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REVIEW ARTICLE

Aneurysmal Subarachnoid Hemorrhage: the Last Decade

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Abstract

Aneurysmal subarachnoid hemorrhage (SAH) affects six to nine people per 100,000 per year, has a 35% mortality, and leaves many with lasting disabilities, often related to cognitive dysfunction. Clinical decision rules and more sensitive computed tomography (CT) have made the diagnosis of SAH easier, but physicians must maintain a high index of suspicion. The management of these patients is based on a limited number of randomized clinical trials (RCTs). Early repair of the ruptured aneurysm by endovascular coiling or neurosurgical clipping is essential, and coiling is superior to clipping in cases amenable to both treatments. Aneurysm repair prevents rebleeding, leaving the most important prognostic factors for outcome early brain injury from the hemorrhage, which is reflected in the neurologic condition of the patient, and delayed cerebral ischemia (DCI). Observational studies suggest outcomes are better when patients are managed in specialized neurologic intensive care units with inter- or multidisciplinary clinical groups. Medical management aims to minimize early brain injury, cerebral edema, hydrocephalus, increased intracranial pressure (ICP), and medical complications. Management then focuses on preventing, detecting, and treating DCI. Nimodipine is the only pharmacologic treatment that is approved for SAH in most countries, as no other intervention has demonstrated efficacy. In fact, much of SAH management is derived from studies in other patient populations. Therefore, further study of complications, including DCI and other medical complications, is needed to optimize outcomes for this fragile patient population.

Keywords Subarachnoid hemorrhage · Functional outcomes · Medical complications · Neurointensive care · Delayed cerebral ischemia · Vasospasm

Introduction/Epidemiology

Spontaneous subarachnoid hemorrhage (SAH) is due to aneurysm rupture in more than 80% of cases [1], with the remaining hemorrhages being nonaneurysmal perimesencephalic (approximately two-thirds) or a variety of other causes (remaining one-third). SAH accounts for 2–7% of all strokes, affecting nine in 100,000 individuals each year in developed countries, although the incidence is declining [2, 3]. For unknown reasons, the incidence is higher in Japan and Finland. The mean patient age has increased from 52 in 1973 to 62 in 2002, and females account for up to two-thirds of those affected, and experience SAH at an older age on average compared to men [4].

Risk factors for SAH are both modifiable and non-modifiable. Known non-modifiable factors include female sex, Japanese or Finnish nationality, and possibly African-American or Hispanic ethnicity [4]. Additionally, genetic markers have been investigated as possible risk factors for SAH and multiple genes were associated with aneurysm formation, including the G572C polymorphism of the interleukin-6 (IL-6) gene [5]. Similarly, Ehlers–Danlos syndrome type 4 is considered a non-modifiable risk factor, as vascular lesions such as aneurysms can develop, although most of the vascular lesions in these patients are not aneurysms [6].

Modifiable risk factors include hypertension, smoking, heavy alcohol use, and possibly sympathomimetic drug use (i.e., cocaine). Hypertension has been found to play a major

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role in the development of SAH. In fact, up to one-fourth of SAH patients have comorbid hypertension, and a baseline increase of systolic blood pressure by 10 mmHg, or diastolic pressure by 5 mmHg, increases the risk of SAH by 20% [7]. Similarly, there is a strong association between SAH and smoking; one meta-analysis found that the age- and sex-adjusted incidence of SAH decreased 2.4% for each 1.0% drop in smoking prevalence among the study population [8]. One explanation suggested that the recent parallel decline in smoking prevalence is a contributing factor to the decreasing incidence of SAH.

Diagnosis

Clinical Features, Computed Tomography, and Lumbar Puncture

The spectrum of SAH presentation ranges from isolated sudden severe headache to death, and many patients present with an altered level of consciousness. However, in the neurologically intact patient with sudden-onset headache, only up to 6% and in other studies, about 1%, would actually have SAH [9], posing a significant diagnostic conundrum as to who should receive radiological studies. Patients with sudden-onset focal neurologic deficits or unexplained altered consciousness, however, should receive a cranial computed tomography (CT) scan without contrast. In the neurologically intact population, many CT scans are done to diagnose one SAH, and although SAH rules exist to guide imaging decisions in patients with sudden headache, the specificity of one such decision rule was only 14% (95% CI 13–16%) for detecting SAH, despite 100% sensitivity [10]. Given the severity of SAH and consequences of missed diagnoses, this is understandable; however, its lack of specificity supports the importance of clinical judgment in decisions to obtain CT scans for neurologically intact patients with sudden-onset headache.

If the initial CT is equivocal, lumbar puncture is traditionally the next diagnostic step (Fig. 1). Cerebrospinal fluid (CSF) erythrocytes or xanthochromia are pathognomonic for SAH, but traumatic taps can confound diagnosis since blood may be mixed with the CSF just due to the lumbar puncture [11]. Some studies suggest that lumbar puncture is not necessary if a third-generation or higher CT scan is obtained within 6 h of headache onset and interpreted as normal by a qualified radiologist [12, 13]. Another approach, however, is to proceed to CT or magnetic resonance angiography (CTA, MRA) or regular MR imaging (MRI) [14]. Some even advocate for performing CTA in patients with unremarkable initial CT and lumbar puncture. These two approaches will uncover abnormalities in approximately 10% of cases, including other causes of headache (intracranial venous thrombosis, reversible cerebral vasoconstriction syndrome, and others) which need to be considered initially in the differential diagnosis of sudden headache, or incidental findings [15].

