Subarachnoid Hemorrhage: Critical Care Management

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Introduction

More than 2,400 years ago, Hippocrates in "*Aphorisms*" (VI, 51) recognized the natural history of spontaneous subarachnoid hemorrhage (SAH) followed by subsequent delayed neurological deterioration *"When persons in good health are suddenly seized with pains in the head, and straightway are laid down speechless, and breathe with stertor, they die in seven days, unless fever come on"*. SAH, nowadays, remains a severe emergency because of the sudden extravasation of blood into the subarachnoid space, still causing, even with modern aggressive medical and surgical therapies, significant morbidity and mortality [1, 2].

The leading cause of non-traumatic SAH is rupture of an intracranial aneurysm, accounting for more than 80 % of SAH cases and for 6 % of total strokes. The general estimated incidence is 8–10 cases per 100,000 inhabitants per year, with important regional differences. Risk factors include hypertension, smoking, alcohol abuse, the use of sympathomimetic drugs (e.g., cocaine) and genetic syndromes, such as autosomal dominant polycystic kidney. The mechanisms of aneurysm formation, growth and subsequent rupture have not yet been fully elucidated. Recent theories recognize an angiogenesis factor, endoglin, as one of the factors involved, but the entire process is probably a multifactorial disease [3–5].

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Clinical Features and Outcome of SAH

Aneurysmal SAH is a heterogeneous disease with different clinical exordia and outcomes. The early mortality rate after aneurysmal SAH remains high at 40 %; 10–20 % of these patients never reach medical attention or die during transportation and around half of the survivors retain some neurological deficit. The time course of the disease can be divided into different phases each contributing to the overall outcome:

1. The severity of the initial hemorrhage: Clinical characteristics, e.g., sudden coma and seizures, observed close to the time of presentation with SAH have negative prognostic implications.
2. The intervention to treat the ruptured aneurysm: Surgical or endovascular aneurysm repair must be performed as soon as possible to prevent the rebleeding.
3. Medical management occurs mainly in neurocritical care and is based on the detection and treatment of cerebral and extracerebral complications. The former leads to delayed cerebral vasospasm with or without delayed ischemic neurological deficits. Other medical complications that negatively affect overall morbidity and mortality include cardiac ischemia and neurogenic pulmonary edema.

Clinical Manifestations

The severity of the clinical presentation with compromised neurological status, from seizures, loss of consciousness or focal neurological deficits, is the strongest prognostic factor in aneurysmal SAH, with the more severe cases (defined as poor-grade or high-grade) more likely to develop cerebral and systemic complications, and need longer stays in the intensive care unit (ICU). Validated scales can describe the severity of the clinical presentation [6]: The Hunt and Hess and the World Federation of Neurological Surgeons (WFNS) scales are currently used to categorize the severity of the clinical presentation at the time of bleeding. A retrospective analysis of more than 2,000 cases shows that severity of initial hemorrhage, clinically graded by the WFNS score, was the major determinant of case fatality at 60 days [7].

The Fisher scale [8], modified by Claassen et al. [9], quantifies the additive risk from SAH thickness and accompanying intraventricular hemorrhage (IVH): 0 – none; 1 – minimal SAH without IVH; 2 – minimal SAH with IVH; 3 – thick SAH without IVH; 4 – thick SAH with IVH. The amount of blood is associated with the risk of vasospasm development: SAH completely filling any cistern or fissure and IVH in the lateral ventricles are both risk factors for delayed cerebral ischemia, and their risk is additive.

