Acute management of aneurysmal subarachnoid haemorrhage

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Key points
Subarachnoid haemorrhage (SAH) accounts for only around 5% of all strokes but is a major cause of death and disability. Eighty-five per cent of SAH occurs because of rupture of an intra-cranial aneurysm. Acute management focuses on maintenance of adequate ventilation, haemodynamic stabilization, minimizing the risks of re-bleeding, and achieving a rapid diagnosis. Subsequent treatment is aimed at securing the bleeding source and preventing delayed neurological deficits and non-neurological complications. Nimodipine substantially decreases the risk of cerebral infarction and poor outcome after aneurysmal SAH.

Subarachnoid haemorrhage (SAH) accounts for about 5% of all strokes and affects 6–12/100 000 of the UK population per year, the majority of whom are young. Mortality is around 50%, with up to 25% dying before reaching hospital. One-third of survivors are dependent for care and almost half will have cognitive impairment sufficient to affect their quality of life.1,2 SAH requires a multi-disciplinary approach to management3 in a neurosciences centre,4 with treatment directed towards securing the ruptured aneurysm, minimizing secondary brain injury, and preventing and treating systemic complications. In 2011, the Neurocritical Care Society issued consensus guidelines for the critical care management of aneurysmal SAH with the aim of improving outcome.4

Pathophysiology
SAH may be due to congenital or acquired conditions, the most common being intracranial aneurysms which account for 85% of cases.2 Other causes include arterio-venous malformations, trauma, and rare conditions such as Moyamoya disease. Hypertension, atherosclerosis, cocaine, alcohol abuse, and smoking increase the risk of SAH. Several inherited conditions, including autosomal-dominant polycystic kidney disease, Ehlers Danlos Type 4, and familial intracerebral aneurysms, can also be associated with SAH. The peak incidence occurs between 40 and 60 yr and SAH is more common in women than men (3:2).2

Most aneurysms occur in the Circle of Willis close to bifurcations. The most common sites for rupture are the posterior communicating artery/internal carotid artery take-off and the anterior cerebral artery (Fig. 1).

SAH occurs as a result of haemodynamic stress. A sudden increase in cerebrovascular arterial pressure results in bleeding into the subarachnoid space with or without intraventricular extension.

Diagnosis
An early accurate diagnosis is essential so that treatment can begin immediately.

Clinical features
The patient typically complains of a sudden onset or ‘thunder clap’ headache, described as ‘the worst in my life’. Associated features include nausea and vomiting, neck stiffness, photophobia, focal neurology, deteriorating level of consciousness, and, in severe cases, cardiac arrest.2 The differential diagnosis includes migraine, meningitis, pituitary apoplexy, and postcoital cephalgia.

Diagnostic imaging
Non-contrast cranial computer tomography (CT) is the first-line investigation and is highly sensitive (95–100% on the first day) for detecting blood in the subarachnoid space.2,3 It is also useful for the diagnosis of complications such as cerebral oedema and hydrocephalus. Magnetic resonance imaging with haemosiderin-sensitive sequences (gradient ECHO or T2-eighted) is also diagnostic but is rarely performed because of the logistical difficulties involved.2,3 In patients with a high index of suspicion for SAH and a normal CT scan, a lumbar puncture is indicated. This should be performed 12 h after the onset of symptoms.2,3 Two to three tubes of cerebrospinal fluid are taken, and the first and last sent for a red blood cell count, bilirubin level, and xanthochromia.5

A CT angiogram may be performed to identify the cause of an SAH. It has a negative predictive value of 82–96% for detecting aneurysms and is most sensitive for those >4 mm in size. A negative CT angiogram may still

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warrant further investigation and digital subtraction angiography (DSA) is the gold standard for diagnosing cause (Fig. 2).2

Grading of SAH

There are more than 40 grading systems that can be used to describe the severity of SAH. The most frequently used are the Hunt and Hess and the World Federation of Neurosurgeons Scale (WFNS) which are both clinical scales, and the Fischer scale which is CT-based (Table 1).6 Most scales are subject to inter- and intra-observer variability but do provide a means of communication between teams, and also prediction of prognosis. The most important predictor of both death and disability is presenting level of consciousness, and, of disability only, a hemiparesis or dysphasia.

Acute management

Initial management is similar to that for other forms of acute brain injury and focuses on cardiorespiratory stabilization to maintain cerebral perfusion and oxygenation. This is achieved by securing the airway, controlling ventilation, and careful arterial pressure management. A PaO2 of >13 kPa and normocapnia (4.5–5.0 kPa) is the initial ventilatory target. In addition, attention must be paid to minimizing the risk of re-bleeding and secondary brain injury.

