

# Aneurysmal subarachnoid hemorrhage: current concepts and updates

Hemorragia subaracnoidea aneurismática: conceitos atuais

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## ABSTRACT

Aneurysmal subarachnoid hemorrhage is a condition with a considerable incidence variation worldwide. In Brazil, the exact epidemiology of aneurysmal SAH is unknown. The most common presenting symptom is headache, usually described as the worst headache ever felt. Head computed tomography, when performed within six hours of the ictus, has a sensitivity of nearly 100%. It is important to classify the hemorrhage based on clinical and imaging features as a way to standardize communication. Classification also has prognostic value. In order to prevent rebleeding, there still is controversy regarding the ideal blood pressure levels and the use of antifibrinolytic therapy. The importance of definitely securing the aneurysm by endovascular coiling or surgical clipping cannot be overemphasized. Hydrocephalus, seizures, and intracranial pressure should also be managed. Delayed cerebral ischemia is a severe complication that should be prevented and treated aggressively. Systemic complications including cardiac and pulmonary issues, sodium abnormalities, fever, and thromboembolism frequently happen and may have an impact upon prognosis, requiring proper management.

**Keywords:** Subarachnoid hemorrhage; aneurysm; brain ischemia, vasospasm

## RESUMO

Hemorragia subaracnoidea aneurismática (aHSA) é uma condição com grande variação de incidência mundialmente. No Brasil, não dispomos de números epidemiológicos exatos. A apresentação clínica mais comum da HSA é a cefaleia, usualmente descrita como a pior da vida. A tomografia de crânio, quando feita nas primeiras 6 horas do ictus, tem uma sensibilidade próxima a 100%. É importante classificar a hemorragia utilizando escalas clínicas e radiológicas, como forma de padronizar a comunicação, e também prever prognóstico. Para prevenção de ressangramento, ainda há controvérsias quanto aos níveis pressóricos ideais e uso de antifibrinolíticos. O tratamento definitivo do aneurisma, por sua vez, é fundamental, seja por meio endovascular ou cirúrgico. Hidrocefalia, crises epilépticas e a pressão intracraniana devem ser manejadas de forma apropriada. Isquemia cerebral tardia é uma complicação grave que deve ser prevenida e tratada agressivamente. Complicações sistêmicas, incluindo cardíacas, pulmonares, anormalidades de sódio, febre e tromboembolismo ocorrem frequentemente e podem ter impacto no prognóstico, necessitando de manejo adequado.

**Palavras-chave:** hemorragia subaracnoidea; aneurisma; isquemia encefálica; vasoespasm

## EPIDEMIOLOGY

Aneurysmal subarachnoid hemorrhage is a condition with considerable incidence variation worldwide. Finland is the country with the highest incidence, with 22.5 patients per 100,000 inhabitants. On the other hand, China has an incidence of 2/100,000. The USA reports 14.5 patients per 100,000 population. However, as 15%-30% of deaths happen before hospital admission, the real incidence of aneurysmal SAH is probably higher<sup>1</sup>. In Brazil, the exact epidemiology of aneurysmal SAH is unknown.

The estimated 30-day mortality rate is 35%, with great morbidity among the survivors (a third of whom require full care, and a third are not able to return to work).

In the past decades, mortality has been decreasing with the technical advances in medicine. A meta-analysis from 2009 has shown that between 1973 and 2002, there has been a 17% reduction in patient fatality<sup>2</sup>.

Risk factors for aneurysmal SAH include female sex, increasing age (with a peak around 50 years-old), smoking, hypertension, alcohol abuse, use of sympathomimetic drugs, familial history of aneurysms or SAH (more than two

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first-degree relatives), and some genetic conditions (autosomal dominant polycystic kidney disease and type IV Ehlers-Danlos syndrome)<sup>3</sup>.

### Clinical presentation and diagnosis

The most common presenting symptom is headache, which is usually described as the worst headache ever felt, is abrupt and peaks in intensity in one hour at most<sup>4</sup>. Around 10–40% of patients have a warning leak or sentinel episode, which is a similar headache that precedes the bleeding by two to eight weeks. The presence of a sentinel episode increases the likelihood of death or disability four-fold<sup>5</sup>.

Nausea and vomiting happens in 77% of the cases, loss of consciousness in 53%, meningismus in 35%, focal deficits in 10%, and Terson syndrome (vitreous hemorrhage associated with SAH) in 40% of patients<sup>3,4,5</sup>.