Prognostic Indicators

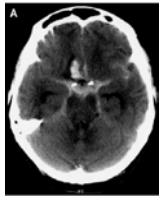
Along with the severity of the clinical presentation and the amount of blood seen at the first computed tomography (CT) scan, aneurysm rebleeding is another major predictor of poor outcome. Rebleeding is a complex and multifactorial event involving hemostasis, pathophysiological and anatomical factors [10–12]. Studies investigating the ultra-early phase, within the first 24 h following aneurysmal SAH, have reported rebleeding in as many as 9–17 % of patients, with most cases occurring within 6 h of initial hemorrhage [13]. Several factors are associated with the risk of rebleeding, among these worse neurological status on admission, larger aneurysm size and high systolic blood pressure. There is general consensus on the need for early blood pressure control in these patients until the aneurysm has been secured although no optimal levels of blood pressure have been recommended. Therefore, treat extreme hypertension in patients with an unsecured, recently ruptured aneurysm. Modest elevations in blood pressure (i. e., mean blood pressure < 110 mm Hg) do not require therapy [14]. Pre-morbid baseline blood pressures should be used to refine targets. Hypotension should be avoided.

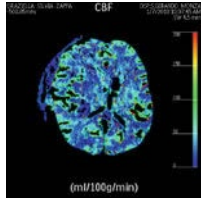
Other elements are also predictive of poor prognosis. Some are related to patient characteristic, such as older age and pre-existing severe medical illness, and others to systemic complications, such as hyperglycemia, fever, anemia, pneumonia and sepsis [15]. Early global cerebral edema on CT scan [16], intraventricular [17] and intracerebral hemorrhage and, above all, the incidence of cerebral vasospasm with delayed ischemic neurological deficits and cerebral infarction are also related to a negative prognosis. Aneurysm size, location, and complex configuration, may increase the risk of periprocedural complications and affect overall prognosis [18, 19].

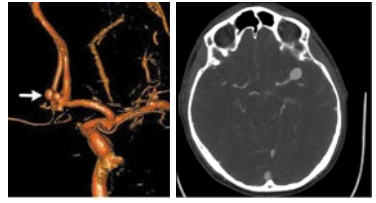
Treatment in high-volume centers with availability of neurosurgical and endovascular services is reasonable [20]: Outcome is influenced by patient volume, with better outcomes occurring in high-volume centers treating more than 60 cases per year [21]. Patients treated at low-volume hospitals are less likely to experience definitive treatment and transfer to high-volume centers may be inadequately arranged.

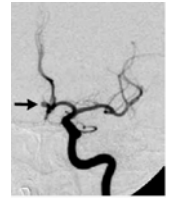
Imaging

Non-contrast head CT scan is a cornerstone in the diagnosis of aneurysmal SAH (Fig. 1). The CT in patients with aneurysmal SAH will show blood in the subarachnoid space, typically in the basal cisterns around the circle of Willis, major fissures, and occasionally intraventricular.









Non-contrast CT

Sensitivity
98-100% < 12 hours
93% < 24 hours
57-85% at 6 days

If positive

Perfusion CT

CBF
CBV
MTT
TTP

Angio CT

Sensitivity 77% -100%
Specificity 79% -100%

DSA

treatment

◀ **Fig. 1** Diagnostic pathway for aneurysmal subarachnoid hemorrhage (SAH). Non-contrast head computed tomography (CT) scan is a cornerstone in the diagnosis of aneurysmal SAH. If positive, in the same session a perfusion CT and an angio CT may be considered. If an aneurysm is detected by angio CT, this investigation may help guide the decision regarding type of aneurysm repair. If angio CT is inconclusive, digital subtraction angiography (DSA) is recommended. DSA could also be useful for determining whether an aneurysm is amenable to coiling or to expedite microsurgery. CBF: cerebral blood flow; CBV: cerebral blood volume; MTT: mean transit time; TTP: time-to-peak

The latest American Heart Association (AHA)/American Stroke Association (ASA) Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage [22] suggest, as an updated recommendation, that CT angiography may be considered in defining aneurysmal SAH. If an aneurysm is detected by CT angiography, this investigation may help guide the decision regarding the type of aneurysm repair. If CT angiography is inconclusive, digital subtraction angiography (DSA) is recommended. Moreover, DSA could be useful for determining whether an aneurysm is amenable to coiling or to expedite microsurgery.