Imaging Findings

Hyperdensities in the subarachnoid spaces and cisterns are the characteristic of SAH [16]. Although accurately measuring the volume and location of SAH is challenging on CT [16], Takemae and colleagues were probably the first to correlate hematoma size and location with subsequent vasospasm and neurological deficit [17]. Fisher et al. subsequently grouped 47 patients with SAH according to the amount of subarachnoid blood and presence of intracerebral (ICH) or intraventricular hemorrhage (IVH) on CT scan, which was then correlated to likelihood of suffering from vasospasm (Table 1) [16]. More recently, the modified Fisher scale was shown to more accurately predict vasospasm in a sample of almost 1400 SAH patients [18].

Clinical researchers have also explored the utility of CT angiography for detecting the vascular lesion responsible for a SAH. Many physicians use digital subtraction angiography (DSA), which provides three-dimensional rotational views, to locate lesions after confirmation of SAH on non-contrast CT. DSA is particularly useful if an aneurysm is complex (large, thrombosed, calcified, or multiple aneurysms), and if endovascular repair will be used for treatment [19]. However, DSA itself carries risks, including neurological deficits at rates as high as 14% [20]. CTA has therefore been explored as an alternative imaging modality [21, 22].

CTA may also reveal a separate cause for SAH or demonstrate that an aneurysm can be surgically clipped. If an aneurysm is detected on CTA, then many neurosurgeons, including the senior author of this review, often can proceed to surgical clipping if indicated, without DSA. A meta-analysis from 2011 that included 50 studies of CTA in the setting of acute SAH reported a pooled sensitivity of 98% (95% CI 97–99%) and a specificity of 100% (95% CI 97–100%) for detecting intracranial aneurysms [23]. It is recommended that some form of angiography be repeated a few days to weeks later in patients for whom an aneurysmal pattern of SAH was noted but no etiology could be identified. A high-quality CTA that does not detect an aneurysm has been suggested to be adequate to exclude one in patients with a nonaneurysmal perimesencephalic pattern of SAH, although many physicians still perform DSA. In these cases, in contrast to patients with an aneurysmal CT SAH pattern, repeat vascular imaging is not necessary [24].

Magnetic resonance imaging is less often considered in the setting of SAH, despite carrying a comparable sensitivity to SAH detection as CT. This is because more patients are ineligible due to being in an agitated state, intubated, or instrumented with equipment that is not compatible with MRI [25]. Nevertheless, MRI can provide data critical to understanding

