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Managing aneurysmal subarachnoid hemorrhage: It takes a team

ABSTRACT

Patients with aneurysmal subarachnoid hemorrhage are at high risk of complications, including rebleeding, delayed cerebral ischemia, cerebral infarction, and death. This review presents a practical approach for managing this condition and its complications.

KEY POINTS

The key symptom is the abrupt onset of severe headache, commonly described as "the worst headache of my life."

Computed tomography without contrast should be done promptly when this condition is suspected.

Outcomes are improved when patients are managed in a high-volume center with a specialized neurointensive care unit and access to an interdisciplinary team.

Early aneurysm repair by surgical clipping or endovascular coiling is considered the standard of care and is the best strategy to reduce the risk of rebleeding.

Medical and neurologic complications are extremely common and include hydrocephalus, increased intracranial pressure, seizures, delayed cerebral ischemia, hyponatremia, hypovolemia, and cardiac and pulmonary abnormalities.

ANEURYSMAL SUBARACHNOID hemorrhage is a devastating condition, with an estimated death rate of 30% during the initial episode.^{1,2} Approximately the same number of patients survive but leave the hospital with disabling neurologic deficits.³

However, better outcomes can be achieved by systems that are able to work as a team on the collective goal of quick intervention to secure the ruptured aneurysm, followed by the implementation of measures to minimize secondary brain injury. Although the search for new diagnostic, prognostic, and therapeutic modalities continues, it is clear that there exists no "silver bullet" that will help all patients. Instead, it is the systematic integration and application of small advances that will ultimately maximize the patient's chances of survival and neurologic recovery.

This review focuses on the management of aneurysmal subarachnoid hemorrhage and its systemic and neurologic complications.

■ ANEURYSM IS THE MOST COMMON CAUSE OF SUBARACHNOID BLEEDING

Aneurysmal subarachnoid hemorrhage, ie, rupture of an intracranial aneurysm, flooding the subarachnoid space with blood, affects about 24,000 Americans each year.^{1,2} A ruptured aneurysm is the most common cause of subarachnoid hemorrhage, accounting for about 85% of cases. Less common causes include idiopathic benign perimesencephalic

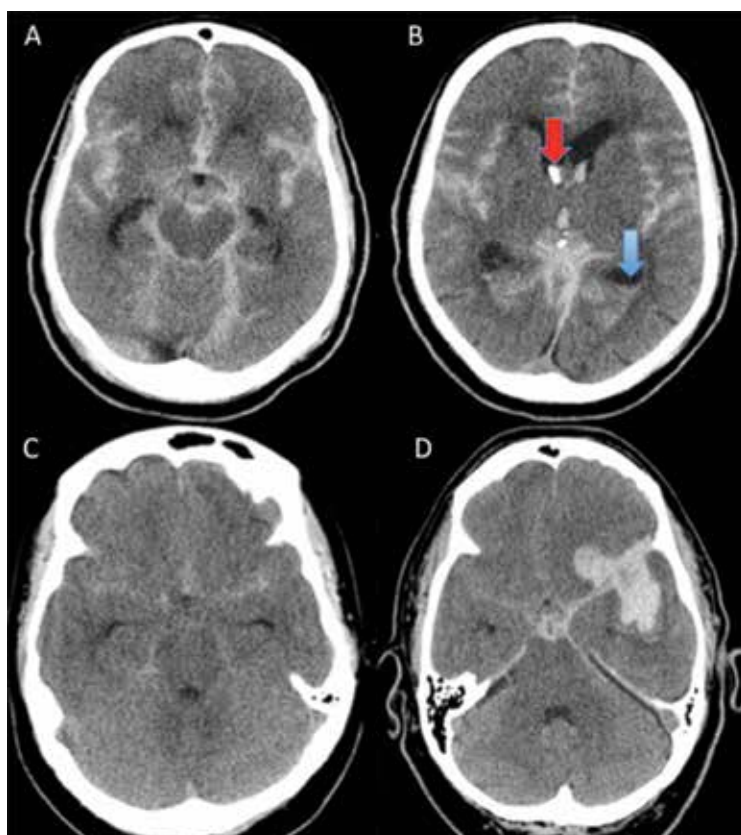


FIGURE 1. Computed tomographic grading scale (no contrast, transverse plane). The thickness of subarachnoid blood is an independent risk factor for angiographic vasospasm and delayed cerebral ischemia (see TABLE 1). **(A)** Modified Fisher 3: a thick layer of subarachnoid blood filling multiple basal cisterns. **(B)** Modified Fisher 4: bilateral intraventricular hemorrhage (blue arrow), and the tip of an external ventriculostomy drain (red arrow). **(C)** Modified Fisher 1. **(D)** Thick subarachnoid layer centered in the left sylvian fissure with rightward subfalcine herniation.

hemorrhage, arteriovenous malformation, dural arteriovenous fistula, and hemorrhagic mycotic aneurysm. These have their own natural history, pathophysiology, and specific treatment, and will not be addressed in this article.

Risk factors for aneurysmal subarachnoid hemorrhage include having a first-degree relative who had the disease, hypertension, smoking, and consuming more than 150 g of alcohol per week.⁴

CLINICAL PRESENTATION AND DIAGNOSIS

The key symptom of aneurysmal subarachnoid hemorrhage is the abrupt onset of severe headache that peaks in intensity over 1 hour,⁵

often described as “the worst headache of my life.” Headache is accompanied by brief loss of consciousness in 53% of cases (conversely, nearly half of patients maintain normal mental status), by nausea or vomiting in 77%, and by meningismus (neck pain or stiffness) in 35%.⁶

These clinical manifestations and risk factors have been incorporated into a decision rule:

Obtain brain imaging if the patient has acute headache reaching maximal intensity within 1 hour, associated with any of the following factors:

- Age 40 or older
- Neck pain or stiffness
- Witnessed loss of consciousness
- Onset during exertion
- “Thunderclap” headache (ie, instantly peaking pain)
- Limited neck flexion on examination.⁵

This decision rule has nearly 100% sensitivity for aneurysmal subarachnoid hemorrhage in clinical practice.⁵ *All patients require brain imaging if they have a severe headache plus either abnormal neurologic findings (eg, a focal neurologic deficit) or a history of cerebral aneurysm.*

Emergency physicians should have a low threshold for ordering noncontrast computed tomography (CT) of the head in patients with even mild symptoms suggesting aneurysmal subarachnoid hemorrhage. Failure to order CT is the most common diagnostic error in this situation.⁶ CT performed within 6 hours of headache onset is nearly 100% sensitive for this condition,⁷ but the sensitivity falls to 93% after the first 24 hours and to less than 60% after 5 days.⁸ In patients who have symptoms highly suggestive of aneurysmal subarachnoid hemorrhage but a normal CT, lumbar puncture is the next diagnostic step.