Surgical and Endovascular Management

After initial stabilization, aimed at restoring respiratory and cardiovascular function, early aneurysm repair should be undertaken, when possible and reasonable, to prevent rebleeding [22]. If a delay in aneurysm treatment occurs, an early, short course of antifibrinolytic therapy prior to aneurysm repair should be considered to reduce the incidence of rebleeding. Prolonged (> 3 days) antifibrinolytic therapy exposes patients to increased adverse effects when the risk of rebleeding is reduced, and should be avoided [14].

Aneurysm obliteration can be achieved by surgical or endovascular methods. The decision regarding aneurysm treatment should be a multidisciplinary decision based on characteristics of the patient and of the aneurysm. The only multicenter randomized trial comparing microsurgical and endovascular repair, the International Subarachnoid Aneurysm Trial (ISAT) [23], randomized more than 2,000 patients with aneurysmal SAH from 42 neurosurgical centers. In this cohort, the risk of death at 5 years was significantly lower in the coiled group, but the proportion of survivors who were independent was not statistically different between the groups, and rebleeding was higher in the coiled group [24]. ISAT has been a strong driver of change in the management of ruptured aneurysms. Nevertheless, the evidence for the advantage of coiling in the long-term should not be assumed from ISAT data.

Neurosurgical clipping should be considered in patients with large (> 50 ml) intraparenchymal hematomas and middle cerebral artery aneurysms. Endovascular coiling should be considered in the elderly (> 70 years), in those presenting with poor-grade (WFNS classification IV/V) aneurysmal SAH, and in those with aneurysms of the basilar apex.

Neurocritical Care Management

Patients with aneurysmal SAH should be treated in multidisciplinary high-volume centers with experienced cerebrovascular surgeons, neuroradiologists and dedicated neurointensive care. Varelas et al. [25] demonstrated that hospital treatment volumes and availability of both endovascular and neurological intensive care services were strong determinants of improved outcomes in aneurysmal SAH.

Vasospasm and Delayed Cerebral Ischemia

Vasospasm refers to narrowing of cerebral arteries subsequent to aneurysmal SAH and has been widely recognized as an unfavorable complication that can be responsible for delayed cerebral ischemia. Vasospasm frequently occurs between days 4 and 21 after bleeding. The initial trigger for arterial narrowing is the contact between the oxyhemoglobin that accumulates after the bleeding at the abluminal side of the vessels.

Dhar and Diringer [26] showed that systemic inflammatory activation is common after SAH even in the absence of infection. Therefore, aneurysmal SAH triggers immune activation sufficient to induce a systemic inflammatory response syndrome (SIRS). A higher burden of SIRS in the initial four days independently predicted symptomatic vasospasm and was associated with worse outcome. Recently, the focus of research into delayed cerebral ischemia has moved from pure cerebral artery constriction towards a more complex, multifactorial etiology [27, 28]. Novel pathological mechanisms have been advocated, including damage to cerebral tissue in the first 72 h after aneurysm rupture, the so called "early brain injury" [29, 30], cortical spreading depression [31], and microthrombosis [32]. A better evaluation of the impact of these pathophysiological mechanisms is essential, if new methodologies for the prophylaxis, diagnosis and treatment of delayed cerebral ischemia are to be developed.

No effective preventive therapy is currently available. Oral nimodipine administration has been confirmed as being associated with an improved neurological outcome, counteracting processes other than vessel narrowing [33]. Euvolemia is recommended until vasospasm is diagnosed.

Several trials investigated the use of drugs to prevent or treat vasospasm, including clazosentan, an endothelin-1 receptor antagonist, and magnesium. Clazosentan has been associated with a dose-dependent reduction in the incidence of angiographic vasospasm but subsequent trials failed to demonstrate any benefit [34, 35]. A phase 3 trial (Intravenous Magnesium sulfate for Aneurysmal Subarachnoid Hemorrhage [IMASH]) did not support any clinical benefit from magnesium infusion over placebo in aneurysmal SAH [36].

