Managing Subarachnoid Hemorrhage in the Neurocritical Care Unit

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KEYWORDS

• Aneurysm • Subarachnoid hemorrhage • Vasospasm • Delayed cerebral ischemia • Neurocritical care

KEY POINTS

- The management of patients with aneurysmal subarachnoid hemorrhage is challenging and requires a multidisciplinary team approach, and is best done at high-volume centers.
- There is a paucity of randomized, blinded, placebo-controlled, prospective trials to aid in the management of aneurysmal subarachnoid hemorrhage.
- The critical care management of aneurysmal subarachnoid hemorrhage varies between patients with microsurgical clipping and those with endovascular occlusion, and the critical care practitioner should be aware of these differences.
- Much of the morbidity from aneurysmal subarachnoid hemorrhage occurs in a delayed manner following the initial hemorrhage. It is the role of the neurocritical care unit to understand and manage these complications.

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) can be a devastating condition that leads to significant morbidity and mortality. Over the past several decades, there has been an overall decrease in the incidence of strokes in high-income countries, but without a concomitant decrease in the incidence of SAH.[1] Unlike other causes of SAH (ie, trauma), aSAH represents a unique physiology, which sets up a cascade of events that leads to further pathologic processes involving multiple organ systems. If a patient survives the initial hemorrhage, it is these pathologic processes that are the source of the significant morbidity and mortality following aSAH. As such, a thorough understanding of these processes and their management are a necessity for any practitioner caring for patients with aSAH. Furthermore, given the complexity of the management of these patients, this care is best done in a dedicated neurocritical care unit (NCCU).

In 2011 and 2012, 2 sets of guidelines were published on the management of aSAH.[2,3] These guidelines by the Neurocritical Care Society and

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the American Heart Association/American Stroke Association (AHA/ASA), and their supporting articles, provide comprehensive reviews of the literature combined with expert consensus opinions. These articles note that there is a paucity of prospective, randomized, placebo-controlled trials in the literature showing that an intervention improves outcome, which might aid in guiding the management of aSAH. In fact, the use of nimodipine (Nimotop) is the only such intervention supported by level 1A class evidence.[3] As such, much of the management of this disease is left to the interpretation of the literature by an experienced clinician. The goal of this article is to review the pertinent literature in a condensed format, in combination with our own experiences in managing these patients, in an attempt to provide a practical aid to those managing this challenging disease in the NCCU.

In addition to reviewing the evidence behind the current management of aSAH in the NCCU, this article is also meant to serve as a practical reference to those who are involved in the day-to-day management of these patients (ie, residents and fellows). To this end a table is included to aid with admission orders, and which can be used as a quick reference on daily NCCU rounds. In their NCCU, we often use a "systems-based" method of rounding, and have organized the table and article in this manner (**Table 1**).

CARE SETTING

The care of patients with aSAH requires a multidisciplinary approach. Team members include neurosurgeons, neurointensivists, neurologists, neuroradiologists, and interventional neuroradiologists. Patients also require specialized critical care nursing with specialized training in neurosciences. We believe that these patients are best served in dedicated NCCUs that treat a high volume of such patients. This scenario is also supported in the literature, which shows that outcomes are improved at high-volume centers.[4] It is also important that patients be transferred expeditiously to the high-volume centers, as rebleeding before transfer or during transfer is reported.[5]

NEUROLOGIC

Hydrocephalus

Hydrocephalus is a known complication of aSAH, first described experimentally in 1928 by Bagley.[6] The incidence of acute hydrocephalus varies widely, and many studies report a range from 15% to 53%.[7–13] The incidence of patients with SAH who go on to require permanent shunting also varies widely in the literature. Shunt rates from 2.3% to 36% have been reported.[7–16] This large variation is likely multifactorial, including varying indications for shunting across institutions and surgeons, effects of clot/blood removal from the subarachnoid space at the time of surgery, and fenestration of the lamina terminalis.

Hydrocephalus following aSAH can be of both the obstructive and the communicating variant. In obstructive hydrocephalus, there may be intraventricular extension of the subarachnoid blood or an intraparenchymal hematoma. In the communicating variant the ventricular system may be free of blood, but the arachnoid granulations may become obstructed by the subarachnoid blood, limiting reabsorption of cerebrospinal fluid (CSF). Recognition of the cause of the patient's hydrocephalus is important, as it can affect the means by which the hydrocephalus is treated (lumbar drain, external ventriculostomy drainage, endoscopic third ventriculostomy, shunt, and so forth).

There are many factors involved in managing hydrocephalus following subarachnoid hemorrhage that are important to the neurointensivist, including ventriculostomy or lumbar drain weaning, risk of aneurysmal rebleeding in the setting of CSF drainage, and indications and timing of permanent CSF diversion (ie, shunting).

The timing of ventriculostomy weaning and removal is not agreed upon. The role of rapid versus gradual weaning from external ventricular drainage (EVD) was examined in a prospective randomized trial by Klopfenstein and colleagues.[17] In this study 81 patients with aSAH with EVDs were randomized to either rapid (24 hours) or gradual (96 hours) wean. This study found no difference in rates of shunt implantation between groups. The gradual-wean group did have longer stays in the intensive care unit (ICU) and hospital. However, we have found that persistence in ventriculostomy weaning is very effective in preventing the need for shunting. Serial EVD clamp trials are effective as long as the amount of CSF draining through the ventriculostomy decreases daily. Although this may lead to a more prolonged EVD wean and ICU/hospital stay, it reduces the number of shunts placed.