There are two alternatives to CT followed by lumbar puncture: ie, noncontrast CT followed by CT angiography,^{9,10} and magnetic resonance imaging followed by magnetic resonance angiography. In patients with suspicious clinical symptoms but negative CT results, CT followed by CT angiography can rule out aneurysmal subarachnoid hemorrhage with a 99% probability.^{9,10} However, CT followed by lumbar puncture remains the standard of care and carries a class I recommendation in the

TABLE 1

Clinical grading scales

Grade	WFNS grading system ¹¹	Hunt and Hess grading system ¹²
Good	1 Glasgow Coma Scale (GCS) 15 without hemiparesis	Asymptomatic or mild headache and slight nuchal rigidity
	2 GCS 14–13 without hemiparesis	Moderate to severe headache, nuchal rigidity, no focal neurologic deficit other than cranial nerve palsy
	3 GCS 14–13 with hemiparesis	Confusion, lethargy, or mild focal neurologic deficit other than cranial nerve palsy
Poor	4 GCS 12–7 with or without hemiparesis	Stupor or moderate to severe hemiparesis
	5 GCS 6–3 with or without hemiparesis	Coma, extensor posturing, moribund appearance

WFNS = World Federation of Neurological Surgeons

TABLE 2

Computed tomographic grading scales for subarachnoid hemorrhage

Grade	Fisher scale ¹³	Modified Fisher scale ¹⁴	Risk of vasospasm ¹⁴
0	—	No subarachnoid or intraventricular hemorrhage	0%
1	No subarachnoid hemorrhage or intraventricular hemorrhage	Minimum or thin subarachnoid hemorrhage, no intraventricular hemorrhage in either lateral ventricle	6%
2	Diffuse, thin subarachnoid hemorrhage, no clot > 1 mm in thickness	Minimum or thin subarachnoid hemorrhage, with intraventricular hemorrhage in both lateral ventricles	15%
3	Localized thick layer of subarachnoid clot > 1 mm in thickness	Thick subarachnoid hemorrhage, no intraventricular hemorrhage	35%
4	Predominant intraventricular hemorrhage or intracerebral hemorrhage without thick subarachnoid hemorrhage	Thick subarachnoid hemorrhage with intraventricular hemorrhage in both lateral ventricles	34%

Risk factors:
Family history
Hypertension
Smoking
Heavy drinking

American Heart Association guidelines for ruling out subarachnoid hemorrhage.⁵

■ GRADING THE SEVERITY OF SUBARACHNOID HEMORRHAGE

Age, the thickness of the blood layer in the subarachnoid space, intraventricular hemorrhage, and the findings of the neurologic ex-

amination at presentation are predictors of long-term outcomes in aneurysmal subarachnoid hemorrhage (FIGURE 1).

Different grading systems used in clinical practice are based on the findings on the initial neurologic examination and on the initial noncontrast CT (ie, the thickness of the blood, and whether intraventricular hemorrhage is present). Among the most widely

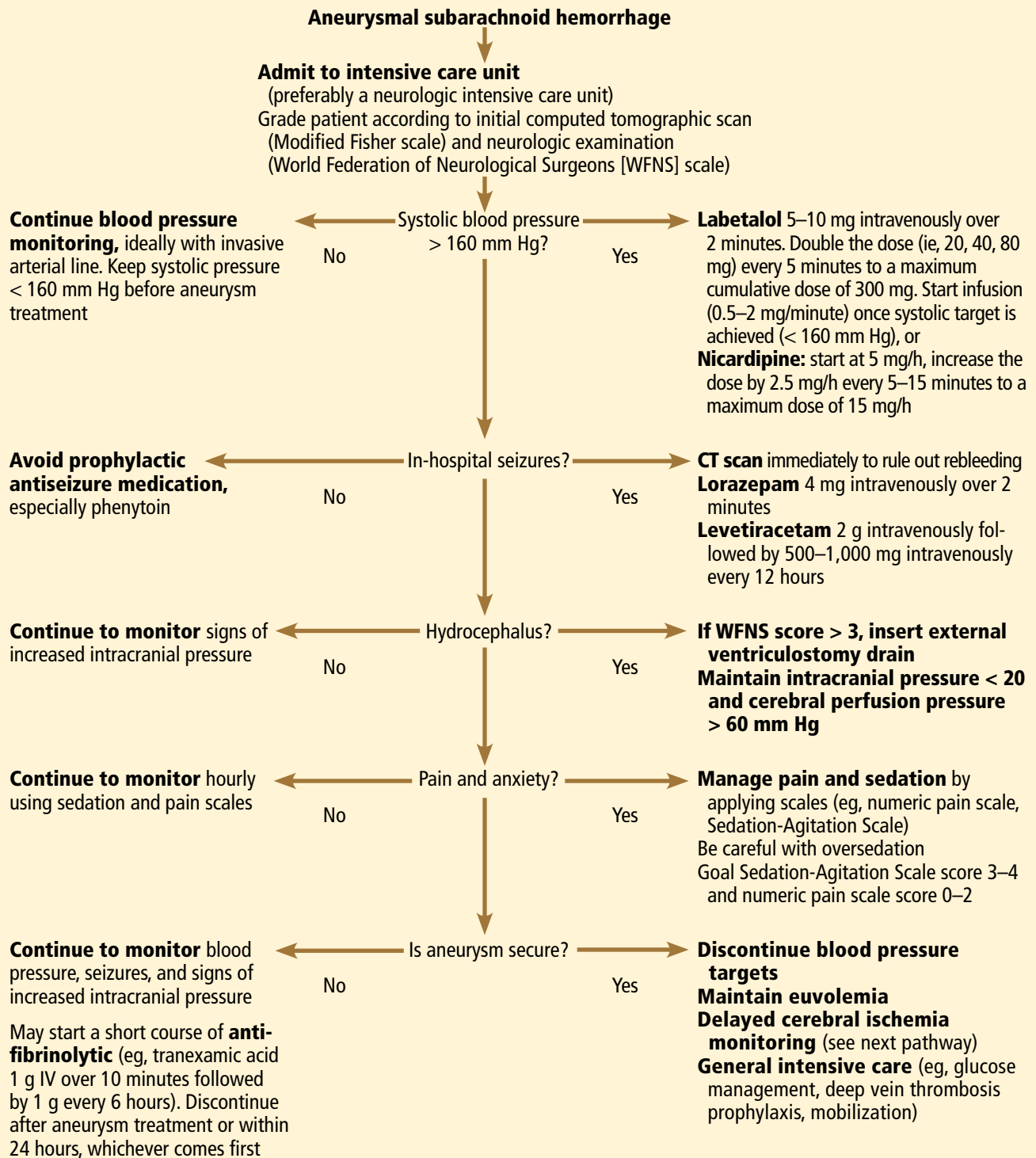


FIGURE 2. Initial management pathway.