Indications for tracheal intubation include:

- unconsciousness (GCS<8),
- reduction in GCS of ≥2 points,
- optimization of oxygenation and ventilation,
- control seizures of seizwe,
- protection of the airway in the absence of laryngeal reflexes.

Extreme hypertension must be treated in patients with an unsecured, recently ruptured aneurysm. A systolic arterial pressure <160 mm Hg (MAP<110 mm Hg) has a lower risk of re-bleeding and should be the aim.3,4 Hypotension (systolic arterial pressure <100 mm Hg) must be avoided. Regular neurological observations, including pupil size and reactivity (pre- and post-intubation), analgesia, normothermia, and glycaemic control, are essential, and, once the diagnosis is confirmed, the patient should be referred to a neuroscience centre.

Management of the ruptured aneurysm

There are two treatment modalities for the management of intracranial aneurysms—surgical clipping or endovascular coiling (Fig. 2). The International Subarachnoid Aneurysm Trial (ISAT) was a multicentre randomized controlled trial that compared endovascular coiling with neurosurgical clipping as treatment for ruptured intracranial aneurysm. The initial findings favoured coiling; the primary outcome (risk of death or dependence at 1 yr) occurred in 23.7% and 30.9% of coiled and clipped patients, respectively, giving an absolute risk reduction of 6–9% in favour of coiling.3,4 Long-term follow-up of ISAT results has revealed that the need for delayed retreatment is significantly higher in coiled patients and there is also a higher, albeit small, long-term risk of re-bleeding after coiling.7 Clipping is now reserved for aneurysms that are unsuitable for coiling, such as those with a wide neck, or in particular locations such as the middle cerebral artery. Advances in endovascular techniques are making coiling more widely applicable. For example, flow diverting stents aim to reconstruct the diseased vessel by redirecting blood flow from the aneurysm, resulting in stasis and thrombosis of the aneurysm, followed by tissue growth over the stent.3

Re-bleeding

The risk of re-bleeding is greatest immediately after the initial haemorrhage, with rates of 5–10% within the first 72 h.4 It is higher in females and in those with poor clinical grade, larger aneurysms, and sentinel bleeds.2,4 Re-bleeding results from a combination of changes in arterial transmural pressure gradients and fibrinolysis of the aneurysmal blood clot. As such, while the aneurysm is
unprotected, the risks of re-bleeding can be minimized by preventing large increases in systemic arterial pressure and large fluctuations in intracranial pressure (ICP) by avoiding coughing and valsalva manoeuvres, using effective analgesia, anti-emetics, and ensuring smooth anaesthesia. Transmural pressure gradients will favour rupture when ICP is rapidly reduced, such as during insertion of an external ventricular drain (EVD). In the absence of mass effect, any other technique that rapidly reduces ICP should also be used with caution in those with an unsecured aneurysm.

Early or ultra-early treatment of the ruptured aneurysm is beneficial in preventing re-bleeds. Antifibrinolytics reduce clot fibrinolysis and may reduce re-bleeding rates by as much as 40%. However, there is currently little evidence for their routine use since the benefits of reduced re-bleeding are offset by poor outcome as a result of treatment-related cerebral ischaemia. Antifibrinolytics should be reserved for short-term use in those at high risk of re-bleeding in whom definitive treatment is delayed.

**Critical care management**

After securing of the aneurysm, the intensive care management of SAH involves treatment of acute complications, optimization of systemic physiology, and the prevention or treatment of delayed neurological deficit (DND) and non-neurological complications. Aggressive treatment by a multidisciplinary team is associated with improved outcome. With the shift to early securing of ruptured aneurysms, DND is now the main cause of death and disability after SAH. DND is any clinically detectable neurological deterioration after initial stabilization, with the exception of re-bleeding. It may be due to delayed cerebral ischaemia (DCI), hydrocephalus, cerebral oedema, fevers, seizures, and electrolyte abnormalities.

**Hydrocephalus**

Twenty to 30% of patients develop hydrocephalus, usually within the first 3 days. Those with poor clinical grade SAH and/or large amounts of subarachnoid and intraventricular blood are at particularly high risk. Hydrocephalus may be delayed in up to 25% of patients. It should be suspected in all patients with neurological deterioration and is diagnosed on cranial CT. The development of acute hydrocephalus necessitates urgent transfer to a neuroscience unit for insertion of an EVD.