After initial ventriculostomy or lumbar drain placement, the risk of aneurysm rebleeding is often quoted as a concern against aggressive CSF drainage in the setting of an unsecured aneurysm. Some data suggest, however, that this is safe. Hellingman and colleagues[18] retrospectively reviewed 34 patients who underwent EVD placement against matched controls with untreated hydrocephalus and a control without ventricular enlargement.

Rebleeding occurred in 21% of patients with treated hydrocephalus as well as untreated hydrocephalus, and 18% of those without hydrocephalus. In the lumbar puncture (LP) group, rebleeding occurred in 5% of patients, in 14% of patients with hydrocephalus without LP, and in none of the controls without hydrocephalus. It was concluded that there was no statistically significant difference between rebleeding in those patients treated with either EVD or LP versus those who were not. McIver and colleagues[19] retrospectively reviewed 304 patients with aneurysmal subarachnoid hemorrhage. Of these patients, 45 had ventriculostomies placed. Rebleeding occurred in 5.4% of patients not undergoing ventriculostomy placement and in 4.4% of those who did undergo ventriculostomy placement. The ability to safely drain CSF following aSAH is important, as there are data to suggest it may lead to a reduction in vasospasm.[20]

Temporary CSF diversion may typically be achieved with ventriculostomy, serial LPs, or lumbar catheter placement. Knowledge of the cause of the hydrocephalus is important, as this may influence a particular approach. We routinely use ventriculostomy as a means to achieve CSF diversion. This approach is well tolerated and, in addition to CSF drainage, allows for accurate measurement of intracranial pressure, which may be important, particularly in high-grade patients with a poor neurologic examination.

Shunt dependence following aSAH varies. Factors predicting the development of shunt-dependent hydrocephalus include age, acute hydrocephalus, ventilation on admission, posterior circulation, and giant aneurysms.[14] Fenestration of the lamina terminalis is a microsurgical maneuver, the utility of which is debated. In our experience, routine fenestration of the lamina terminalis is associated with an 80% decrease in the incidence of shunt-dependent hydrocephalus.[8] We routinely perform this straightforward microsurgical technique in all cases of aSAH where access to the lamina terminalis is easily obtainable (ie, fronto-spheno-temporal [pterional] craniotomies). However, the issue of fenestrating the lamina terminalis is debated, as some literature suggests it does not reduce the incidence of shunt-dependent hydrocephalus.[15] The AHA guidelines do not recommend this maneuver, and classify the evidence as level IIIB.[3]

Seizures

Seizures after aSAH hemorrhage are common. One retrospective review found a prevalence of 15.2% in 547 patients.[21] Seizure frequency in subarachnoid hemorrhage after surgery was 9.4% in the 307 patients studied prospectively by Ohman.[22] Furthermore, in this study a history of hypertension was found to be a significant risk factor for the development of epilepsy after aSAH and surgery. Epilepsy developed in 7% of 247 patients alive with follow-up 12 months after aSAH.[23] Subdural hematoma and cerebral infarction were predictors of epilepsy.

The risk of seizures in patients undergoing clip occlusion or coil embolization of ruptured aneurysms was assessed in the International Subarachnoid Aneurysm Trial (ISAT).[24] There was an overall incidence of seizures in 10.9% of the patients. Among those patients randomized to endovascular intervention, 8.3% had seizures, whereas 13.6% of patients randomized to open surgery had seizures, a difference that was found to be significant. Furthermore, on long-term follow-up after discharge, the risk of seizures was also significantly greater in the neurosurgical group. The study also identified the following risk factors for developing seizures: younger age, Fisher grade greater than 1 on computed tomography (CT), delayed ischemic neurologic deficit due to vasospasm, thromboembolic complication, and middle cerebral artery (MCA) location of the aneurysm.

Lanzino and colleagues[25] reviewed 56 articles from 1980 to 2010 on the topic of the incidence and treatment of seizures after aneurysmal subarachnoid hemorrhage. Seizures occurred at the time of SAH in 4% to 26% of patients. Only a small proportion of patients had a seizure after admission but before aneurysm treatment. This review also addressed the role of anticonvulsants after SAH. The study notes that there are no randomized controlled trials addressing the safety and efficacy of antiepileptics in SAH. The AHA/ASA guidelines are similarly vague, stating that "the use of prophylactic anticonvulsants may be considered in the immediate post-hemorrhagic period."[3] There are data to suggest that the use of phenytoin (Dilantin, Phenytek) for seizure prophylaxis is associated with poor functional outcome.[26]

The duration of prophylactic anticonvulsant use is also not well agreed upon. A short course of phenytoin (3 days), however, may be equivalent to a longer (7-day) course, but with fewer side effects in preventing seizures.[27] While the routine use of antiepileptic drugs (AEDs) in SAH is common, it is not trivial. A study pooling the data of 3552 patients from 4 prospective, randomized, double-blind, placebo-controlled trials from 1991 to 1997 looked at the outcomes in patients with subarachnoid hemorrhage treated with AEDs.[28] In this study, 65.1% of patients received antiepileptic drugs. Patients who received treatment with AEDs had a worse outcome based on the Glasgow Outcome

