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The Critical Care Management of Aneurysmal Subarachnoid Hemorrhage

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Additional information is available at the end of the chapter

1. Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is a neurosurgical emergency that results from the rupture of an aneurysm in the subarachnoid space (see figure 1). SAH carries a high mortality rate, estimated at 45%; additionally, a significant amount of patients are left with impaired neurologic function [1]. The critical care management of SAH requires an appreciation of both neurologic and general critical care principles; it is best thought of as a systemic multi-organ disease.

1.1. Epidemiology & morbidity

The clinical burden of aneurysmal SAH is immense. Case fatality approaches 50%, and approximately 1 in 8 patients die prior to reaching the hospital [2]. Of those that survive, nearly 50% will have significant functional impairment [3]. Aneurysmal SAH accounts for approximately 85% of all non-traumatic SAH. Approximately 30,000 Americans are affected annually [1]. The incidence of aneurysmal SAH ranges from 6-21/100,000 patient years [4].

1.2. Risk factors

Risk factors for development of aneurysmal SAH can be categorized as modifiable and non-modifiable. Modifiable risk factors include cocaine abuse, hypertension, and cigarette smoking [4]. It is estimated that cigarette use increases the risk of aneurysmal SAH by a factor of 3.7-3.9 [5]. Non-modifiable risk factors include sex, ethnicity, family history, and collagen-vascular diseases. The female:male ratio for aneurysmal SAH is approximately 2:1 [6]. The incidence of aneurysmal SAH is higher amongst people of Finnish and Japanese descent; and the incidence of aneurysmal SAH is almost three times greater in Finland than other parts of the world [4]. The incidence of intracranial aneurysms is higher in patients

with collagen vascular diseases, such as Marfan's Syndrome, Ehlor's-Danlos Disease, Neurofibromatosis Type 1, and Autosomal dominant polycystic kidney disease [7].
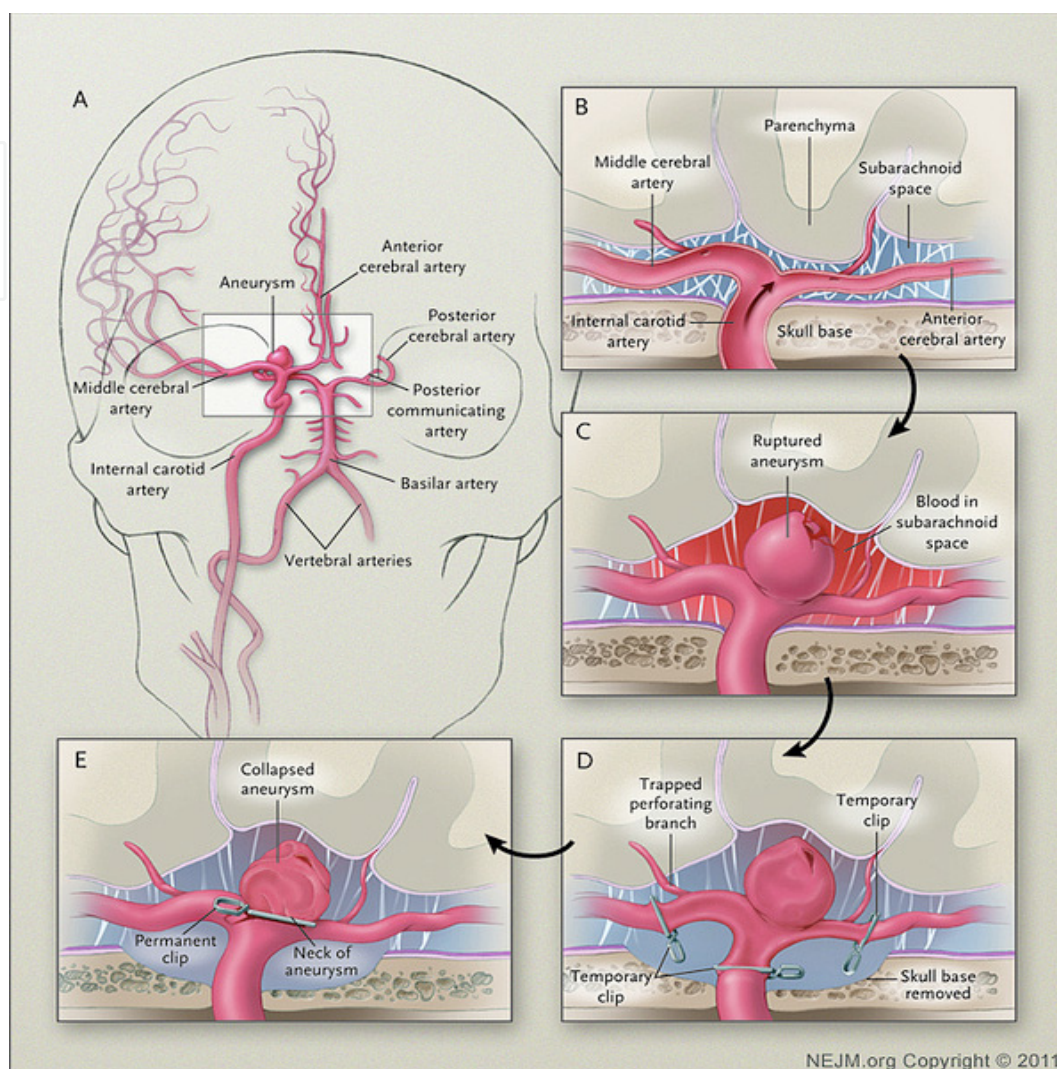
Borrowed with permission: Ellegala D, Day A. (2005) Ruptured Cerebral Aneurysms. New England Journal of Medicine. 352: 121-124