DEVELOPED BY THE AUTHORS IN COLLABORATION WITH THE ST. MICHAEL'S HOSPITAL SUBARACHNOID HEMORRHAGE COMMITTEE (DRS. ANDREW BAKER, SIMON ABRAHAMSON, ADITYA BHARATHA, JULIAN SPEARS, ALBERTO GOFFI, DIPANKA SARMA, ANDREA RIGAMONTI, ZUL KARDARELI, WALTER MONTANERA, AND R. LOCH MACDONALD). PRESENTED AT THE 11TH ANNUAL MEETING OF THE NEUROCRITICAL CARE SOCIETY, OCTOBER 2013, PHILADELPHIA, PA.

used are those developed by Hunt and Hess¹² and by the World Federation of Neurological Surgeons¹¹ (WFNS), and the CT grading scales (Fisher¹³ or its modified version¹⁴) (TABLES 1 AND 2). With either the Hunt and Hess scale or the WFNS scale, the higher the score, the worse the patient's probable outcome. Scores on both Fisher scales correlate with the risk of angiographic vasospasm. The higher the grade, the higher the risk of angiographic vasospasm.

The VASOGRADE score—a combination of the WFNS score and the modified Fisher scale—stratifies patients at risk of delayed cerebral ischemia, allowing for a tailored monitoring strategy.¹⁵ There are three variations:

- VASOGRADE green—Modified Fisher 1 or 2 and WFNS 1 or 2
- VASOGRADE yellow—Modified Fisher 3 or 4 and WFNS 1, 2, or 3
- VASOGRADE red—WFNS 4 or 5.

After the initial bleeding event, patients with aneurysmal subarachnoid hemorrhage are at high risk of delayed systemic and neurologic complications, with poor functional outcomes. Delayed cerebral ischemia holds the greatest risk of an unfavorable outcome and ultimately can lead to cerebral infarction, disability, and death.^{6,7}

■ INITIAL MANAGEMENT

After aneurysmal subarachnoid hemorrhage is diagnosed, the initial management (FIGURE 2) includes appropriate medical prevention of rebleeding (which includes supportive care, blood pressure management, and, perhaps, the early use of a short course of an antifibrinolytic drug) and early transfer to a high-volume center for securing the aneurysm. The reported incidence of rebleeding varies from 5% to 22% in the first 72 hours. “Ultra-early” rebleeding (within 24 hours of hemorrhage) has been reported, with an incidence as high as 15% and a fatality rate around 70%. Patients with poor-grade aneurysmal subarachnoid hemorrhage, larger aneurysms, and “sentinel bleeds” are at higher risk of rebleeding.¹⁶

Outcomes are much better when patients are managed in a high-volume center, with a specialized neurointensive care unit¹⁷ and access to an interdisciplinary team.¹⁸ Regardless

of the initial grade, patients with aneurysmal subarachnoid hemorrhage should be quickly transferred to a high-volume center, defined as one treating at least 35 cases per year, and the benefit is greater in centers treating more than 60 cases per year.¹⁹ The higher the caseload in any given hospital, the better the clinical outcomes in this population.²⁰

Treating cerebral aneurysm:

Clipping or coiling

Early aneurysm repair is generally considered the standard of care and the best strategy to reduce the risk of rebleeding. Further, early treatment may be associated with a lower risk of delayed cerebral ischemia²¹ and better outcomes.²²

Three randomized clinical trials have compared surgical clipping and endovascular repair (placement of small metal coils within the aneurysm to promote clotting).

The International Subarachnoid Aneurysm Trial²³ showed a reduction of 23% in relative risk and of 7% in absolute risk in patients who underwent endovascular treatment compared with surgery. The survival benefit persisted at a mean of 9 years (range 6–14 years), but with a higher annual rate of aneurysm recurrence in the coiling group (2.9% vs 0.9%).²⁴ Of note, this trial included only patients with aneurysms deemed suitable for both coiling and clipping, so that the exclusion rate was high. Most of the patients presented with good-grade (WFNS score 1–3), small aneurysms (< 5 mm) in the anterior circulation.

A single-center Finnish study²⁵ found no differences in rates of recovery, disability, and death at 1 year, comparing surgery and endovascular treatment. Additionally, survival rates at a mean follow-up of 39 months were similar, with no late recurrences or aneurysmal bleeding.

Lastly, the Barrow Ruptured Aneurysm Trial^{26,27} found that patients assigned to endovascular treatment had better 1-year neurologic outcomes, defined as a modified Rankin score of 2 or less. Importantly, 37.7% of patients originally assigned to endovascular treatment crossed over to surgical treatment. The authors then performed intention-to-treat and as-treated analyses. Either way, patients treat-

Have a low threshold for ordering noncontrast CT

Outcomes are much better when patients are managed in a high-volume center

ed by endovascular means had better neurologic outcomes at 1 year. However, no difference in the relative risk reduction in worse outcome was found on 3-year follow-up, and patients treated surgically had higher rates of aneurysm obliteration and required less aneurysm retreatment, both of which were statistically significant.

The question that remains is not whether to clip or whether to coil, but whom to clip and whom to coil.²⁸ That question must be answered on a patient-to-patient basis and requires the expertise of an interventional neuroradiologist and a vascular neurosurgeon—one of the reasons these patients are best cared for in high-volume centers providing such expertise.

MEDICAL PREVENTION OF REBLEEDING

Blood pressure management

There are no systematic data on the optimal blood pressure before securing an aneurysm. Early studies of hemodynamic augmentation in cases of ruptured untreated aneurysm reported rebleeding when the systolic blood pressure was allowed to rise above 160 mm Hg.^{29,30} A recent study evaluating hypertensive intracerebral hemorrhage revealed better functional outcomes with intensive lowering of blood pressure (defined as systolic blood pressure < 140 mm Hg) but no significant reduction in the combined rate of death or severe disability.³¹ It is difficult to know if these results can be extrapolated to patients with aneurysmal subarachnoid hemorrhage. Current guidelines^{3,32} say that before the aneurysm is treated, the systolic pressure should be lower than 160 mm Hg.