Table 1
Admission orders and rounding template for patients with aSAH in the NCCU

System	Orders	Notes
General	Admit to NCCU, neurosurgery, attending of record	
Neurologic	Noncontrast head CT	
	Conventional 4-vessel cerebral-angiogram	
	Aneurysm precautions	Dark, quiet room, limited interruptions
	Levetiracetam 1 g q12 h	Seizure prophylaxis
	q6 h Na/K checks	To monitor for CSW/SIADH
	Na goal: 135–145	May be adjusted depending on patient's clinical status and evidence of cerebral edema
	Ventriculostomy-if symptomatic hydrocephalus	Pop-off set to 15–20 mm Hg in setting of unsecured aneurysm. After aneurysm occlusion, pop-off may be lowered depending on clinical scenario
	Dexamethasone (Decadron) 4 mg q6 h × 24 h	
	Daily TCDs	
	Nimodipine 60 mg q4 h × 21 d	
Cardiac	SBP goal <160	Nicardipine (Cardene) continuous infusion if needed. SBP goal may be liberalized if vasospasm/DCI
	MAP goal >70	
	Baseline ECG	
	Baseline echocardiogram	
Pulmonary	Incentive spirometry	
	Chest radiograph	On admission and then daily if intubated
	Ventilator settings if patient requires mechanical ventilation	

Renal	IV fluids: 0.9% normal saline at 150 mL/h Goal euvolemia	May use 2% or 3% hypertonic saline based on sodium goal Volume status goal may change as clinical scenario changes (ie, goal hypervolemia in setting of vasospasm/DCI)
GI	NPO on admission Pantoprazole (Protonix) 40 mg q24 h	Resume enteral feeds when clinically stable GI ulcer prophylaxis
ID	Follow temperature curves Periprocedural antibiotics Fever workup if T_{max} >38.4°C	Initiate cooling measures if persistently febrile despite antipyretics Cefazolin 1–2 g × 1 for EVD or lumbar drain placement Cefazolin 1–2 g q8 × 3 doses for craniotomy (may use clindamycin 600 mg if cefazolin allergy) Urine analysis, blood and urine cultures, CXR, ± CSF studies/culture
Endocrine	Glucose checks q4 h while NPO Insulin sliding scale	 Glucose goal ≤150 mg/dL
Hematology	Hemoglobin goal ≥10 g/dL	
DVT prophylaxis	Compression stockings Sequential compression devices Unfractionated heparin 5000 units SC q8–12 h	 Start 24 h after stable head CT or after craniotomy
Check labs	BMP, CBC, coags, type and screen, UA/urine culture, urine pregnancy test (if applicable)	
Consent	Consent for angiogram, intraoperative angiogram, ventriculostomy, craniotomy	Done at time of admission to NCCU

Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; BMP, basic metabolic panel; CBC, complete blood count; coags, coagulation panel; CSF, cerebrospinal fluid; CSW, cerebral salt wasting; CT, computed tomography; CXR, chest radiography; DCI, delayed cerebral ischemia; DVT, deep venous thrombosis; ECG, electrocardiography; EVD, external ventricular drainage; GI, gastrointestinal; ID, infectious disease; IV, intravenous; MAP, mean arterial pressure; NCCU, neurocritical care unit; NPO, nothing by mouth; q, every; SBP, systolic blood pressure; SC, subcutaneous; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TCD, transcranial Doppler ultrasonography; UA, urinalysis.

Scale, and were more likely to have vasospasm, neurologic deterioration, cerebral infarction, and elevated temperatures during hospitalization. We routinely use levetiracetam (Keppra), 500 to 1000 mg every 12 hours, for seizure prophylaxis. This medication has a favorable side-effect profile in comparison with phenytoin. The duration of therapy is tailored to the individual patient, and takes into account the extent and location of SAH/intraparenchymal hemorrhage and the presence or absence of seizures.

Rebleeding

Rebleeding rates after aSAH vary in the literature. Starke and Connolly,[29] on behalf of the participants of the International Multidisciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage, recently published a review of the literature on this topic. Early studies (through 1990) showed that rebleeding rates for untreated aneurysms were 4% within the first 24 hours, 1% to 2% per day for the next 14 days, 50% for the first 6 months, and 3% per year following this. In the ISAT trial, approximately 2.1% of patients rebled before treatment.[30] In the International Cooperative Study on the Timing of Aneurysm Surgery, rebleeding occurred in 6% of patients with planned surgery for days 0 to 3 and 22% in patients with planned surgery for days 15 to 32.[31] In this study, after the initial effects of the hemorrhage and vasospasm, rebleeding was the next largest cause of poor results.[32] This finding has led to the standard of care that aneurysms should be occluded as soon as possible following rupture.