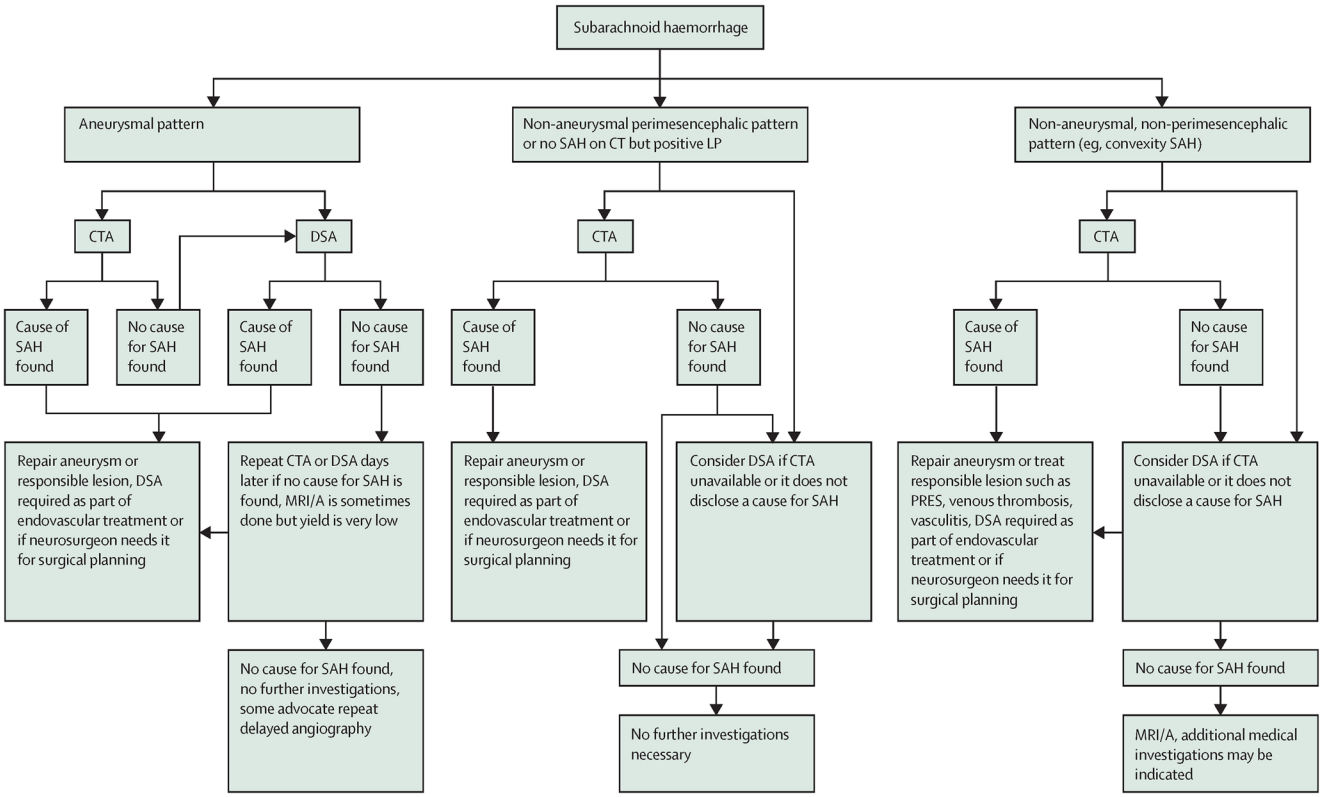

Fig. 1 An algorithm for investigation of patients with subarachnoid hemorrhage with CT or lumbar puncture. SAH, subarachnoid hemorrhage; CTA, CT angiography; MRA, MR angiography; DSA, digital subtraction angiography; LP, lumbar puncture; PRES, posterior reversible encephalopathy syndrome (reprinted with permission from Macdonald and Schweizer TA [1]

the clinical sequelae of an SAH, including brain injury in the acute phase. A small retrospective cohort study found that high-grade patients were significantly more likely to have increased lesion volume on DWI and on FLAIR, such that a 10-mL volume increase was associated with a doubling and 34% increase, respectively, in the likelihood of a 1-point increase in the Hunt–Hess scale [26]. Finally, in a study of brain injury in rats, thicker SAH on MRI both with and without IVH was associated with larger lesion volume on T2 imaging, increased ventricular volume, and decreased neurological functioning [27].

MR angiography (MRA) has also been explored as an alternative to DSA in the assessment of vascular narrowing. A study published in 2000 found significant agreement between these modalities in assessing the caliber of the anterior and middle cerebral arteries, but only moderate agreement for the internal carotid artery [28]. Subsequent comparisons of arterial diameters measured by time of flight MRA versus DSA found that the two modalities correlated best in images

Table 1 Clinical and subarachnoid blood grading scales

World Federation of Neurological Surgeons	Hunt and Hess	Fisher scale	Modified Fisher scale
0 N/A	N/A	N/A	No subarachnoid blood
1 GCS 15	Mild headache	No subarachnoid blood	Minimal/diffuse/thin SAH, no IVH
2 GCS 13–14, no motor deficit	Moderate/severe headache, cranial nerve palsy, nuchal rigidity	Diffuse/thin sheet	Minimal/diffuse/thin SAH with IVH
3 GCS 13–14, motor deficit present	Lethargy/confusion, mild focal deficit	Thick layer/clot	Thick cisternal clot, no IVH
4 GCS 7–12	Stuporous, hemiparetic, mild decerebrate posturing	Diffuse/none with ICH/IVH	Thick cisternal clot, with IVH
5 GCS 3–6	Coma, decerebrate posturing	N/A	N/A

GCS, Glasgow coma scale

of severe vasospasm, but that overall approximately one-third of MRA found results similar to DSA while almost 45% of MRA overestimated vascular narrowing [29]. Further study of MRA is needed, especially as the technology improves and yields more detailed diagnostic information. While MRA has the same feasibility limitations as MRI, it also has reduced sensitivity and specificity for aneurysm detection and surgical planning [30]. In a study of over 200 patients with nontraumatic SAH, MRA and DSA measured arterial lumen with similar accuracy, but inaccuracies in the measurement of aneurysm neck width impacted aneurysm modeling in 3D time of flight MRA [31].

Treatment

Initial Resuscitation and Triage

For patients with SAH, there is a strong correlation between hospital patient volume and outcome [32]. Controlling for confounding factors, SAH patients have better outcomes at centers that treat many patients, have specialized neurovascular teams and neurointensive care or similar units, or are teaching centers [33, 34]. An important tenet of resuscitation is to prevent hypoxia. However, there is emerging evidence that hyperoxia has potentially deleterious effects, including vasoconstriction, decreased cardiac output, aggravation of delayed cerebral ischemia (DCI), and increased risk of poor functional outcome [35]. Data on the effects of hyperoxia predominantly samples patients with systemic illnesses, so the applicability of the derived thresholds to SAH patients is unknown, and further research will be needed to identify these thresholds in the SAH population [36].

Reducing the risk of rebleeding until the aneurysm is repaired is thought to require blood pressure monitoring and control within some range [12, 37]. The blood pressure target depends on patient age, pre-existing hypertension, admission blood pressure, cardiac function, and intracranial pressure. Guidelines generally agree that only extreme fluctuations require treatment, but recommended thresholds vary given the lack of RCTs addressing this topic [37–39]. Nimodipine should be prescribed immediately, which often helps control the blood pressure [12, 38]. Hypotension is also dangerous, since it may reduce cerebral perfusion pressure, especially if the intracranial pressure is elevated. Doerfler et al. studied the effect of hypotension (systolic blood pressure < 90 mmHg), hyperglycemia, and hypoxia on the outcomes of 421 patients with aSAH [40]. Patients that developed hypotension had more than three times the risk of poor outcome compared to those that did not.