In patients with these symptoms, the threshold for an emergency physician to order a noncontrast brain computed tomography (CT) should be low. When performed within six hours of the ictus, it has a sensitivity of nearly 100%. It falls to 93% after 24 hours and to less than 60% after five days<sup>4</sup>.

The traditional next step after a high suspicion of aneurysmal SAH and a negative CT has always been a lumbar puncture to look for blood or xanthochromia in the cerebrospinal fluid. Although it is still a class I, level of evidence B recommendation according to current guidelines, this approach is now a matter of debate. Some claim that since the incidence of SAH is low and it can be difficult to distinguish between

SAH and puncture-related trauma, lumbar puncture is no longer of great value<sup>5</sup>.

Another approach after a negative head CT is to perform a brain magnetic resonance imaging. Some sequences, such as fluid-attenuated inversion recovery, proton density, and gradient-echo are highly sensitive to blood.

A negative CT should not be enough to rule out SAH in high suspicion cases<sup>3,4,5</sup>.

In order to look for aneurysms > 3mm, CT angiography has a sensitivity that approaches 100% and is comparable with the gold standard—digital subtraction angiography. The latter has the limitation of being noninvasive and not universally available method. More recently, CT angiography performed in 64-row multislice scanners and 320-detector row scanners has proven to have an excellent sensitivity and specificity for the detection of even small aneurysms (< 3 mm)<sup>6</sup>.

### Clinical and radiological scales

After the diagnosis of SAH, it is important to classify the hemorrhage based on clinical and imaging features. Classifications are important because they carry prognostic value and standardize communication. The strongest predictors of outcomes are the severity of neurological impairment on admission and the amount of blood in the subarachnoid space.

The most used clinical scales are the Hunt and Hess, and the World Federation of Neurological Surgeons scales (Table 1)<sup>3,4</sup>.

Regarding radiological scales, the most used are the original Fisher Scale, and the modified Fisher Scale (Table 2).

**Table 1.** Clinical scales (World Federation of Neurological Surgeons and Hunt and Hess Scales).

SAH grade	World Federation of Neurological Surgeons Scale	Hunt and Hess scale
1 (good)	GCS 15, no motor deficit	Asymptomatic or mild headache and slight nuchal rigidity
2 (good)	GCS 14-13, no motor deficit	Moderate to severe headache, nuchal rigidity, no focal Neurologic deficit other than cranial nerve palsy
3 (good)	GCS 14-13, motor deficit	Confusion, lethargy, or mild focal neurologic deficit Other than cranial nerve palsy
4 (poor)	GCS 12-7, with or without motor deficit	Stupor or moderate-to-severe hemiparesis
5 (poor)	GCS 6-3, with or without motor deficit	Coma, extensor posturing, moribund appearance

GCS: Glasgow coma scale.

**Table 2.** Radiological Scales (Fisher and Modified Fisher Scales).

Grade	Original Fisher	Modified Fisher
0	-	No SAH or IVH
1	No SAH or IVH	Minimum or thin SAH, no IVH in either lateral ventricle
2	Diffuse, thin SAH, no clot > 1 mm in thickness	Minimum or thin SAH, with IVH in both lateral ventricles
3	Localized thick layer of subarachnoid clot > 1 mm in thickness	Thick SAH, no IVH
4	Predominant IVH or intracerebral hemorrhage without thick SAH	Thick SAH with IVH in both lateral ventricles

SAH: subarachnoid hemorrhage; IVH: intraventricular hemorrhage

**Table 3.** Clinica land radiological scale (Vasograde).

Vasograde	World Federation of Neurological Surgeons	Modified Fisher
Green	01/02	01/02
Yellow	01/03	03/04
Red	04/05	Any

The main goal of the radiological scales is to predict the risk of developing delayed cerebral ischemia (DCI)/vasospasm. However, in the original Fisher scale, a patient with grade 3 bleeding had more chances of developing DCI/vasospasm than a patient with grade 4.

According to the modified Fisher Scale, an SAH completely filling any cistern or fissure, and intraventricular blood in both lateral ventricles, has a higher risk of developing DCI. Not identified as a risk factor, intraparenchymal hemorrhage was left out of the new classification.