Many risk factors can help to predict rebleeding. Naidech and colleagues[33] looked at 574 patients enrolled in the Columbia University SAH Outcomes project. Rebleeding occurred in 6.9% of patients, 73% of which occurred in the first 3 days. In their multilogistic regression model, independent predictors of rebleeding were Hunt-Hess grade on admission and maximal aneurysm diameter. Of note, rebleeding was associated with a decrease in survival with functional independence. Timing of rebleeding was also related to Hunt-Hess grade. Patients with higher grades (IV and V) rebled earlier than those with lower grades. Rebleeding time did not correlate with aneurysm size. Patients with rebleeding have worse outcomes compared with those who do not, including higher rates of brain death and poor outcomes.[34]

Risk of rebleeding following treatment of ruptured intracranial aneurysms was studied in the Cerebral Aneurysm Rerupture After Treatment (CARAT) study,[35] which looked at 1001 patients across 9 centers treated with either coil embolization or surgical clipping. In this study there were 19 reruptures following treatment, 58% of which led to death. Degree of aneurysm occlusion was associated with the risk of rerupture. There was no statistically significant difference between rebleeding risk following coil embolization in comparison with surgical clipping.

Given the important finding that rebleeding is associated with worse outcomes, many have sought to identify interventions that can reduce this risk. As mentioned earlier, early aneurysm occlusion is one such intervention that has been an important development in the management of these patients. Another intervention that has been studied is the use of antifibrinolytic therapy, which has been evaluated mainly with the antifibrinolytics tranexamic acid (Lysteda, Cyklokapron) and ε-aminocaproic acid (EACA) (Amicar). The use of tranexamic acid (TXA) and EACA has been studied extensively. The goal of this therapy is to prevent clot dissipation by means of inhibiting fibrinolysis. However, despite the theoretical benefits, clinical outcomes have been varied.

In 2003 a Cochrane review looked at the use of antifibrinolytic therapy in aSAH, and concluded there was no benefit for poor outcome or death.[36] There was a reduction in rebleeding but this was countered by the increased risk of cerebral ischemia, therefore the review rejected the routine use of antifibrinolytic therapy in aSAH.

Given worse outcomes from delayed ischemia in patients treated with antifibrinolytics, more recent studies have evaluated the potential benefit of a short course of antifibrinolytic therapy. A prospective, randomized controlled trial published in 2002 looked at the use of early TXA (1 g) at the time of SAH diagnosis and 1 g every 6 hours until the aneurysm was occluded.[37] However, treatment with TXA did not exceed 72 hours. A total of 505 patients were randomized (254 to TXA, and 251 to control). Rebleeding decreased from 10.8% in controls to 2.4% in the treatment group. A prospective observational study looked at the use of EACA at the time of SAH diagnosis, but continued only for a maximum of 72 hours.[38] The study compared 73 patients treated with EACA and 175 patients not treated with EACA. This protocol resulted in a significant decrease in bleeding among those patients treated with EACA (2.7%) versus non-EACA treated patients (11.4%). Of importance, as had been previously seen in trials with prolonged use of antifibrinolytic therapy, there were no differences in ischemic complications between those treated and those not treated. There was, however, an increase in the incidence of deep venous thrombosis (DVT) in the treatment

group. There was no statistically significant difference in outcome between cohorts.

Given these data, the AHA/ASA SAH guidelines offer a Class IIA recommendation that it is reasonable to give antifibrinolytic therapy for less than 72 hours in patients with an unavoidable delay in aneurysm occlusion, a significant risk of rebleeding, and no medical contraindication.[3] We currently do not routinely use antifibrinolytic therapy. However, we do aim to treat all ruptured aneurysms within 24 hours of admission, thereby reducing the risk of rerupture.

Vasospasm and Delayed Cerebral Ischemia

Nomenclature

aSAH is associated with significant morbidity and mortality. Much of the morbidity is secondary to cerebral ischemia, which can occur in a delayed manner (ie, several days after the ictus). If severe enough, the ischemia can lead to brain tissue infarction. Although this has often been correlated with angiographic vessel narrowing ("vasospasm"), vasospasm can occur without ischemia/infarction, and ischemia/infarction can occur without vasospasm.[39] Vasospasm has been a well-known sequela of SAH since early descriptions by Robertson[40] in 1949 and Ecker and Riemenschneider[41] in 1951. Owing to the large variability in nomenclature, an international ad hoc panel of experts was assembled to propose a universal definition of delayed cerebral ischemia (DCI) to standardize outcome measures.[42] The investigators correctly observe that the diagnosis of DCI is one of exclusion. We make the diagnosis of DCI when there is a deterioration in the neurologic examination, etiology such as hydrocephalus, cerebral salt wasting (CSW), infection, and hemorrhage have been ruled out, and the deterioration improves with triple-H therapy within 6 to 12 hours; or, if there is no improvement, an angiogram is obtained to show radiographic vessel narrowing. It is important to recognize failure to respond to therapy, as lack of early improvement leads to a high risk of poor outcomes and thus may be an indication for conventional angiography.[43]

It is important to distinguish vasospasm (a radiographic finding) from clinical deterioration secondary to DCI, which can be a multifactorial process that includes vessel narrowing (ie, vasospasm).[42,44] A prospective study of 508 patients with subarachnoid hemorrhage also supports the notion that DCI is a more meaningful definition than arterial narrowing alone.[45] Given the significant morbidity and mortality associated with vasospasm and DCI, over the past several decades a significant effort has been made to establish monitoring and interventions that can improve outcomes from this process. A comprehensive review of all of these trials and measures is beyond the scope of this article; however, an outline follows of what we believe to be the most important, including transcranial Doppler ultrasonography (TCD), calcium-channel blockers, triple-H therapy, endovascular therapy, endothelin receptor antagonists, and statins.

