Multidisciplinary management and emerging therapeutic strategies in aneurysmal subarachnoid haemorrhage

Alejandro A Rabinstein, Giuseppe Lanzino, Eelco F M Wijdicks

The management of patients with aneurysmal subarachnoid haemorrhage demands expertise to anticipate, recognise, and promptly treat the many neurological and systemic complications. For this reason, these patients are best cared for in high-volume medical centres with multidisciplinary teams and should preferably be treated in a specialised intensive care unit. Endovascular occlusion and surgical clipping provide complementary alternatives for the treatment of aneurysms. Perfusion scans are redefining the way we detect delayed ischaemia as a growing body of evidence indicates that monitoring vessel diameter is insufficient to prevent cerebral infarctions. Statins, endothelin antagonists, and magnesium sulfate infusion are among the novel strategies being tested for neuroprotection and attenuation of vasospasm. The effectiveness of these treatments is supported by strong experimental data and they represent a new generation of therapeutic options developed from the understanding that vasospasm is primarily caused by endothelial dysfunction.

Introduction

The rupture of an intracranial aneurysm is a neurological emergency. The urgency of the situation might not seem intuitively obvious because many patients present only with a headache and initially have a nearly normal neurological examination. In the first 24 h, rebleeding is a major risk and can lead to early morbidity or even brain death. After the aneurysm is secured (ie, excluded from the circulation), the patient enters a new phase punctuated by cerebral vasospasm and decreased cerebral perfusion. Avoiding secondary damage then becomes the primary goal of care. Some patients present in a much worse clinical condition, requiring complex management of pulmonary oedema, cardiac failure, and arrhythmias. Other patients need emergency evacuation of a cerebral haematoma or decompressive craniectomy to control mass effect.

There has been a notable change in the management of aneurysmal subarachnoid haemorrhage (aSAH) over the past decade. In this era of neurointervention and neurointensive care, a multidisciplinary team is required to respond to the needs of the patient. Mortality from aSAH is decreasing and we are making progress in the understanding of its complex pathophysiology. Furthermore, new management strategies have emerged and their use might enable more patients to return to a good or even a full level of functioning.

In this Review, we first provide a practical overview of the care of patients with aSAH from the time of their first hospital assessment. Second, we highlight recent diagnostic and therapeutic advances and discuss promising new treatment options. This Review is not intended to be a guideline or to represent practice recommendations and we do not strictly follow the rules of evidence-based medicine. When evidence is available, we present a critical assessment of its strengths and weaknesses; when there is no evidence available, we offer recommendations based on our experience.

Initial management

In the emergency department

The acute physiological abnormalities caused by the rupture of an intracranial aneurysm can be devastating. Probably no other acute neurological illness provokes the extent of sudden increase in intracranial pressure and sympathetic outflow as that produced by aSAH. Sudden death occurs in 10–15% of individuals at the time of rupture.21 Coma from intracranial hypertension and cardiopulmonary complications caused by neurocardiogenic injury are common among survivors with extensive haemorrhage. Thus, the initial phase of care of patients with aSAH can be very challenging, yet this period is less well studied.

Diagnosis of aSAH

Diagnosis is suspected by the clinical signs and symptoms but must be confirmed by brain imaging or CSF analysis. CT scanning has a high sensitivity for the detection of subarachnoid blood (>95%).4 CT scans also offer valuable information to estimate the risk of delayed vasospasm; a recent modification to the classic Fisher grading score recognises that the presence of not only cisternal but also intraventricular blood increases the risk of vasospasm and this modified scale should preferentially be used (table 1).24 The score described by Hijdra and colleagues has greater predictive power than the Fisher score, but is less often used because it is more laborious. Only early CT scans should be used to estimate the risk of vasospasm; scans that are done more than 48 h after the time of bleeding lose predictive value.11 The most common causes for aSAH with false negative CT scans are small haemorrhages and delayed presentation. Clinical suspicion of aSAH with a negative CT scan demands that a lumbar puncture is done.12–16 CSF should be centrifuged and examined for xanthochromia, which can be present as early as 6 h after the haemorrhage and is uniformly evident 12 h later.12 Spectrophotometric analysis is more sensitive than visual inspection of the CSF, but visual inspection has good specificity.16 Although
MRI is rarely used for the initial diagnosis of aSAH, haemosiderin-sensitive sequences (such as gradient echo, T2*, and susceptibility-weighted imaging) have a high sensitivity for the diagnosis of any form of intracranial haemorrhage. In fact, MRI scans are more sensitive than CT scans when scanning is done several days after the onset of the bleeding.2

Scoring clinical severity

The severity of neurological impairment on presentation is one of the strongest predictors of outcome. As the Hunt and Hess score10 relies on some subjective information, we favour the simplicity and objectivity of the World Federation of Neurological Surgeons scoring system (table 2).19

In the intensive care unit

After ensuring adequate ventilation, oxygenation, and circulation, initial care should be focused on recognising early complications and preventing rebleeding. Patients should be referred to high-volume centres with continuous availability of a multidisciplinary team (including cerebrovascular neurosurgeons, endovascular specialists, neurointensivists, brain rehabilitation physicians, dedicated physical, occupational, and speech therapists, and nurses with expertise in SAH) and admitted to the intensive care unit, ideally one specialised in neurosciences.20–22

The most common cerebral complications on presentation are acute hydrocephalus and global brain oedema. Acute hydrocephalus responds rapidly to ventricular drainage and the resulting clinical improvement can be dramatic.21 Global brain oedema visible on CT scans is a marker of poor prognosis and treatment is often ineffective in these cases.24 Nonetheless, as some patients who improve after aggressive initial resuscitation (endotracheal intubation, stabilisation of cardiopulmonary function, ventriculostomy when indicated, occasionally osmotherapy) can achieve a favourable outcome,25 discontinuation of intensive care and life-support measures during the first 12–24 h is not advisable.

Important aspects of early medical care in aSAH include analgesia, antiemesis, fluid administration, blood pressure control, and general preventive measures (eg, stool softeners to avoid straining, H2 receptor blockers or proton-pump inhibitors for prophylaxis of gastroduodenal ulcers, and intermittent pneumatic compression of the legs to minimise the risk of deep vein thrombosis). Analgesia can be achieved with paracetamol, tramadol, or narcotics. Hypotonic solutions should be avoided in fluid prescription. Severe hypertension should be treated, but there is little evidence to guide the criteria to initiate antihypertensive treatment. On the basis of indirect evidence from retrospective data, systolic blood pressure greater than 160 mm Hg might be associated with increased risk of rebleeding.24 Hence, this cutoff point is often used to initiate treatment with intravenous boluses of labetolol or nicardipine infusion. However, it is prudent to avoid sudden drops in perfusion pressure because this could cause ischaemia, particularly in patients with increased intracranial pressure.