Summarizing, in the original Fisher Scale, when compared with grade 1, grade 2 has na odds ratio (OR) of 1.3; grade 3 has an OR of 2.2; and grade 4 has an OR of 1.7 for developing DCI/vasospasm. In the modified Fisher Scale, when compared with grades 0/1, grade 2 has an OR of 1.6; grade 3 has an OR of 1.6; and grade 4 has an OR of 2.2<sup>7,8</sup>.

The VASOGRADE scale combines clinical and radiological features (Table 3). It positively correlates with the risk of DCI. When compared with green, the yellow VASOGRADE has an OR of 1.31, and the red has an OR of 3.19 for developing DCI/ vasospasm<sup>9</sup>.

## PATHOPHYSIOLOGY

When an aneurysm ruptures, blood pours into the subarachnoid space leading to a Sharp and sudden increase in intracranial pressure, jeopardizing cerebral perfusion pressure and leading to global ischemia. This is the postulated mechanism of the loss of consciousness that happens in about 50% of the patients. Also, the blood itself mechanically damages the brain, contributing to global ischemia.<sup>10,11</sup>

There is a massive sympathetic tone increase that starts to cause systemic complications (acute lung injury, neurogenic pulmonary edema, cardiac dysfunction) and a systemic inflammatory syndrome develops.

This series of events is part of what is called early brain injury, a process that starts Just after the aneurysmal rupture and is characterized by microcirculatory constriction, microthrombosis, disruption of the blood-brain barrier, vasogenic and cytotoxic edema, endothelia land neuronal death<sup>10,11</sup>

## Prevention of rebleeding

After the diagnosis, the next step includes measures to avoid rebleeding. The incidence of rebleeding ranges from 7–22% in the first three days. In the first 24 hours, it is called ultra-early rebleeding, with na incidence of 15% and a

mortality rate as high as 70%. Patients with larger aneurysms and poor grade SAH are at higher risk<sup>4</sup>.

Whenever possible, patients should be transferred to a high-volume center, defined as at least 35 SAH, but ideally > 60 SAH treatments per year. There is data showing that mortality is inversely proportional to the number of patients treated. A 24% reduction in mortality per year is estimated for each 100 patients treated. It is also important to have a neurological intensive care unit and a multidisciplinary team<sup>1,12</sup>.

Management of blood pressure (BP) is na important part of the treatment, although there are no controlled, randomized trials regarding this topic. The American Heart Association guidelines establish that before the aneurysm is treated, systolic BP should remain below 160 mmHg<sup>1</sup>. The European and the Neurocritical Care Society guidelines recommend a mean BP less than 110 mmHg, also taking into account premorbid baseline pressures<sup>13</sup>.

Ideally, drugs of choice for lowering BP should be titratable and short acting, such as nicardipine or labetalol. In Brazil, the most commonly used drug is sodium nitropruside. After the aneurysm is secured, BP lowering medications should be withheld, unless there are signs of hypertensive crisis<sup>1,4</sup>.

Antifibrinolytic therapy, which is a controversial topic, may play a role in the prevention of rebleeding. In some studies, antifibrinolytics were associated with good results. A Swedish study showed a decrease in rebleeding from 10.4% to 2.8% with the use of tranexamic acid 1g 6/6 hours, for a maximum of 72 hours. A Cochrane review, on the other hand, concluded that although antifibrinolytic therapy reduces rebleeding, this benefit is outweighed by the increase in ischemic events<sup>1,4,13</sup>.

According to the guidelines, when there is na unavoidable delay in securing the aneurysm and no contraindications, na early short-course of antifibrinolytics may be reasonable<sup>1,13</sup>.

There is an ongoing randomized, multicentric trial that Will possibly answer this question. It is testing 1 g of tranexamic acid Just after the diagnosis of SAH followed by continuous infusion of 1 g per eight hours to a maximum of 24 hours (4 g maximum), against placebo<sup>14</sup>.

The most effective way to prevent rebleeding, however, is to definitively secure the aneurysm, which can be achieved by endovascular coiling or surgical clipping.

Two randomized trials have compared both strategies, the International Subarachnoid Aneurysm Trial and the Barrow Ruptured Aneurysm Trial. With a follow-up of 18 years, the former trial showed a 23% relative reduction of the risk of death or dependence in patients who underwent coiling instead of clipping (number needed to treat of 14). However, obliteration rates were higher in the surgical group. It should be emphasized that the aneurysms included were considered appropriate for both methods of treatment, and were, in their majority, small and from the anterior circulation<sup>15</sup>.

