The adult respiratory distress syndrome can reduce lung compliance, requiring increased levels of positive end expiratory pressure (PEEP). A PEEP greater than 15 can cause increased intracranial pressure; therefore, intracranial pressure should be monitored in patients with reduced levels of consciousness who require increasing levels of PEEP.
- Sedation may be necessary to prevent ventilator-induced agitation, which can increase intracranial pressure.
- If long-term ventilation is required, tracheostomy may be necessary to prevent tracheomalacia or stenosis.

Pulmonary complications

- Neurogenic pulmonary edema is a rare but dangerous complication of subarachnoid hemorrhage. Patients may present with rapid-onset dyspnea; production of pink, frothy sputum; and reduction in oxygen saturation. This may be complicated by reversible decompensation of the left ventricle. Treatment involves increasing PEEP to 10 to 15 mm Hg, adding diuretics, and consideration of early administration of an alpha-blocking agent, such as chlorpromazine.
- Hypervolemic therapy administered during management of vasospasm increases the risk of pulmonary edema. Hemodynamic monitoring with arterial line and Swan-Ganz catheters may be necessary to guide management. Morphine (a pulmonary vasodilator) and loop diuretics can be used cautiously to avoid acute decreases in blood pressure.
- Any critically ill, immobile patient is at risk for nosocomial pneumonia, adult respiratory distress syndrome, aspiration pneumonia, and pulmonary embolus. Appropriate surveillance of ventilated patients with clinical examination, chest radiography, and arterial blood gas testing is essential.

Prophylaxis for deep venous thrombosis

- The incidence of deep venous thrombosis in patients with subarachnoid hemorrhage is approximately 2%, even in those receiving standard prophylactic measures. The incidence of pulmonary embolism in these patients is approximately 1% to 2%.
- Use of pneumatic compression devices and compression stockings should be standard in every patient with subarachnoid hemorrhage.
- After clipping of the aneurysm, subcutaneous heparin is safe.
- Some advocate weekly ultrasonography of the lower extremities in immobile patients.

Emerging therapies

Vasospasm management

- The mechanism of vasospasm is incompletely understood but is probably related to blood breakdown products. Factors postulated to play a role in vasospasm include vasoactive free radicals and the balance of vasoconstricting agents (endothelin and eicosanoid) and vasodilating agents (prostacyclin and endothelium-derived relaxation factor). Ongoing drug trials are evaluating medications aimed at these potential mechanisms of vasospasm.
- **Tirilazad** is a 21-aminosteroid reported to reduce lipid peroxidation and stabilize cell membranes. Results of studies on the prevention of vasospasm have been equivocal. A European trial [15, Class I] showed reduced mortality rates and improved outcome in patients receiving 6 mg/kg per day for 10 days. No statistically significant difference in symptomatic vasospasm was seen, however. A North American trial [16, Class I] did not show any change in outcome or any difference in symptomatic vasospasm. Several differences between the studies may account for the difference in outcomes. In the European study, 50% of patients received phenytoin, and intravenous nimodipine was used. In the North American trial, all patients received oral nimodipine, and 90% received phenytoin. Phenytoin may reduce concentrations of tirilazad. Currently, phenytoin is not more efficacious than standard management and is more expensive.
- A randomized, controlled multicenter trial [17, Class I] evaluated the role of **intracisternal tissue plasminogen activator** in the prevention of delayed cerebral ischemia. The overall incidence of angiographic vasospasm was similar in both the group receiving tissue plasminogen activator and the control group. In one subset of patients with thick subarachnoid clot, a 56% relative reduction of severe vasospasm was found. No difference was seen in the rate of bleeding complications or in outcome. Further studies are needed to identify the best candidates for thrombolytic therapy and the optimal dose and timing of this therapy.
- **Hypothermia** may suppress neurotoxic glutamate release and reduce intracellular calcium accumulation, and it has been used with some success in patients with head trauma. Mild hypothermia (33° to 35°C) is being tried in some patients with subarachnoid hemorrhage [18, Class III]. Additional controlled studies are needed to determine which patients may benefit.
- A retrospective study showed a reduced risk of development of delayed cerebral ischemia in patients who were receiving **aspirin** before developing subarachnoid hemorrhage [19].

Aneurysm management

- Ongoing efforts are being made to overcome the technical difficulties of **endovascular procedures** and techniques.
- **Intravascular stents** have been used in combination with GDC coils in wide-based or fusiform aneurysms. The stent acts as a neck to the aneurysm to contain the coils [20].

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