Placement of an external ventricular drain (EVD) may be indicated emergently and can be life-saving in patients with acute hydrocephalus [12]. The only other common indication for emergency surgery is for patients with space-occupying ICH, usually secondary to ruptured middle cerebral artery aneurysms. Many grading scales have been proposed for assessing the neurologic and clinical condition of patients with SAH [41–43]. Common data element (CDE) recommendations suggest that the Glasgow coma scale (GCS) and World Federation of Neurological Surgeons (WFNS) grading system be used (Table 1) [44]. These systems are useful for estimating the patient's prognosis, for guiding monitoring and treatment, and for clinical studies [45].

Rebleeding

Rebleeding prior to aneurysm repair is a serious complication of SAH [46]. Meta-analysis of 14 studies including 5693 patients reported rebleeding in 7–26% of patients (mean 13%) [47], with the majority occurring within 3 days of the initial bleed regardless of aneurysm size [48]. Factors associated with rebleeding were temporal proximity to the first hemorrhage, higher blood pressure and systolic blood pressure variability [49], worse neurologic grade, ICH or IVH, and larger aneurysm size [50–52]. Even after controlling for pre-rebleeding factors such as neurological grade and aneurysm size, patients with rebleeding had a significantly lower chance of survival with functional independence [48].

Prevention of rebleeding includes treating acute hypertension, repairing the aneurysm as soon as possible, and administering antifibrinolytic drugs. However, most rebleeds occur within 6 h of aSAH, making prevention difficult [47]. Hasan et al. measured blood and intra-aneurysmal pressures in 11 humans during induced hypertension and found nearly equal changes in the blood and aneurysm pressures [53], suggesting that reducing blood pressure and transmural pressure difference across the aneurysm wall specifically could reduce rebleeding. Confirmatory data, however, are sparse. Oheda et al. reported that emergently reducing systolic blood pressure to < 140 mmHg in a consecutive series of 309 patients did not reduce the risk of rebleeding and, in fact, patients meeting this target pressure had higher rates of early rebleeding [54]. Furthermore, the effect of increasing the pressure gradient across the aneurysm wall by reducing intracranial pressure through CSF drainage must also be considered.

Administering antifibrinolytic drugs prior to aneurysm repair has been proposed to reduce rebleeding, but no evidence for clinical benefit has been documented. This strategy remains investigational [55]. The Ultra-early Tranexamic Acid After SAH (ULTRA) is a multicenter open-label trial investigating whether patients receiving TXA immediately after nontraumatic SAH have better neurological outcome and decreased mortality. Recruitment is ongoing at the time of publication [56].

Aneurysm Repair

Clinicians must consider whether, when, and how to repair an aneurysm. Prediction of outcome after SAH is sufficiently inaccurate such that almost all patients should have the ruptured aneurysm repaired, with exceptions perhaps being cases with impaired brainstem reflexes and motor posturing that does not improve with ventricular drainage or multiple adverse medical comorbidities, such as advanced age and hypertension [45, 57]. Guidelines recommend the ruptured aneurysm be repaired as soon as possible [37–39]. Although evidence to support this practice is sparse and meta-analyses of observational studies do not provide strong evidence, there are no logical reasons to delay aneurysm repair. The main question is then whether emergent aneurysm repair, akin to management of ischemic stroke with thrombectomy, compares to the more-common approach of repairing the aneurysm within 24 or so hours. It has been challenging, even in retrospective and post hoc analyses, to show any benefit to emergency repair [58]. Oudshoorn and colleagues compared adjusted risks of death and dependency among 1238 patients who had aneurysm repair within 24 h vs. 24 to 72 h of aSAH [59]. The adjusted risk ratio for death and dependency for treatment within 24 h was 1.4 (95% CI 1.1–1.7).

RCTs demonstrated that endovascular coiling was associated with a lower risk of death and dependency at 1-year follow-up and that this benefit persisted for at least 10 years [60–62]. Guidelines recommend endovascular aneurysm repair of ruptured aneurysms amenable to this treatment with variable levels of enthusiasm, and endovascular coiling is now used to repair most ruptured aneurysms in the USA [63]. Nevertheless, endovascular repair uses an expanding variety of coils, stents, and devices that were not tested in RCTs and in cases that would not have been included in the original studies [64]. It is assumed that the risk–benefit ratio for these treatments is favorable. The chosen method to repair a ruptured aneurysm should include input from experts in different repair modalities and incorporate clinical and radiologic factors such as patient age; clinical condition (including presence of large intracranial hematomas that need emergent evacuation and any associated illnesses); the size, shape, and location of the ruptured aneurysm; any additional aneurysms; the certainty as to which one bled; the estimated risks of treatment by clipping or coiling; available equipment; and individual skill level [65]. In particular, given the better long-term resistance to recurrence, rebleeding, and the requirement for retreatment, surgical clipping may be a preferred option in very young patients [66].