The Barrow Ruptured Aneurysm Trial had a follow-up of six years and showed no relevant differences between coiling and clipping for anterior circulation aneurysms. Regarding posterior circulation aneurysms, endovascular treatment was superior, although obliteration rates were lower<sup>16</sup>.

Recently, a new study was published with contrasting results compared with the trials mentioned above. It was a controlled, non randomized study that used an administrative dataset of more than 8,000 patients from Europe, Australia, and the USA, and compared outcomes after endovascular coiling and surgical clipping in aneurysmal SAH. In a multivariable logistic regression, the OR for 14-day patient fatality after coiling compared to clipping was 1.7 (95% CI 1.1–2.7); for 90-day patient fatality, 1.28 (95% CI 0.91–1.82); and for 90-day poor functional outcome, 0.78 (95% CI 0.6–1.01). The conclusion was that, in clinical practice, endovascular treatment was associated with a higher 14-day patient fatality and nonsuperior outcomes at 90 days<sup>17</sup>. A severe limitation of this analysis is that there was likely indication bias. It is possible that patients with the worst clinical condition were those treated by endovascular methods.

In summary, it is still unclear who are the best candidates for clipping or coiling. Patient characteristics, topography and size of the aneurysm, as well as treatment expertise in treating brain aneurysms, should all be taken into account.

For aneurysms considered technically suitable for both methods, coiling may be preferred especially for those in the posterior circulation (particularly at the basilar artery apex), in poor grade SAH, and in elderly patients.

For patients with large hematomas, with middle cerebral artery aneurysms, or those in whom bypass revascularization is deemed necessary, surgical clipping may be a better option, as well as for those who are Young and may benefit from a method with higher durability<sup>15</sup>.

There is also some debate regarding the Best moment to perform the procedure – early (within 72 hours) or ultra-early (within 24 hours). The formal recommendation is to perform as early as is feasible<sup>1</sup>.

A retrospective, non randomized trial analyzed treatment < 24 hours versus 24-72 hours after the ictus and concluded that it can be safely performed in the day time, in up to 72 hours, instead of as an emergency<sup>18</sup>.

There is an ongoing randomized, single-center Chinese study comparing early surgery (up to three days), intermediate surgery (four to seven days) and late surgery (more than seven days) in patients with poor grade SAH<sup>19</sup>.

## Hydrocephalus

Hydrocephalus can occur in acute (our focus here) or chronic stages, in up to 50% of patients after SAH. When it leads to decreased level of consciousness, it requires an external ventricular drain. Up to 30% of those who

present with poor grade SAH may become a good grade after drainage<sup>1,4</sup>.

Lumbar drainage may also be an option; however, large hematomas and obstructive hydrocephalus are contraindications<sup>5</sup>.

There is some concern about the theoretical risk of rebleeding when the aneurysm is not yet treated (due to the increase of transmural pressure caused by fluid removal). Some studies claim that drainage is safe<sup>20</sup>, and some claim that it increases re-rupture risk. A recent meta-analysis and systematic review found no association between drainage and rebleeding, with an OR of 3.92 (18.5% of rebleeding in the external ventricular drain group versus 6.4% of rebleeding in the group that did not need an external ventricular drain), with a median time of one hour from the insertion of the drain until the rebleed<sup>21</sup>.

Another controversy is whether to maintain a continuous or intermittent drainage and how to wean the external ventricular drain or lumbar drain. What is usually warranted is to perform intermittent cerebrospinal fluid drainage and attempt an early clamp trial<sup>22</sup>.

Some studies claim that rapid weaning (immediate closure and observation for 24 hours) leads to reduced days of intensive care unit stay and the same rate of permanent shunts, compared with gradual weaning (over 96 hours with daily step-up followed by closure after 24 hours)<sup>23</sup>.

Multicenter prospective studies regarding the best management of the external ventricular drain are, therefore, warranted.

## Seizures

Seizures can occur when the aneurysm ruptures, perioperatively (usually represents a re-rupture) or later (beyond the scope of this review) and their incidence ranges between 4-26%.

Guidelines state that a short course (3-7 days) of seizure prophylaxis may be used in the immediate post-bleeding period; however, this has a low level of evidence. Phenytoin should be avoided due to its effects on cognitive outcomes, incidence of vasospasm, and CT infarcts. The effects of other antiepileptic drugs are less clear. Levetiracetam is increasingly being used and seems to be a good option<sup>1,13</sup>.