Calcium channel blockers

Nimodipine (60 mg every 4 h for 21 days by enteral route) is started on admission to the intensive care unit. The use of this calcium channel blocker to decrease the risk of delayed ischaemic damage and poor functional outcome is supported by level I evidence (ie, from randomised controlled trials).27 Of note, oral nimodipine does not decrease angiographic vasospasm and its benefit has been attributed to neuroprotection. In trials that have tested calcium antagonists with more potent vasodilatory effects (eg, intravenous nicardipine), these drugs reduced angiographic vasospasm but did not prevent delayed ischaemia; falls in arterial blood pressure that induced cerebral hypoperfusion might have given rise to the negative results in these studies. Thus, when using nimodipine, it is important to ensure that systemic blood pressure is not compromised. If nimodipine causes hypotension, the dose of the medication can be halved and given every 2 h.

Anticonvulsants

We do not recommend the use of prophylactic anticonvulsants. Phenytoin has been associated with poor outcome in aSAH.24 The reasons for this detrimental

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**Table 2**: Comparison of the traditional Fisher radiological grading scale and a proposed modified grading scale

<table>
<thead>
<tr>
<th>Fisher scale</th>
<th>Modified Fisher scale</th>
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<tbody>
<tr>
<td>0</td>
<td>No SAH or IVH</td>
</tr>
<tr>
<td>1</td>
<td>Minimum or thin SAH, no IVH in either lateral ventricle</td>
</tr>
<tr>
<td>2</td>
<td>Minimum or thin SAH with IVH in both lateral ventricles</td>
</tr>
<tr>
<td>3</td>
<td>Thick SAH, no IVH in either lateral ventricle</td>
</tr>
<tr>
<td>4</td>
<td>Thick SAH with IVH in both lateral ventricles</td>
</tr>
</tbody>
</table>

The modified Fisher scale incorporates the effect of IVH on the risk of vasospasm and delayed ischaemic damage. Delayed cerebral ischaemia can be predicted by the appearance of the initial CT scan of the brain. SAH=subarachnoid haemorrhage. IVH=intraventricular haemorrhage.

**Table 2**: Clinical grading scales for patients presenting with aneurysmal subarachnoid haemorrhage

<table>
<thead>
<tr>
<th>Hunt and Hess grading system</th>
<th>WFNS grading system</th>
</tr>
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<tbody>
<tr>
<td>I Asymptomatic or mild headache</td>
<td>GCS sum score 15 without hemiparesis</td>
</tr>
<tr>
<td>II Moderate to severe headache, nuchal rigidity, no focal deficits other than cranial nerve palsy</td>
<td>GCS sum score 14–13 without hemiparesis</td>
</tr>
<tr>
<td>III Confusion, lethargy, or mild focal deficits other than cranial nerve palsy</td>
<td>GCS sum score 14–13 with hemiparesis</td>
</tr>
<tr>
<td>IV Stupor or moderate to severe hemiparesis</td>
<td>GCS sum score 12–7 with or without hemiparesis</td>
</tr>
<tr>
<td>V Coma, extensor posturing, moribund appearance</td>
<td>GCS sum score 6–3 with or without hemiparesis</td>
</tr>
</tbody>
</table>

WFNS=World Federation of Neurological Surgeons. GCS=Glasgow coma scale.
Conventional cerebral angiogram showing a small ruptured intracranial aneurysm in the left A1 segment of the anterior cerebral artery (A, arrow), which is much better visualised on the three-dimensional rotational image (B, arrow).

These non-invasive techniques are quite sensitive for the detection of aneurysms that are 4 mm or larger, but might still miss very small aneurysms. Nevertheless, the sensitivity of these techniques continues to improve.

**Surgical clipping versus endovascular coiling**

Surgical clipping and endovascular coiling are both effective methods to exclude the ruptured aneurysm from the circulation. There has been much debate on the relative merits of these interventions, with some neuro-interventionalists firmly preferring one technique over the other. These techniques should not be seen to be in competition with each other but rather as complementary. Certain aneurysms are best approached with open surgery (eg, those with a very wide neck or that incorporate branching vessels) and others are more suitable for endovascular treatment (eg, basilar tip aneurysms).

The most rigorous study done so far to compare the two treatment techniques is the International Subarachnoid Aneurysm Trial (ISAT). In this study, more than 2100 patients with ruptured aneurysms were randomly assigned to receive craniotomy and clipping or endovascular coiling across multiple centres (mostly European). Clinical equipoise was demanded for enrolment in the trial: that is, the responsible neurosurgeons and interventionalists had to agree that the aneurysm was comparably suitable for treatment with either procedure (which explains the small number of posterior circulation aneurysms randomised and the large number of patients screened in relation to those randomised). The results of this trial showed that endovascular coiling was associated with a lower risk of death or dependency at 1 year compared with surgical clipping (absolute risk reduction 7·4% and relative risk reduction 23·9%).

The benefit of coiling on functional outcome remained significant for a mean of 9 years (range 6–14 years), despite a higher risk of rebleeding than with clipping.

Rebleeding from the treated aneurysm during the first year occurred in seven patients allocated to endovascular therapy versus two patients in the surgical arm. Although still very low, rebleeding after 1 year was also more frequent in the endovascular group (11 patients) than in the surgical group (two patients). Complete angiographic occlusion of the aneurysm in ISAT was achieved in 66% of the cases who received endovascular coiling, arguably a suboptimum proportion. Re-treatment was done 4–6 times more commonly after primary endovascular therapy (17·4%) than after surgical clipping (3·8%). Experience in the USA confirms that rebleeding is rare after treatment of ruptured aneurysm with clipping or coiling and late re-treatment is more often necessary after coiling. It is therefore advisable to monitor coiled aneurysms with follow-up angiograms to ensure timely identification and treatment of a recurrence. The ideal intervals between studies, length of surveillance, and relative value of non-invasive angiograms are unknown.
Age remains an important consideration when deciding the treatment technique to secure the aneurysm. Endovascular coiling was associated with better functional outcome than neurosurgical clipping in a subgroup of elderly patients (>65 years of age) in ISAT who presented with good clinical grade and SAH from small ruptured aneurysms in the internal carotid artery or posterior communicating artery. Conversely, patients with middle cerebral artery aneurysms had better outcomes with neurosurgical clipping than with endovascular treatment. Clinical results were similar with both techniques when the ruptured aneurysm was located in the anterior communicating or anterior cerebral artery region. Meanwhile, some have argued that the advantage of endovascular coiling over surgical clipping cannot be assumed for patients younger than 40 years of age. The reasoning behind this argument is that younger patients can tolerate surgery better than older individuals, and therefore they are more likely to benefit from the better long-term protection given by clipping.