**Seizures and anticonvulsants**

Clinical seizures are uncommon, occurring in only 1–7% of patients. In patients with an unsecured aneurysm, they are often a sign of a re-bleed. Although seizures should be treated aggressively, the use of prophylactic anticonvulsants is associated with a worse outcome after SAH and not recommended. Phenytoin in particular is associated with higher levels of cerebral vasospasm, cerebral infarction, pyrexia, and worse neurological outcome. Anticonvulsants have an unknown potential to lessen the impact of non-convulsive seizures, and patients with poor grade SAH who deteriorate or fail to improve should have an electroencephalogram to exclude non-convulsive status epilepticus.

**DCI and vasospasm**

DCI occurs in more than 60% of patients, with the greatest risk between days 4 and 10 after the SAH, and is associated with worse outcome. DCI and vasospasm are often assumed to be synonymous but DCI can occur in the absence of vasospasm and often affects more than one vascular territory (see below). It may be classified in a variety of ways, taking into account both clinical and diagnostic criteria. The Neurocritical Care Society’s
consensus guidelines recommend the following classification for consistency:4

- DCI is neurological deterioration related to ischaemia (unrelated to treatment of the aneurysm) that persists for >1 h and has no other cause (e.g. hydrocephalus, seizures, or metabolic).
- Vasospasm is arterial narrowing demonstrated angiographically or with Doppler ultrasonography, with corresponding clinical symptoms and signs.

Patients with poor grade SAH, large subarachnoid blood load, intraventricular haemorrhage, and smokers are particularly at risk for the development of vasospasm. Pathological changes occur within intracranial arteries causing thickening of the vessel walls and narrowing of the lumen, impaired vascular relaxation, and associated impairment of vascular reactivity and autoregulation. Together these result in reduced cerebral blood flow (CBF) and ischaemia in affected areas.

**Diagnosis**

Up to 70% of patients with SAH develop vasospasm on angiography and, of these, 30% have clinical symptoms. Clinical symptoms include reduced level of consciousness, changes to speech, or the development of focal motor deficits and onset may be sudden or insidious. Diagnosis is often difficult, particularly in patients who already have a neurological deficit or in those who are sedated. Of note, both vasospasm and DCI may be asymptomatic.

It is imperative to monitor patients appropriately and to make a timely and correct diagnosis of DCI so that treatment can be begin early with the aim of preventing irreversible neurological deficits and mortality. In addition to clinical symptoms and signs, the following techniques can be used to aid diagnosis:4

- Transcranial Doppler ultrasonography is a non-invasive bed-side technique that measures blood flow velocity in basal cerebral arteries. It is a useful diagnostic and monitoring tool for vasospasm, with a high specificity but moderate sensitivity. A diagnosis of vasospasm is made if flow velocities are >120 cm s⁻¹, velocities increase (>50 cm s⁻¹ day⁻¹ from baseline) or the Lindegaard ratio (ratio of flow velocity in ipsilateral middle cerebral and internal carotid arteries) is >3. This technique is operator-dependent and, because it measures flow velocity, is able only to assess relative changes in CBF.
- CT angiography (CTA) is highly specific (85–95%) for the diagnosis of angiographic vasospasm but has a tendency to overestimate the degree of stenosis. It is often used as a screening tool for vasospasm reducing the need for DSA.
- DSA is the gold standard for detecting vasospasm but is unable to assess the adequacy of brain tissue perfusion.
- CT perfusion imaging provides information on regional brain tissue perfusion. A delayed mean transit time (>6.4 s) with arterial narrowing on CTA can be used to predict the need for DSA and intervention for vasospasm. It is best when used for anterior circulation vasospasm.

**Treatment**

Since DCI is reversible, it is an obvious target for prevention and treatment.

**Nimodipine and other calcium channel antagonists**

Nimodipine is a dihydropyridine calcium channel antagonist and prevents Ca²⁺ influx to cells at L-type calcium channels. It was originally developed for the management of hypertension and its exact mode of action in the treatment of SAH is incompletely understood. It is, however, a safe and cost-effective treatment to prevent DCI and improve outcome after SAH, with level 1 evidence to support its use.³ In the British aneurysm nimodipine trial, there was a 34% (CI 13–50%) and 40% (CI 20–55%) reduction in cerebral infarction and poor outcome, respectively, in patients receiving nimodipine compared with placebo. Nimodipine should be given enterally whenever possible (60 mg 4 hourly) but may be given i.v. on the intensive care unit. As it is important that systolic arterial pressure is not compromised, the dose may be halved and administered 2 hourly to reduce the incidence of hypotension. Nimodipine should be started when a diagnosis of SAH is made and continued for 21 days.

