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## Spontaneous subarachnoid haemorrhage

Jan Claassen, MD,

Soojin Park, MD

Department of Neurology, Columbia University Irving Medical Center, New York Presbyterian Hospital, New York, NY, USA

### Abstract

Subarachnoid haemorrhage (SAH) is the third most common subtype of stroke. Incidence has decreased over past decades, possibly in part related to lifestyle changes such as smoking cessation and management of hypertension. Approximately a quarter of patients with SAH die before hospital admission; overall outcomes are improved in those admitted to hospital, but with elevated risk of long-term neuropsychiatric sequelae such as depression. The disease continues to have a major public health impact as the mean age of onset is in the mid-fifties, leading to many years of reduced quality of life. The clinical presentation varies, but severe, sudden onset of headache is the most common symptom, variably associated with meningismus, transient or prolonged unconsciousness, and focal neurological deficits including cranial nerve palsies and paresis. Diagnosis is made by CT scan of the head possibly followed by lumbar puncture. Aneurysms are commonly the underlying vascular cause of spontaneous SAH and are diagnosed by angiography. Emergent therapeutic interventions are focused on decreasing the risk of rebleeding (ie, preventing hypertension and correcting coagulopathies) and, most crucially, early aneurysm treatment using coil embolisation or clipping. Management of the disease is best delivered in specialised intensive care units and high-volume centres by a multidisciplinary team. Increasingly, early brain injury presenting as global cerebral oedema is recognised as a potential treatment target but, currently, disease management is largely focused on addressing secondary complications such as hydrocephalus, delayed cerebral ischaemia related to microvascular dysfunction and large vessel vasospasm, and medical complications such as stunned myocardium and hospital acquired infections.

### Introduction

Spontaneous subarachnoid haemorrhage (SAH) is the third most common type of stroke and frequently related to aneurysmal rupture.<sup>1</sup> In this Seminar, we will primarily focus on aneurysmal SAH, but spontaneous SAH that lacks imaging evidence of aneurysms will also be discussed whereas traumatic or other non-spontaneous causes will be omitted. There is a trend towards a decreasing worldwide incidence of SAH<sup>2,3</sup> possibly related to public health

Correspondence to: Assoc Prof Jan Claassen, Department of Neurology, Columbia University Irving Medical Center, New York Presbyterian Hospital, New York, NY 10032, USA, jc1439@cumc.columbia.edu.

Contributors

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interventions and lifestyle modifications, due to reduced rates of smoking and management of hypertension.<sup>3–6</sup> Poor-grade SAH is associated with high morbidity and mortality and is managed aggressively with advanced neurosurgical, interventional neuroradiological, and neurocritical care strategies that have shown good functional outcomes.<sup>7–11</sup> Novel strategies to prevent and treat early brain injury, delayed cerebral ischaemia, seizures, and other medical complications might hold promise to improve outcomes further. Common data elements to standardise research efforts for patients with SAH have been published.<sup>12</sup>

## Epidemiology and risk factors

Worldwide, almost 500 000 patients have aneurysmal SAH annually.<sup>13</sup> An incidence of 8 cases of spontaneous SAH per 100 000 person-years was reported in a meta-analysis including 75 studies from 32 countries (analysing 8176 patients, 67 746 051 person-years).<sup>3</sup> Despite regional differences, SAH incidence has declined over past decades from a high of 10 per 100 000 person-years in 1980 to 6 in 2010, or by 1·7% annually between 1955 and 2014. The incidence changes differ by country and range between a decrease of 59% in Japan to 14% in North America, which might be related to differences in smoking prevalence.<sup>3</sup> Early case fatality remains high, as up to one-quarter of patients with aneurysmal SAH do not reach the hospital or die in the emergency room.<sup>14</sup>

The underlying causes of decreasing SAH incidence are uncertain but are possibly related to improved management of hypertension and the cessation of smoking. On a population basis, the incidence of SAH—adjusted by age and sex—decreased by 7·1% per mm Hg reduction in systolic blood pressure and by 2·4% with every percent decrease in smoking prevalence.<sup>3</sup> Aspirin use has been associated with a decreased risk of aneurysm rupture, but also with an increased risk of rebleeding once rupture has occurred.<sup>15</sup> A notable exception to the overall decreasing rates of aneurysmal SAH is China. Stroke burden (including SAH) is increasing in China, particularly in rural areas, and is blamed on the quality of primary stroke prevention, socioeconomic factors, and the high prevalence of risk factors such as hypertension and smoking.<sup>6</sup> Worldwide, women have a 1·3 times greater relative risk of developing SAH than men. Furthermore, the mean age of patients with SAH increased from 52 to 62 years between 1973 and 2002.<sup>7</sup>

The prevalence of unruptured intracranial aneurysms is estimated at approximately one in 20–30 adults<sup>16</sup> (3·2%) in a population without diagnosed comorbidity. The mean age of patients with unruptured aneurysms is 50 years, and the prevalence is twice as high in women as in men.<sup>17</sup> Widespread imaging for headaches and non-specific complaints has yielded large cohorts of patients with unruptured aneurysms. Familial clustering of intracranial aneurysms and aneurysmal SAH clearly suggest a genetic contribution and genome-wide association studies identified a number of loci with common variants.<sup>18</sup> Part of the genetic correlation with intracranial aneurysms might be driven by genetic risk factors for potentially modifiable conditions and behaviours including smoking and hypertension.<sup>19</sup> A genetic predisposition for insomnia raised the risk of both aneurysm formation and aneurysmal SAH, but these findings need replication. A positive family history of aneurysmal SAH, defined as two affected first-degree relatives, accounts for

11% of events whereas autosomal dominant polycystic kidney disease accounts for 0.3% of events.<sup>20</sup>

Hypertension, smoking, and female sex have been identified as the most consistent risk factors for unruptured intracranial aneurysms.<sup>4,5</sup> Screening for intracranial aneurysms with MR or CT angiography might be beneficial in patients with two or more first-degree relatives who have had aneurysmal SAH.<sup>21</sup> Among people without a history of aneurysm but with a family history, the rate of de novo aneurysm detection was 3% in individuals who had previously had two negative screens.<sup>21</sup>

Hypertension, older age, larger aneurysm size, posterior circulation aneurysm, and irregular aneurysm shape (ie, those with a daughter sac) have been implicated as risk factors for aneurysmal rupture.<sup>22–24</sup> Based on pooled analysis of individual patient data from 8382 participants in six prospective cohort studies, a prediction tool for rupture of incidentally diagnosed aneurysms was developed called the PHASES score.<sup>22</sup> The score generated by the prediction tool takes into account the population (P), hypertension (H), patient age (A), aneurysm size (S), earlier SAH (E), and site of aneurysm (S). Haemodynamic stress and vessel wall injury and the inhibition of its repair have all been linked to hypertension, smoking, cocaine ingestion, heavy alcohol use, oestrogen compounds, hypercholesterolaemia, and diabetes as risk factors for aneurysm formation and rupture.<sup>25–28</sup>

## Clinical presentation, signs and symptoms, and diagnosis

The most common clinical presentation of spontaneous SAH is sudden onset of thunderclap headaches that are very painful, unexpected, and intense from the onset.<sup>29</sup> These headaches are the only symptom in half of SAH cases. The presentation can be non-specific and headaches are one of the most common complaints of patients seen in an emergency room. Signs and symptoms in patients with aneurysmal SAH can occur due to mass effect or embolic strokes from the aneurysm itself, or from direct or indirect effects of the haemorrhage.