Once vasospasm involves the large arteries and is angiographically visible, approximately 50 % of patients develop delayed cerebral ischemia [37]. Data on prophylactic angioplasty of the basal cerebral arteries and antiplatelet prophylaxis

are inconclusive. Neurointensivists must always watch for the occurrence of vasospasm in patients with aneurysmal SAH. We suggest the following sequence to identify vasospasm and delayed ischemic neurological deficits (Fig. 2):

- Frequent clinical examination, looking for a new focal deficit or reduced consciousness. Symptomatic vasospasm is defined as the development of new focal neurological signs, deterioration in level of consciousness, or both, when other possible causes of worsening (for example, hydrocephalus, seizures, metabolic derangement, infection, or over- sedation) have been excluded. Delayed cerebral ischemia is defined as symptomatic vasospasm or the appearance of new infarction on CT or magnetic resonance imaging (MRI) when the cause is felt to be attributable to vasospasm.
- Daily transcranial Doppler (TCD), widely described in the literature as a safe and useful tool to measure increase in cerebral blood flow velocities as a sign of cerebral vessel narrowing. TCD is a simple and non-invasive bedside screening tool to detect vasospasm; its sensitivity and specificity in identifying vasospasm is good for middle cerebral arteries [38]. TCD vasospasm is commonly defined as a mean flow velocity in any vessel > 120 cm/s.
- In selected patients, we use continuously invasive probes (thermal diffusion flowmetry, Hemedex) to quantify regional cerebral blood flow (rCBF) and continuous electroencephalography (cEEG) to trend CBF changes. In fact, CBF more closely reflects fuel delivery than does cerebral perfusion pressure (CPP).

Whenever clinical deterioration is identified, TCD reveals significant increased velocity or thermal diffusion flowmetry shows a flow reduction, we move to the next step, requiring the transport of the patient outside the ICU.

- Perfusion imaging (perfusion CT) may be more accurate for identifying delayed cerebral ischemia than anatomic imaging. Perfusion CT is a promising technology: CBF and MTT (mean transit time) have the highest overall diagnostic accuracy [39, 40]. Threshold values of 35 ml/100 g/min for CBF and 5.5-second MTT are suggestive of delayed cerebral ischemia on the basis of the patient population utility method.
- DSA is still the gold-standard technique but it is invasive and time-consuming. Angiographic vasospasm is defined as moderate-to-severe arterial narrowing on digital subtraction angiography. We move to this next step, after perfusion CT, only when an endovascular treatment is planned.

Once vasospasm occurs, induction of hypertension with high mean arterial pressure (MAP) to counteract vessel narrowing is recommended for patients with delayed cerebral ischemia unless cardiac status excludes it. Cerebral angioplasty and/ or selective intra-arterial vasodilator therapy is reasonable in patients with symptomatic cerebral vasospasm, particularly those who do not respond rapidly to hypertensive therapy. Once delayed cerebral ischemia is likely, other neuroprotective strategies must be employed, including sedation, hypothermia and CPP optimization. Derangements in cerebrovascular autoregulation, the intrinsic capacity of the cerebral arteries to maintain constant CBF despite changes in CPP, are involved in the development of delayed cerebral ischemia following aneurysmal SAH.