## Increased intracranial pressure

High intracranial pressure is a frequently complication that may develop due to brain edema, intraparenchymal hemorrhage, hydrocephalus, or rebleeding. Intracranial pressure should be aggressively treated with head of bed elevation, sedation, analgesia, hyperosmolar therapy, normal ventilation (short periods of hyperventilation only as a bridge to therapy), cerebrospinal fluid drainage and, in refractory cases, barbiturate sedation, decompressive craniectomy, or hypothermia<sup>4,10</sup>. Most of the recommendations



for the treatment of elevated intracranial pressure come from traumatic brain injury.

### Delayed cerebral ischemia: definition and pathophysiology

Delayed cerebral ischemia occurs in up to 30% of the patients after SAH, usually within the first two weeks after the bleeding. It is defined as the occurrence of any focal neurological impairment or decrease of at least two points on the Glasgow Coma Scale, that lasts for at least one hour, is not apparent immediately after the aneurysm occlusion and cannot be attributed to other causes (hydrocephalus, infection, electrolyte disturbance, or seizure).

The risk of DCI is correlated mainly with the amount of cisterna and intraventricular blood on initial neuroimaging (as discussed previously in the Fisher/modified Fisher scale). The risk is also higher in patients with a poor neurological examination post-resuscitation (as discussed previously in the World Federation of Neurological Surgeons/Hunt and Hess scales).

Traditionally, DCI has been related to arterial vasospasm. However, more recent evidence suggests that it has a complex pathophysiology with multiple postulated mechanisms, even occurring in territories without spasm<sup>10,11,25</sup>.

Currently, DCI is attributed to arterial vasospasm, microthrombosis, inflammation, microcirculation dysfunction and cortical spreading depolarization/ischemia.

Arterial vasospasm happens in 70% of the patients between days 3-14 post-bleeding. Its severity is related to the amount, thickness and persistence of blood.

Its main driver is the release of hemoglobin contents, leading to inflammation, oxygen free radical reactions, endothelial injury, increase in the expression of endothelin 1, and reduction in nitric oxide. Some studies show cerebral infarction in 3%, 10%, and 46% of patients with no/mild, moderate or severe vasospasm, respectively. Not only the spasm itself and its severity, but collateral bloodflow, brain metabolic demand, and BP levels also play a role in DCI<sup>11</sup>.

As will be discussed later, some drugs have been able to reduce arterial spasm but not DCI, and others were able to reduce DCI and poor outcomes, but with no change in vasospasm.

Microthrombosis seems to be abundant in regions correlated with vasospasm and DCI. The presence of blood and its products activate inflammatory pathways and lead to endothelial cell activation and damage. There is breakdown of the blood vessel basal lamina, destruction of collagen type IV, and hyperactivation of matrix metalloproteinase 9, which together cause mural thrombus formation and release of microemboli.

A large arterial spasm also injures the endothelium, leading to platelet adherence, coagulation and propagation of the microemboli formation. The clotting process is fundamental to stopping the bleeding but generates a

self-perpetuated prothrombotic mechanism. Some studies correlate a high level of von Willebrand factor with the occurrence of DCI<sup>11,25</sup>.

Inflammation also plays a major role in DCI. In SAH, there are inflammation-related genes with increased mRNA expression, upregulation of genes encoding membrane receptors, extracellular matrix components, cell adhesion molecules and proapoptotic proteins. With the rupture of the blood-brain barrier, inflammatory cells infiltrate the clot and the arteries, leading to increased expression of inflammatory cytokines, endothelin 1, reactive oxygen species, and trigger oxidative stress.

In summary, after SAH there is a massive expression of proinflammatory cytokines, an invasion of inflammatory cells, and a proinflammatory state develops, which seems to contribute to arterial spasm and DCI<sup>11,25</sup>.

It is likely that microvascular constriction and dysfunction also play a role in the development of DCI. After SAH, at first there is pial arteriole constriction caused by altered vascular reactivity due to endothelial injury. Arteriolar smooth muscle is dysfunctional and the presence of blood increases vasoconstriction<sup>11</sup>.

Cortical spreading depolarization is a Gray matter depolarization wave that propagates at a speed of 2-5 mm per minute, leading to depression in brain electrical potential (spreading depolarization) and electrical activity (spreading depression). Cortical arterioles usually respond to depolarization with vasodilation and hyperemia. However, after SAH, vasoconstriction may occur, leading to waves of cortical hypoperfusion (cortical spreading ischemia) and brain damage.