Loss of consciousness is seen in between 26% and 53% of patients with aneurysmal SAH,<sup>30–32</sup> a range likely to be explained primarily by referral bias. This disorder of consciousness might be brief or more prolonged and is associated with poor clinical grade, more subarachnoid and intraventricular blood on admission CT, and higher frequency of global cerebral oedema. Other symptoms of aneurysmal SAH include neck pain or stiffness, emesis, focal cranial nerve abnormalities (ie, third nerve palsy with posterior communicating artery aneurysms), seizures, or focal supratentorial deficits such as hemiparesis. The neurological examination is categorised using World Federation of Neurological Surgeons<sup>33</sup> or Hunt Hess<sup>34</sup> scales (table).

Misdiagnosis of patients with good-grade SAH continues to be a problem, putting patients at higher risk of rebleeding, delayed cerebral ischaemia (DCI), and procedural complications.<sup>35</sup> Particularly in resource-limited settings, clinically based decision instruments enable alert patients with headache that warrant additional diagnostic studies to be identified. The Ottawa SAH rule<sup>29</sup> incorporates information on demographics and clinical

presentation to trigger additional diagnostic testing: age 40 years or older, neck pain or stiffness, witnessed loss of consciousness, onset of headache during exertion, instantaneous onset of headache, or limited neck flexion on examination. This scale applies only to alert patients older than 15 years, with new severe non-traumatic headache reaching a maximum intensity within 1 h, and without new neurological deficits, a history of aneurysms, SAH, brain tumours, or recurrent headaches. This scale allows practitioners to rule out SAH without requiring a CT scan in some low-risk patients, or would prompt a CT scan to seek SAH or other bleeding in high-risk patients (sensitivity for SAH 100%, specificity 12.7%).<sup>36</sup>

### Diagnostic investigations

Diagnosis of SAH is based on pre-test probability accounting for history and clinical examination. This traditionally relies on non-contrast head CT scanning (figure 1), followed by lumbar puncture if CT is negative for patients with clinical symptoms concerning for SAH. CT timing in relation to onset of clinical symptoms determines the sensitivity to identify subarachnoid blood. A CT within 6 h of a thunderclap headache can have 98.7% sensitivity.<sup>37</sup> In a multicentre, implementation science study of 3672 patients combining the Ottawa SAH rule with information obtained from CT scans acquired within 6 h of headache onset, the diagnosis of SAH can be made with some reliability (sensitivity 95.5%, specificity 100%); importantly SAH might be missed in 5% of patients.<sup>36</sup> Given the gravity of missing an aneurysmal SAH diagnosis and the high morbidity associated with rebleeding, these decision rules have limited impact for patients in resource-rich settings.<sup>38</sup> Conditions that mimic SAH include pseudo SAH following primary cardiac arrest, which has a distinct CT appearance dissimilar to true SAH.<sup>39</sup> MRI is currently not widely used to diagnose aneurysmal SAH, but some studies demonstrate a similar performance to CT.<sup>40</sup>

Vascular imaging, such as CT angiography or digital subtraction angiography, should be obtained for all patients presenting without recent trauma or imaging evidence of SAH (typically head CT) or lumbar puncture. Angiography will not identify an aneurysm in approximately 15% of patients<sup>41</sup> and half of these are perimesencephalic SAH.<sup>42</sup> Repeat angiography reveals aneurysms in 2–8% of those with initially negative vascular imaging<sup>42</sup> with a slightly higher incidence of aneurysms in those with a family history of aneurysmal SAH.<sup>43</sup> 30% of patients with SAH have multiple aneurysms<sup>44</sup> and a ruptured aneurysm might be identified on the basis of blood location from the initial CT scan, and aneurysm size and morphological features.<sup>45,46</sup>

### Perimesencephalic SAH

Perimesencephalic SAH is a type of non-aneurysmal spontaneous SAH with a distinct imaging appearance and a more benign clinical course. The diagnosis is made from a CT scan (obtained within 72 h of onset) and increasingly with a single high-quality CT angiogram.<sup>47</sup> The CT scan demonstrates predominance of subarachnoid blood immediately anterior to the midbrain or pons, with smaller amounts of blood extending to the perimesencephalic and basal Sylvian cisterns, foramen magnum, interhemispheric fissure, and lateral ventricles. CT angiography excludes aneurysms as the bleeding cause. Additional diagnostic work-up (including digital subtraction angiography) is controversial as state-of-the-art CT angiography is highly sensitive for the detection of aneurysms.<sup>48</sup> The incidence

of perimesencephalic SAH is approximately 0.5 per 100 000 person-years and men are affected slightly more often than women (unlike aneurysmal SAH), but no clear risk factors have been identified. Complications such as rebleeding, hydrocephalus, DCI, and poor outcomes are rare.

### Differential diagnosis

SAH diagnosis relies on obtaining an accurate history that then triggers the diagnostic work-up outlined above. The differential for patients with spontaneous SAH who have no aneurysm found on angiography is broad and includes but is not limited to perimesencephalic SAH, reversible cerebral vasoconstriction syndrome (RCVS),<sup>49</sup> and cortical vein thrombosis. Trauma is the underlying cause in most patients who present with SAH, and trauma history might not always be obvious. The clinical course and management of patients with traumatic SAH is fundamentally different and not the focus of this Seminar. Importantly, aneurysmal SAH with associated loss of consciousness might cause secondary traumatic brain injury. The blood pattern in classic traumatic SAH is predominantly located in the cortical sulci<sup>50</sup> whereas the location of aneurysmal SAH is usually in the basal cisterns. Although rare, intracranial artery dissection from trauma can also result in SAH.<sup>51</sup> RCVS is a clinical diagnosis and acquiring an accurate history is crucial. The RCVS2-score takes into account thunderclap headache, carotid artery involvement, presence of vasoconstrictive triggers, sex, and presence of SAH and provides a structured approach to diagnosis of RCVS.<sup>49</sup>

## Acute management

### Aneurysm treatment

Despite differences in health-care systems, admission to high-volume centres—defined as institutions that care for at least 35 patients with SAH annually—is an important predictor of good outcomes.<sup>52–54</sup> Aneurysm treatment within 72 h of symptom onset is recommended.<sup>55</sup> Treatment within this timeframe compared with treatment within the first 24 h of symptom onset did not consistently improve outcomes in a meta-analysis of 4667 patients with poor-grade aneurysmal SAH,<sup>56</sup> but earlier treatment remains an active topic of discussion.