**Management of patients with poor clinical grade**

Management of poor-grade patients is particularly challenging because these patients are most often intubated and sedated. Thus, physical examination cannot be reliably used to detect signs of delayed ischaemia. Invasive and non-invasive brain monitoring techniques can be used for these patients. Measurements and techniques include venous oximetry (by jugular bulb catheters), brain tissue oxygen tension (by probes such as the Licox catheter, GMS, Kiel-Mielkendorf, Germany), cerebral microdialysis, continuous EEG, and continuous catheters), brain tissue oxygen tension (by probes such as the Licox catheter, GMS, Kiel-Mielkendorf, Germany), cerebral microdialysis, continuous EEG, and continuous monitoring (85 cm/s)62 and values greater than 115 cm/s as detected by single photon emission computed tomography. A lower threshold velocity has been recommended for the ultrasonographic definition of basilar artery vasospasm monitoring (85 cm/s)62 and values greater than 115 cm/s reliably identified patients at risk of brainstem ischaemia as detected by single photon emission computed tomography. A basilar to vertebral artery ratio of greater than three with mean velocities faster than 85 cm/s might further increase the diagnostic accuracy of transcranial doppler for the detection of basilar artery vasospasm.63

**Vasospasm and systemic complications**

**Diagnosis of vasospasm**

The risk of vasospasm increases between 3 and 7 days after aSAH, although earlier vasospasm can occur and might be associated with poor outcome. Fewer than 4% of deficits occur after day 13. More than 60% of patients with aSAH develop cerebral vasospasm during the hospital course, but only about 30% will become symptomatic. Cerebral vasospasm tends to be more severe in younger patients with poor neurological grade, thick subarachnoid clot, intraventricular haemorrhage, and history of smoking. The onset of symptomatic vasospasm can be sudden or gradual and insidious. Headache and increasing neck stiffness are non-specific signs. Patients will commonly present with increasing confusion, delirium, or decreased consciousness, with or without focal deficits. Techniques available for monitoring vasospasm and cerebral perfusion are listed in table 3.

Transcranial doppler ultrasonography is a widely accepted method for screening and monitoring of vasospasm. However, transcranial doppler has inherent limitations: it is operator dependent and does not provide useful information in patients with poor temporal ultrasonographic windows (a problem often encountered in older women). The sensitivity and specificity of transcranial doppler for the diagnosis of symptomatic vasospasm and subsequent cerebral infarction on CT scans range from 70% to 80%. Transcranial doppler results correlate adequately with findings on digital subtraction angiography when vessels can be well insonated. The sensitivity differs depending on the vessel involved; it is highest for the middle cerebral artery but lower for intracranial internal carotid and anterior cerebral arteries. In one study, the negative predictive value for middle cerebral artery velocities of less than 120 cm/s was 94% and the positive predictive value for middle cerebral artery velocities greater than 200 cm/s was 87% for transcranial doppler monitoring compared with digital subtraction angiography, the gold standard method for the diagnostic assessment of cerebral vasospasm. An increase in mean flow velocity of more than 50 cm/s over 24 h is also a reliable marker of vasospasm. Use of the intracranial to extracranial vessel mean flow velocity ratio (known as the Lindegaard ratio) helps to discriminate between vasospasm and hyperaemia; velocities three times higher in the middle cerebral artery than in the extracranial internal carotid artery are indicative of angiographic vasospasm, and a ratio of six indicates severe angiographic vasospasm. A lower threshold velocity has been recommended for the ultrasonographic definition of basilar artery vasospasm monitoring (85 cm/s)62 and values greater than 115 cm/s reliably identified patients at risk of brainstem ischaemia as detected by single photon emission computed tomography. A basilar to vertebral artery ratio of greater than three with mean velocities faster than 85 cm/s might further increase the diagnostic accuracy of transcranial doppler for the detection of basilar artery vasospasm.
The major advantages of digital subtraction angiography are high accuracy and ability to undertake endovascular treatment of existing vasospasm immediately. However, this technique is an invasive procedure that requires the presence of a qualified neurointerventionalist, often demands general anaesthesia, and is associated with small risks of contrast nephropathy and stroke. Additionally, digital subtraction angiography might not identify vasospasm in up to a quarter of patients with aSAH who develop radiological infarctions.\(^{37}\)

CT angiography has a good correlation with digital subtraction angiography for the identification of vasospasm in proximal arterial segments.\(^{38}\) Agreement between CT angiography and conventional angiography is close to 90% in cases of severe vasospasm, with excellent agreement among different observers.\(^{46}\) Discrepancies between the two tests are more common when vasospasm is mild or moderate.\(^{47}\) When CT angiography is used to study vasospasm, the axial source and three-dimensional images must be examined for symmetry and calibre of the cerebral vessels. Having a baseline CT angiography at presentation is useful to be able to assess interval changes in vessel diameter. Metal artifacts from clips or coils often diminish the quality of the images.

CT perfusion is being increasingly used for the diagnosis of vasospasm. Good correlation with digital subtraction angiography has been reported. Absolute cerebral blood flow values of less than 25 mL/100 g/min and mean transit times greater than 6·5 s are associated with severe vasospasm and high risk of delayed ischaemic deficits.\(^{47}\) A mean transit time with a threshold of 6·4 s was the most sensitive parameter for the diagnosis of cerebral vasospasm (as confirmed by angiogram), with a negative predictive value of 98·7%.\(^{48}\) CT perfusion and CT angiography had a higher positive predictive value than transcranial doppler in this study.\(^ {49}\) Other investigators have identified delayed time to peak as the most reliable predictor of delayed cerebral ischaemia.\(^{50}\) In practice, visual inspection of CT perfusion maps can be reliably used to evaluate hypoperfusion (figure 2).\(^ {51}\) CT perfusion maps can show decreased perfusion in areas with mild or no macrovascular vasospasm on CT angiography, thus enabling recognition of ischaemic risk that would otherwise remain unnoticed.\(^ {52,53}\) In fact, findings on CT perfusion studies have better predictive values than those of CT angiography for the diagnosis of delayed cerebral ischaemia in patients who have clinical signs of deterioration.\(^ {54}\) Radiation exposure is a disadvantage that limits the suitability of CT perfusion as a serial test.