Figure 1. The arterial blood supply to the brain is located primarily in the subarachnoid space (Panel B). Aneurysm formation occurs in the subarachnoid space (Panel C), which must be surgically accessed to provide definitive treatment of the aneurysm (Panel E).

2. Diagnosis

2.1. Clinical presentation

The classic presentation of a patient with aneurysmal SAH is thunderclap headache, often described as the "worst headache of my life." It is generally abrupt in onset and reaches maximal intensity instantly. However, this classic description is seen in only 50% of patients presenting with aneurysmal SAH [8]. Conversely, in those patients prospectively screened for acute severe headache, only 6-17% were demonstrated to have SAH [9,10]. Common

features at presentation can include seizure, loss of consciousness, and nausea and emesis preceding onset of headache [9]. The concept of 'sentinel headache' remains controversial; it is thought to be related to changes in the wall of the aneurysm versus a microbleed. A sentinel headache generally presents as a severe headache lasting greater than an hour, but diagnostic evaluation does not lead to the confirmation of SAH. These patients are at higher risk for early re-bleeding and aneurysmal SAH. The estimated relative odds ratio is 2.5-3.8 increase in early re-bleeding in patients who present initially with a sentinel headache [11].

2.2. Physical examination

Patients with aneurysmal SAH can have a variety of examination findings at presentation. These may range from a headache without focal neurologic deficits to being comatose. Most commonly, patients may have a depressed level of consciousness or confusional state. Cranial nerve palsies are also frequently seen as a direct result of an aneurysm; though cranial nerve 6 palsy may be a sign of elevated intracranial pressure. Focal weakness is also noted in a small percentage of patients. Fundoscopic examination may reveal subhyaloid hemorrhages and papilledema. Clinical correlation with outcome is best defined by the Hunt & Hess grading scale (see Table 1) [12].

2.3. Neuro-imaging

In addition to clinical presentation, the vast majority of SAH is diagnosed with correlating neuro-imaging. Non-contrast Head CT is the preferred modality of choice for the initial evaluation. Retrospective analysis has reported a sensitivity of 91-100% [13]. The sensitivity of non-contrast head CT diminishes as time elapses from the time of onset. It is best during the first 24 hours and diminishes to 85% at 5 days and subsequently to 50% at 1 week [14]. False negatives may occur in patients with anemia and is dependent upon the experience of the reading neuroradiologist [15]. MRI offers a higher sensitivity to detect SAH in patients presenting outside of first 48 hours after onset; however MRI is not readily available at most institutions and some patients may not be suitable for MRI. The FLAIR (fluid attenuated inversion recovery) and GRE (gradient echo) sequences are the most reliable method for detection of SAH in MRI [16].

Detection of aneurysms is best with catheter digital subtraction angiography, which remains the gold standard. In our practice, we perform a CT angiogram at admission, which carries a 85-98% sensitivity in comparison to catheter angiography. On average, 10-20% of patients with non-traumatic SAH will have a non-diagnostic catheter angiogram [17]. Practice varies in terms of repeat angiography; our current practice is to repeat an angiogram between 10-14 days.

2.4. Lumbar puncture

Cerebro-spinal fluid (CSF) analysis remains an essential aid in diagnosis in CT-Negative patients presenting with acute onset of severe thunderclap headache. Lumbar puncture

should ideally occur 6-12 hours after onset of symptoms to optimize sensitivity. Lysis of red cells and the formation of oxyhemoglobin and bilirubin produce xanthochromia, ideally detected visually by inspection and confirmed by spectophotometry. CSF can remain positive for up to 7 days following ictus [18].

2.5. Classification

Various classifications exist for SAH. These range from clinical grading systems to radiographic scales. The most commonly used scales are Hunt & Hess, and World Federation of Neurological Surgeons (WFNS) scales [19]. (See Table 1)

Grade	Hunt & Hess	WFNS	Survival
1	Asymptomatic or minimal headache and slight nuchal rigidity	GCS 15, no motor deficit	70%
2	Moderate to severe headache, nuchal rigidity, no neurology deficit other than cranial nerve palsy	GCS 13-14, no motor deficit	60%
3	Drowsy, confusion, or mild focal deficit	GCS 13-14, motor deficit	50%
4	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances	GCS 7-12 with or without motor deficit	20%
5	Deep coma, decerebrate rigidity, moribund appearance	GCS 3-6 with or without motor deficit	10%

Adapted from - Rosen et al. (2005) Subarachnoid Hemorrhage Grading Scales: A Systemic Review. Neurocrit Care. 2: 110-118.

Table 1. Clinical grading scales for aneurysmal SAH and percent survival correlated with Hunt & Hess.