Monitoring for vasospasm and DCI

Monitoring for the development of vasospasm and DCI remains an important role of the NCCU. In addition to serial neurologic examinations and imaging studies (ie, CT, CT perfusion, and conventional angiography), TCD is an important method for evaluating the cerebral vasculature. Despite the widespread use of TCD, however, its accuracy in predicting DCI and vasospasm is limited.[46,47] In a review of 441 patients with aSAH, almost 40% of patients with DCI did not have TCD velocities above the vasospasm threshold of 120 cm/s.[46] We use TCD data as an adjuvant to the clinical examination and other diagnostic modalities (such as CT perfusion scanning), and will follow trends in TCD velocities, but elevation in these numbers alone without clinical evidence of DCI does not lead them to make interventions.

Calcium-channel blockers

There are few multi-institutional, randomized, placebo-controlled, double-blind trials in the neurosurgical literature on improvement of outcomes that are available to guide management. The use of nimodipine following aSAH, however, represents one such trial.[48] The use of nimodipine following aSAH was pioneered by Allen and colleagues[48] at Johns Hopkins University School of Medicine. In this trial, 125 neurologically intact patients with aSAH were randomized to either nimodipine or placebo for 21 days. Only 1 patient of 56 treated with nimodipine versus 8 of 60 in the placebo group developed a persistent deficit from cerebral arterial spasm ($P = .03$).

Recently, a meta-analysis was completed looking at the use of calcium antagonists for aSAH.[49,50] The review included 16 trials with 3361 patients. Three of these trials included magnesium sulfate. Oral nimodipine provided a relative risk of 0.67 (95% confidence interval [CI] 0.55–0.81) for poor outcome. There was no statistically significant reduction for other calcium-channel antagonists alone or with intravenous nimodipine. Calcium-channel antagonists overall reduced the occurrence of secondary ischemia with a relative risk of 0.66 (95% CI 0.59–0.75). Based on this evidence, the investigators

recommend oral nimodipine, 60 mg every 4 hours for 21 days[50]; this is also our practice.

As already mentioned, it has been hypothesized that magnesium sulfate may also reduce the risk of DCI and poor outcome after aSAH. The MASH-2 (Magnesium for Aneurysmal Subarachnoid Hemorrhage) trial was a phase 3 randomized, placebo-controlled, multicenter trial aimed at addressing this question.[51] Patients were randomized to magnesium sulfate, 64 mmol/d, or placebo. There were 606 patients in the magnesium group and 597 in the placebo group. Poor outcome was found in 26.2% of patients receiving magnesium and in 25.3% of patients receiving placebo (relative risk 1.03, 95% CI 0.85–1.25). Based on this evidence and an updated review of meta-analysis data, the investigators do not recommend intravenous magnesium sulfate after aSAH. We do not use magnesium sulfate in managing these patients.

Triple-H therapy

The treatment of vasospasm following subarachnoid hemorrhage has classically been the so-called triple-H therapy, consisting of hypertension, hypervolemia, and hemodilution. This therapy evolved from 1972 to 1982, initially as monotherapies and subsequently as a combination of all 3.[52–55] The relative importance of each component of triple-H therapy has recently come under review. The literature seems to support that of each component; hypertension is the most important in increasing cerebral blood flow (CBF) and/or oxygenation, whereas hypervolemia does not increase CBF.[56–58] Further studies are needed to best identify the role triple-H therapy should play in managing vasospasm/DCI, as it is not a benign therapy and is associated with many complications, including pulmonary edema, hyponatremia, and myocardial infarction.[59] Furthermore, accurate hemodynamic management of these patients often requires invasive catheter lines. We routinely use the PiCCO (Pulsion Medical Systems SE, Feldkirchen, Germany) catheter system in preference to traditional Swan-Ganz catheters in managing these patients.

In patients with unsecured, unruptured aneurysms, hypertensive, hypervolemia therapy seems to be safe and does not lead to rupture.[60] When hypotension is a concern, if nimodipine administration results in unwanted lowering of blood pressure, we will routinely change the dosage from 60 mg every 4 hours to 30 mg every 2 hours. This change often will mitigate the antihypertensive effects of this calcium-channel blocker while maintaining the total daily dose.

During triple-H therapy, we aim for a mean arterial pressure goal that is 20% above the patient's baseline. If this fails to produce a favorable response in the patient, it will then be increased by another 10% of the new baseline. Extrapolating from the ischemic stroke guidelines, this elevation will be continued up to a systolic blood pressure of 220 mm Hg or diastolic blood pressure of 120 mm Hg.[61]

Endovascular management of vasospasm

Balloon catheter for angioplasty for vasospasm in aSAH was introduced in 1984.[62] In their review of the literature, Hoh and Ogilvy[63] found a 62% rate of clinical improvement following balloon angioplasty, although this was associated with a 5% major complication rate and 1.1% rate of vessel rupture. The decision to proceed with angioplasty rather than intra-arterial vasodilators is beyond the scope of this article. For a recent review of the literature, see Kimball and colleagues.[64] We proceed with angiography in patients with suspected DCI/vasospasm who do not improve clinically within 6 to 12 hours of initiation of triple-H therapy. If vasospasm is found radiographically, it is treated with either angioplasty or intra-arterial vasodilators.