Much of the initial management is focused on minimising the risk of rebleeding (figure 2). In natural history studies, this complication is seen in 8–23% of patients and carries a very high morbidity and mortality.<sup>57</sup> Patients with a high clinical grade, hypertension, intracerebral or intraventricular haemorrhage, and larger aneurysms are at particular rebleeding risk, especially early after the bleed.<sup>58</sup> Short-term antifibrinolytic therapy was considered as a strategy to reduce the rebleeding risk as most rebleeding occurs within 24 h of SAH onset.<sup>59</sup> In the ultra-early tranexamic acid after subarachnoid haemorrhage study, 480 patients were randomised to receive 24 h of tranexamic acid (1 g bolus followed by 1 g given every 8 h) and 475 received standard care.<sup>60</sup> Aneurysm repair was performed within 24 h with a median of 14 h from onset to treatment. There was no difference in the primary study endpoint, defined as a good clinical outcome (modified Rankin scale score 0–3) at 6 months, between treatment arms (odds ratio [OR] 0.86, 95% CI 0.66–1.12). Rebleeding after randomisation and before aneurysm treatment occurred at similar rates in both groups

(10% with tranexamic acid and 14% in controls; OR 0.71, 95% CI 0.48–1.04). This trial demonstrated the lack of benefit from short-term tranexamic acid administration if aneurysm securement is early. Patients for whom early aneurysm treatment cannot be performed might still benefit from short-term antifibrinolytic therapy, but risks of this approach are uncertain given the available data. Hypertension is frequently encountered following SAH and might promote rebleeding. Most treatment protocols aim to keep systolic blood pressure below a threshold with cutoffs varying between 160 mm Hg and 180 mm Hg.<sup>55,61</sup> The benefits of platelet transfusions outside of thrombocytopenia remain uncertain.<sup>62</sup>

Aneurysm treatment is focused on preventing blood entry into the aneurysm (eg, clipping or coiling). The International Subarachnoid Aneurysm Trial (ISAT), the largest interventional randomised aneurysmal SAH clinical trial to date, randomly assigned 2143 patients with aneurysmal SAH to clipping or coil embolisation. Endovascular coiling was associated with a higher chance of independent survival than clipping 1 year after the haemorrhage and among patients suitable for both treatments,<sup>63</sup> with a persistently lower chance of death or dependency measured by the modified Rankin scale score at 10 years.<sup>64</sup> There was a persistent but small increase in rates of rebleeding among patients who had undergone coiling in a study with 10–18.8 year follow-up, but the risk of death and disability from rebleeding was small (one in 1397 patient-years in the endovascular group and one in 2041 patient-years in the neurosurgery group).<sup>64</sup> Among ISAT patients who survived hospitalisation, there was no difference in functional recovery at 5 years<sup>65</sup> or beyond.<sup>64</sup> In post-hoc analysis, ISAT investigators suggested that pretreatment delays might have been to blame for higher in-hospital mortality for patients who underwent clipping.<sup>66</sup> In a large multicentre examination of coiling versus clipping in clinical practice across 24 centres from Europe, USA, and Australia (n=9159), coiling was associated with higher 14-day case fatality and non-superior 90-day outcomes.<sup>67</sup> Discussions are ongoing regarding the generalisability of these findings related to case ascertainment, group differences such as pretreatment delays, technical advances over the past two decades since the last enrolment into ISAT, and unbalanced operator experience. Apart from complications unique to clipping (eg, retraction injury) or coiling (eg, coil migration), all approaches might be complicated by intraprocedural rupture.

Advances in microsurgical and interventional neuroradiological techniques provide novel treatment options even for challenging aneurysms such as wide-necked or bifurcation aneurysms, blister aneurysms, or arteries arising from within the aneurysm. In selecting treatment approaches, physicians expertise as well as location of the aneurysm, aneurysm characteristics (ie, branch arteries incorporated into the aneurysm dome, size, neck width, fusiform shape, and calcification), and the parent artery anatomy (ie, bifurcation aneurysm or parent artery flow dynamics) must be considered. Intravascularly placed devices might need antiplatelet medications, which complicates management of patients with SAH who need ventricular drain or shunt placements. A comprehensive discussion of all possible neurosurgical and interventional neuroradiological treatment approaches is beyond the scope of this Seminar as innovative technological advances are constantly providing novel opportunities to manage challenging cases.

Several secondary complications can occur after aneurysmal SAH, including early brain injury, elevated intracranial pressure (ICP), and DCI. The underlying pathophysiology is complex, probably overlapping, and only partly understood. Frequently implicated mechanisms include inflammation, microvascular dysfunction, dysfunction of brain metabolism, haematological abnormalities, and cortical spreading depolarisation. Better understanding of these pathomechanisms might help apply targeted therapies in clinical practice.

### Early brain injury

Early brain injury is an emerging concept of injury sustained within the first 72 h following aneurysmal rupture with global cerebral oedema as the most prominent imaging manifestation.<sup>68</sup> Early brain injury is associated with cerebral metabolic distress,<sup>69</sup> inflammation,<sup>70,71</sup> platelet activation,<sup>71</sup> and cortical spreading depolarisation.<sup>72</sup> Animal models implicate early activation of the innate immune response followed by microglia and astrocytic activation<sup>73</sup> with disruption of the blood–brain barrier.<sup>74</sup> Early brain injury, as defined by imaging criteria, is common and the risk of poor outcomes is doubled in patients with early brain injury compared with patients without early brain injury.<sup>68</sup> Brain oedema can be quantified using the subarachnoid haemorrhage early brain oedema score (SEBES),<sup>75</sup> which was recently found to be associated with ICP and outcomes in a cohort of 745 patients.<sup>76</sup> Novel treatments for early brain injury are being studied that might have a potentially larger impact than interventions aimed at vasospasm or DCI.

### ICP, herniation, and hydrocephalus

Patients with poor-grade aneurysmal SAH can develop mass effect from intracerebral haemorrhage or brain oedema. Surgery to remove clots or hemicraniectomy can decrease mortality. Hypertonic saline is as effective as mannitol for treatment of increased ICP in aneurysmal SAH; however, the optimal dose and treatment strategy, or whether it improves outcomes, is unclear.<sup>77</sup> Hydrocephalus (figure 1) is seen in 12–31% of patients with aneurysmal SAH depending on factors such as hospital ascertainment and presence of intraventricular blood,<sup>78,79</sup> with casting of the fourth ventricle portending a poor prognosis.<sup>80</sup> Emergent management includes placement of an external ventricular drainage catheter, which is complicated by tract haemorrhages in approximately 15% of patients,<sup>81</sup> most being clinically insignificant. Little data exist on the safety of neurosurgical procedures for patients taking dual antiplatelets. A single-centre case series suggests that external ventricular drainage (EVD) placement with dual antiplatelets (which might be started after aneurysm treatment using stent-assisted coiling or flow-diverters) was associated with a higher risk of additional haemorrhage than without dual antiplatelets (27% vs 8%), but no increase in symptomatic bleeding was seen.<sup>82</sup> In a preliminary, retrospective cohort study, the same investigators found no increase in bleeding rates in patients undergoing ventriculoperitoneal shunt placement with dual antiplatelets.<sup>83</sup> Methodological limitations of this study do not allow conclusions about the safety of this approach. Ventriculitis might complicate the course in approximately a quarter of patients managed with a ventricular drain, but diagnosis is largely clinical due to the unreliability of standard biochemical and microbiological measures.<sup>84</sup>