Delayed Cerebral Ischemia

Neurological deterioration following SAH most commonly occurs 3–14 days following the initial hemorrhage and has been associated with a vasospastic narrowing of cerebral arteries (Fig. 2). The ensuing infarction, disability, and death have been frequently associated with severe vasospastic narrowing [67]. This phenomenon has been described with a wide range of terminology, including vasospasm (VSP), angiographic VSP (aVSP), delayed ischemic neurologic deficit, delayed cerebral ischemia (DCI), delayed cerebral infarction, delayed ischemic deficit, delayed neurologic deficit, secondary cerebral ischemia, clinical vasospasm, and symptomatic vasospasm [68]. Angiographic VSP is the recommended nomenclature for describing a demonstrated, transient narrowing of cerebral arteries on CT, MR, or DSA, while DCI is the recommended term to describe the post-SAH delayed clinical deterioration after other potential identifiable causes have been ruled out [68]. DCI can lead to infarction, which should appear on CT or MRI within the first 2 weeks or so after SAH and not be present within approximately 3 days of a first SAH. To attribute the infarction to a DCI event, this new infarction should also not have been present within 24–48 h of aneurysm repair, and should not be due to other identifiable causes such as aneurysm repair complications, encephalomalacia, or herniation. Studies have shown that DCI and delayed cerebral infarction together correlate better with unfavorable clinical outcome than aVSP [69].

A review of over 230 publications in the SAH literature found that 13,490 patients from a pooled population of 31,168 (43%) had findings consistent with aVSP [70]. The incidence rose to 67% when angiography was performed specifically during the time of aVSP. Finally, DCI was found to occur in 10,445 of 32,188 (33%) patients. Along with admission neurologic condition and rebleeding, DCI and cerebral infarction remain among the top three causes of morbidity and mortality following aSAH [71]. After controlling for admission neurological condition, a study by Stienen et al. found that rebleeding (OR 7.7, 95% CI 3.0–19.7) and cerebral infarction due to DCI (OR 3.7, 95% CI 1.9–6.9) were the strongest predictors of in-hospital mortality [46]. Another study which applied controlled multivariate analyses to national-level data found an association between opioid abuse and transient cerebral ischemic events following aSAH [72]. In the setting of the ongoing opioid epidemic in the USA, these findings suggest utility in screening patients for opioid abuse to identify individuals who may benefit from increased clinical monitoring for post-SAH ischemic events.

Although the diagnosis of DCI is based on clinical features and investigations to exclude other causes of neurologic deterioration, DCI often does not occur in isolation. Many patients have other complications that also contribute to their neurologic decline. Of note, diagnosing DCI no longer requires the presence or occurrence of aVSP (Figs. 3, 4, and 5). While this represents a departure from traditional teaching, one impetus for the change pertained to studies of clazosentan, which revealed that this medication did not improve clinical outcome