MRI, particularly diffusion-weighted imaging, has greater sensitivity than does CT for the diagnosis of acute ischaemia related to vasospasm.\(^ {75-79}\) Perfusion-weighted imaging might also provide useful information (figure 3). Abnormal perfusion-weighted imaging might be used to predict neurological deficits with greater sensitivity than transcranial doppler.\(^ {80}\) As with CT perfusion, perfusion-weighted MRI can be used to identify hypoperfusion in territories not affected by substantial angiographic vasospasm (most often the basal ganglia and watershed regions).\(^ {81}\) Mismatch between perfusion-weighted imaging and diffusion-weighted imaging can be used to identify ischaemic penumbra in patients with vasospasm.\(^ {82}\)

Testing of vasomotor reactivity by use of transcranial doppler with CO2 challenge can be done at the bedside. This method was a very sensitive early predictor of vasospasm in a recent small series.\(^ {83}\) Monitoring regional and local oxygenation with jugular bulb catheters and brain probes (such as the Licox catheter) remains confined to some specialised centres.\(^ {44}\) Whether decreases in the oxygen concentration in brain tissue indicate a risk of ischaemia or a very early marker of established ischaemic damage is unclear. Other methods to monitor regional brain perfusion, such as thermal diffusion intracranial microprobes, are still mostly experimental.

**Treatment of vasospasm**

Initial evaluation should involve assessment of volume status. It is important to ensure that the patient does not become volume depleted, sometimes a challenging task

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**Table 3: Most commonly used techniques to diagnose and monitor vasospasm and cerebral ischaemia**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter angiography</td>
<td>Most sensitive for large-vessel spasm</td>
<td>Invasive</td>
</tr>
<tr>
<td></td>
<td>Enables measurement of cerebral circulation time</td>
<td>Labour intensive</td>
</tr>
<tr>
<td></td>
<td>Can be combined with intra-arterial treatment</td>
<td>Cannot be repeated too often</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iodine use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiation exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Need for transportation</td>
</tr>
<tr>
<td>Transcranial doppler</td>
<td>Non-invasive</td>
<td>Depends on presence of bone windows</td>
</tr>
<tr>
<td></td>
<td>Done at bedside</td>
<td>Operator-dependent</td>
</tr>
<tr>
<td></td>
<td>Can be done daily to follow trends*</td>
<td>Does not assess the microcirculation well</td>
</tr>
<tr>
<td></td>
<td>Good correlation with catheter angiography</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can be combined with CO2 challenge to test VMR</td>
<td></td>
</tr>
<tr>
<td>CT angiography</td>
<td>Non-invasive</td>
<td>Cannot be repeated too often</td>
</tr>
<tr>
<td></td>
<td>Can be combined with CT perfusion</td>
<td>Iodine use</td>
</tr>
<tr>
<td></td>
<td>Good correlation with catheter angiography</td>
<td>Radiation exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Need for transportation</td>
</tr>
<tr>
<td>CT perfusion</td>
<td>Evaluates actual cerebral perfusion</td>
<td>Cannot be repeated too often</td>
</tr>
<tr>
<td></td>
<td>Quantifiable measures</td>
<td>Iodine use</td>
</tr>
<tr>
<td></td>
<td>Can detect ischaemia even without detected angiographic vasospasm</td>
<td>Radiation exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Need for transportation</td>
</tr>
<tr>
<td>Magnetic resonance angiography</td>
<td>Non-invasive</td>
<td>Cannot be repeated too often</td>
</tr>
<tr>
<td></td>
<td>Can be combined with DWI/PWI</td>
<td>Need for transportation</td>
</tr>
<tr>
<td>MRI with DWI/PWI</td>
<td>Measures actual cerebral perfusion</td>
<td>Cannot be repeated too often</td>
</tr>
<tr>
<td></td>
<td>Easy identification of ischaemic penumbra</td>
<td>Need for transportation</td>
</tr>
<tr>
<td>Single photon emission</td>
<td>Measures cerebral perfusion</td>
<td>Cannot be combined with vessel imaging in the same session</td>
</tr>
<tr>
<td>computed tomography</td>
<td></td>
<td>Radioactive exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Need for transportation</td>
</tr>
<tr>
<td>Jugular oximetry</td>
<td>Regional measure of brain oxygenation</td>
<td>Invasive</td>
</tr>
<tr>
<td></td>
<td>Can be measured frequently</td>
<td>Susceptible to artifact</td>
</tr>
<tr>
<td>Brain tissue O2</td>
<td>Local measure of brain oxygenation</td>
<td>Invasive</td>
</tr>
<tr>
<td></td>
<td>Continuous measure</td>
<td>Very limited spatial resolution</td>
</tr>
<tr>
<td>VMR-vasomotor reactivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI-diffusion-weighted imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWI-perfusion-weighted imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous transcranial doppler monitoring is also possible.</td>
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in patients with excessive natriuresis. The ideal protocol for salt and volume replacement has not been established. We prefer 0.9% saline solution in patients with normal serum sodium concentrations and 1-5% sodium chloride in patients who develop hyponatraemia, which can be given via peripheral veins. Other concentrations of saline solution (3%, 7.5%) have been used, as well as colloid solutions (most commonly albumin in 5% and 25% solution). Supplemental 5% albumin solution limits loss of fluid and sodium by decreasing glomerular filtration rate, which leads to a decrease in the total amount of fluids required to maintain an adequate volume status.91 However, there is no evidence to support the routine use of colloid solutions in aSAH, and crystalloid solutions should be standard fluid therapy.

The main goal of fluid management in patients without clinical vasospasm is to maintain neutral fluid balance taking into account insensible losses (eg, fluid lost by evaporation of sweat). Some protocols require invasive central venous pressure monitoring with a recommended pressure of between 6 mm Hg and 8 mm Hg and a pulmonary capillary wedge pressure of between 8 mm Hg and 12 mm Hg. However, non-invasive methods to monitor intravascular fluid status are becoming available and might be preferable.84 Prophylactic hypervolaemia is not recommended; this strategy did not improve cerebral blood flow or prevent symptomatic vasospasm or delayed ischaemic damage in a randomised controlled study,85 and it can be associated with increased risk of cardiopulmonary complications owing to fluid overload.

Since its description,86 haemodynamic augmentation therapy has become the mainstay of medical treatment of cerebral vasospasm in patients with aSAH.92 The objective of haemodynamic augmentation is to improve cerebral perfusion by overcoming the increased vascular resistance imposed by vasospasm. Although the efficacy of this treatment has not been tested in randomised controlled trials,87 the benefits of implementing such augmentation are supported by lower levels of evidence and can be seen in practice.