There is no specific drug of choice, but a short-acting, titratable medication is preferable. Nicardipine is a very good option, and labetalol might be an appropriate alternative.³³ Once the aneurysm is secured, all anti-hypertensive drugs should be held. Hypertension should not be treated unless the patient has clinical signs of a hypertensive crisis, such as flash pulmonary edema, myocardial infarction, or hypertensive encephalopathy.

Antifibrinolytic therapy

The role of antifibrinolytic therapy in aneurysmal subarachnoid hemorrhage is controversial

and has been studied in 10 clinical trials. In a Swedish study,³⁴ early use of tranexamic acid (1 g intravenously over 10 minutes followed by 1 g every 6 hours for a maximum of 24 hours) reduced the rebleeding rate substantially, from 10.8% to 2.4%, with an 80% reduction in the mortality rate from ultra-early rebleeding. However, a recent Cochrane review that included this study found no overall benefit.³⁵

An ongoing multicenter randomized trial in the Netherlands will, we hope, answer this question in the near future.³⁶ At present, some centers would consider a short course of tranexamic acid before aneurysm treatment.

DIAGNOSIS AND TREATMENT OF COMPLICATIONS

Medical complications are extremely common after aneurysmal subarachnoid hemorrhage. Between 75% and 100% of patients develop some type of systemic or further neurologic derangement, which in turn has a negative impact on the long-term outcome.^{37,38} In the first 72 hours, rebleeding is the most feared complication, and as mentioned previously, appropriate blood pressure management and early securing of the aneurysm minimize its risk.

NEUROLOGIC COMPLICATIONS

Hydrocephalus

Hydrocephalus is the most common early neurologic complication after aneurysmal subarachnoid hemorrhage, with an overall incidence of 50%.³⁹ Many patients with poor-grade aneurysmal subarachnoid hemorrhage and patients whose condition deteriorates due to worsening of hydrocephalus require the insertion of an external ventricular drain (FIGURE 1).

Up to 30% of patients who have a poor-grade aneurysmal subarachnoid hemorrhage improve neurologically with cerebrospinal fluid drainage.⁴⁰ An external ventricular drain can be safely placed, even before aneurysm treatment, and placement does not appear to increase the risk of rebleeding.^{39,41} After placement, rapid weaning from the drain (clamping within 24 hours of insertion) is safe, decreases length of stay in the intensive care unit and hospital, and may be more cost-effective than gradual weaning over 96 hours.⁴²

Increased intracranial pressure

Intracranial hypertension is another potential early complication, and is frequently due to the development of hydrocephalus, cerebral edema, or rebleeding. The treatment of increased intracranial pressure does not differ from the approach used in managing severe traumatic brain injury, which includes elevating the head of the bed, sedation, analgesia, normoventilation, and cerebrospinal fluid drainage.

Hypertonic saline has been tested in several studies that were very small but nevertheless consistently showed control of intracranial pressure levels and improvement in cerebral blood flow measured by xenon CT.⁴³⁻⁴⁷ Two of these studies even showed better outcomes at discharge.^{43,44} However, the small number of patients prevents any meaningful conclusion regarding the use of hypertonic saline and functional outcomes.

Barbiturates, hypothermia, and decompressive craniectomy could be tried in refractory cases.⁴⁸ Seule et al⁴⁹ evaluated the role of therapeutic hypothermia with or without barbiturate coma in 100 patients with refractory intracranial hypertension. Only 13 patients received hypothermia by itself. At 1 year, 32 patients had achieved a good functional outcome (Glasgow Outcome Scale score 4 or 5). The remaining patients were severely disabled or had died. Of interest, the median duration of hypothermia was 7 days, and 93% of patients developed some medical complication such as electrolyte disorders (77%), pneumonia (52%), thrombocytopenia (47%), or septic shock syndrome (40%). Six patients died as a consequence of one of these complications.

Decompressive craniectomy can be life-saving in patients with refractory intracranial hypertension. However, most of these patients will die or remain severely disabled or comatose.⁵⁰

Seizure prophylaxis is controversial

Seizures can occur at the onset of intracranial hemorrhage, perioperatively, or later (ie, after the first week). The incidence varied considerably in different reports, ranging from 4% to 26%.⁵¹ Seizures occurring perioperatively, ie, after hospital admission, are less frequent and are usually the manifestation of aneurysm rebleeding.²⁴

Seizure prophylaxis remains controversial, especially because the use of phenytoin is associated with increased incidence of cerebral vasospasm, infarction, and worse cognitive outcomes after aneurysmal subarachnoid hemorrhage.^{52,53} Therefore, routine prophylactic use of phenytoin is not recommended in these patients,³ although the effect of other antiepileptic drugs is less studied and less clear. Patients may be considered for this therapy if they have multiple risk factors for seizures, such as intraparenchymal hematoma, advanced age (> 65), middle cerebral artery aneurysm, craniotomy for aneurysm clipping, and a short course (≤ 72 hours) of an antiepileptic drug other than phenytoin, especially while the aneurysm is unsecured.³

Levetiracetam may be an alternative to phenytoin, having better pharmacodynamic and kinetic profiles, minimal protein binding, and absence of hepatic metabolism, resulting in a very low risk of drug interaction and better tolerability.^{54,55} Because of these advantages, levetiracetam has become the drug of choice in several centers treating aneurysmal subarachnoid hemorrhage in the United States.