2.6. Differential diagnosis

Not all non-traumatic SAH is necessarily aneurysmal; however all non-traumatic SAH is treated as aneurysmal unless it is evident from clinical history or radiographic imaging that it is low risk. Most commonly, angiographic negative SAH is secondary to perimesencephalic hemorrhages. These compromise 10% of all SAH and two-thirds of non-traumatic SAH with negative angiograms. Blood is generally located ventral to brainstem in the prepontine and perimesencephalic cisterns. Generally, intraventricular hemorrhage (IVH) is rare. The average patient with perimesencephalic SAH is above the age of 50 and has less severe deficits. Rebleeding and vasospasm are infrequent in these patients [17].

Most SAH is in fact traumatic; however a collaborating history is not always obtained. Of those patients that have non-traumatic, non-aneurysmal SAH, intradural dissection is a concern; this is typically of the vertebral artery. Rupture of arteriovenous malformations (AVM) can occasionally extravasate blood into the cisternal space. Additionally, Arteriovenous Dural fistulas, mycotic aneurysms, pituitary apoplexy, and moya moya

disease should remain on the differential, though there is generally additional history to suggest these. Cerebral vasculitis should remain a diagnosis of exclusion in patients with unexplained subarachnoid hemorrhage. The pattern of SAH on neuroimaging directs further work up. A non-classic pattern of cisternal hemorrhage suggests perimesencephalic or AVM related SAH. Blood present in the cortical sulci is generally thought to be traumatic, though can be associated with AVM rupture and vasculitis [17].

3. Management

The critical care management of aneurysmal SAH can be thought of as three distinct phases: Immediate management (prior to securing the culprit aneurysm), entrapment of the aneurysm, and post entrapment management. Technical aspects and surgical management in entrapment of the aneurysm are described elsewhere [20, 21]. In this chapter we focus primarily on critical care management of aneurysmal SAH and potential complications.

3.1. Immediate management

The major risk of fatality following aneurysmal SAH occurs within the first 24 hours and is related to the risk of re-rupture of the aneurysm. Rebleeding occurs primarily within the first 8 hours and is present in 9-17% of patients within the first 72 hours [22]. Rebleeding carries a significant mortality rate – up to 50% [17]. Therefore, prevention of rebleeding is key in management.

Management in the 1980's of aneurysmal SAH incorporated the use of antifibrinolytics to diminish the risk of rebleeding. In these patients, antifibrinolytics were continued for weeks at a time. However, this practice was subsequently abandoned when further studies suggested that though rebleeding was diminished, complications of delayed cerebral ischemia, primarily vasospasm, increased and there was little difference in outcomes [23].

Recently, there has been renewed interest in the use of short-term (12-48 hours) antifibrinolytic therapy. Because complications of delayed cerebral ischemia and vasospasm generally occur after day 3, and the greatest risk of re-rupture is within the first 48 hours, a short duration of antifibrinolytic therapy may improve outcomes. A significant reduction in the rate of rebleeding, 11% to 2.5% has been observed in patients treated with an early short course of the antifibrinolytic tranexamic acid [24]. However, no study to date has been powered adequately to assess clinical outcome benefit with early short duration antifibrinolytic therapy. One study, however, has shown an increase in the rate of DVT's associated with the use antifibrinolytic therapy [25]. The Neurocritical Care Society's consensus statement on management of SAH recommends considering an initial early short course of an antifibrinolytic with early definitive treatment of the aneurysm [26]. Our current practice is to utilize antifibrinolytic therapy as early surgery/intervention is being arranged.

No clear hemodynamic goals have been defined in patients with aneurysmal SAH prior to entrapment of the aneurysm. Practice varies from center to center with the general consensus that elevated blood pressure raises the concern for early rebleeding. Early studies

reported that induced hypertension and hypervolemia were associated with aneurysmal rebleeding and hemorrhagic transformation; however, further studies have failed to demonstrate this link. The consensus statement from the Neurocritical Care Society observed that modest hypertension (SBP <160mmHg, MAP < 110mmHg) was not associated with rebleeding [26].

Hydrocephalus is a frequent complication of aneurysmal SAH and is seen in 15-30% of SAH patients. The clinical impact of hydrocephalus is variable. Patients may be asymptomatic to obtunded. CSF diversion thru ventriculostomy generally resolves hydrocephalus and often times, a marked improvement is noted in level of consciousness [1]. Our clinical practice is to place ventriculostomies in all Hunt and Hess Grade 3 or higher aneurysmal SAH.

3.2. Securing the aneurysm

The key treatment of aneurysmal SAH is securing or trapping the aneurysm, thereby reducing the probability of rebleeding. Patients who have early surgery, within the first 72 hours, had an overall mortality rate equivalent to patients with delayed surgery (days 11-32); however, those with early surgery had significantly better clinical recovery [27]. The general consensus is that aneurysms should be secured within the first 24-48 hours following rupture The technical aspects and surgical management in entrapment of the aneurysm are beyond the scope of this chapter and are described elsewhere [20, 21]

3.3. Post entrapment management

The majority of the length of stay for aneurysmal SAH patients occurs post-surgical trapping. It is during this time that patients remain at high risk for neurologic deterioration secondary to vasospasm, delayed cerebral ischemia, seizures, hyponatremia, and other complications.