Haemodynamic augmentation is also traditionally known as “triple H” therapy for its components: hypervolaemia, hypertension, and haemodilution. However, there is substantial controversy with regard to the relative value of these components. Induction of haemodilution is now used less often because the improvements in cerebral blood flow related to diminished blood viscosity do not produce a net benefit if the fall in haematocrit compromises oxygen delivery to the brain.88 Meanwhile, more recent studies have questioned the usefulness of hypervolaemia.89 In one study,90 induced hypertension improved regional cerebral blood flow and brain tissue oxygenation, but these benefits disappeared after induction of hypervolaemia. Other investigators found induced hypertension to be more effective and safer than hypervolaemia in achieving improved brain oxygenation.91 Nonetheless, there are data that lend support to the usefulness of hypervolaemia. Saline boluses (15 mL/kg over 1 h) increased regional cerebral blood flow as measured by PET scans in brain regions most vulnerable to ischaemia.92 The value of induction of hypervolaemia might depend on the baseline volume status of the patient. Administration of fluids might benefit truly euvoelaemic patients, but not those who are already volume expanded before the diagnosis of symptomatic vasospasm. In fact, attempts to produce increased hypervolaemia in patients with volume expansion might provoke complications from fluid overload.

Several vasopressors can be used to induce hypertension, including phenylephrine, norepinephrine, and dopamine. Vasopressin is an effective vasopressor, but is not commonly used in patients with aSAH because of its potential to exacerbate hyponatraemia.
augmentation of cardiac output with inotropics (eg, dobutamine and milrinone) is preferred in some centres and data are available to support this strategy.\(^9\)

About 10–20% of patients treated with haemodynamic augmentation have complications, mostly pulmonary oedema and, much less commonly, myocardial ischaemia and cardiac arrhythmias.\(^5,9\) Increased cerebral oedema, posterior reversible encephalopathy syndrome, and haemorrhagic conversion of ischaemic stroke are complications rarely seen in practice.\(^9\) Endovascular therapy should be pursued when signs of clinically significant fluid overload become evident. Cardiopulmonary complications that demand acute, aggressive treatment with diuretics and vasodilators must be avoided as those interventions almost invariably lead to cerebral ischaemia in patients with active vasospasm.

Panel 1: Our guiding principles for the management of aneurysmal subarachnoid haemorrhage

**Recommendations:**
- Admit patient to an intensive care unit with specialised nursing care
- Be part a multidisciplinary team
- Assess patient for cardiopulmonary neurogenic injury
- Optimise oxygenation
- Treat hydrocephalus promptly and aggressively
- Order nimodipine
- Secure the aneurysm as soon as possible
- Pursue endovascular occlusion if feasible
- Consider early surgical decompression if raised intracranial pressure
- Maintain euvoalma\(^*\)
- Do neurological examinations very frequently
- Monitor brain perfusion, not just vessel diameter
- Augment blood pressure if hypoperfusion is present
- Pursue angioplasty or intra-arterial drugs if hypoperfusion is refractory
- Keep patient’s body temperature normal
- Maintain blood sugar concentrations, ideally between 80 and 150 mg/dL
- Monitor serum sodium concentrations and use hypertonic intravenous fluids if hyponatraemia is present
- Use preventive measures against deep vein thrombosis

**Cautions:**
- Do not give up on poor-grade patients
- Do not minimise the importance of sleepiness
- Do not use frequent or large doses of sedatives or narcotics
- Do not order fluid restriction\(^†\)
- Do not infuse hypotonic intravenous solutions
- Do not induce prophylectic hypervolaemia
- Do not overload patients with fluids, even if they have vasospasm
- Do not reduce blood pressure after aneurysm treatment
- Do not prescribe phenytoin
- Do not give glucocorticosteroids regularly
- Do not rely on a single monitoring modality for vasospasm or hypoperfusion
- Do not accept neurological deficits and functional impairment as unavoidable

*\(^*\)Mild hypervolaemia is reasonable in patients with symptomatic vasospasm. \(^†\)Not to be confused with free water restriction, which is appropriate in hyponatraemic patients.

Endovascular therapies for vasospasm include transluminal balloon angioplasty and super-selective intra-arterial infusion of vasodilators.\(^9,99\) Although not proven effective in randomised controlled studies, these interventions are reasonable options in patients who are refractory to medical therapy or when haemodynamic augmentation is considered unsafe owing to poor cardiovascular reserve. Angioplasty is highly effective in relieving focal vasospasm that involves the proximal segments of the major intracranial vessels at the level of the circle of Willis.\(^99\) Early treatment seems to maximise the chances of averting ischaemia from severe vasospasm.\(^99\) The effects of angioplasty are durable and the procedure is relatively safe when done by experienced neurointerventionalists (although arterial wall rupture, dissection, local thrombosis, and reperfusion injury are possible). Intra-arterial vasodilators can ameliorate distal and diffuse vasospasm, but their effects are transient. Papaverine was the first drug used for this indication; however, this drug is neurotoxic and can increase intracranial pressure and also provoke seizures, transient cortical blindness, and irreversible brain injury.\(^101\) Nimodipine,\(^102\) nicardipine,\(^103,104\) and verapamil\(^105\) have since emerged as safer alternatives.

**Treatment of medical complications**

The presentation and course of aSAH can be associated with several neurological and systemic complications.\(^9\) Panel 1 summarises our practical recommendations for the management of aSAH, including measures to prevent and treat the most common complications.

Fever\(^96\) and hyperglycaemia\(^107–109\) are associated with worse outcome in aSAH. The detrimental effects of these physiological alterations in aSAH seem to be at least partly independent of the presence of vasospasm.\(^96,109\) Nonetheless, fever and hyperglycaemia have been associated with symptomatic vasospasm\(^100–102\) and could exacerbate ischaemic neuronal damage in these patients. The value of intensive treatments to maintain normothermia and normoglycaemia needs to be formally studied.