The presence of elevated potassium concentrations, the reduced levels of nitric oxide and other metabolic changes favor the occurrence of cortical spreading depolarization. Some studies temporally and spatially correlate cortical spreading depolarization with DCI. Depolarizations that last longer than 60 minutes may be strongly correlated with infarction<sup>10,11,25</sup>.

### Delayed cerebral ischemia: prevention and monitoring

In order to prevent DCI, the only pharmacologically approved therapy is nimodipine 60 mg every four hours for 21 days. It has been shown to reduce cerebral infarction, poor outcome and death, but not to reduce angiographic spasm<sup>24</sup>. If hypotension occurs, the dose can be divided in 30 mg every two hours or reduced to 30 mg every four hours. This recommendation is a class I, level of evidence A, according to current guidelines<sup>1,13</sup>.

Hyponatremia and hypovolemia frequently occur after SAH, are associated with DCI, and should be avoided. The target is normal serum sodium and euolemia, which can be achieved by isotonic crystalloid fluid resuscitation. If needed, fludrocortisone may be an option.

The previous classic “triple H therapy” (hypertension, hemodilution, and hypervolemia) is no longer recommended as there is no evidence that it improves neurological outcomes and it can increase the risk of cardiac dysfunction, pulmonary edema, and infection.

There have been multiple failed attempts to prevent DCI by targeting its complex pathophysiology. Clinical trials with magnesium, clazosentan (antagonist of endothelin 1 receptor), aspirin, heparin, erythropoietin, nicardipine, methylprednisolone, prophylactic use of balloon angioplasty, intra-arterial or intravenous milrinone, and even with intrathecal drugs, have all been unsuccessful to date. Consequently, none of these therapies are formally recommended<sup>4,25</sup>.

Delayed cerebral ischemia is considered a reversible condition if treated promptly. Monitoring, recognition, and aggressive treatment are fundamental. Among those patients who are awake, frequent neurological examination is the gold standard for detecting DCI. However, in those with poor grade SAH, its detection is frequently challenging due to the decreased level of consciousness or the use of sedation, leading to the need of advanced monitoring strategies<sup>4,25</sup>.

Transcranial Doppler is a non-invasive test that allows indirect evaluation of proximal large vessel cerebral blood flow based on blood velocities. It can be performed at the bedside and be repeated whenever needed. Middle cerebral artery mean velocities < 120 cm/s have a high negative predictive value for vasospasm, and velocities > 180 cm/s or 200 cm/s have a high positive predictive value. The Lindegaard Index is defined by the middle cerebral artery mean cerebral blood flow velocity divided by the extracranial internal carotid artery mean cerebral blood flow velocity, and has fewer systemic hemodynamic variations. When it is > 3, the index indicates vasospasm, and > 6 indicates severe vasospasm. Serial examinations are also important as an increase of 50 cm/s in 24 hours is also a “red flag”<sup>6,25</sup>.

Sensitivity and specificity of transcranial Doppler for vasospasm diagnosis varies widely between authors, ranging from 39-94% and 70-100%, respectively<sup>26</sup>. It is considered by the American Heart Association/American Stroke Association guideline as class IIa, level of evidence B, and by the Neurocritical Care Society guideline as having a moderate quality of evidence, with strong recommendation<sup>1,13</sup>.

Continuous electroencephalography (EEG) is a useful method for the detection of DCI and has the advantages of being non-invasive, monitoring broad regions of the brain and detecting epileptiform discharges and electrographic crises. In the presence of cortical spreading depolarization and cortical ischemia, EEG changes may precede the occurrence of symptoms. The most sensitive EEG patterns for the prediction of DCI are reduction in the alpha/delta ratio and decrease of alpha variability<sup>10,25</sup>. The presence of interictal discharges, especially when starting several days after the bleeding, may also be correlated with an increased risk of DCI<sup>27</sup>.

Computed tomographic (CT) perfusion is an appealing method since it allows for the evaluation of spasm of large and small vessels and their functional consequences on cerebral blood flow. The most accepted cutoff values are a mean transit time > 5–6.5 seconds and/or regional cerebral blood flow < 25–40 ml/100 g/min<sup>6,10</sup>.