Management during this period relies on close serial neurologic assessment, and prompt management of complications.

Traditionally, patients with aneurysmal SAH have been treated with triple H therapy – consisting of hypervolemia, hemodilution, and hypertension. As our understanding of aneurysmal SAH advances, this strategy has changed significantly.

3.3.1. Volume status

Monitoring volume status in critically ill patients can be challenging, but remains essential to optimizing medical care. Patients with aneurysmal SAH frequently develop hypovolemia and hyponatremia as a consequence of cerebral salt wasting syndrome. Retrospective studies demonstrate an increase in ischemia and worse outcomes in patients with hypovolemia [28].

Fluid balance does not necessarily reflect intravascular volume [29]. Some have advocated CVP while others rely on PAC to optimize volume status. CVP appears to be unreliable as

an indicator of volume status and the use of routine PAC is cumbersome and the risks outweigh the benefits [30, 31]. Few have shifted to beside ultrasound and distensibility of the inferior vena cava [32]. However, none of these measures of intravascular volume have proven reliable. A combination of both invasive and non-invasive monitoring in conjunction with other clinical indicators of volume status provide the best guide for targeting therapy [26].

Induced hypervolemia has been investigated in two prospective randomized trials – no benefit was found in vasospasm or clinical outcome [33, 34]. Therefore, our clinical practice is to target euvolemia. Preferred volume of choice is isotonic crystalloid [26]. Mineralocorticoid supplementation with fludrocortisone has demonstrated the reduction in need of intravenous fluids needed to maintain euvolemia [35].

3.3.2. Prophylactic measures

3.3.2.1. Nimodipine

Calcium antagonists have been studied as agents to reduce the incidence of vasospasm associated with aneurysmal SAH. To date, nimodipine, a member of the dihydropyridine family of calcium antagonists, has been the only medication shown to have significant improvement in clinical outcome in patients with aneurysmal SAH [37]. Typical dosing is 60mg every 4 hours orally and is continued for 21 days. Treatment with nimodipine led to a relative risk reduction of 24% for poor outcome [37].

3.3.2.2. Magnesium

Magnesium has attracted study in patients with aneurysmal SAH as it is a non-competitive calcium antagonist with important vascular and potential neuroprotective effects [38]. Dosing and optimal magnesium levels are not well agreed upon; however, hypomagnesemia is related to a worse outcome. Studies have yielded conflicting results. The largest trial to date did not demonstrate any outcome difference between those targeted with hypermagnesemia [39]. A second Phase III study, MASH-II, is currently underway. Our current practice is to target Magnesium levels between 2.0 and 3.0 mg/dL, and to avoid hypomagnesemia pending results of MASH-II [26].

3.3.2.3. Statins

The many beneficial effects of statins have made them targets for consideration as prophylactic agents in aneurysmal SAH patients. Clinical trials have, however, not demonstrated a consistent beneficial effect. A meta-analysis suggested that there may be a reduction in delayed cerebral ischemic (DCI) with statins, however, patients in these studies had a higher rate of DCI than typically reported elsewhere [40]. Another meta-analysis of 4 randomized trials showed no benefit with statin prophylaxis in Trans-Cranial Doppler (TCD) detected vasospasm, functional outcome, or mortality [41].

Though no studies have directly addressed continuing or withdrawing statins in patients with aneurysmal SAH, there is data from patients with ischemic stroke and myocardial

infarction that suggests acute statin withdrawal can worsen outcome [42, 43]. Until further data is available from clinical trials, the consensus is not to initiate treatment with a statin; however, one should be continued if it has been prescribed prior to aneurysmal SAH [26].

3.3.2.4. Seizure

Seizures may occur with aneurysmal rupture; patients may also develop chronic epilepsy following aneurysmal SAH. The incidence of seizures during the acute phase of aneurysmal SAH varies: studies estimate a range between 8-30% [1]. Other estimates are more conservative ranging between 1-7% at the time of rupture [21]. Continuous EEG monitoring in patients with poor grade SAH demonstrated a 10-20% prevalence of non-convulsive seizures [44]. Risk factors for developing seizures include age > 65 years, thick subarachnoid clot, rupture of a middle cerebral artery aneurysm, and intraparenchymal hemorrhage [45].

Prophylactic treatment of seizures has been commonplace; however, recent studies have investigated the benefit and risks involved [26]. Prophylactic use with phenytoin has been demonstrated to lead to worse outcomes [46]. Shorter duration prophylaxis has been advocated and a 3-7 day course of prophylaxis is general practice. Other anti-epileptic agents have been investigated and levetiracetam has been shown to be equally efficacious in reducing early seizures as well as improved functional recovery in comparison to those patients treated with phenytoin [47]. The current recommendation is to consider using short-term (3-7 days) of agents other than phenytoin, such as levetiracetam, for seizure prophylaxis. For patients with poor grade SAH with unexplained neurologic deterioration, continuous EEG monitoring is recommended [26].