Inflammation and endothelin receptor antagonists and statins

As discussed earlier, DCI is a major source of morbidity following subarachnoid hemorrhage. Vasospasm is thought to play at least some role in this process. Laboratory evidence supports the hypothesis that vasospasm is at least partially mediated by inflammatory processes.[65–68] Given this theory, considerable efforts have been made to evaluate promising therapies aimed at the inflammatory nature of vasospasm/DCI.

Endothelin, a vasoconstrictor, is thought to be a potential mediator of vasospasm, produced by a variety of cell types, including leukocytes in the CSF.[69,70] As such, there have been efforts to show that endothelin antagonists (such as clazosentan) can improve vasospasm, and therefore improve outcomes in aSAH. The CONSCIOUS trials (Clazosentan to Overcome Neurologic Ischemia and Infarction Occurring after Subarachnoid Hemorrhage) have sought to answer this question. CONSCIOUS-1 was a randomized, double-blind, placebo-controlled phase 2b dose-finding trial, which found that clazosentan significantly decreased moderate and severe angiographic vasospasm in a dose-dependent manner.[71] Encouragingly the investigators also found that there was some evidence suggesting a decrease in morbidity and mortality related to vasospasm. However, the study, was not powered to detect differences in clinical outcome.

The CONSCIOUS-2 trial was a randomized, double-blind, placebo-controlled phase 3 trial to assess the efficacy in reducing all-cause mortality, vasospasm-related new infarcts, delayed ischemic neurologic deficit secondary to vasospasm, and rescue therapy for vasospasm in patients with aSAH undergoing surgical clipping.[72] The study failed to show any significant benefit in clazosentan use. The CONSCIOUS-3 trial aimed to assess the same question in aSAH patients undergoing endovascular coiling.[73] This study was ended prematurely given the results of the CONSCIOUS-2 trial. The study did show a significant reduction of vasospasm-related morbidity and all-cause mortality at the high dose, but there was no statistically significant improvement in patient outcome. A recent review of the literature further supports these findings, and do not support the use of endothelin receptor antagonists for patients with aSAH.[74]

Given the proposed inflammatory nature of vasospasm and DCI, the use of statins has also been proposed and studied as a possible means to improve outcomes. Two recent meta-analyses, however, have failed to suggest that there is a significant enough benefit to warrant its routine use.[75,76] We do not routinely use endothelin antagonists in patients with aSAH. Furthermore, we do not routinely start patients on statins when admitted with aSAH, but will continue them if the patient had been using the medication before the hemorrhage.

CARDIAC

Troponin elevation following subarachnoid hemorrhage is a well-known phenomenon. Elevation in troponin I was found to be associated with an increased risk of left ventricular dysfunction, pulmonary edema, DCI, and death or poor functional outcomes in a cohort of 253 patients at the time of discharge.[77] Cardiac dysfunction following aSAH (also known as stunned myocardium, and the more recently proposed neurogenic stress cardiomyopathy) presents a challenge to the management of these patients.[78] It manifests as an increase in troponins, multiterritorial regional wall-motion abnormalities on echocardiogram, electrocardiogram abnormalities, a chest radiograph with pulmonary edema, and a normal coronary angiogram.[78] These findings are important, as their presence may hinder the treatment of vasospasm and DCI. Tako-tsubo cardiomyopathy is a subset of cardiomyopathy that can be seen following aSAH, particularly in postmenopausal women.[79,80] It is important to be aware of the diagnosis of cardiomyopathy following subarachnoid hemorrhage, as this has implications in the augmentative therapy needed in DCI (ie, inotropic pressors may be more appropriate than vasoconstrictors). Cardiomyopathy, whether preexisting or secondary to aSAH, can be detrimental in the setting of vasospasm when hemodynamic augmentation (triple-H therapy) is required. We previously reported on the successful use of an intraaortic balloon counterpulsation pump in such a setting.[81]

Although the causality has not been well established, it has been shown that bradycardia, tachycardia, and nonspecific ST-wave and T-wave abnormalities have been associated with mortality following aSAH.[82]

PULMONARY

Pulmonary complications have been reported in 22% of patients with aSAH, with pneumonia and congestive heart failure being the most common.[83] In their study of 305 patients, Friedman and colleagues[83] found that the incidence of symptomatic vasospasm was higher in patients with pulmonary complications. This finding is important, as it may relate to the fact that optimal treatment of vasospasm/DCI can be limited by the presence of pulmonary complications. Mechanisms by which pulmonary function is impaired following subarachnoid hemorrhage include pneumonia, pulmonary edema, atelectasis, acute lung injury, and acute respiratory distress syndrome.[84–86]

RENAL

Fluid Balance

An understanding of the fluid balance of patients with aSAH is important,[87] as is sodium balance, which is closely linked to fluid physiology. Standard calculations of fluid-balance measurements do not accurately predict actual circulating blood volumes as measured by pulse dye densitometry.[88] Given these findings, in a prospective controlled study Hoff and colleagues[89] used pulse dye densitometry to measure blood volumes daily in 102 patients in the first 10 days following SAH. In the intervention group, fluid management was based on blood-volume measurements, compared with the control group in which fluid management was based on fluid balance. The investigators found that severe hypovolemia (defined as blood volume <50 mL/kg) was seen more often in patients being managed by fluid calculation alone.