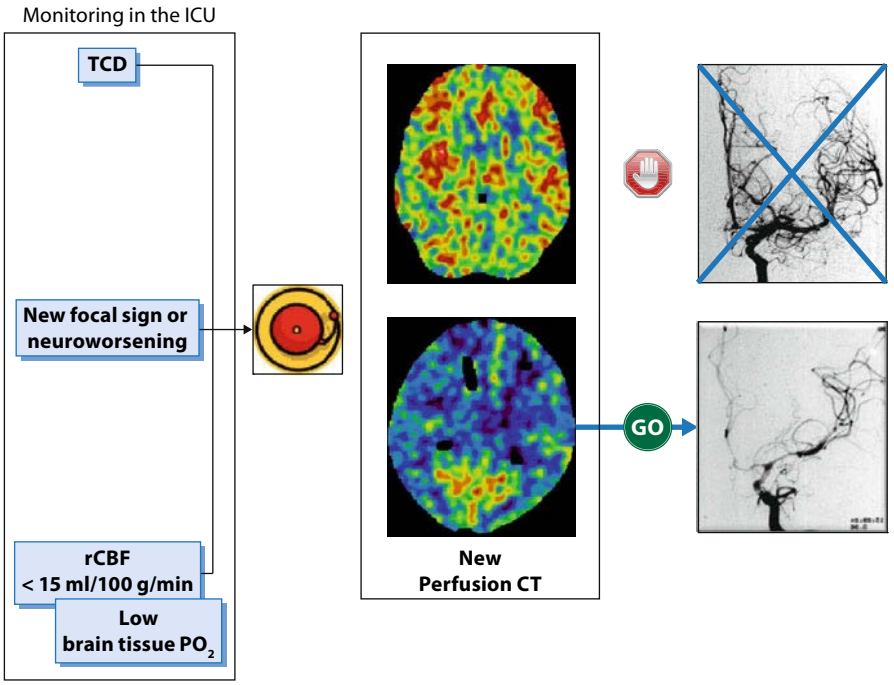


Fig. 2 Sequence to identify vasospasm and delayed ischemic neurological deficit. Each time a clinical deterioration is identified, transcranial Doppler (TCD) reveals significant increased velocity, or thermal diffusion flowmetry shows a flow reduction, we perform perfusion imaging (perfusion computed tomography [CT]) for a better evaluation of cerebral blood flow (CBF) and mean transit time (MTT) (see text). We move to digital subtraction angiography (DSA) after perfusion CT only when a perfusion disturbance is identified or/and an endovascular treatment is planned

High intracranial pressure (ICP) and persistent autoregulatory failure after SAH are independently associated with the occurrence of delayed cerebral infarction and may be an important cofactor in addition to vasospasm itself. Assessment of the status of cerebrovascular autoregulation, measuring the ability of vessels to autoregulate with the pressure reactivity index (PRx), would identify patients with an increased risk of delayed ischemic neurological deficits.

Multimodal brain monitoring is extensively used in various neurocritical care units. Different tools (e.g., brain tissue oxygen tension [PbO_2] and cerebral microdialysis) can help clinicians in detecting metabolic and CBF derangements, mainly in those patients suffering from high-grade aneurysmal SAH. Interestingly, in a recent paper, Chen et al. [41] analyzed a population of patients with low-grade aneurysmal SAH. Patients underwent brain monitoring with PbO_2 and microdialysis. The lactate/pyruvate ratio (LPR) and the frequency of brain hypoxia and energy dysfunction at different ICP and CPP values were analyzed. Interestingly, markers of reduced CBF and metabolic derangements were present in some patients, even in the absence of ICP/CPP disturbance, stressing the importance of these additional tools in managing low grade aneurysmal SAH.

Hydrocephalus and High Intracranial Pressure

Intracranial hypertension (high ICP) can occur in patients with aneurysmal SAH. The pathophysiology can be multifactorial, including acute hydrocephalus, reactive hyperemia and global ischemic insult with brain edema. The latter generally occurs at the onset of the bleeding. Once the aneurysm ruptures, a sudden discharge of blood into the basal cisterns with an acute increase in ICP and reduction in CBF can be immediately fatal. In surviving patients, acute hydrocephalus is likely to occur because the blood clot obstructs CSF flow, or CSF reabsorption is reduced. Acute hydrocephalus has been reported in 15–87 % of patients in different studies [11, 14] and is usually managed by cerebrospinal fluid (CSF) diversion with external ventricular drainage (EVD) or lumbar drainage depending on the clinical scenario.

In patients with high ICP and acute hydrocephalus, ICP monitoring is reasonable and continuous ICP values are desirable as increasing MAP is necessary to sustain CPP and maintain adequate cerebral perfusion.