3.3.2.5. DVT

Aneurysmal SAH induces a prothrombotic condition that can lead to an increase in deep venous thrombosis (DVT), and pulmonary embolism (PE). Incidence of DVT varies between 1.5-1.8%, with poor grade SAH having a higher incidence [48].

Conventionally, sequential compression devices (SCDs), unfractionated heparin, and low-molecular weight heparin have been used. One meta-analysis showed all were similarly effective in preventing DVT, but there was a trend towards higher rates of hemorrhage (intracerebral and non-cerebral) in those with low molecular weight heparins [49]. Timing of initiation is controversial, but generally, it is felt safe to assume pharmacologic prophylaxis after 24 hours from onset. Similarly, pharmacologic prophylaxis should be held 24 hours before and after intracranial procedures [26].

3.3.2.6. Glycemic control

Hyperglycemia is often diagnosed in patients with SAH; numerous studies have associated admission hyperglycemia with poor clinical grade and outcome [50]. The optimal range of glycemic control in patients with aneurysmal SAH is unknown. One study has shown improved outcomes with tight glycemic control: 80-140mg/dL, achieved thru insulin infusion [51]. However, when tightened to 80-110mg/dL, outcomes were worse secondary to episodic hypoglycemia and vasospasm [52]. Extrapolating data from other critically ill

populations suggests that patients on insulin infusions are more likely to develop hypoglycemia [53]. Microdialysis studies have shown cerebral glucose levels to decrease, even without systemic hypoglycemia [54]. Based on the available data, hypoglycemia should be avoided and system glycemic control should target < 200mg/dL [26].

3.3.2.7. Pyrexia

Fever is very common in patients with SAH; studies report between 41-72% of patients with aneurysmal SAH will have fever. Fever is independently associated with poor outcome in retrospective studies of SAH [55]. As such, aggressive work up of fever is obligatory to look for underlying infection, drug reaction, or thrombosis. No clinical trial has prospectively examined induced normothermia and outcome; however, given the increased morbidity with fever, it is prudent to manage pyrexia [56]. Strategies to decrease fever include medications such as acetaminophen, and NSAIDs. More aggressive devices include cooling blankets, and intravascular temperature modulation devices. The deleterious effects of aggressive cooling can include shivering and should be monitored for and aggressively combated [26].

3.3.2.8. Anemia

Anemia develops in over 50% of patients with Aneurysmal SAH and Hemoglobin concentrations decrease to less than 11g/dL in more than 80% of patients [57]. Because under normal circumstances when cerebral oxygen delivery demands metabolic demand, these levels are well tolerated. However, patients with aneurysmal SAH are at risk for developing vasospasm and DCI; their metabolic needs may not be met.

The optimal target hemoglobin in this patient population is not known. Retrospective studies have demonstrated that higher hemoglobin concentrations were associated with good functional outcomes [58]. PET imaging studies show an improvement in delivery of cerebral oxygen when hemoglobin is improved from 8g/dL to 10g/dL thru red cell transfusion [59]. However, evidence from broader based critically ill patients suggest that there is lower mortality in patients with a restrictive transfusion strategy [60].

Current guidelines suggest minimizing blood loss from blood drawing, as well as consideration of packed red cells to maintain hemoglobin concentrations between 8-10g/dL. Patients with DCI are the most likely to benefit from this higher transfusion strategy [26].

3.3.3. Complications of aneurysmal subarachnoid hemorrhage

Direct neurologic complications include cerebral vasospasm and delayed cerebral ischemia. Acute hydrocephalus and a diminished threshold for seizures have been discussed previously. Systemic complications of aneurysmal SAH include cardiac, pulmonary, and electrolyte abnormalities (see Figure 2). Fever, anemia, hyperglycemia are also common and have been discussed previously.
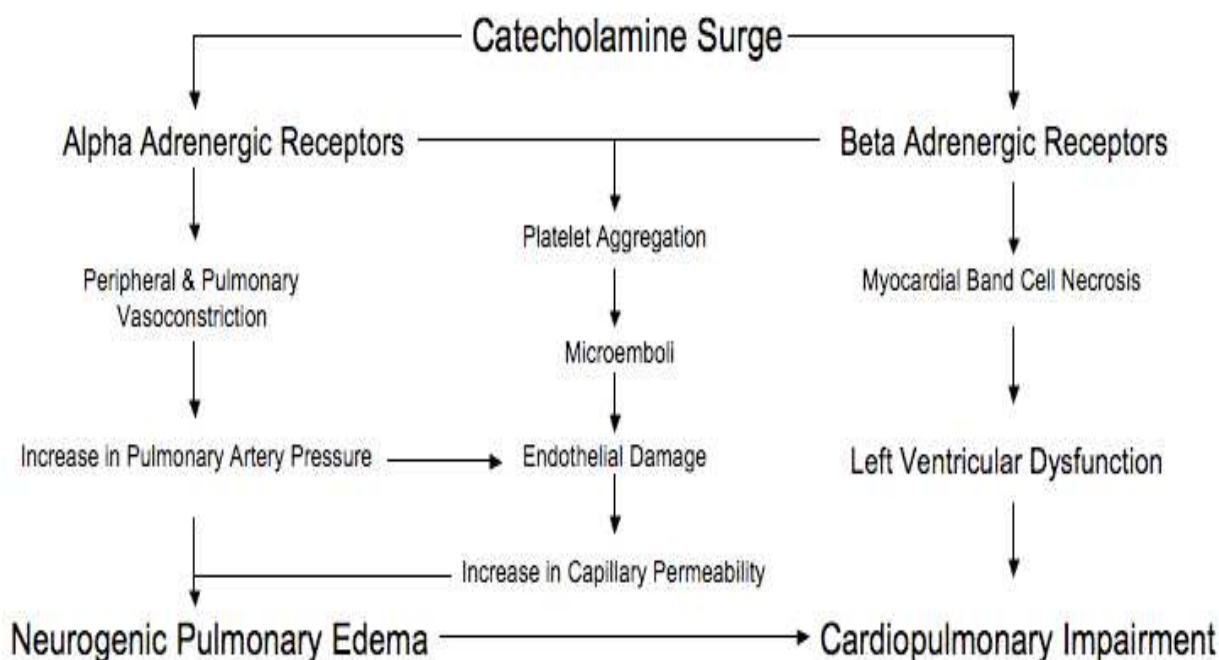
Adapted from – Coppadoro A, Citerio G (2011) Subarachnoid Hemorrhage: An Update for the Intensivist. Minerva Anestesiologica. 77: 74-84.