## DCI

DCI occurs in 20–30% of patients with aneurysmal SAH and continues to have a substantial impact on outcome.<sup>85,86</sup> Traditionally, large vessel vasospasm induced by haemoglobin and other blood products had been thought to be the primary cause of DCI, but recent evidence suggests a more complex and multifactorial mechanistic understanding. Predictors of DCI and vasospasm include poor neurological examination (ie, high World Federation of Neurosurgical Surgeons score), high amounts of subarachnoid and ventricular blood, large aneurysm size, cigarette smoking, hyperglycaemia, hydrocephalus, pre-existing diabetes, and female sex.<sup>87,88</sup> Patients with spontaneous SAH but no aneurysm detected on angiography rarely develop DCI, even if the blood pattern on CT scan suggests an underlying aneurysm.<sup>89</sup> However, patients with non-aneurysmal SAH require cerebrospinal fluid (CSF) diversion at similar rates to those with aneurysmal SAH if the blood pattern on imaging is similar to the classic aneurysmal SAH pattern and at much higher rates when compared with patients with perimesencephalic SAH.<sup>89</sup>

Timely detection or, if possible, prediction of DCI is crucially important for management of DCI. A combination of clinical and radiological factors can both increase the pre-test probability and should factor into clinical monitoring for DCI, including loss of consciousness at ictus and high clinical grade with large amounts of subarachnoid and intraventricular blood (captured by scales including the Hijdra score and modified Fisher scale; figure 1).<sup>90–94</sup> Diagnosis is primarily based on the clinical examination but, particularly in poor-grade patients, clinical changes can go undetected even in carefully monitored settings. Most protocols rely on serial neurological assessments for timely detection of DCI possibly supported by an assessment of vasospasm, such as transcranial doppler, CT angiography and CT perfusion studies, or digital subtraction angiography.<sup>95</sup> Whereas transcranial doppler is less frequently used for the detection of vasospasm in the USA,<sup>96</sup> a recent meta-analysis suggests some benefit over digital subtraction angiography<sup>97</sup> (figure 3). Follow-up catheter angiography remains widely practised as it allows not only diagnosis, but also administration of vasodilators to prevent stroke.

Several novel imaging and electrophysiological approaches have been introduced to detect DCI onset. Quantitative electroencephalogram (EEG) measures can be incorporated into prediction algorithms to generate pre-test probability scores for DCI for a patient on any given day.<sup>98</sup> CT angiography alone might not be reliable for diagnosing vasospasm,<sup>99</sup> but early CT perfusion might have promise for predicting DCI.<sup>100</sup> Other approaches in comatose patients with SAH at high risk of DCI can incorporate invasive brain monitoring including brain tissue oxygen, cerebral microdialysis, electrocorticography, and intracortical EEG.<sup>101,102</sup> Exploring physiological data recorded as part of general critical care, such as heart rate and blood pressure, might offer low-cost approaches to detect DCI in the future.<sup>103</sup>

DCI and outcomes did not improve despite lower vasospasm rates in the CONSCIOUS-2 and 3 trials,<sup>104,105</sup> supporting the notion of a more complex underlying pathophysiology.<sup>106</sup> Implicated mechanisms include vascular dysfunction with a larger focus on the microvasculature, systemic inflammation, cortical spreading depolarisation, and autoregulatory failure. The initial ICP elevation during aneurysm rupture with ictal global



hypoperfusion has been implicated as a trigger for microvascular dysfunction. Additionally, microthrombosis in distal arteries might play a role.<sup>107</sup>

Prophylactic administration of oral nimodipine, but not other calcium-channel blockers, is supported by systematic meta-analyses based largely on one randomised clinical trial<sup>108</sup> and is recommended in clinical guidelines. Despite having potentially advantageous bioavailability, sustained release microparticle formulations of nimodipine (EG-1962) did not decrease the rate of vasospasm or reduce poor outcomes.<sup>109</sup> The long-term goal in the acute management of aneurysmal SAH includes the administration of targeted cerebro-protective agents<sup>110</sup> but, other than nimodipine, none have thus far been identified.<sup>111</sup>

Some studies have indicated lower rates of DCI and better outcomes with low-dose heparin<sup>112</sup> or antiplatelet therapy.<sup>113</sup> Recent studies also suggest that the meningeal lymphatic system has a central role in the clearance of erythrocytes from the CSF in aneurysmal SAH.<sup>114</sup> Little is known about the potential role of dysfunction of the paravascular glymphatic system in promoting neuroinflammation in DCI.<sup>115</sup> Numerous studies have implicated inflammation in the pathophysiology of DCI but, on closer inspection, many investigators have explored vastly divergent mechanisms and insufficiently differentiated between physiological responses to the initial injury and pathophysiological events that further promote damage. Systemic pro-inflammatory cytokines and cellular mediators including myeloid and lymphoid lineage cells are elevated following aneurysmal SAH, correlating temporally with the development of DCI. Studies implicate microglial activation mediated by inflammation in brain injury, attributed to DCI and poor outcome.<sup>116,117</sup> Spreading depolarisations are large depolarising waves that propagate slowly across the cortex and reflect metabolic collapse with underlying ATP-dependent ion pump breakdown.<sup>118</sup> In SAH animal models and patients with aneurysmal SAH, spreading depolarisation has been implicated in the DCI mechanism,<sup>119</sup> independent of angiographic vasospasm.<sup>120</sup> Autoregulatory failure is seen as a downstream process in aneurysmal SAH and other acute brain injuries, probably related to several underlying mechanisms, further promoting brain injury.<sup>121</sup> These insights into potential DCI mechanisms open up the prospect for novel approaches for DCI prevention and the hope to improve outcomes.

To treat patients with DCI, induced hypertension is practised widely even though high-level evidence to support this approach is lacking. A large retrospective, multicentre, observational study found induced hypertension to be an effective strategy for preventing DCI-related cerebral infarcts.<sup>122</sup> A randomised controlled, open-label trial was stopped early due to lack of effect on cerebral perfusion and slow enrolment.<sup>123</sup> Early clinical improvement in the group that underwent induced hypertension did not translate into better long-term functional outcomes. Hypervolaemia and haemodilution, part of the abandoned concept of triple-H therapy, might be harmful.<sup>124</sup> Failure of medical treatment approaches to treating DCI might be predicted by neurogenic cardiac injury.<sup>125</sup> Excessive induced hypertension can be complicated by posterior reversible encephalopathy syndrome (PRES),<sup>126</sup> seizure, and ictal-interictal electrical activity.<sup>127</sup> In an open-label, single-site pilot study (n=108), a targeted approach involving advanced haemodynamic monitoring with algorithmic goal-directed blood pressure interventions reduced DCI rates and improved functional outcomes at 3 months.<sup>128</sup> The benefits of balloon angioplasty are controversial,

but a recent case series suggests possible benefits from intra-arterial administration of vasodilators, if applied early and repeatedly in severe vasospasm.<sup>129</sup> Early magnesium administration following SAH (within 6 h of the bleed) to supranormal levels was not beneficial in a meta-analysis of five randomised controlled trials.<sup>130</sup>