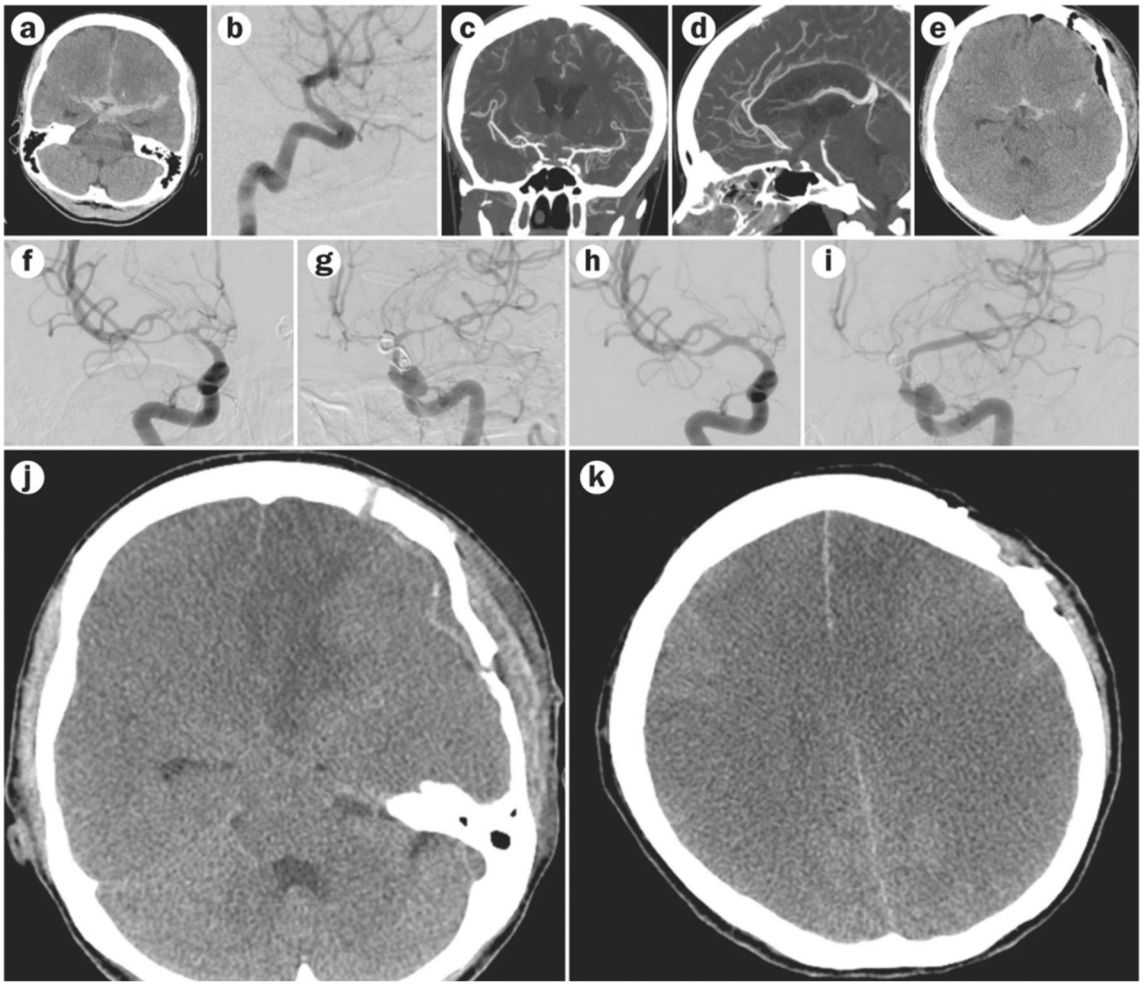

Fig. 2 CT scan, cerebral angiography, and development of angiographic vasospasm and DCI after SAH. A 40-year-old woman was admitted to hospital with SAH caused by a small aneurysm of the precommunicating segment of the left anterior cerebral artery (**a**). Oblique view of left internal carotid artery angiogram (**b**). Diffuse thick SAH was evident on CT scan, WFNS grade was 2, and the cerebral arteries were of normal caliber. Coronal view of CT angiography (**c**). Sagittal view of CT angiography (**d**). Axial view of CT angiography (**e**). The aneurysm was clipped on the day of admission and the postoperative CT scan did not show hypodensities. Her consciousness deteriorated and she developed right hemiparesis, which did not improve with induced hypertension. Catheter angiography showed severe diffuse vasospasm 4 (**f**) and 5 days (**g**) after SAH. Balloon and pharmacological angioplasty with milrinone was performed 4 and 5 days after SAH. Angiograms after treatment with balloon and pharmacological angioplasty (**h**, **i**). Multiple cerebral infarcts developed days later and the patient died (**j**, **k**, reprinted with permission from Macdonald RL: Delayed neurological deterioration after subarachnoid haemorrhage. Nat Rev. Neurol 2014:10 44–58)

despite effectively reducing aVSP [73]. These findings also support those of a previous systematic review and meta-analysis of RCTs studying the effects of pharmacological interventions on aVSP, DCI, and clinical outcome in patients following aSAH. This meta-analysis found that despite significant reductions in the risk of developing aVSP (risk ratio [RR] 0.80 95% CI 0.70–0.92), there was no statistically significant effect on reducing poor clinical outcomes (RR 0.93 95% CI 0.85–1.03) [74].

Although diagnostic tests for DCI should theoretically show regions of cerebral ischemia [75], this is not easily measured and the diagnosis is more commonly made based on surrogate findings such as if cerebral perfusion is reduced in a brain region that previously received adequate perfusion prior to suspected DCI onset. Because arterial diameter is a critical determinant of cerebral blood flow, aVSP is commonly used to support the diagnosis of DCI. CTA and CT perfusion are increasingly used to diagnose aVSP and determine if it is severe enough to reduce cerebral blood flow. Several other methods may also be used to support a DCI diagnosis, including focal, invasive methods to directly monitor brain tissue oxygen content, blood analysis for metabolites elevated during ischemia, and thermal diffusion flowmetry to measure blood flow. Transcranial Doppler (TCD) ultrasound can also be used to predict and detect changes in cerebral artery flow velocity, the pulsatility index, and autoregulation response, each of which may be altered during aVSP. In the Transcranial Doppler and CTA for Investigating Cerebral vasospasm in SAH (TACTICS) study, CTA detected vasospasm in 95% of patients but was not a good predictor of subsequent