Nicardipine may be applied topically (implanted into clip for clipping aneurysm) or intra-arterially during DSA for treatment of vasospasm. It is effective for up to 48 h. Studies have shown a reduction in the incidence of vasospasm and DCI, with improved outcome.⁴
**Triple H therapy**

Triple H therapy is the use of hypertension, hypervolaemia, and haemodilution to improve CBF and oxygen delivery in the treatment of DCI and vasospasm. Its use is controversial and a recent systematic review found no controlled studies showing a positive effect from any component of triple H therapy, although some individual studies have shown a benefit from hypertension alone. It is most important to avoid hypovolaemia and hypotension.

The aim of arterial pressure control is to maintain cerebral perfusion and oxygenation by optimizing cerebral perfusion pressure (CPP) and CBF. CPP is determined by the difference between the mean arterial pressure and the ICP, and CBF is affected by factors in addition to CPP such as blood vessel diameter and blood viscosity. In vasospasm, the diameter of cerebral vessels is reduced, increasing the resistance to blood flow. Increased arterial pressure is required to overcome this resistance and maintain CBF and prevent ischaemia. Although there is little evidence to support the beneficial effects of hypertension, a recent study found that a CPP of <70 mm Hg in high-grade SAH was associated with an increase in brain tissue hypoxia and metabolic crises, both of which are associated with death or poor outcome. Other studies have demonstrated that induced hypertension improves CBF independent of volume status. The recent consensus guidance recommends arterial pressure augmentation in the treatment of vasospasm, and simultaneous assessment of changes in neurological function.

Although hypervolaemia may increase CBF after SAH, it is associated with increased morbidity from complications such as pulmonary oedema. Haemodilution is now the goal and prophylactic hypervolaemia should be avoided. Volume status must be carefully monitored throughout the acute episode. Boluses of isotonic crystalloids can be used to improve CBF while initiating other therapies. Glucose-containing fluids should be avoided. Hydrocortisone and fludrocortisone have a role in patients with persistent hypovolaemia and associated hypotension.

Haemodilution is associated with improved blood rheology and possibly with increased CBF, but also with reduced cerebral oxygen delivery. Traditionally, a haematocrit of 0.3 was the target during triple H therapy, but current consensus recommendation is against haemodilution.

Over 80% of SAH patients develop anaemia during their hospital stay, and precautions to minimize blood loss must be taken. Anaemia is associated with worse outcome, but the optimum haemoglobin concentration is unknown. Current guidance recommends a haemoglobin concentration between 8 and 10 g dl⁻¹, with consideration given to higher concentrations in resistant DCI.

**Magnesium**

Magnesium is neuroprotective and having vasodilatatory properties, both of which could be of benefit in SAH. Although some studies have suggested that hypermagnesaemia reduces the risk of poor outcome and DND, a recent large clinical trial (Intravenous Magnesium Sulfate in Aneurysmal Subarachnoid Haemorrhage—IMASH) and subsequent meta-analysis identified no beneficial effect of magnesium on the incidence of DCI and outcome. The optimal magnesium concentration is not known and further studies are required. Hypomagnesaemia should be avoided, but induced hypermagnesaemia is not recommended.

**Statins**

Statins are HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA reductase) reductase inhibitors used in the management of hypercholesterolaemia. They have been found to ameliorate glutamate-mediated excitotoxicity, attenuate the production of reactive oxygen species in brain injury, up-regulate e-NOS, and diminish the inflammatory reaction by modulating the cytokine response. Current evidence for the use of statins in the treatment of SAH and prevention of DCI and vasospasm is equivocal. Recently published meta-analyses and systematic reviews found no beneficial effects on mortality or neurological recovery between patients treated with statins and those who were not, despite some evidence supporting their use from phase 2 trials and observational data. There are no published phase 3 trials, but the results of the SimvaSTatin in Aneurysmal Subarachnoid Haemorrhage trial (STASH) trial (http://clinicaltrials.gov/ct2/show/NCT00731627), investigating the outcome effects of statins after SAH, are awaited. Current guidance recommends that patients on statins before an SAH should have these drugs continued, but that the introduction of statins de novo should only be considered in selected patients at high risk of DCI and vasospasm.

**Endovascular treatment**

Endovascular treatment options have been developed in an attempt to reduce the morbidity and mortality associated with DCI and vasospasm. Aggressive endovascular treatment may improve neurological outcome without the risks associated with other treatments such as triple H therapy. Suggested criteria for the use of endovascular treatment include a new neurological deficit without other cause, no CT evidence of cerebral infarction, failure of medical therapy, and vasospasm on angiography. Treatment options are angioplasty, intra-arterial vasodilator therapy, or a combination of the two. At present, there is no concrete evidence for the optimal timing or method of endovascular treatment for vasospasm. Prophylactic use is, however, thought to involve greater risk than benefit and is not recommended.