Addressing this question, a survey was sent to 25 high-volume aneurysmal subarachnoid hemorrhage academic centers in the United States. All 25 institutions answered the survey, and interestingly, levetiracetam was the first-line agent for 16 (94%) of the 17 responders that used prophylaxis, while only 1 used phenytoin as the agent of choice.⁵⁶

A retrospective cohort study by Murphy-Human et al⁵⁷ showed that a short course of levetiracetam (≤ 72 hours) was associated with higher rates of in-hospital seizures compared with an extended course of phenytoin (eg, entire hospital stay). However, the study did not address functional outcomes.⁵⁷

Continuous electroencephalographic monitoring may be considered in comatose patients, in patients requiring controlled ventilation and sedation, or in patients with unexplained alteration in consciousness. In one series of patients with aneurysmal subarachnoid hemorrhage who received continuous monitoring, the incidence of nonconvulsive status epilepticus was 19%, with an associated mortality rate of 100%.⁵⁸

The question is not whether to clip or coil, but whom to clip and whom to coil

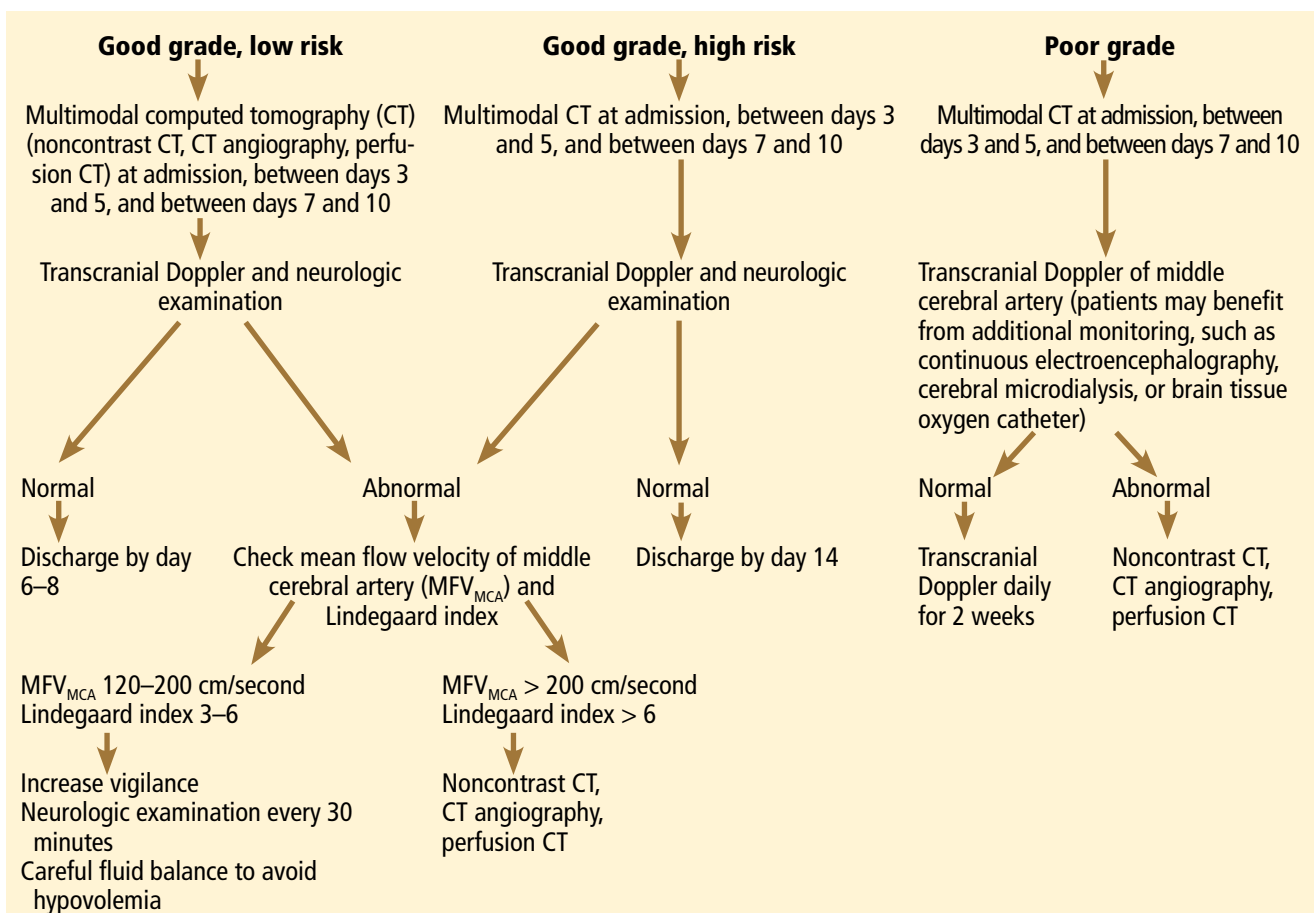


FIGURE 3. Monitoring pathway for delayed cerebral ischemia.

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Continuous quantitative electroencephalography is useful to monitor and to detect angiographic vasospasm and delayed cerebral ischemia. Relative alpha variability and the alpha-delta ratio decrease with ischemia, and this effect can precede angiographic vasospasm by 3 days.^{59,60}

Delayed cerebral ischemia

Delayed cerebral ischemia is defined as the occurrence of focal neurologic impairment, or a decrease of at least 2 points on the Glasgow Coma Scale that lasts for at least 1 hour, is not apparent immediately after aneurysm occlusion, and not attributable to other causes (eg, hyponatremia, fever).⁶¹

Classically, neurologic deficits that oc-

curred within 2 weeks of aneurysm rupture were ascribed to reduced cerebral blood flow caused by delayed large-vessel vasospasm causing cerebral ischemia.⁶² However, perfusion abnormalities have also been observed with either mild or no demonstrable vasospasm.⁶³ Almost 70% of patients who survive the initial hemorrhage develop some degree of angiographic vasospasm. However, only 30% of those patients will experience symptoms.

In addition to vasospasm of large cerebral arteries, impaired autoregulation and early brain injury within the first 72 hours following subarachnoid hemorrhage may play important roles in the development of delayed cerebral ischemia.⁶⁴ Therefore, the modern concept of delayed cerebral ischemia monitoring should

focus on cerebral perfusion rather than vessel diameter measurements. This underscores the importance of comprehensive, standardized monitoring techniques that provide information not only on microvasculature, but also at the level of the microcirculation, with information on perfusion, oxygen utilization and extraction, and autoregulation.

Although transcranial Doppler has been the most commonly applied tool to monitor for angiographic vasospasm, it has a low sensitivity and negative predictive value.³⁷ It is nevertheless a useful technique to monitor good-grade aneurysmal subarachnoid hemorrhage patients (WFNS score 1–3) combined with frequent neurologic examinations (FIGURE 3).