Swan-Ganz catheterization is one means of invasive measurement of hemodynamic parameters. However, there are numerous complications associated with this method.[90] One more recent method of monitoring volume status is by means of

transpulmonary thermodilution monitoring with the PiCCO system.[91] The effectiveness of the PiCCO system, compared with conventional pulmonary artery catheter–derived measurements, was compared in 16 patients with subarachnoid hemorrhage.[92] Cardiac output by the PiCCO system showed high correlation and low error compared with conventional catheter-based measurements. Once the accuracy of the PiCCO system was validated in the 16 patients, 100 subsequent patients were then randomized to either PiCCO or traditional catheters and the outcomes compared. Patients receiving early goal-directed therapy by PiCCO had decreased occurrences of vasospasm and cardiopulmonary complications compared with those managed by standard management based on use of central venous or pulmonary artery catheters. In the NCCU, we prefer the use of the PiCCO system to Swan-Ganz catheterization when more precise hemodynamic monitoring is needed beyond a central venous line.

Fluid-balance goals should constantly be assessed in patients with aSAH. The role of prophylactic hypervolemia has been studied. Eighty-two patients were randomized to either hypervolemia or euvolemia in a prospective randomized trial following aneurysm clipping.[58] There was no benefit in CBF in the patients randomized to hypervolemia. Similarly, in their study of 32 patients randomized to triple-H therapy or euvolemia, Egge and colleagues[93] did not find any benefit to prophylactic triple-H therapy. Given these data and the complications associated with hypervolemia, we aim for a goal of euvolemia unless otherwise indicated (ie, vasospasm/DCI). To this end, 0.9% normal saline is routinely used as maintenance fluids. In the setting of CSW or syndrome of inappropriate antidiuretic hormone secretion (SIADH), however, hypertonic saline may be required.

Sodium Goals

Derangements in maintenance levels of blood sodium are common in aSAH. Sodium levels are important, as outcomes have been associated with abnormal valves.[94] Two common causes of hyponatremia in patients with aSAH are CSW and SIADH. In CSW there is a renal loss of sodium, resulting in diuresis and hypovolemia, whereas in SIADH there is a retention of free water, leading to euvolemia or hypervolemia.[95] It is important to distinguish the 2 disorders clinically, as treatment will vary depending on the origin of the hyponatremia. We have previously reported favorable experience using 3% sodium chloride/acetate for hyponatremia in 29 patients with symptomatic vasospasm.[96] Most patients with hyponatremia after aSAH have CSW and not SIADH.

Corticosteroids have been used to treat hyponatremia in aSAH. In one randomized, placebo-controlled trial, hydrocortisone (Cortef) was effectively used to prevent hyponatremia, although there was no overall difference in patient outcome.[97] Fludrocortisone (Florinef) has also been shown to be effective in preventing natriuresis in randomized studies.[98,99] A recent study showed that early use of fludrocortisone was effective in preventing symptomatic vasospasm, but had no effect on overall outcomes.[100] We use fludrocortisone when the diagnosis of CSW has been made by presence of excessive diuresis accompanied by declining levels of blood sodium; we do not routinely use corticosteroids in a prophylactic manner.

INFECTIOUS DISEASE

Fever

Fever following subarachnoid hemorrhage is common. Predictors include poor Hunt-Hess grade and the presence of intraventricular hemorrhage.[101] Of importance, refractory fever following SAH is associated with increased mortality and worse outcomes.[101,102] Despite this, the role of fever reduction in improving outcomes is not well known. The side effects of treating fever either by pharmacologic means (ie, potential antiplatelet effects of nonsteroidal anti-inflammatories) or by cooling devices such as cooling blankets and intravascular devices (ie, shivering) must be weighed against the potential benefit in reducing the patient's temperature. In the NCCU, we treat fevers (>38.4°C) first with acetaminophen, and simultaneously send a diagnostic workup for the etiology of the fever and treatment of identifiable causes. If this is ineffective, methods of cooling such as surface cooling devices are used. Initial fever workup consists of urine analysis, urine culture, blood cultures, and chest radiography. CSF studies are sent on patients with ventriculostomies or lumbar catheters. If the patient has had an intracranial procedure but does not have a CSF drain in place, consideration is given to LP to obtain CSF in the appropriate clinical setting. Thorough investigation to identify and treat infectious causes of fever is prudent, as both pneumonia and bloodstream infections are independently associated with death or severe disability at 3 months.[103] Of importance is that delayed fever may also be present in the setting of vasospasm.[104]

Periprocedural Antibiotics

Periprocedural antibiotics are given for invasive procedures involving the central nervous system.