## Seizures

Seizures might be seen at the time of haemorrhage, during acute hospitalisation, and as a long-term consequence of aneurysmal SAH. Underlying mechanisms for seizures following aneurysmal SAH are incompletely understood but might include neuroinflammation<sup>131,132</sup> and cerebral hyperaemia.<sup>127</sup> Both phenomena might be seen immediately before seizure onset as well as during the seizure and feed into a vicious cycle promoting a pro-ictal state. Many in-hospital seizures are exclusively electrographic and some are recorded only on intracortical electrodes.<sup>133</sup> Electrographic seizures following aneurysmal SAH have been associated with poor functional and cognitive outcomes.<sup>134</sup> It remains unclear exactly how seizures affect outcome, but in acute brain injury, compensatory mechanisms for increased metabolic demand might be impaired.<sup>135</sup> Long-term epilepsy is infrequent but associated with worse outcomes<sup>136</sup> and is less likely in patients who underwent coil embolisation.<sup>137</sup> Before aneurysm treatment, short-term seizure prophylaxis might be considered given the fear of rebleeding,<sup>61</sup> but administration beyond this very early phase is highly controversial. Risk stratification using the seizure after aneurysmal subarachnoid haemorrhage risk (SAFARI) score might allow identification of high-risk patients who could benefit from prophylaxis, but this remains unproven. The SAFARI score takes into account patients aged 60 years and older, seizure before hospitalisation, ruptured anterior circulation aneurysm, and hydrocephalus requiring CSF diversion.<sup>138</sup> A small, underpowered, prospective, single-centre, randomised, open-label trial (duration of prophylaxis after subarachnoid haemorrhage trial) suggests that prolonged seizure prophylaxis with levetiracetam might only benefit patients with aneurysmal SAH with imaging evidence of early brain injury.<sup>139</sup>

## Medical complications

Medical complications are frequently seen in patients with severe aneurysmal SAH and have a major impact on outcomes.<sup>140,141</sup> General critical care complications including bacteraemia, central line infections, urinary tract infections, aspiration pneumonia, and deep venous thrombosis are common and require meticulous critical care strategies for prevention, early detection, and targeted treatment.<sup>140</sup> Hospital-acquired infections are an established contributor to poor outcomes and have been associated with nutritional deficiencies, specifically low glutamine levels.<sup>142</sup> Normoglycaemia is a goal of critical care, but overly aggressive insulin strategies can lead to intracerebral hypoglycaemia in aneurysmal SAH.<sup>143</sup> Anaemia has been associated with poor outcomes,<sup>144</sup> but whereas guidelines<sup>61</sup> support transfusions for patients who are clearly anaemic (haemoglobin <7 g/dL), higher haemoglobin targets are controversial.<sup>145</sup> Adequate oxygenation is a cornerstone of resuscitation strategies, but hyperoxia should be prevented.<sup>146</sup> Initiation of chemical deep vein thrombosis prophylaxis using unfractionated heparin within 24 h of aneurysm treatment is extrapolated from other patient populations and is supported by guidelines. It is associated with low bleeding risk,<sup>147</sup> but controversy persists.<sup>148</sup> Optimal fluid resuscitation strategies

are unclear, and simply following the fluid balance is not as valuable as understanding volume status and cerebral blood flow. Higher fluid intake has been associated with hospital complications and poor outcome,<sup>149</sup> but causality is unproven. Avoiding hypovolaemia is likely to be crucial, and fluid titration is encouraged to achieve this.

Cardiac dysfunction (biomarker, electrocardiographic, or wall-motion abnormality) is associated with greater risk of DCI and poor outcomes.<sup>150</sup> Stress cardiomyopathy is common in patients with aneurysmal SAH, affecting the heart globally with severely decreased left ventricular ejection fraction or regional wall-motion abnormalities.<sup>151</sup> The clinical challenge is to differentiate stress cardiomyopathy from acute coronary syndromes, as both disorders can share the characteristics of chest pain, electrocardiogram changes, and elevation in cardiac troponin.<sup>152</sup> The admission electrocardiogram can be helpful in differentiating these.<sup>153</sup>

Respiratory dysfunction can develop, particularly in patients with high-grade aneurysmal SAH,<sup>154,155</sup> and can result from neurogenic pulmonary oedema, fluid overload from DCI management, left heart dysfunction, and adult respiratory distress syndrome. Hyponatraemia following aneurysmal SAH due to the syndrome of inappropriate antidiuretic hormone or cerebral salt-wasting<sup>156,157</sup> is common and complicated by longer stays in intensive care units and hospitals.<sup>158</sup> In practice, it is difficult to differentiate between these and fluid restriction can be harmful for patients with aneurysmal SAH. Management focuses on maintaining euvolaemia. Hyponatraemia is of particular concern in patients with elevated ICP and brain swelling as it can promote both. For these patients, administration of sodium chloride solution (eg, 2% hypertonic saline) or fludrocortisone can be pursued. Patients with aneurysmal SAH often have fevers, which has been linked to worse outcomes. Central fevers can occur with or without infections, leading to potentially unnecessary antibiotic administration in some patients.<sup>159</sup> Fever prevention can reduce secondary brain injury<sup>160</sup> and improve outcomes,<sup>161</sup> as brain hypoxia worsens with fever after aneurysmal SAH. Pharmacological antipyretics might not be sufficient, so adjunctive strategies for normothermia might be needed.

Approximately 22% of patients with aneurysmal SAH who are acutely managed with EVDs will need permanent CSF diversion and require shunt placement, most commonly connecting the ventricles to the peritoneal space. Prevalence of shunt dependency varies widely (18–27%)<sup>162</sup> and patients requiring a shunt have worse long-term functional outcomes.<sup>163</sup> The optimum modes of CSF drainage (intermittent *vs* continuous), EVD weaning (rapid *vs* gradual), and EVD wean timing (following aneurysm securement *vs* time of vasospasm risk) are uncertain.<sup>164</sup> Early mobilisation might be beneficial for all patients with aneurysmal SAH including those with EVDs.<sup>165</sup>

Timing of tracheostomy and percutaneous endoscopic gastrostomy is controversial. A retrospective case series of haemorrhagic stroke, including aneurysmal SAH, suggests that early tracheostomy and percutaneous endoscopic gastrostomy might be associated with decreased length of stay.<sup>166</sup> However, no difference was seen in 6-month functional outcomes in 382 patients with severe ischaemic stroke, intracerebral haemorrhage, or

aneurysmal SAH randomly assigned to early ( 5 days of intubation) versus delayed tracheostomy ( 10 days).<sup>167</sup>

## Long-term management

After hospital discharge, patients with aneurysmal SAH should be followed up by a neurologist or neurosurgeon. Repeat vascular imaging is often obtained, especially in patients who had aneurysm coiling, given concerns about long-term durability.<sup>64</sup> Given the technological advances in imaging technology, gadolinium-enhanced MR angiography is emerging as an alternative to digital subtraction angiography for follow-ups. Up to 8% of patients are readmitted within 30 days, and 14% of these have potentially preventable conditions (eg, dehydration, pneumonia, and urinary tract infection).<sup>168</sup> Long-term antiseizure medications are only considered for patients with seizures during hospital admission or following hospital discharge. Patients with aneurysmal SAH frequently remain on long-term antipsychotic, pain, and antiseizure medications, which can be decreased with appropriate follow-up.<sup>169</sup>