Figure 2. Cardio-pulmonary complications of aneurysmal SAH are related to the surge in catecholamines.

3.3.3.1. Cardiac complications

Cardiac complications following aneurysmal SAH are frequent and range from hemodynamic instability to cardiac arrhythmias to myocardial injury and heart failure. Given the high prevalence of cardiac complications, all patients with aneurysmal SAH should have an ECG, cardiac enzymes, and echocardiogram on admission.

ECG abnormalities most commonly seen following aneurysmal SAH are ST segment alterations, prominent U waves, QT-prolongation and other conduction abnormalities. Older age, hyperglycemia, and longer length of state are associated with atrial fibrillation and atrial flutter [61].

Troponin I is elevated on admission in 20-34% of patients with aneurysmal SAH. Studies have suggested that elevated troponin I is an independent risk factor for severe disability and death at hospital discharge. Higher grade SAH, IVH, and loss of consciousness at ictus have all been associated with elevated troponin I [62].

Acute heart failure and myocardial injury are most commonly seen in higher-grade SAH patients; the most severe form is neurogenic stunned myocardium. The surge of catecholamine release associated with SAH is thought to be responsible for neurogenic stunned myocardium, however the exact mechanism remains poorly understood. The classic

pathologic findings are myocardial contraction band necrosis. Presentation includes transient lactic acidosis, cardiogenic shock, pulmonary edema, widespread T wave inversions, and reversible wall motion abnormalities [63]. One prospective study revealed a 18% (35% in Grade III-V) prevalence of wall motion abnormalities on echocardiogram in patients with aneurysmal SAH [64]. Takotsubo cardiac myopathy, also known as apical ballooning syndrome, is a subset of stunned myocardial injury seen most commonly in post-menopausal women and is associated with pulmonary edema and prolonged mechanical ventilation [65].

3.3.3.2. Pulmonary complications

Pulmonary complications are frequent (22%) and include impairment in gas exchange, pneumonia (20%), pulmonary edema (14%), and pulmonary embolism (0.3) [61]. These represent common manifestations of pulmonary disease in general critical care patients. Patients with aneurysmal SAH are however prone to develop aspiration pneumonias given a higher frequency of impaired consciousness. Thus, vigilant aggressive pulmonary toilet and aspiration precautions are important.

Neurogenic pulmonary edema (NPE) is associated with various neurologic insults, including SAH, seizures, and traumatic brain injury. It is thought to be a result of massive sympathetic discharge and catecholamine release at ictus, resulting in vasoconstriction and an increase in MAP with subsequent shift of intravascular volume to a lower-resistance pulmonary bed. The role of cardiac dysfunction in association aneurysmal SAH also contributes to pulmonary edema in these patients. NPE is associated with poor outcomes and is seen in patients with higher grade SAH. These patients are challenging to manage. Maintaining euvolemia in SAH patients decreases the risk of vasospasm; and it is well accepted that hypovolemia increases risk of vasospasm. Thus, cautious use of diuretic therapy is indicated when oxygenation and/or hemodynamic instability as a result of heart failure develop [66].

3.3.3.3. Hyponatremia

Hyponatremia is prevalent in up to 57% of patients with aneurysmal SAH [67]. It is the most commonly encountered electrolyte abnormality in NeuroScience ICU's. Severe hyponatremia is associated with seizures, and worsening of cerebral edema. In patients with aneurysmal SAH, hyponatremia is associated with increasing risk of vasospasm, likely secondary to its association with hypovolemia [68].

Hyponatremia in the setting of aneurysmal SAH can either be caused by Cerebral salt wasting (CSW) or the Syndrome of Inappropriate Antidiuresis (also known as Syndrome of Inappropriate Antidiuretic Hormone – SIADH). The proportion of patients with CSW versus SIADH as the cause of hyponatremia in aneurysmal SAH varies depending on the study, but CSW is more likely. Distinguishing CSW and SIADH is of clinical importance as the management is different, and can adversely affect outcomes in patients with aneurysmal SAH [68].