One meta-analysis concluded that SAH patients with an abnormal CT perfusion are 23 times more likely to develop DCI, with a sensitivity of 84% and specificity of 77%. Another meta-analysis showed that an increase in mean transit time during hospitalization of 1.5 seconds or more, or a reduction of cerebral blood flow of 11.9 mL/100 g/min, was diagnostic for DCI<sup>28,29</sup>.

Monitoring brain tissue partial pressure oxygenation is a non-invasive, direct method that measures continuous but regional levels of oxygen, and may detect early changes in brain oxygenation, preceding ischemic damage and clinical manifestations. Levels < 20 mmHg are a warning sign, and < 15 mmHg require immediate intervention.

Cerebral microdialysis measures interstitial levels of glucose, lactate, pyruvate and glutamate. The most-studied markers of anaerobic metabolism and thus indicators of cerebral ischemia are the lactate-pyruvate ratio and glucose levels. A lactate-pyruvate ratio > 40 and/or glucose < 0.5 mM may be indicators of DCI.

Partial pressure oxygenation and cerebral microdialysis have proven to be more accurate than the classic evaluation by intracranial pressure and cerebral perfusion pressure, as hypoxia and a cellular energy crisis may occur even with normal intracranial pressure and cerebral perfusion pressure<sup>10</sup>.

### Delayed cerebral ischemia: treatment

The first step of DCI treatment is usually a normal saline bolus (15 mL/kg) in order to increase cerebral blood flow to ischemic areas and maintain euolemia and normal cerebral blood volume.

Triple H therapy is not recommended as part of DCI treatment as it leads to high complication rates and has not proven to be beneficial. Hypervolemia alone has proven to be ineffective and detrimental, raising the chances of pulmonary and cerebral edema, infections, coagulopathies, prolonged ventilator weaning, and longer intensive care unit stay. Hemodilution may reduce oxygen delivery and raise cerebral ischemic volume.

Normovolemic-induced hypertension using vasopressors, however, remains a cornerstone of first line treatment for DCI. The aim is to improve cerebral blood flow and cerebral oxygenation, and clinical response may be seen in up to 70% of the patients. Norepinephrine, dopamine or phenylephrine may be used, depending on the clinical scenario. Nowadays, the recommendation is to induce hypertension unless the patient is already hypertensive or there is a formal contraindication.

Blood pressure should be raised in a stepwise fashion and titrated to clinical response or improvement of multimodal parameters. Lack of response in 30 minutes should trigger escalation of BP targets. Most centers use a maximal target of systolic BP 220 mmHg, mean arterial pressure 140 mmHg or cerebral perfusion pressure 120 mmHg. Once there is resolution of DCI, the therapy is maintained for 24–48 hours of stable symptoms, and then slowly withdrawn<sup>10,11,25</sup>.

The Hypertension Induction in the Management of Aneurysmal Subarachnoid Haemorrhage with Secondary Ischaemia study was the first randomized trial aiming to evaluate induced hypertension as a treatment for DCI<sup>30</sup>. It was prematurely interrupted with 41 patients (the original design aimed to include 240 patients) due to lack of effect on cerebral perfusion and slow recruitment. The group with induced hypertension had an adjusted risk ratio for poor outcome of 1.0 (95% CI 0.6–1.8) and risk for serious events 2.1 (95% CI 0.9–5.0). Due to the premature interruption, it was underpowered to support induced hypertension as a therapy for DCI. It demonstrated, however, that serious adverse effects may happen with elevated BP. There are several criticisms of the study, such as the small number of patients (only 21 in the hypertension group), possibly an insufficient target of BP and the lack of a better selection of patients<sup>30</sup>. New trials addressing this topic are still needed.

After hypertension, the next step in the treatment of DCI (tier two) may be cardiac output augmentation with dobutamine or milrinone, attempting to improve brain perfusion. Milrinone is a selective inhibitor of phosphodiesterase type III isoenzyme with inotropic and vasodilator properties. It has a short half-life (around 50 minutes)—the reason why it is used as continuous infusion<sup>13,25</sup>.

The Montreal Neurological Hospital published their protocol in 2012<sup>31</sup>, with extensive experience with the drug. Their protocol consisted of a bolus of 0.1–0.2 mg/kg intravenous milrinone, followed by a continuous intravenous infusion of 0.75 mcg/kg/min – 1.25 mcg/kg/min. If there is hypotension, vasopressors should be initiated, aiming for a mean arterial pressure of 90 mmHg. The infusion should be maintained for 72 hours of stable symptoms and then weaning is initiated, decreasing 0.25 mcg/kg/min every 28–48 hours. If symptoms recur, the protocol should be restarted. A total of 88 patients were followed, five deaths occurred and 48.9% of the surviving patients returned to their basal condition and 75% had a modified Rankin scale  $\leq 2$ . No significant collateral effects were reported<sup>31</sup>.