## Outcomes

Large meta-analyses have shown that case fatality rates of patients with aneurysmal SAH have decreased in the past decades by 0.8% per year, which might be linked to improved surgical and medical management.<sup>7</sup> Similar to other acute brain injuries, most patients with poor-grade illness die following withdrawal of life-sustaining therapies.<sup>170</sup> Up to a third of SAH survivors will experience decreased quality of life, attentional deficits, cognitive impairment, depression, and reduced activities of daily living.<sup>171,172</sup> Poor cognitive outcomes have been linked to DCI, white matter abnormalities, and pituitary gland volume loss.<sup>173–175</sup> Results from a large cohort of patients with aneurysmal SAH, who were followed up over 10 years within ISAT, suggested that quality of life in patients who underwent coiling was superior to those who underwent clipping.<sup>9</sup> Standardised neuropsychological assessments might predict long-term return to work in patients with aneurysmal SAH.<sup>176</sup> The potential for good functional outcomes in patients with poor-grade aneurysmal SAH supports aggressive early resuscitation strategies.<sup>10</sup>

Prediction of long-term outcomes is challenging;<sup>177</sup> however, families demand early guidance. Based on population statistics, prognostication scores such as the functional recovery expected after subarachnoid haemorrhage score,<sup>178</sup> SAFIRE score,<sup>79</sup> and subarachnoid haemorrhage international trialists score<sup>179</sup> have been developed. Nihilism based on age should be avoided, as favourable outcomes are not infrequent in older adults.<sup>11</sup> The limited relevance of these scores to prognosticating in individual patients cannot be overstated. To achieve more precise outcome predictions, a personalised medicine approach incorporating biomarkers and genetics might be more promising.<sup>180</sup>

Differences in resource allocation are major drivers of disparities in aneurysmal SAH outcomes and need to be addressed in health-care reform efforts going forward.<sup>181</sup> Improvements in neurological services including the application of a multidisciplinary approach, specialised intensive care units, and focused management protocols might be

associated with better outcomes for patients with aneurysmal SAH in both high-income<sup>183</sup> and low-and-middle income countries.<sup>184</sup>

## Future directions

Common data elements aimed at standardisation of research efforts for patients with SAH will facilitate future studies.<sup>12</sup>

## Aneurysm treatment

Worldwide, most aneurysms are treated with coil embolisation and ongoing trials are addressing the benefits of clipping versus coiling in patients eligible for clipping who were underrepresented or excluded from previous trials such as ISAT.<sup>185</sup> Numerous ongoing trials are exploring the benefits of newly developed neurosurgical and neuroradiological technology to allow for treatment of the most challenging aneurysms.

## Management of secondary complications

Patients with poor-grade aneurysmal SAH are at higher risk of occult DCI, and might warrant invasive multimodality neuromonitoring for brain hypoxia or ischaemia, or metabolic or electrographic derangements to trigger timely intervention.<sup>102</sup> An optimal cerebral perfusion pressure (CPP) might exist for patients with high-grade aneurysmal SAH, below which there is increased risk of brain hypoxia and poor outcome.<sup>186</sup> ICP and CPP monitoring alone might be insufficient to detect cerebral compromise, as brain hypoxia and metabolic crisis can exist with normal ICP.<sup>187</sup> Invasive monitoring including cerebral microdialysis can identify ischaemic patterns that precede clinical deterioration (figure 4),<sup>188</sup> and it might play an important role in detecting silent ischaemia in unconscious patients. Multimodality monitoring catheters should be inserted in the watershed anterior cerebral artery territory (anterior cerebral artery to middle cerebral artery) ipsilateral to the maximal blood load or to ruptured aneurysms (if symmetrical blood and on the non-dominant side).<sup>189</sup> If placed in response to neurological deterioration, catheter placement is guided by the location of the tissue most at risk. Cortical spreading depolarisations on subdural electro-corticography reflect metabolic collapse. Prolonged clusters result in infarction,<sup>190</sup> while the number of episodes is correlated with outcome.<sup>191</sup> Technical guidance exists for what is currently a complex process of data acquisition, analysis, and interpretation,<sup>192</sup> but it is not yet known whether treatment strategies are effective or improve outcome.

Prevention of ischaemic strokes related to DCI remains a focus of investigation. Following the clazosentan to overcome neurological ischaemia and infarction occurring after SAH (CONSCIOUS) trials, which demonstrated biological efficacy to prevent vasospasm but failed to show an effect on functional outcomes, clazosentan is currently being evaluated in an international placebo-controlled trial to determine the impact primarily on clinical deterioration due to DCI and secondarily on the risk of ischaemic strokes and 3-month functional outcomes. In Japan, clazosentan was approved for prevention of vasospasm, vasospasm-related cerebral infarction, and ischaemic symptoms after aneurysmal SAH in 2022, following the completion of two Japanese studies of endovascular coiling and surgical clipping, respectively.<sup>193</sup> A small pilot trial of long-acting statins showed a signal for

lower large vessel spasm without affecting DCI.<sup>194</sup> Manipulation of the peripheral cellular immune response might offer novel targets, while non-specific, broad immunomodulatory therapies have largely been equivocal at best.<sup>111,195</sup> Targeting spreading depolarisations might offer new therapeutic targets to reduce DCI including phosphodiesterase inhibitors,<sup>196</sup> N-methyl-D-aspartate antagonists such as ketamine,<sup>197</sup> and possibly valproic acid.<sup>198</sup> Ongoing trials are investigating the benefit of intrathecal nicardipine,<sup>199</sup> remote ischaemic preconditioning,<sup>200</sup> stellate ganglion block,<sup>201</sup> and neurapheresis using a lumbar drainage filtration system.<sup>202,203</sup>

Cerebral autoregulation, under normal conditions, aims to maintain constant nutrient and oxygen supply to the brain. This mechanism is impaired acutely after aneurysmal SAH and dynamic assessment of cerebral autoregulation using transcranial doppler or near-infrared spectroscopy might identify patients at risk of DCI.<sup>204</sup> A pilot cohort of 31 patients showed that assessing personalised outer limits of cerebral autoregulation using invasive (ie, ICP) and non-invasive (ie, near infrared spectroscopy) measurements is feasible in aneurysmal SAH, and exceeding personalised limits of autoregulation was associated with poor functional outcomes.<sup>205</sup> It is not yet known whether manipulating blood pressure to stay within optimal limits prevents DCI or improves outcomes. Advanced haemodynamic monitoring with algorithmic goal-directed blood pressure interventions reduced the rate of DCI and improved outcome at 3 months in a small randomised trial (n=108).<sup>128</sup>

Shunt prediction models<sup>206</sup> and clinical trials investigating EVD management that focused on shortening EVD duration while decreasing shunt dependency have the potential to improve long-term outcomes.