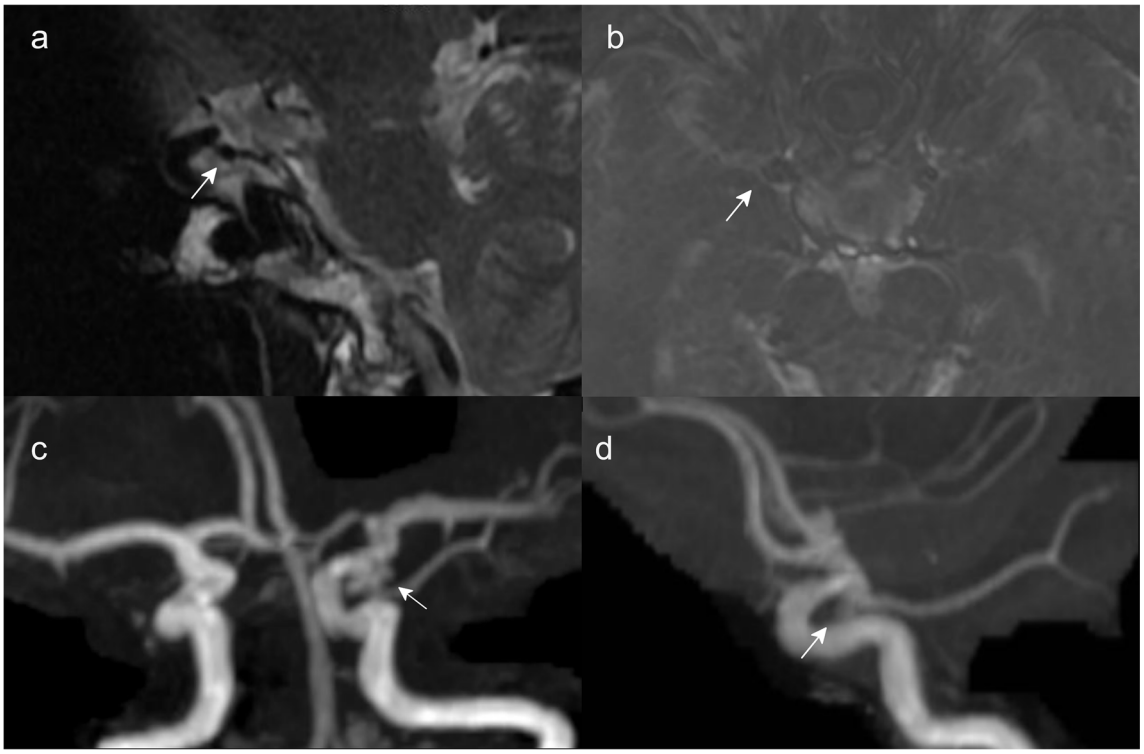

Fig. 3 This female was 64 years old in 2014 when she underwent MRI of the cervical spine for investigation of neck pain (**a**). The sagittal T2 weighted image shows an area of low signal intensity at the right internal carotid artery–posterior communicating artery junction. This can only be appreciated knowing the subsequent course of events. She also had a history of low back pain, fibromyalgia, migraines, hepatitis B, hypertension, narcotic dependence, and major depressive disorder. In 2016 an MRI and MR angiogram were obtained because of headaches (**b**–**d**). In retrospect, a right posterior communicating artery aneurysm is present

DCI [76]. These characteristics, in combination with the known operator-dependent variability in TCD findings, suggest that TCD may play a more useful role in monitoring trends and deviations in cerebral perfusion over time rather than as a single diagnostic measurement.

An ongoing area of interest is the prediction of DCI. Accurately predicting DCI would facilitate efficient patient triaging and would allow healthcare providers to focus prophylactic measures and rescue therapies on patients who would likely see the greatest benefit from them [77–79]. To date, some of the most important factors that have been identified as contributors to DCI are the presence of ICH and IVH, as well as the aSAH volume, location, density, and clearance rate. Worsening clinical grade and loss of consciousness at ictus have also shown strong associations with the occurrence of DCI, and potential associations with cigarette smoking, preexisting hypertension, diabetes mellitus, and cocaine use may also exist [80]. Increasing age is also associated with DCI [81]. Furthermore, women appear to suffer from more angiographic vasospasm, DCI, and, in one study, cerebral infarctions, although only young women appeared to have worsened outcomes than their male counterparts [81, 82]. Reasons for difference on the basis of sex are currently under investigation, and further research will be needed to uncover their drivers.

Recent studies have also found that the VASOGRADE, which combines the WFNS and the modified Fisher scores, had a favorable performance for predicting the occurrence of DCI following surgical clipping for aSAH, and had better predictive results than clinical and radiological scores, including the WFNS, Hunt and Hess, modified Fisher scale, and Subarachnoid Hemorrhage Early Brain Edema scores [83]. However, all clinical and radiological scores, including VASOGRADE, demonstrated worse predictive performance in patients treated with endovascular coiling. Another recent systematic review and meta-analysis which included 53 studies found that the Fisher scale, modified Fisher scale, and Hijdra sum score all correlated well with DCI [84].

Prevention

Prevention of DCI represents an important goal that should substantially reduce the morbidity and mortality of patients with SAH. Previously reported strategies for preventing DCI have included accelerating clot clearance by administering subarachnoid fibrinolytic drugs, lumbar drainage, fenestration of the lamina terminalis, subarachnoid space lavage, and head shaking [12, 37–39, 80, 85, 86]. While most published guidelines do not comment on or recommend lumbar drainage, guidelines from Japan mention that intrathecal tPA or cisternal