Neurogenic pulmonary oedema tends to occur early after aneurysm rupture.\(^101\) This oedema is thought to be caused by the sudden increase in sympathetic activation, leading to increased hydrostatic pressure (which probably accounts for most cases) or increased alveolar permeability.\(^101\) Although the oedema might be massive initially, it responds well to ventilatory support with a high level of positive end-expiratory pressure. Neurogenic pulmonary oedema is more common in patients with poor clinical grades, and patients with this complication might be more prone to vasospasm, although this association might not be independent but instead associated with the severity of the SAH. The differential diagnoses include cardiogenic pulmonary oedema and pneumonia (related to aspiration or mechanical ventilation).\(^103\)
Neurocardiogenic injury can be provoked by excessive sympathetic stimulation. The resulting cardiomyopathy is known as apical ballooning syndrome or takotsubo cardiomyopathy because of the echocardiographic appearance.\(^{116-118}\) Takotsubo syndrome is also more common in patients with poor clinical grade at presentation. Typically, the disorder manifests over the first 48 h with signs of left ventricular dysfunction and reverses spontaneously over the subsequent 2–3 weeks. There might also be a slight increase in cardiac enzymes in the serum,\(^{119}\) but prominent increases in these chemical markers or major ischaemic changes in the electrocardiogram should raise suspicion of myocardial ischaemia.\(^{120}\)

Hyponatraemia after aSAH, although frequently observed, is most often asymptomatic. However, very low (eg, <120 mEq/L) or very rapid decline in serum sodium concentrations can cause a depressed level of consciousness and trigger seizures. The main mechanism is cerebral salt wasting, although the syndrome of inadequate secretion of antidiuretic hormone (SIADH) might contribute.\(^{121-124}\) The major risk is volume contraction caused by excessive natriuresis, which increases the risk of cerebral ischaemia from vasospasm. Salt and fluid replacements are the mainstay of therapy. Hypertonic saline solutions (eg, 1·5% or 3%) and fludrocortisone are useful treatment options and can be combined. Hyponatraemia is independently associated with worse prognosis after aSAH,\(^{125}\) probably because this event happens in patients with severe disturbances of hypothalamic function caused by massive haemorrhage in the basal cisterns. Although diabetes insipidus is infrequent in patients with aSAH, it can occur and should be investigated in patients with substantial polyuria and increasing sodium concentrations.

Non-infectious fever (often referred to as central fever) is common in patients with aSAH,\(^{112}\) however, infections (such as pneumonia, bacteremia, and ventriculitis) should always be excluded first in febrile patients because they are not infrequent and demand prompt antibiotic treatment. Non-infectious fever tends to start earlier (within the first 3 days) than fever caused by infection\(^{112}\) and might develop preferentially in patients with intraventricular haemorrhage.\(^{126}\) Non-infectious fever might also be associated with increased risk of vasospasm.\(^{127}\) Patients with this type of fever typically have persistently increased body temperatures (instead of spikes) and absent or mild leukocytosis, but the predictive value for risk of vasospasm of these variables remains to be determined.

Anaemia is consistently associated with worse outcomes in patients with SAH.\(^{127-129}\) However, blood transfusions might be detrimental.\(^{127,130}\) At present, the ideal haemoglobin level that should be used as a cutoff for transfusion is unclear. A prospective, randomised controlled trial to compare liberal versus conservative transfusion protocols in a population with strictly standardised medical care is needed to answer this important question.

Venous thromboembolism can be prevented by the combined use of stockings and intermittent pneumatic compression.\(^{131}\) Enoxaparin increases the risk of intracranial bleeding\(^{132}\) and should not be used for prevention of thrombosis. The safety of subcutaneous low-dose heparin remains untested in aSAH.

**New therapies for prevention of cerebral ischaemia and neuroprotection**

Substantial progress is being made in the understanding of the pathophysiology of cerebral vasospasm, which is increasingly regarded as a disorder that predominantly

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**Panel 2: Therapies tested in controlled trials of patients with aneurysmal subarachnoid haemorrhage for prevention of vasospasm and delayed cerebral ischaemic damage**

<table>
<thead>
<tr>
<th>Evidence supports*</th>
<th>Evidence does not support</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral nimodipine</strong></td>
<td><strong>Prophylactic hypervolaemia</strong></td>
</tr>
<tr>
<td>Four trials (pooled 853) indicated a combined relative risk of death and dependency of 0·67 (95% CI 0·55–0·81)(^{134-137})</td>
<td>Two randomised trials (pooled n=114) showed no difference in cerebral blood flow, symptomatic vasospasm, or cerebral infarction(^{138-139})</td>
</tr>
<tr>
<td><strong>Antiplatelet therapy</strong></td>
<td><strong>Enoxaparin</strong></td>
</tr>
<tr>
<td>Seven trials (pooled n=1385) showed no significant benefit on functional outcome or rate of delayed cerebral ischaemia(^{140})</td>
<td>One trial (n=170) showed no improvement in functional outcome and possible increased risk of additional intracranial haemorrhage(^{141})</td>
</tr>
<tr>
<td><strong>Tirilazad</strong></td>
<td><strong>Prophylactic angioplasty</strong></td>
</tr>
<tr>
<td>Four trials (pooled n=3552) with combined results showed no significant effect on functional outcome or rate of cerebral infarction(^{142-143})</td>
<td>One trial (n=170) showed no benefit on functional outcome and treatment carried risk of fatal vessel rupture(^{144})</td>
</tr>
<tr>
<td><strong>Intravenous nicardipine</strong></td>
<td><strong>Intravenous magnesium sulphate</strong></td>
</tr>
<tr>
<td>One trial (n=886) showed reduction in symptomatic vasospasm but without improvement in functional outcome(^{145})</td>
<td></td>
</tr>
</tbody>
</table>

**Studies in progress**

- Endothelin antagonist (clazosentan)
- CONSCIOUS-2\(^{146}\) and CONSCIOUS-3\(^{147}\) trials
- Statins
- STASH trial\(^{148}\)
- Magnesium sulfate
- MASH-II\(^{149}\) and IMASH trials\(^{59}\)
- Albumin
- ALISAH trial\(^{53}\)
- Lumbar drainage
- LUMAS trial\(^{53}\)

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*CONSCIOUS=Clazosentan to Overcome Neurological Ischaemia and Infarction Occurring After Subarachnoid Hemorrhage. STASH=Simvastatin in Aneurysmal Subarachnoid Haemorrhage. MASH=Magnesium Sulfate in Aneurysmal Subarachnoid Haemorrhage. IMASH=Intravenous Magnesium Sulfate in Aneurysmal Subarachnoid Haemorrhage. ALISAH=Treatment of Subarachnoid Hemorrhage with Human Albumin. LUMAS=Lumbar Drainage in Subarachnoid Haemorrhage. Fasudil, an intracellular calcium antagonist with presumed complex neuroprotective actions (eg, as a Rho kinase inhibitor) is only widely used in Japan. One trial lends support to its use,\(^{147}\) but these results have not been replicated.*
affects the endothelial function and microcirculation. Robust theoretical rationale and strong experimental data have led to the design of clinical trials that investigate novel therapies for vasospasm and protection against delayed ischaemic damage. Panel 2 summarises the current state of the evidence for various therapeutic options tested for this indication in clinical trials.