Impaired consciousness is frequent after aneurysmal SAH particularly at the onset of bleeding<sup>30</sup> and in patients with early clinical deterioration.<sup>207</sup> Challenges for the precise assessment of consciousness are frequently encountered fluctuations in consciousness<sup>208</sup> and the potential dangers associated with stopping sedation, such as brain tissue hypoxia and elevated ICP.<sup>209</sup> However, precise assessments of consciousness are crucial as they heavily inform goals of care discussions and are fundamental for the detection of secondary complications, such as DCI. Measures beyond the behavioural examination have been explored. Computational analysis of the EEG at rest or in combination with clinical features correlates with the behavioural examination and might be able to support predictions of recovery of consciousness earlier than the clinical examination can.<sup>210</sup> Functionally connected networks in the brain that underlie acute disorders of consciousness can be detected by use of resting-state MRI or coherence analysis of the EEG.<sup>211</sup> EEG and MRI can help to identify brain activation of motor commands in clinically unresponsive patients, a phenomenon also known as cognitive motor dissociation or covert consciousness.<sup>212</sup> 39% of behaviourally unresponsive patients with SAH can be diagnosed with cognitive motor dissociation in the intensive care unit compared with approximately 15–20% of behaviourally unresponsive patients with other injuries such as traumatic brain injury, intracerebral haemorrhage, or cardiac arrest. Cognitive motor dissociation is independently associated with short-term recovery of consciousness and better 1-year functional recovery.<sup>213,214</sup> Underlying mechanisms and how to support recovery are uncertain and currently being investigated. Potential treatment options include

neurostimulants such as amantadine, but safety and efficacy in this patient population are unproven.

### Ictal-interictal continuum

Invasive brain monitoring has shown that, in patients with aneurysmal SAH, seizures can be recorded from intracortical electrodes without a surface correlate and that seizures are associated with increased metabolic demand.<sup>215</sup> In patients with epilepsy, increased regional cerebral blood flow compensates for elevated metabolic demand within seconds. This compensatory response can be delayed in patients with SAH and acute brain injury by up to 10 min, which is possibly related to impaired vasoreactivity. These highly localised seizures are associated with worse functional outcomes at 3 months when compared with seizures that are more widespread, and they probably represent a surrogate marker of neuronal disconnection. Following acute brain injury, the EEG might not only reveal seizures, but also EEG patterns that are clearly abnormal but do not meet classic seizure criteria. Examples of these patterns include rhythmic discharges such as lateralised or generalised periodic discharges, also known as the ictal-interictal continuum. Management of these patterns is controversial<sup>216</sup> and invasive brain monitoring supports more aggressive treatment for high-frequency than low-frequency ictal-interictal discharges.<sup>217</sup>

### Conclusion

Despite overall improvements in outcome, aneurysmal SAH continues to have a major public health impact with a mean age of onset in the mid-fifties, leading to many years of reduced quality of life. Active areas of investigation are in the categories of optimising early management approaches, goal-directed haemodynamic and perfusion-guided management, personalised medicine for prognostication, and cerebroprotection.

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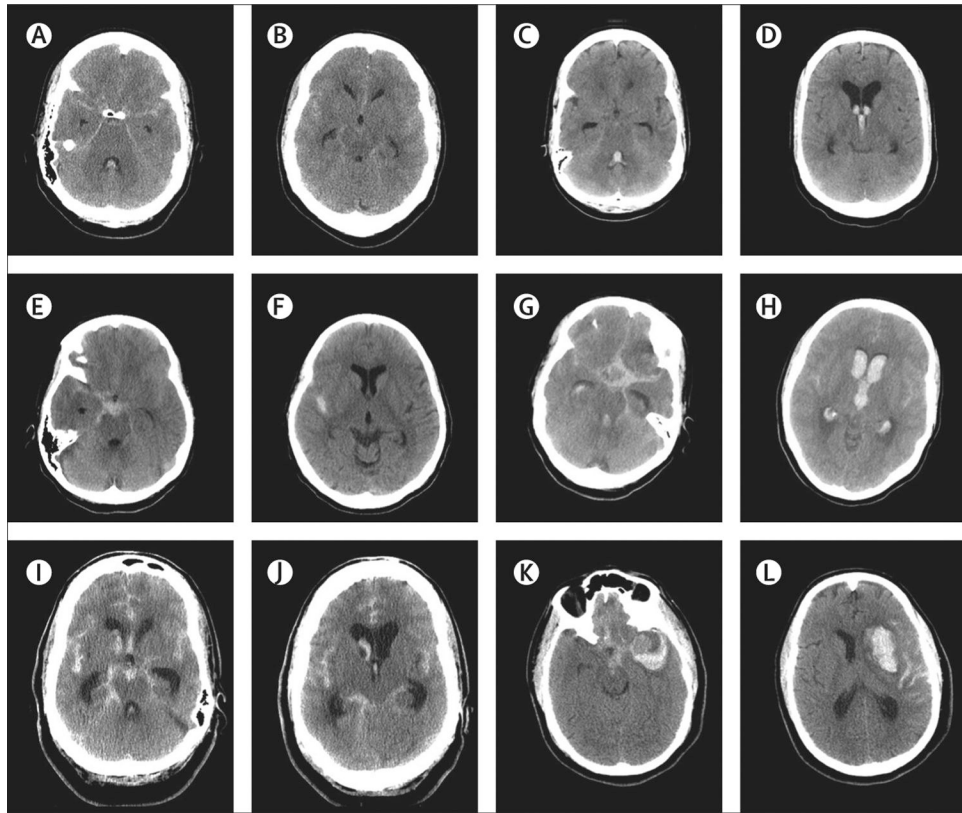


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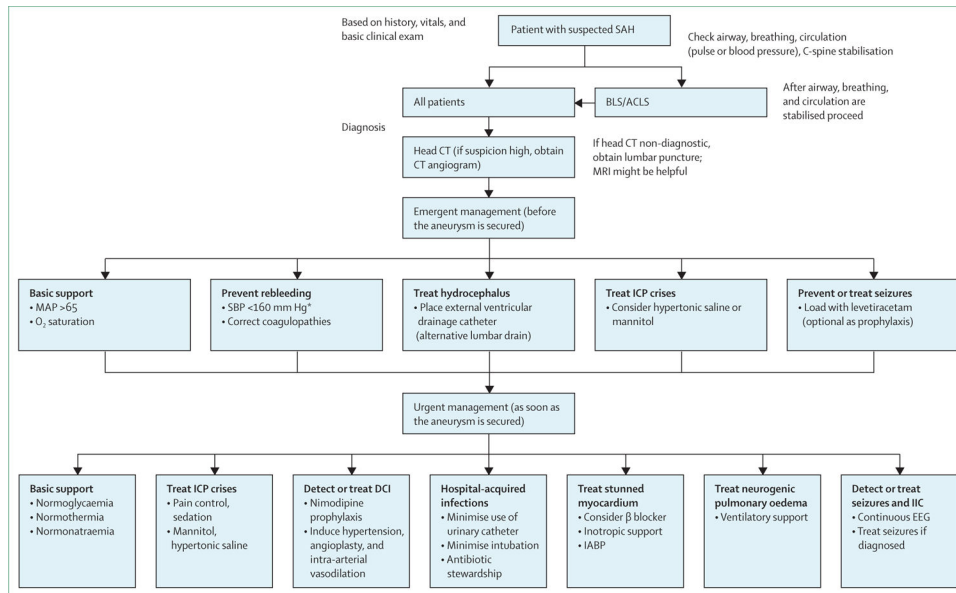
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### Search strategy and selection criteria

We searched SCOPUS, Web of Science, Embase, MEDLINE, Cochrane Central Register of Controlled Trials, and PubMed (Jan 1, 2015–Feb 28, 2021) using the search terms “subarachnoid haemorrhage”, “subarachnoid hemorrhage”, “sub-arachnoid”, and “subarachnoid”. We selected publications in English regarding humans within the past 5 years that were commonly referenced as well as highly regarded older publications. We also searched reference lists of articles identified by this search strategy and selected the relevant articles. Review articles and book chapters are cited to provide readers with further details and references.