CSW is a result of natriuresis: loss of sodium resulting in loss of free water leading to hyponatremia; it is thus a hypovolemic hyponatremia. SIADH results from inappropriate anti-diuresis and is thus a euvolemic hyponatremia. Distinguishing the two is often difficult. Generally, patients with SIADH have decreased urine output in comparison to CSW. Urine osmolality is generally lower to normal in patients with CSW and high in patients with SIADH. Urine sodium levels are elevated in both. However, these are not always reliable; volume status, if determined reliably, is likely the most accurate method for distinguishing CSW from SIADH [69].

The mechanism of CSW is not completely understood. It is thought to result from interference of sympathetic input to the kidney and from elevated circulating natriuretic factors seen after cerebral injury [68].

CSW in patients with aneurysmal SAH are treated with Na supplementation and restoration of volume. This is achieved thru the use of salt tablets and hypertonic saline solutions. Mineralocorticoid supplementation is useful to increase Na and volume; typically, fludrocortisone is used. Therapy is targeted to maintain Na >135 [68].

More recently, the vasopressin receptor antagonist conivaptan has become available. It may cause an increase in diuresis and lead to a negative fluid balance. Though originally intended for the treatment of SIADH, it has been used cautiously in the hyponatremic patient with aneurysmal SAH [70].

3.3.3.4. Systemic Inflammatory Response (SIRS)

The catecholamine release associated with aneurysmal subarachnoid hemorrhage along with pro-inflammatory cytokines can lead to SIRS. The presence of SIRS criteria on admission (body temperature, heart rate, respiratory rate, and white blood cell count) in patients with aneurysmal SAH is a significant independent predictor of vasospasm and hydrocephalus. It is also associated with a higher mortality and morbidity rate [71].

3.3.3.5. Vasospasm and delayed cerebral ischemia

Vasospasm refers to the narrowing and vasoconstriction of cerebral arteries following aneurysmal SAH; it is prevalent in 70% of patients with aneurysmal SAH. Delayed cerebral ischemia refers specifically to the clinical and neurologic deterioration, often related to severe cerebral vasospasm, and occurs in 20-30% of patients with aneurysmal SAH.

The best predictor of cerebral vasospasm is thickness of cisternal clot and intraventricular hemorrhage, as seen on CT scan [72]. The Fisher and modified Fisher grading scales are used to predict expected risk of vasospasm (see table 2) [73].

Cerebral vasospasm typically starts after post-bleed day 3 and can extend thru 21 days, though most cases resolve within 14 days. The generation of microemboli, cortical spreading ischemia, and microcirculatory spasm are thought to add to DCI [74, 75]. (See Figure 3)

Grade	Fisher Scale	Percent with Symptomatic Vasospasm	Modified Fisher Scale	Percent with Symptomatic Vasospasm
1	Focal Thin	21%	Focal or Diffuse Thin SAH, no IVH	24%
2	Diffuse Thin SAH	25%	Focal or Diffuse Thin SAH, with IVH	33%
3	Thick SAH Present	37%	Thick SAH Present, no IVH	33%
4	Focal or Diffuse thin SAH with significant ICH or IVH	31%	Thick SAH Present, with IVH	40%

Adapted from – Frontera et al. (2006) Prediction of Symptomatic Vasospasm After Subarachnoid Hemorrhage: The Modified Fisher Scale. Neurosurgery. 58: 21-26

Table 2. Fisher and Modified Fisher grading scales for aneurysmal SAH with percentage of patients within grade with symptomatic vasospasm.
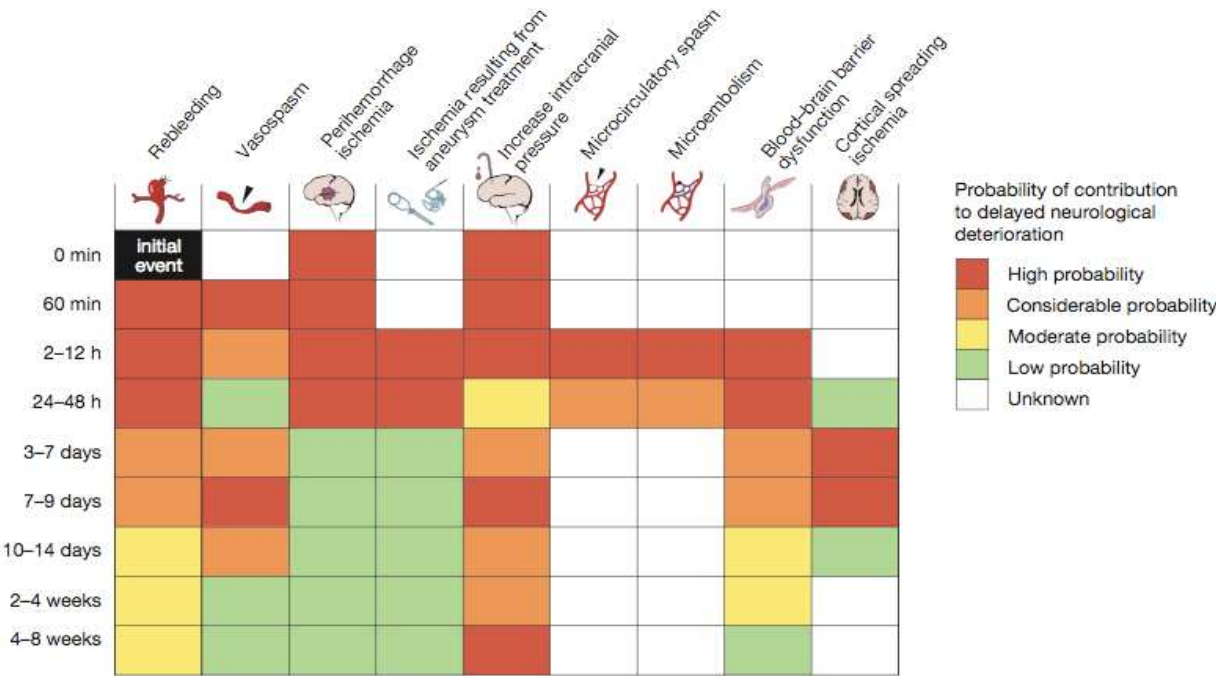
Borrowed with permission: MacDonald R et al. (2007) Cerebral Vasospasm After Subarachnoid Hemorrhage: The Emerging Revolution. Nature Clinical Practice Neurology. 3: 256-263.