**Statin**

Independent of their effects on reducing cholesterol, statins also have pleiotropic effects that include amelioration of glutamate-mediated excitotoxicity, attenuated production of reactive oxygen species, up-regulation of endothelial nitric oxide synthase, and diminished inflammatory reaction by modulation of the cytokine response. In two small randomised trials, statin treatment provided benefit across various endpoints, including ultrasonographically defined vasospasm, duration of impaired autoregulation, vasospasm-related delayed ischaemic deficits, improved functional, physical, and psychosocial outcome at 6 months, and reduction in all-cause mortality. Statin therapy was safe in both these small trials; specifically, there were no severe cases of myositis or hepatitis reported. The favourable results observed in one of these trials might be partly explained by the poor outcomes seen in the placebo group.

However, the results of studies that have investigated statins in SAH have not been consistently favourable. Data from two other small, randomised controlled studies indicated no differences in the rate of vasospasm-related infarcts or functional outcomes between statin-treated patients and controls. In fact, the most recent meta-analysis of available randomised studies concluded that there is no evidence to support a beneficial effect of statins in SAH. Furthermore, after the first reports indicating beneficial effects of statin use on vasospasm, centres that modified their practice and began giving statin therapy to all their patients with SAH have subsequently reported no improved outcomes among statin-treated patients compared with historical controls treated at the same institutions. Therefore, although preliminary data on the use of statins for the prevention of severe vasospasm seem encouraging, early promising results must be confirmed in larger, multicentre trials before statins can be recommended for this indication (table 4). One such trial (the STASH [Simvastatin in Aneurysmal Subarachnoid Haemorrhage] trial) is currently underway.

**Endothelin antagonists**

Endothelin-1 is the most potent physiological vasoconstrictor, and increased activity of endothelin-1 seems to play a major part in the pathogenesis of cerebral vasospasm. This vasoconstrictor is postulated to work through nuclear signal transduction pathways. There has been substantial interest in the development of endothelin-1 receptor antagonists for the treatment of cerebral vasospasm, particularly in drugs that block the activation of endothelin-1A receptors as they have been specifically implicated as mediators of cerebral vessel constriction.

After encouraging results from a phase 2a study, data from a double-blind trial (the CONSCIOUS-1 [Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage] trial) indicated that intravenous clazosentan, an endothelin-1 receptor antagonist, reduced moderate or severe angiographic vasospasm in a dose-dependent manner (66% for the high dose vs 23% for placebo in the intention-to-treat analysis), but did not improve clinical outcomes. In a post-hoc analysis that used a stricter definition for vasospasm-related infarctions and central adjudication of endpoints, clazosentan was associated with a trend towards better clinical outcomes. However, as results for clinical outcomes were positive only after the substantial modifications implemented in the post-hoc analysis, the strength of these conclusions is diminished.

Systemic hypotension, anaemia, pulmonary complications (probably related to fluid retention), and death were more common in the treatment arms than in the placebo group. However, most fatalities were caused by intraoperative complications; hence, they were not thought to be related to the drug under investigation. The discrepancy between angiographic and clinical outcomes might be explained by systemic complications or the

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**Table 4: Prospective comparative clinical studies that have investigated statins for the treatment of aneurysmal subarachnoid haemorrhage**

<table>
<thead>
<tr>
<th>Statin type and dose</th>
<th>Population size</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised, placebo-controlled trial</td>
<td>80</td>
<td>Reduced vasospasm, reduced severe vasospasm, decreased duration of impaired autoregulation, reduced delayed ischaemic deficits related to spasm, reduced mortality, improved functional outcome</td>
</tr>
<tr>
<td>Randomised, placebo-controlled trial</td>
<td>39</td>
<td>Reduced symptomatic vasospasm, attenuated serum markers of brain injury</td>
</tr>
<tr>
<td>Randomised, placebo-controlled trial</td>
<td>39</td>
<td>No difference in vasospasm, delayed cerebral infarctions, or functional outcome</td>
</tr>
<tr>
<td>Randomised, placebo-controlled trial</td>
<td>32</td>
<td>No difference in vasospasm, delayed cerebral infarctions, or functional outcome, better lipid panel but no difference in other laboratory markers</td>
</tr>
<tr>
<td>Observational, historical control trial</td>
<td>150</td>
<td>No difference in vasospasm, delayed cerebral infarctions, or functional outcome</td>
</tr>
<tr>
<td>Observational, historical control trial</td>
<td>340</td>
<td>No difference in symptomatic spasm, functional outcome, in-hospital mortality, or length of hospital stay</td>
</tr>
<tr>
<td>Observational, historical control trial</td>
<td>130</td>
<td>No difference in vasospasm, symptomatic spasm, or functional outcome and mortality at discharge</td>
</tr>
</tbody>
</table>

Modified from Rabinstein, with permission from Springer.
possibility that other mechanisms in addition to vasospasm could substantially affect prognosis in these patients. Two more studies (CONSCIOUS-2 and CONSCIOUS-3 in clipped and coiled patients, respectively) investigating this endothelin antagonist are in progress.

Magnesium sulfate

Hypomagnesia occurs in about half the patients with SAH and its presence is correlated with a high risk of delayed ischaemic deficits and a poor 3-month outcome. Magnesium antagonises voltage-gated calcium channels and has cerebral vasodilator properties. Data from animal studies indicate that magnesium might be neuroprotective and might reverse cerebral vasospasm and decrease delayed ischaemic deficits.

Results from pilot studies have established the feasibility of magnesium sulfate infusion for patients with SAH. Subsequently, the MASH (Magnesium in Aneurysmal Subarachnoid Hemorrhage) Study Group reported the results of a randomised controlled study of 283 patients with aSAH, in which a continuous infusion of magnesium sulfate (64 mmol/L per day) was started within 4 days of aneurysm rupture and continued until day 14 after occlusion of the aneurysm. This treatment was associated with a 34% reduction in the risk of delayed cerebral ischaemia (hazard ratio 0.66; 95% CI 0.38–1.14) and a risk reduction in poor functional outcome at 3 months of 23% (risk ratio 0.77; 0.54–1.09). However, confidence intervals were wide and included 1.0 for both endpoints. Data from another placebo-controlled study indicated a lower incidence of symptomatic vasospasm in patients receiving magnesium infusion (23%) versus that noted in the placebo group (43%), but without differences in functional outcome. The high rate of symptomatic vasospasm in the placebo arm of this study could have affected the comparison in favour of the magnesium group. In randomised studies that have compared magnesium sulfate infusion versus intravenous nimodipine, similar outcomes in both groups were reported. Although magnesium infusion seems to be safe, it can induce hypotension, hypocalcaemia, and bradycardia.