Seizures

No randomized, controlled trials exist to guide decisions on prophylaxis or treatment of seizures. The majority of SAH patients with seizures had seizure onset before medical evaluation and delayed seizures occurred in 3 % to 7 % of patients. Benefits from prophylactic anticonvulsive therapy are still unclear. Therefore, routine use of anticonvulsant prophylaxis with phenytoin is not recommended after SAH [14].

In the neurocritical care setting, it seems reasonable to monitor the occurrence of seizures with clinical examination and EEG. cEEG is becoming a crucial component of neurocritical care and should be considered in patients with low-grade SAH who fail to improve or who have neurological deterioration of undetermined etiology. Lindgren and co-workers analyzed the frequency of non-convulsive status epilepticus (NCSE) in sedated and ventilated aneurysmal SAH patients. The main finding of this study supported the use of cEEG and showed how continuous sedation in aneurysmal SAH patients in need of controlled ventilation was associated with a low frequency of clinical and subclinical seizures [42].

Claassen et al. described some relationships between constant epileptiform discharges after SAH and mortality [43]. The absence of sleep potentials and the presence of repetitive epileptiform activity in the form of periodic lateralized epileptiform activity are prognostic indicators of a poor neurological outcome as repetitive epileptiform activity is a marker of ischemic damage that cannot be seen on brain imaging. Thus, once seizures and epileptic activity are suspected and diagnosed, treatment is compulsory given the detrimental consequences.

Management of Medical Complications

Sodium Abnormalities

Hyponatremia is frequently seen following aneurysmal SAH. Hyponatremia is a severity marker of SAH, being more frequent in low-grade patients. Hyponatremia is sustained from different mechanisms. A key point to interpret the origin of these abnormalities is the accurate investigation of the volemic state of patients by some combination of central venous pressure (CVP), intrathoracic volume measurements, and fluid balance. The cerebral salt wasting syndrome (CSWS) is the result of excessive secretion of natriuretic peptides and causes sodium reduction from excessive natriuresis. Therefore CSWS, defined as the renal loss of sodium during intracranial disease, is a hypovolemic hyponatremic condition linked with natriuresis and decrease fluid volume. CSWS is more common in patients with low clinical grade, ruptured anterior communicating artery aneurysms, and hydrocephalus, and it may be an independent risk factor for poor outcome [27]. Mineralocorticoid administration has been investigated in different studies and seems to be associated with a better control of hyponatremia and reduced administration of crystalloids.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is caused by elevated serum vasopressin activity, and represents a euvolemic hyponatremic state. Fluid restriction in SIADH is indicated but with caution because as it has been associated with an incidence of cerebral infarction. Sodium balance should be calculated on a daily basis and hydrocortisone could be used to overcome the excessive natriuresis [28].

Stunned Myocardium

Cardiac dysfunction after SAH is referred to as ‘neurogenic stunned myocardium’ and can represent a critical care challenge [2, 44]. Cardiopulmonary complications can develop immediately after the bleeding and clinical findings vary from no symptoms with mildly raised troponin enzymes through to cardiogenic shock, reduced left ventricular function, congestive heart failure and pulmonary edema in approximately 10 % of patients. Clinical features of neurogenic stunned myocardium include electrocardiogram (EKG) abnormalities, increase in serum markers that decays within days, chest x-ray suggestive of pulmonary edema, echocardiogram regional wall motions abnormalities (RWMA) and a coronary angiogram with normal coronary arteries. Baseline cardiac assessment with serial enzymes, EKG, echocardiography and cardiac output monitoring is recommended, especially in patients with evidence of myocardial dysfunction [14]. The most widely accepted theory on the pathogenesis of aneurysmal SAH-induced myocardial dysfunction relies on massive catecholamine release [45]. At the time of bleeding, a sudden increase in ICP may cause sympathetic activation via hypothalamic damage. Histological studies have shown myocardial changes, known as myocardial

contraction band necrosis, which refers to a specific form of myocyte injury with hypercontracted sarcomeres and interstitial mononuclear inflammatory response. Myocardial stunning can be challenging and carries great implications in terms of therapy [46]. In fact, patients who develop vasospasm are at high risk of delayed cerebral ischemia. Sustaining CBF and adequate oxygen delivery via implementation of CPP is mandatory. Consequently, MAP needs to be sustained by fluid and vasopressors (usually with phenylephrine) given that CPP = MAP – ICP.