CT angiography is a good noninvasive alternative to digital subtraction angiography. However, it tends to overestimate the degree of vasoconstriction and does not provide information about perfusion and autoregulation.⁶⁵ Nevertheless, CT angiography combined with a CT perfusion scan can add information about autoregulation and cerebral perfusion and has been shown to be more sensitive for the diagnosis of angiographic vasospasm than transcranial Doppler and digital subtraction angiography (FIGURE 4).⁶⁶

Patients with a poor clinical condition (WFNS score 4 or 5) or receiving continuous sedation constitute a challenge in monitoring for delayed neurologic deterioration. Neurologic examination is not sensitive enough in this setting to detect subtle changes. In these specific and challenging circumstances, multimodality neuromonitoring may be useful in the early detection of delayed cerebral ischemia and may help guide therapy.⁶⁷

Several noninvasive and invasive techniques have been studied to monitor patients at risk of delayed cerebral ischemia after subarachnoid hemorrhage.⁶⁶ These include continuous electroencephalography, brain tissue oxygenation monitoring (P_{tO_2}), cerebral microdialysis, thermal diffusion flowmetry, and near-infrared spectroscopy. Of these techniques, P_{tO_2} , cerebral microdialysis, and continuous electroencephalography (see discussion of seizure prophylaxis above) have been more extensively studied. However, most of the studies were observational and very small, limiting any recommendations for using these

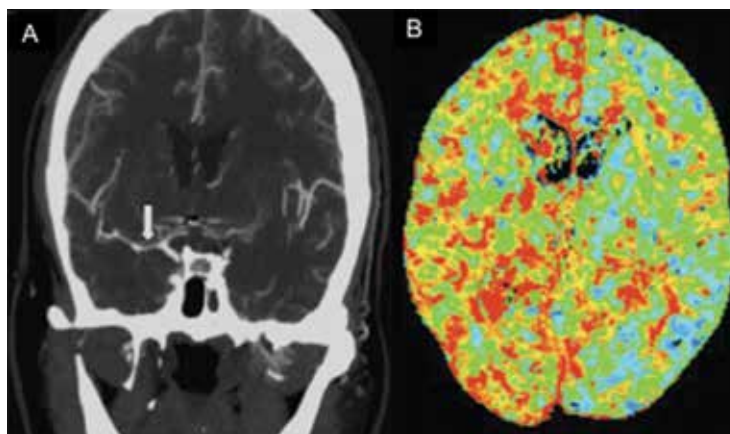


FIGURE 4. Multimodal computed tomography (CT) of the head. **(A)** CT angiography in the coronal plane shows severe vasospasm in the right middle cerebral artery (white arrow). **(B)** CT perfusion shows an asymmetric mean transit time. The right hemisphere displays more grades of red, representing a longer time required for blood to pass through tissue.

techniques in routine clinical practice.⁶⁸

P_{tO_2} is measured by inserting an intraparenchymal oxygen-sensitive microelectrode, and microdialysis requires a microcatheter with a semipermeable membrane that allows small soluble substances to cross it into the dialysate. These substances, which include markers of ischemia (ie, glucose, lactate, and pyruvate), excitotoxins (ie, glutamate and aspartate), and membrane cell damage products (ie, glycerol), can be measured. Low P_{tO_2} values (< 15 mm Hg) and abnormal microdialysis findings (eg, glucose < 0.8 mmol/L, lactate-to-pyruvate ratio > 40) have both been associated with cerebral ischemic events and poor outcome.⁶⁸

Preventing delayed cerebral ischemia

Oral nimodipine 60 mg every 4 hours for 21 days, started on admission, carries a class I, level of evidence A recommendation in the management of aneurysmal subarachnoid hemorrhage.^{3,32,69} It improves clinical outcome despite having no effect on the risk of angiographic vasospasm. The mechanism of improved outcome is unclear, but the effect may be a neuroprotective phenomenon limiting the extension of delayed cerebral ischemia.⁷⁰

If hypotension occurs, the dose can be lowered to 30 mg every 2 hours. Whether to discontinue nimodipine in this situation is controversial. Of note, the clinical benefits of nimodipine

Guidelines:
Before treating the aneurysm, the systolic pressure should be < 160 mm Hg