Meta-analyses of available studies indicate that magnesium sulfate infusion might be beneficial. However, trials done so far have not had adequate statistical power owing to their small size, and the different designs limits the validity of a pooled analysis of their results (table 5). Hence, at present, the evidence is insufficient and larger randomised controlled trials, such as the ongoing MASH-II trial, are needed to determine the safety and efficacy of magnesium sulfate infusion before it can be recommended for patients with aSAH.

Other investigational therapies

Microthrombosis and microembolism can occur in aSAH. However, data from trials that have investigated antiplatelet drugs showed no conclusive benefit. Enoxaparin did not prevent ischaemia and was associated with an increased rate of additional intracranial bleeding.

Impaired cerebrovascular relaxation related to damage in the nitric oxide system has been implicated in the pathogenesis of cerebral vasospasm. Preliminary evidence has suggested that nitric oxide donors, such as intraventricular sodium nitroprusside, might ameliorate cerebral vasospasm. This treatment strategy has strong theoretical and experimental rationale and further investigations are warranted.

Albumin was traditionally used in aSAH to promote volume expansion and haemodilution. However, albumin might also be protective against cerebral ischaemia. In one retrospective analysis, the incidence of vasospasm was similar in groups treated with and without albumin, but there was a trend towards better 3-month outcomes in patients who received albumin. A multicentre trial (the ALISAH [Treatment of Subarachnoid Hemorrhage with Human Albumin] study) to test different doses of albumin infusion is underway.

A multicentre study tested the value of prophylactic angioplasty of major intracranial vessels in patients with high risk of vasospasm (Fisher grade 3). Patients treated with prophylactic angioplasty had a slight reduction in the incidence of delayed ischaemic neurological deficits (23–5%) compared with the standard care group (31–8%).

<table>
<thead>
<tr>
<th>Magnesium infusion</th>
<th>Population size</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised, single-blind, placebo-controlled trial</td>
<td>To maintain serum concentrations 4–5.5 mg/dL, for 10 days</td>
<td>No difference in symptomatic spasm or functional outcome</td>
</tr>
<tr>
<td>Randomised, double-blind, placebo-controlled trial</td>
<td>64 mmol/L per day until day 14</td>
<td>283 Reduction in delayed cerebral infarctions and poor outcome (but wide CIs including 1.0)</td>
</tr>
<tr>
<td>Randomised, double-blind, placebo-controlled trial</td>
<td>20 mmol bolus, then 80 mmol per day until day 14</td>
<td>60 Reduction in symptomatic vasospasm</td>
</tr>
<tr>
<td>Randomised versus intravenous nimodipine trial</td>
<td>0–4 mmol/kg bolus, then 1–2 mmol/kg daily for 7–21 days</td>
<td>304 No differences between the groups</td>
</tr>
<tr>
<td>Randomised, single-blind, placebo-controlled trial</td>
<td>Adjusted to maintain serum concentration of twice the baseline until day 12</td>
<td>58 No differences in delayed ischaemia or functional outcome Higher rates of hypotension and hypocalcaemia MgSO₄ infusion stopped in 52% of patients owing to side-effects</td>
</tr>
</tbody>
</table>

Table 5: Prospective randomised clinical studies that have investigated magnesium infusion for the treatment of aneurysmal subarachnoid haemorrhage
but no benefit in functional outcome at 3 months. Although overall mortality was similar in both groups (21\% with prophylactic angioplasty vs 18·8\% in controls), three patients died of vessel rupture from prophylactic angioplasty. Unless further research that is focused on well selected patients can indicate unquestionable benefits on functional outcome, prophylactic angioplasty cannot be recommended because of its invasiveness and inherent risk of vessel rupture. 

In a non-randomised, single-centre study, lumbar drainage was associated with substantially lower rates of symptomatic vasospasm and vasospasm-related cerebral infarction compared with no CSF drainage. However, these findings need to be replicated. Lumbar drains are safe in selected patients with aSAH, but this still needs to be tested in larger populations. Enhancing cisternal blood clearance by simultaneous lumoperitoneal lavage and low frequency head shaking have been suggested as alternative therapy options, although the usefulness of these techniques remains unproven.

Conclusions and future directions

The care of patients with aSAH is undergoing changes that hold great promise for improving patient outcomes. Over the past few years, we have learned about the value of endovascular coil occlusion and embraced its use, enhanced our understanding of the mechanisms leading to secondary brain ischaemia, and found new ways to identify brain tissue at risk of ischaemic damage through perfusion scans. We are now learning how to optimise the use of these new diagnostic modalities and how to evaluate new therapeutic strategies developed from strong theoretical rationale and experimental data. We are abandoning old concepts that defined vasospasm and predicted delayed ischaemia solely on the basis of the calibre of major intracranial arteries and are focusing on the evaluation of cerebral perfusion and the correction of the endothelial dysfunction that causes microcirculatory failure.

Nevertheless, there is still much more to learn. For example, we need to determine the mechanisms of acute brain damage at the time of the bleeding and the early events that trigger delayed vasospasm. We have to define the optimum blood pressure that we should target before the ruptured aneurysm is secured. We need more data on the rates of complete aneurysm occlusion with new techniques of embolisation (eg, stent-assisted coiling, bioactive coils), which can then be used as a comparison with upcoming modalities, such as flow diversion. The optimum timing of perfusion scans and the best method for implementation of haemodynamic augmentation in patients with symptomatic vasospasm are yet to be established. Furthermore, the value of multimodal brain monitoring needs to be determined and the most useful monitoring techniques in poor-grade patients need to be identified. In patients with persistent hydrocephalus, we should identify more reliable predictors of the need for ventriculoperitoneal shunting. The results of randomised trials should help to determine the safety and efficacy of endothelin antagonists, statins, magnesium sulfate, and lumbar drainage. Randomised studies are also needed to evaluate the risks and benefits of transfusions in anaemic patients and to assess the best target for insulin treatment in those with hyperglycaemia. These and other crucial questions demand answers, and increased collaborative research will be essential to acquire them.

Contributors

AAR undertook the literature search and wrote the paper. GL and EFMW helped with the literature search and contributed additional references and made critical revisions to the paper.

Conflicts of interest

AAR and EFMW have no conflicts of interest. GL serves on the advisory board for Actelion and Edge Therapeutics and has received unrestricted educational grants from Synthes and ev3.

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