However, if catecholamines themselves cause neurogenic stunned myocardium, then phenylephrine, along with other available sympathomimetic drugs, may be harmful [47]. In selected cases, other strategies can be adopted to sustain CPP or cardiac output after aneurysmal SAH (e.g., milrinone, dobutamine and intra-aortic balloon pump counterpulsation).

Fever

Fever is the most common medical complication in patients suffering from aneurysmal SAH and has been widely associated with neurological deterioration in neurocritical care patients [48]. Non-infectious (central) fever has been associated with the amount of blood (the severity of injury) and the development of vasospasm. Fever affects cerebral metabolism and small increases in temperature can exacerbate ischemic brain damage via an imbalance between substrate delivery and metabolic needs. Temperature elevations have also been associated with cerebral hyperemia, edema worsening and elevated ICP. Therefore, temperature monitoring and aggressive fever control is reasonable in the acute phase of aneurysmal SAH in order to reduce the burden of the secondary insult [14]. Core body temperature reduction (hypothermia) as a neuroprotective strategy is still under investigation.

Glucose Control

Hyperglycemia is commonly identified during initial evaluation of patients with aneurysmal SAH. Accurate glycemic control must be part of the general critical care management of patients with aneurysmal SAH. In fact, prolonged hyperglycemia is associated with an increased ICU length of stay, increased risk of death or severe disability and is an independent predictor of death or severe disability. An independent association between hyperglycemia and symptomatic vasospasm has also been described and elevated blood glucose levels at the time of admission were prognostic of unfavorable outcome, defined as death, vegetative state, or severe disability at 12 months.

Hypoglycemia (serum glucose < 80 mg/dl) should be avoided. Serum glucose should be maintained around 140 mg/dl. There are reports of cerebral microdialysis findings of cerebral metabolic crisis and low cerebral glucose in SAH patients being treated with insulin infusions, even in the absence of systemic hypoglycemia

[49]. If microdialysis is being used, serum glucose may be adjusted to avoid low cerebral glucose [14].

Deep Venous Thrombosis

Deep venous thrombosis occurs relatively frequently after aneurysmal SAH, especially in patients immobilized because of poor neurological status. Heparin-induced thrombocytopenia has been described in several studies [22]. Early identification and targeted treatment are recommended and prophylaxis (with subcutaneous heparinoids and external pneumatic compression sleeves) is reasonable for patients who are comatose and admitted to the neurocritical care unit.

Conclusion

Aneurysmal SAH is a complex disease with different degrees of clinical severity. Patients' characteristics and neurological impairment at the time of bleeding can be summarized using international scales. The optimal management of SAH has not been fully established yet. Several topics are still under debate. However, management of patients with aneurysmal SAH requires a multidisciplinary approach in a high volume hospital. Early aneurysm repair is compulsory as re-rupture is frequent and associated with poor prognosis.

Recently, the AHA/ASA updated the guidelines for the evaluation and treatment of patients with SAH and the Neurocritical Care Society released guidelines summarizing the current state of art and areas of uncertainty in treatment of aneurysmal SAH [14, 22].

Efforts to improve outcome after aneurysmal SAH should focus on the medical complications that contribute to poor outcome together with delayed cerebral ischemia. Given the multifactorial etiology underling delayed cerebral ischemia and the cascade of events that happen at the onset of bleeding (mainly CBF reduction), new monitoring tools, such as perfusion CT, cEEG, microdialysis and PbO_2 should be routinely promoted to optimize cerebral physiology.

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