We use cefazolin (Ancef, Kefzol) unless the patient has an allergy or contraindication, in which case clindamycin (Cleocin) is substituted. One dose is given immediately before placement of ventriculostomy or lumbar drain. For patients undergoing craniotomy, antibiotics are continued for an additional 24 hours after surgery while in the NCCU.

ENDOCRINE

Glucose Control

Persistently elevated glucose (>200 mg/dL for 2 or more consecutive days), has been shown to result in patients being 7 times more likely of having a poor outcome at 10 months after treatment for aSAH than those patients who did not have persistently elevated glucose.[105] Furthermore, elevated glucose levels at admission are also associated with an increased risk of poor outcome.[106] Prolonged elevated glucose (ie, over a week) is also associated with worse outcomes.[107] However, treatment of hyperglycemia can lead to increased incidence of hypoglycemia, which has been shown, in both the SAH literature and the general medical literature, to be associated with worse outcomes.[108,109] As such, we place patients on an insulin sliding scale to target a glucose goal of 150 mg/dL or less at the time of admission. Continuous insulin infusions are only used when hyperglycemia is refractory to intermittent subcutaneous insulin dosing regimens.

HEMATOLOGY

Anemia

The ideal hemoglobin goal in patients with aSAH is not certain. Early animal data suggested that a hematocrit near 30% was optimal for protecting the brain in a canine model of ischemia.[110] Subsequently, several human studies have shown that anemia and lower hemoglobin values are associated with worse outcomes in patients with aSAH, and that higher hemoglobin is associated with improved outcomes.[111–114] A recent prospective, randomized trial randomized 44 patients to a hemoglobin goal of at least either 10 or 11.5 g/dL to evaluate the safety of this practice.[115] Although those in the higher hemoglobin group received more transfusions, this was found to be safe with similar safety and outcome end points. This finding is an important one for the SAH population, as studies from the critical care literature have suggested that a higher hemoglobin goal is not necessarily better and may actually result in worse outcomes.[116] We aim for a hemoglobin goal of at least 10 g/dL, and transfuse accordingly.

Deep Venous Thrombosis

The incidence of DVT in patients with SAH varies. Ray and colleagues[117] report an incidence of 18% in 250 patients with aSAH over a 4-year period, and Mack and colleagues[118] report an incidence of 3.4% in 178 patients who had screening lower extremity Doppler ultrasonography. A recent meta-analysis looking at venous thromboembolism (VTE) prevention, with pooled data from 30 studies with a total of 7779 patients, showed that low molecular weight heparin and intermittent compression devices were effective in decreasing the rate of VTE.[119]

Typically all patients at our center receive compression stockings and sequential compression devices at the time of admission. We will typically hold medical thromboprophylaxis until definitive treatment of the aneurysm. At this point, 5000 units unfractionated heparin given subcutaneously every 8 to 12 hours is begun, starting 24 hours after treatment. We do not routinely use low molecular weight heparin, although this may be considered for patients at high risk for DVT.[120] Rates of intracranial hemorrhage vary depending on the method of prophylaxis used. Lowest rates were seen if no heparin was used (0.04 per 1000 patients), and was 0.35 per 1000 patients if unfractionated heparin was used. Rates were highest in the group receiving low molecular weight heparin (1.52 per 1000 patients).[119]

NCCU MANAGEMENT OF ENDOVASCULAR VERSUS SURGICALLY TREATED PATIENTS

It should be noted that patients treated endovascularly rather than with surgical clipping of aneurysms following aSAH present unique challenges, which vary with treatment modality. Some aneurysms are best treated with endovascular therapy (ie, mid-basilar aneurysms), whereas others are best treated with microsurgical clipping (ie, MCA aneurysms). However, the decision of whether to treat a particular aneurysm with microsurgical clipping versus endovascular occlusion is complex and beyond the scope of this article. We have previously reviewed this literature, and in general favor surgical clipping over endovascular therapy in aSAH patients.[121] Regardless of which treatment modality is ultimately used, it is important that those caring for these patients in the NCCU recognize the differences in their management. Patients who have had coil embolization or stent-assisted coil embolization, may require antiplatelet therapy, which creates a challenge if the patient requires subsequent invasive interventions (ventriculostomy, lumbar drain, craniotomy, and so

forth). For example, rates of hemorrhagic complications associated with ventriculostomy placement in aSAH patients undergoing stent-assisted coiling, and thus on dual antiplatelet therapy, are higher than those undergoing coiling without a stent.[122] Patients who have undergone craniotomies are susceptible to postoperative complications (eg, wound infections, postoperative hematoma) that patients treated by endovascular means are not. It is important for the practitioner caring for these patients to be aware of these differences.

SUMMARY

aSAH can be a devastating disease. Those patients who survive the initial hemorrhage are best cared for in specialized NCCUs with personnel well trained in the management of this disease. Despite the progress made over the last decades, there still remains a paucity of high-quality evidence with which to guide the management of these patients. This article aims to provide those caring for these patients with a brief review of some of the literature combined with our own experiences. **Table 1** provides an outline for admission orders and a daily rounding template based on this experience, to help those who take on the challenge of managing this disease.

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