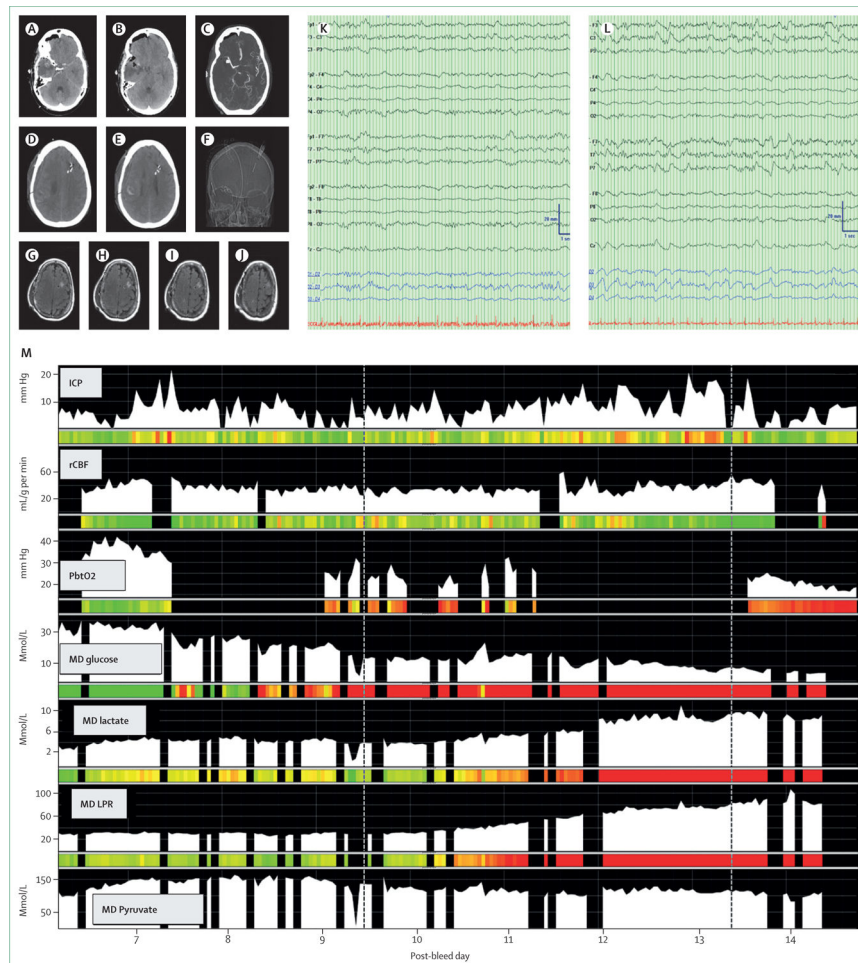
**Figure 1: Neuroimaging of patients with aneurysmal subarachnoid haemorrhage**  
 Head CT demonstrating modified Fisher scores 1 (A, B), 2 (C, D), 3 (E, F), 4 (G, H), hydrocephalus (I, J), and intracerebral haemorrhage (K, L).



**Figure 2: Management approach for patients with aneurysmal subarachnoid haemorrhage**  
 SAH=subarachnoid haemorrhage. BLS=basic life support. ACLS=advanced cardiac life support. ICP=intracranial pressure. MAP=mean arterial pressure. SBP=systolic blood pressure. DCI=delayed cerebral ischaemia. IIC=ictal-interictal continuum. IABP=intra-aortic balloon pump. EEG=electroencephalogram. \*As per US guidelines (European guidelines recommend <180 mm Hg).



**Figure 3:**  
Digital subtraction angiography of patient demonstrating right, multilobulated middle cerebral artery bifurcation aneurysm



**Figure 4: Patient with aneurysmal SAH and DCI diagnosed with multimodality monitoring and cognitive-motor dissociation**

A 73-year-old woman who presented with severe headache and loss of consciousness. She was diagnosed with aneurysmal subarachnoid haemorrhage (SAH) (A, B; Hunt Hess 4, mFS 4) from an aneurysm at the right middle cerebral artery (CT angiography; C). Operative treatment failed at an outside hospital before she was transferred to a tertiary care centre. She arrived in deep coma with a coma recovery scale-revised score of 9 out of 23 that quickly deteriorated to 7. To support detection of delayed cerebral ischaemia (DCI), on post-bleed day 5 the decision was made to place a multimodality monitoring bundle into the left frontal lobe (placement on the right was impossible due to the previous craniotomy) including measurements for intracranial pressure (ICP), brain oxygenation (PbtO<sub>2</sub>), brain temperature, regional cerebral blood flow (rCBF), cerebral microdialysis (MD), and surface and intracortical electroencephalogram (EEG). Baseline EEG demonstrated a minor breach over the right hemisphere but otherwise symmetric EEG (K). On post-bleed day 10 she was diagnosed with DCI triggered by focal changes on surface EEG (L) and PbtO<sub>2</sub>, rCBF, cerebral glucose, pyruvate and rising lactate and lactate-pyruvate ratio (LPR) (M, first dotted line). On post-bleed day 13 she was diagnosed with cognitive motor dissociation using the motor command protocol while the coma recovery scale-revised remained unchanged

at 7 (M, second dotted line). She was severely disabled at 3 months (Glasgow outcome scale-extended of 3) post-injury.

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**Table:**

Clinical and imaging scales

	Clinical grading scale		Imaging grading scale	
	WFNS scale	Hunt Hess scale	Modified Fisher scale	SEBES
Prediction purpose	Outcome	Outcome	Delayed cerebral ischaemia	Quantify oedema
Range	1–5	1–5	0–4	0–4
Criteria	..	..	Quantify location and extent of SAH and IVH	At two levels in each hemisphere: (1) effacement of sulci or (2) disruption of grey-white matter
Grade				
0	..	..	No SAH	..
1	GCS 15	Mild headache	Thin SAH, no IVH	..
2	GCS 13–14, no motor deficit	Moderate to severe headache, cranial nerve palsy, nuchal rigidity	Thin SAH, with IVH	..
3	GCS 13–14, with motor deficit	Lethargy or confusion, mild focal deficit	Thick SAH, no IVH	..
4	GCS 7–12	Stupor, hemiparesis	Thick SAH, with IVH	..
5	GCS 3–6	Coma, decerebrate posturing	..	..

WFNS=World Federation of Neurological Surgeons. SEBES=subarachnoid hemorrhage early brain oedema score. GCS=Glasgow coma scale. SAH=subarachnoid haemorrhage. IVH=intraventricular haemorrhage.

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