**Antiplatelet therapy**

Since microthrombosis might play a role in DCI, antiplatelet drugs have been used to try and prevent it. A Cochrane review published in 2007 suggested a non-significant trend towards an outcome benefit from antiplatelet agents but this was offset by an increased risk of haemorrhagic complications. Antiplatelet therapy is currently
only indicated when a stent is deployed in the treatment of a ruptured aneurysm. 3

**Non-neurological complications**

Up to 40% of SAH patients develop at least one severe, life-threatening medical complication during their hospital admission and are responsible for about one-quarter of deaths after SAH. 13 They include cardiorespiratory, hepatic, renal, and biochemical abnormalities.

**Fever**

Fever is common and associated with worse outcome after SAH. 1,3 Temperature should be monitored routinely and a pyrexia investigated for an infective cause. During the ‘at risk’ period for DCI and vasospasm, routine anti-pyretic medication, and other measures, such as cooling, should be undertaken to treat the fever. 4

**Glucose control**

Hyperglycaemia is a marker of the severity of SAH and associated with a worse outcome, vasospasm, and systemic infections. 1,3,4 Tight glycaemic control may be detrimental because of the risk of hypoglycaemia. Normal serum glucose levels may be associated with cerebral hypoglycaemia and metabolic crises after brain injury. Optimum blood glucose levels are not known, but current guidance recommends maintaining them between 4.5 and 11.0 mmol litre\(^{-1}\) and avoiding hypoglycaemia and large swings in blood glucose concentration. 4

**Cardiac complications**

Cardiac complications are common, occurring in 49–100% of patients, particularly in those with poor grade SAH. They are often reversible but are associated with poor outcome. 1,4 Brain injury results in a massive catecholamine release with increased sympathetic outflow and dysfunction of the autonomic nervous system. This results in a hyperdynamic circulation with increased myocardial oxygen demand and workload. As a result, transient myocardial ischaemia and failure may occur. Independent of the systemic catecholamine effects, norepinephrine is released from sympathetic nerve terminals and this may lead to the neurogenic stunned myocardium syndrome. 4

Transient ECG changes occur very frequently. These are most commonly T-wave morphological changes, ST segment changes, and prolongation of the QTc interval. These are usually asymptomatic, but 4–8% of patients go on to develop clinical significant arrhythmias. Although ECG changes are not independent predictors of mortality, elevated troponin I, CK-MB, and ST depression are associated with poor outcome and DND. It is often difficult to differentiate between neurogenic cardiac injuries and an acute ischaemic coronary event. Serial ECGs, and also markers of cardiac injury, that is, troponin levels and an echocardiogram, should be monitored routinely in poor grade patients. The peak troponin level in neurogenic cardiac injury is usually lower after a coronary event. Ventricular dysfunction is often transient and usually of limited clinical significance. More rarely, a Takotsubo-type cardiomyopathy may develop and this is associated with poor outcome. 14 Treatment of cardiac complications is supportive, with continuing management of the underlying brain injury. 5

**Pulmonary complications**

Pulmonary complications are common after SAH with up to 80% of patients having impaired oxygenation at some time. They include aspiration pneumonitis, neurogenic or cardiogenic pulmonary oedema, pneumonia, acute lung injury, or ARDS. Treatment is supportive with the aim of maintaining cerebral oxygenation and perfusion.

**Sodium balance**

Sodium disturbances occur commonly and it is important to monitor serum sodium regularly. 15 Hyponatraemia may be due to the administration of excessive hypotonic fluids, the cerebral salt wasting syndrome, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH). 1 Correct diagnosis is key. Although the standard treatment for SIADH is fluid restriction, this might be ill advised after SAH, particularly in those at risk of DCI. Hydrocortisone or fludrocortisone treatment may be of benefit. 4

**Venous thrombo-embolism**

Prevention of venous thrombo-embolism (VTE) is imperative. All patients should have mechanical VTE prophylaxis initiated on admission, but the timing of pharmacological prophylaxis is more contentious. Low molecular weight heparins are associated with an increased bleeding risk and initiation of treatment should therefore follow a multi-disciplinary team discussion. It is usual to wait until after the ruptured aneurysm is secured. 4

**Conclusion**

SAH is a common cause of stroke with a high incidence of morbidity and mortality. Outcome is improved when treatment is provided by a multidisciplinary team in a high-volume neuroscience centre. 4 The major focus of treatment is to prevent re-bleeding by early securing of the ruptured aneurysm and the prevention of secondary brain injury by identification and treatment of complications including DCI.

**Declaration of interest**

None declared.

**References**

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Please see multiple choice questions 13–16.