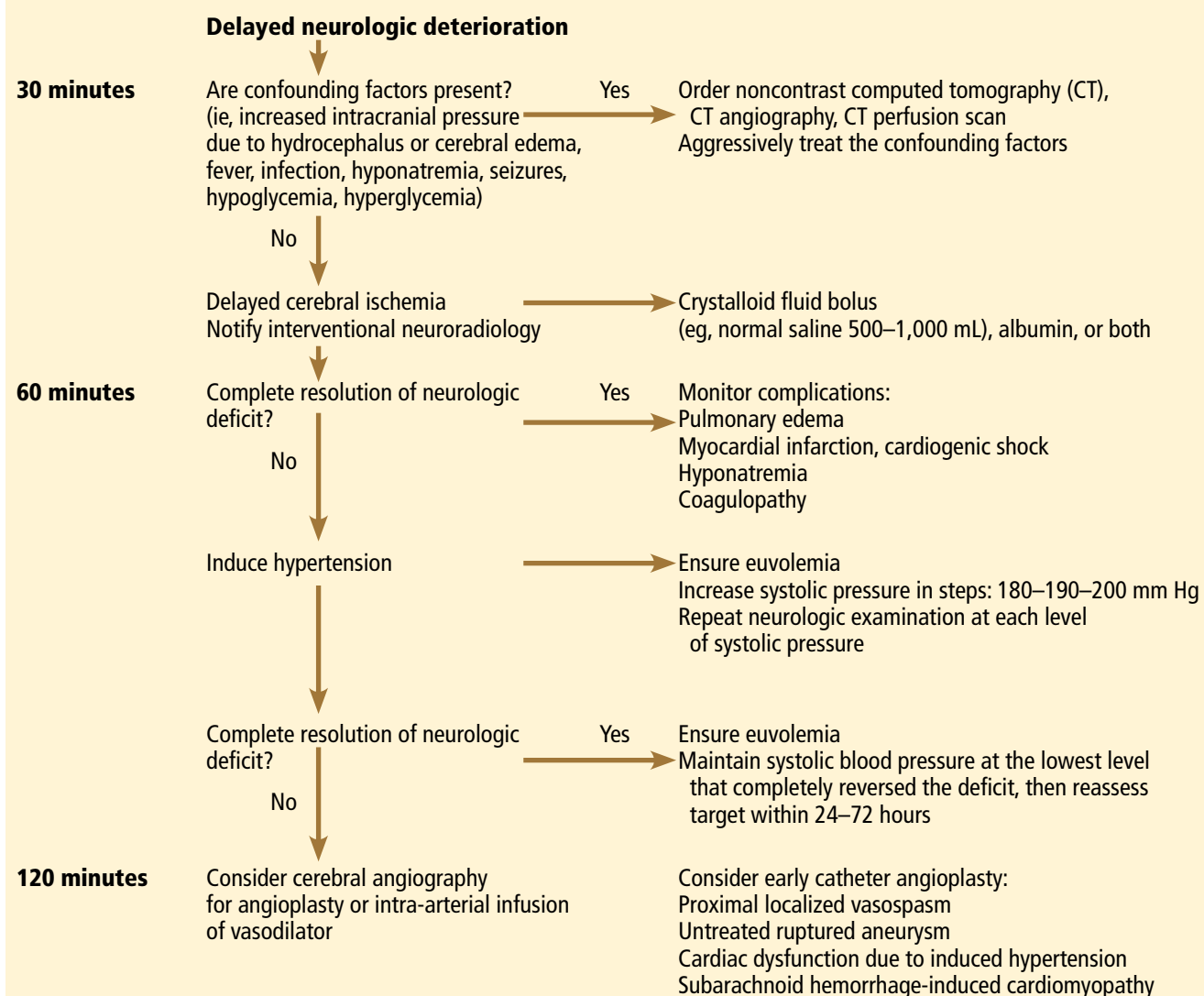


FIGURE 5. Care pathway for delayed cerebral ischemia.

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have not been replicated with other calcium channel blockers (eg, nicardipine).⁷¹

Prophylactic hyperdynamic fluid therapy, known as “triple-H” (hypervolemia, hemodilution, and hypertension) was for years the mainstay of treatment in preventing delayed cerebral ischemia due to vasospasm. However, the clinical data supporting this intervention have been called into question, as analysis of two trials found that hypervolemia did not improve outcomes or reduce the incidence of de-

layed cerebral ischemia, and in fact increased the rate of complications.^{72,73} Based on these findings, current guidelines recommend maintaining euvolemia rather than prophylactic hypervolemia in patients with aneurysmal subarachnoid hemorrhage.^{3,32,69}

■ TREATING DELAYED CEREBRAL ISCHEMIA

Hemodynamic augmentation

In patients with neurologic deterioration due to delayed cerebral ischemia, hemodynamic

augmentation is the cornerstone of treatment. This is done according to a protocol, started early, involving specific physiologic goals, clinical improvement, and escalation to invasive therapies in a timely fashion in patients at high risk of further neurologic insult (FIGURE 5).

The physiologic goal is to increase the delivery of oxygen and glucose to the ischemic brain. Hypertension seems to be the most effective component of hemodynamic augmentation regardless of volume status, increasing cerebral blood flow and brain tissue oxygenation, with reversal of delayed cerebral ischemic symptoms in up to two-thirds of treated patients.^{74,75} However, this information comes from very small studies, with no randomized trials of induced hypertension available.

The effect of a normal saline fluid bolus in patients suspected of having delayed cerebral ischemia has been shown to increase cerebral blood flow in areas of cerebral ischemia.⁷⁴ If volume augmentation fails to improve the neurologic status, the next step is to artificially induce hypertension using vasopressors. The blood pressure target should be based on clinical improvement. A stepwise approach is reasonable in this situation, and the lowest level of blood pressure at which there is a complete reversal of the new focal neurologic deficit should be maintained.^{3,29}

Inotropic agents such as dobutamine or milrinone can be considered as alternatives in patients who have new neurologic deficits that are refractory to fluid boluses and vasopressors, or in a setting of subarachnoid hemorrhage-induced cardiomyopathy.^{76,77}

Once the neurologic deficit is reversed by hemodynamic augmentation, the blood pressure should be maintained for 48 to 72 hours at the level that reversed the deficit completely, carefully reassessed thereafter, and the patient weaned slowly. Unruptured unsecured aneurysms should not prevent blood pressure augmentation in a setting of delayed cerebral ischemia if the culprit aneurysm is treated.^{3,32} If the ruptured aneurysm has not been secured, careful blood pressure augmentation can be attempted, keeping in mind that hypertension (> 160/95 mm Hg) is a risk factor for fatal aneurysm rupture.

Endovascular management of delayed cerebral ischemia

When medical augmentation fails to completely reverse the neurologic deficits, endovascular treatment can be considered. Although patients treated early in the course of delayed cerebral ischemia have better neurologic recovery, prophylactic endovascular treatment in asymptomatic patients, even if angiographic signs of spasm are present, does not improve clinical outcomes and carries the risk of fatal arterial rupture.⁷⁸

SYSTEMIC COMPLICATIONS

Hyponatremia and hypovolemia

Aneurysmal subarachnoid hemorrhage is commonly associated with abnormalities of fluid balance and electrolyte derangements. Hyponatremia (serum sodium < 135 mmol/L) occurs in 30% to 50% of patients, while the rate of hypovolemia (decreased circulating blood volume) ranges from 17% to 30%.⁷⁹ Both can negatively affect long-term outcomes.^{80,81}

Decreased circulating blood volume is a well-described contributor to delayed cerebral ischemia and cerebral infarction after aneurysmal subarachnoid hemorrhage.^{80–82} Clinical variables such as heart rate, blood pressure, fluid balance, and serum sodium concentration are usually the cornerstones of intravascular volume status assessment. However, these variables correlate poorly with measured circulating blood volumes in those with aneurysmal subarachnoid hemorrhage.^{83,84}

The mechanisms responsible for the development of hyponatremia and hypovolemia after aneurysmal subarachnoid hemorrhage are not completely understood. Several factors have been described and may contribute to the increased natriuresis and, hence, to a reduction in circulating blood volume: increased circulating natriuretic peptide concentrations,^{85–87} sympathetic nervous system hyperactivation,⁸⁸ and hyperreninemic hypoaldosteronism syndrome.^{89,90}

Lastly, the cerebral salt wasting syndrome, described in the 1950s,⁹¹ was thought to be a key mechanism in the development of hyponatremia and hypovolemia after aneurysmal subarachnoid hemorrhage. In contrast to the syndrome of inappropriate antidiuretic hor-

The benefits of nimodipine have not been replicated with other calcium channel blockers

none, which is characterized by hyponatremia with a normal or slightly elevated intravascular volume, the characteristic feature of cerebral salt wasting syndrome is the development of hyponatremia in a setting of intravascular volume depletion.⁹² In critically ill neurologic and neurosurgical patients, this differential diagnosis is very difficult, especially in those with aneurysmal subarachnoid hemorrhage in whom the clinical assessment of fluid status is not reliable. These two syndromes might coexist and contribute to the development of hyponatremia after aneurysmal subarachnoid hemorrhage.^{92,93}