A systematic review showed that the literature is still very poor regarding milrinone and DCI, with no randomized or case controlled studies published, leading to very low level of evidence regarding this topic<sup>32</sup>.

Recently, a randomized controlled study that aimed to compare milrinone plus hyperdynamic therapy was stopped due to lack of eligible subjects<sup>33</sup>.

If medical therapy fails, the next step is endovascular therapy (mechanical dilation with balloon angioplasty and/or pharmacological dilation with intra-arterial drugs).

Balloon angioplasty appears safe, with reported neurological improvement rates as high as 90%. The mechanism of action is related to the stretching and disruption of degenerative muscle and proliferative components in the media of spastic arteries. It is limited to proximal vessels. Potential complications are vessel perforation, reperfusion injury, distal embolism and thrombosis. Recurrence is rare.

Intra-arterial therapy has the advantages of distal penetration, and is easier and safer to perform. It has a transitory effect (depending on the half life of the drug), and recurrence often happens. There is also a theoretical risk of increased intracranial pressure secondary to vasodilation and systemic hypotension. Nowadays, the most used drugs are nicardipine, verapamil and milrinone<sup>25,34</sup>.

A recent meta-analysis of 55 studies on intra-arterial therapy reported 89% angiographic improvement, 57% neurological improvement, 66% good clinical outcome and 9% deaths<sup>35</sup>.

Other interventions such as intrathecal drugs (milrinone, sodium nitroprusside, nicardipine), aortic flow diversion, intra-aortic balloon pump counter-pulsation are experimental strategies under investigation.

## SYSTEMIC COMPLICATIONS

Sodium and water abnormalities are common after SAH, with hyponatremia occurring in 30–50% of patients, hypovolemia in 17–30%, both being associated with negative outcomes. The pathophysiology is not completely understood, but increased natriuretic peptide concentrations, sympathetic nervous system hyperactivation and hyperreninemic hypoaldosteronism may contribute.

Hyponatremia may be due to the syndrome of inappropriate antidiuretic hormone (normal intravascular volume) or cerebral salt wasting syndrome (depleted intravascular volume).

Water restriction should be avoided in treating hyponatremia due to the risk of developing DCI. Hypertonic fluids and fludrocortisone are better options<sup>1,4</sup>. Especially in poor grade patients, early intensive hemodynamic monitoring may improve outcomes<sup>36</sup>.

Cardiac complications are related to sympathetic hyperactivity and catecholamine-induced myocardial dysfunction, and are also associated with poor outcomes. Positive cardiac enzymes, electrographic changes, arrhythmias, motion wall abnormalities, stunned myocardium and cardiogenic shock may occur<sup>4</sup>.

A meta-analysis demonstrated that motion wall abnormalities, increased cardiac enzymes, increased brain natriuretic peptide, Q and T waves and ST segment abnormalities were associated with worse outcomes,

increased mortality and increased the occurrence of DCI<sup>37</sup>. Treatment is mainly supportive.

Pulmonary complications occur in 20-30% of patients with a positive association of DCI with death. Pneumonia, acute respiratory distress syndrome, cardiogenic or neurogenic pulmonary edema and pulmonary embolism may occur<sup>4</sup>.

Fever is the most common medical complication after SAH and should be aggressively treated, aiming for normothermia. It can be infectious or noninfectious, with the latter being a diagnosis of exclusion<sup>1,4,13</sup>.

Glucose management is of major importance. Hypo- and hyperglycemia are correlated with an energetic crisis and worse prognosis. Serum glucose levels 80-180 mg/dl seem to be reasonable<sup>1,4,13</sup>.

Prevention of deep venous thrombosis should be practiced in all SAH patients. Before the aneurysm is safe, compression devices must be used. Chemical prophylaxis can be started 24 hours after surgery<sup>1,13</sup>.

## CONCLUSION

In conclusion, SAH is a disease with high morbimortality, whose treatment goes through several distinct phases ranging from the imminent risk of rebleeding to late cerebral ischemia. The approach in an intensive care setting is crucial to minimize the risks of complications and to optimize the clinical prognosis of patients with SAH.

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