Figure 3. Complications and risk against time in aneurysmal SAH

Cerebral vasospasm is the highest contributing factor to morbidity in patients with aneurysmal SAH. Cerebral vasospasm may have evolved as a protective measure to prevent re-rupture of a cerebral aneurysm; however, its diffuse cerebral effects are deleterious and add significant morbidity to aneurysmal SAH. Vasospasm is thought to occur secondary to blood product degradation in the subarachnoid space. Deoxy-hemoglobin and oxy-hemoglobin decrease perivascular nitric oxide and increase endothelin-1 respectively. The net result is a pathologic prolongation of calcium in smooth muscle, leading to an increase in spasm, apoptosis, and vascular remodeling [75].

Monitoring for vasospasm is of great value in the management of aneurysmal SAH. TCD, CT Angiography with perfusion imaging, and conventional digital subtraction angiography are options for monitoring for cerebral vasospasm.

The advantages of TCD are its noninvasive low risk profile; however it's sensitivity is variable and dependent on the skill of the ultrasonographer. Many patients have poor trans-cranial windows, making monitoring with TCD's difficult, if not impossible. Mean flow velocities are typically utilized for detection of vasospasm. Using a mean fellow velocities less than 120cm/s has a 94% negative predictive value for cerebral vasospasm. Mean flow velocities greater than 130cm/s have been proposed as the threshold for mild-moderate vasospasm; this carries a 73% sensitivity and 100% specificity for detecting vasospasm. Mean flow velocities greater than 200cm/s reliably predict moderate to severe angiographic vasospasm. The Lindegaard ratio compares intracranial MCA mean flow velocity to extracranial ICA mean flow velocity; the advantage of a ratio is to distinguish hyperemic states from vasospasm. Ratios greater 4 are suggestive of vasospasm; a ratio greater than 6 reliably predicts cerebral vasospasm [76].

CT angiography has a 87-95% percent sensitivity for angiographic vasospasm, but carries a high negative predictive value approaching 99%. However, CT angiography and perfusion are cumbersome and may pose additional risk to the patient secondary to iodinated contrast. CT angiography with perfusion may be a surveillance option for patients who have poor TCD windows [26].

Non-interventional strategies to combat cerebral vasospasm include the traditional triple H model. Augmenting MAP has been utilized to decrease DCI associated with cerebral vasospasm [74]. Our practice utilizes MAP goals between 110-140 to treat cerebral vasospasm.

Few centers have utilized intrathecal calcium antagonists. Some have utilized intrathecal nicardapine with success in decreasing flow velocities as measured by TCD's [77]. Multicenter randomized trials utilizing have yet to be completed demonstrating efficacy.

The trigger for intervention varies between centers. Many centers choose an aggressive intervention including endovascular delivery of local intra-arterial verapamil (and other calcium antagonists) that have an immediate effect with resulting local vasodilatation. Specific management of interventional management of vasospasm associated with

aneurysmal SAH are described in more detail elsewhere [78]. The current gold standard for refractory cerebral vasospasm includes angioplasty in conjunction with intra-arterial delivery of calcium channel antagonists [26].

4. System based practice

Most patients with aneurysmal SAH are treated at small volume centers seeing fewer than 18 cases per year. Mortality is substantially greater at small volume centers compared to larger high volume referral centers [79]. Moreover, studies suggest that the utilization of a dedicated neurocritical care team is associated with improvement in hospital discharge disposition in patients with aneurysmal SAH [80].

5. Conclusion

Aneurysmal SAH is a complex critical illness with multisystem complications that requires the close attention of a dedicated neurocritical care team. Mortality and morbidity are high; the likelihood of a good outcome depends on presentation grade and careful and diligent management of complications.

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