Hoff et al^{83,84} prospectively compared the clinical assessment of fluid status by critical and intermediate care nurses and direct measurements of blood volume using pulse dye densitometry. The clinical assessment failed to accurately assess patients' volume status. Using the same technique to measure circulating blood volume, this group showed that calculation of fluid balance does not provide adequate assessment of fluid status.^{83,84}

Hemodynamic monitoring tools can help guide fluid replacement in this population. Mutoh et al⁹⁴ randomized 160 patients within 24 hours of hemorrhage to receive early goal-directed fluid therapy (ie, preload volume and cardiac output monitored by transpulmonary thermodilution) vs standard therapy (ie, fluid balance or central venous pressure). Overall, no difference was found in the rates of delayed cerebral ischemia (33% vs 42%; $P = .33$) or favorable outcome (67% vs 57%; $P = .22$). However, in the subgroup of poor-grade patients (WFNS score 4 or 5), early goal-directed therapy was associated with a lower rate of delayed cerebral ischemia (5% vs 14%; $P = .036$) and with better functional outcomes at 3 months (52% vs 36%; $P = .026$).

Fluid restriction to treat hyponatremia in aneurysmal subarachnoid hemorrhage is no longer recommended because of the increased risk of cerebral infarction due to hypovolemic hypoperfusion.⁸²

Prophylactic use of mineralocorticoids (eg, fludrocortisone, hydrocortisone) has been shown to limit natriuresis, hyponatremia, and the amount of fluid required to maintain euvolemia.^{95,96} Higher rates of hypokalemia and hyperglycemia, which can be easily treated,

are the most common complications associated with this approach. Additionally, hypertonic saline (eg, 3% saline) can be used to correct hyponatremia in a setting of aneurysmal subarachnoid hemorrhage.⁷⁹

Cardiac complications

Cardiac complications after subarachnoid hemorrhage are most likely related to sympathetic hyperactivity and catecholamine-induced myocyte dysfunction. The pathophysiology is complex, but cardiac complications have a significant negative impact on long-term outcome in these patients.⁹⁷

Electrocardiographic changes and positive cardiac enzymes associated with aneurysmal subarachnoid hemorrhage have been extensively reported. More recently, data from studies of two-dimensional echocardiography have shown that subarachnoid hemorrhage can also be associated with significant wall-motion abnormalities and even overt cardiogenic shock.^{98–100}

There is no specific curative therapy; the treatment is mainly supportive. Vasopressors and inotropes may be used for hemodynamic augmentation.

Pulmonary complications

Pulmonary complications occur in 20% to 30% of all aneurysmal subarachnoid hemorrhage patients and are associated with a higher risk of delayed cerebral ischemia and death. Common pulmonary complications in this population are mild acute respiratory distress syndrome (27%), hospital-acquired pneumonia (9%), cardiogenic pulmonary edema (8%), aspiration pneumonia (6%), neurogenic pulmonary edema (2%), and pulmonary embolism (1%).^{101–103}

SUPPORTIVE CARE

Hyperthermia, hyperglycemia, and liberal use of transfusions have all been associated with longer stays in the intensive care unit and hospital, poorer neurologic outcomes, and higher mortality rates in patients with acute brain injury.¹⁰⁴ Noninfectious fever is the most common systemic complication after subarachnoid hemorrhage.

Antipyretic drugs such as acetaminophen and ibuprofen are not very effective in reduc-

Fluid restriction to treat hyponatremia in aneurysmal subarachnoid hemorrhage is no longer recommended

ing fever in the subarachnoid hemorrhage population, but should still be used as first-line therapy. The use of surface and intravascular devices can be considered when fevers do not respond to nonsteroidal anti-inflammatory drugs.

Although no prospective randomized trial has addressed the impact of induced normothermia on long-term outcome and mortality in aneurysmal subarachnoid hemorrhage patients, fever control has been shown to reduce cerebral metabolic distress, irrespective of intracranial pressure.¹⁰⁵ Maintenance of normothermia (< 37.5°C) seems reasonable, especially in aneurysmal subarachnoid hemorrhage patients at risk of or with active delayed cerebral ischemia.¹⁰⁶

Current guidelines^{3,32,69} strongly recommend avoiding hypoglycemia, defined as a serum glucose level less than 80 mg/dL, but suggest keeping the blood sugar level below 180 or 200 mg/dL.

At the moment, there is no clear threshold for transfusion in patients with aneurysmal subarachnoid hemorrhage. Current guidelines suggest keeping hemoglobin levels between 8 and 10 g/dL.³

Preventing venous thromboembolism

The incidence of venous thromboembolism after aneurysmal subarachnoid hemorrhage varies widely, from 1.5% to 18%.¹⁰⁷ Active surveillance with venous Doppler ultrasonography has found asymptomatic deep vein thrombosis in up to 3.4% of poor-grade aneurysmal subarachnoid hemorrhage patients receiving pharmacologic thromboprophylaxis.¹⁰⁸

In a retrospective study of 170 patients, our group showed that giving drugs to prevent venous thromboembolism (unfractionated heparin 5,000 IU subcutaneously every 12 hours

or dalteparin 5,000 IU subcutaneously daily), starting within 24 hours of aneurysm treatment, could be safe.¹⁰⁹ Fifty-eight percent of these patients had an external ventricular drain in place. One patient developed a major cerebral hemorrhagic complication and died while on unfractionated heparin; however, the patient was also on dual antiplatelet therapy with aspirin and clopidogrel.¹⁰⁹

Current guidelines suggest that intermittent compression devices be applied in all patients before aneurysm treatment. Pharmacologic thromboprophylaxis with a heparinoid can be started 12 to 24 hours after aneurysm treatment.^{3,109}

A TEAM APPROACH

Patients with subarachnoid hemorrhage need integrated care from different medical and nursing specialties. The best outcomes are achieved by systems that can focus as a team on the collective goal of quick intervention to secure the aneurysm, followed by measures to minimize secondary brain injury.

The modern concept of cerebral monitoring in a setting of subarachnoid hemorrhage should focus on brain perfusion rather than vascular diameter. Although the search continues for new diagnostic, prognostic, and therapeutic tools, there is no “silver bullet” that will help all patients. Instead, it is the systematic integration and application of many small advances that will ultimately lead to better outcomes.

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