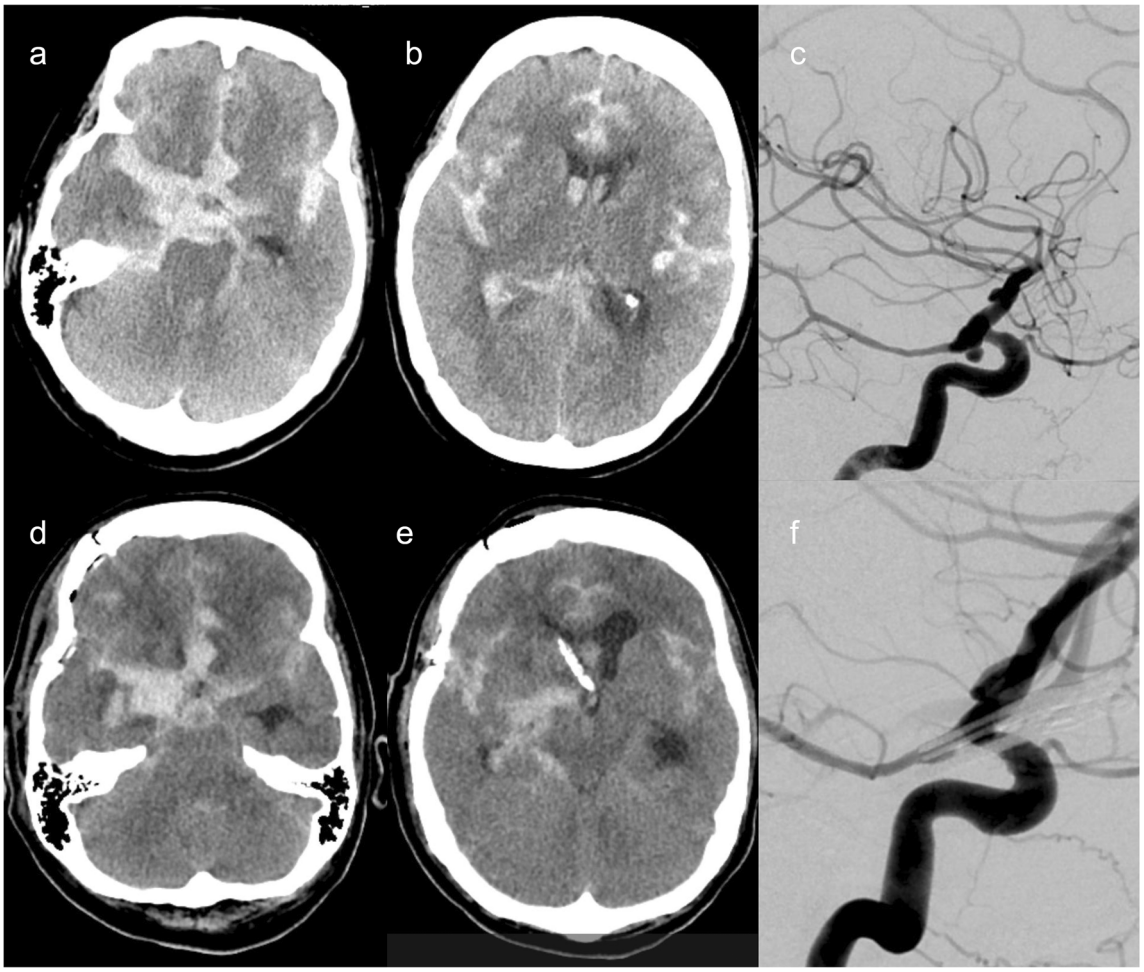

Fig. 4 In 2019 at the age of 69, a patient came to the emergency department with sudden onset of constant moderate to severe left shoulder pain radiating up her neck to her head. Her initial blood pressure was 234/111. No specific diagnosis was made and she was discharged after her blood pressure was controlled. She returned 14 days later after collapsing unconscious with a Glasgow coma score of 6 and WFNS grade 5. A CT scan showed diffuse thick SAH with intraventricular hemorrhage (modified Fisher 4, **a**, **b**). Right internal carotid angiography showed a right posterior communicating artery aneurysm (**c**). The aneurysm was repaired by neurosurgical clipping and an external ventricular catheter was inserted. Postoperative CT scan showed decreased SAH (**d**, **e**) and an intraoperative angiogram showed successful aneurysm repair (**f**)

urokinase irrigation are useful based on moderate evidence [86]. Currently, there are promising RCTs investigating the usefulness of fibrinolytic drugs and lumbar drainage in the post-SAH setting, although they will require further assessment in future RCTs with larger sample sizes [87–89].

The fact that DCI presents with delayed onset following SAH is an important characteristic of the condition, as it provides a window following SAH during which neuroprotective interventions may be initiated to potentially prevent or decrease the risk of DCI. Among the neuroprotective interventions that have been investigated, magnesium, simvastatin, and clazosentan have been the most widely studied, with disappointing results [90–92].

Recently, goal-directed hemodynamic therapy (GDHT) has been proposed as a method for reducing the risk of DCI after SAH. Given that optimized targets for the administration of hemodynamic augmentation methods have not been well-defined, GDHT aims to address this issue by applying advanced hemodynamic monitoring to guide volume therapy. The results from a prospective RCT investigating the risk reducing effects of a GDHT protocol for DCI were reported by Anetsberger et al. [93]. This study of 108 patients randomly assigned to GDHT or standard therapy found that the GDHT group had significantly lower odds of DCI (odds ratio: 0.324; 95% CI 0.11–0.86; $p = 0.021$), and a significantly greater proportion of patients achieving good outcome at 3 months, as measured by a GOS score of 5.

Currently, orally administered nimodipine is the only drug approved by the U.S. Food and Drug Administration to improve patient outcomes following aSAH, as it has been found to improve neurological outcome and reduce DCI [94–98]. Recently, results were published from an RCT comparing the efficacy of oral nimodipine to a sustained release formulation administered directly into the ventricles via EVD [99].

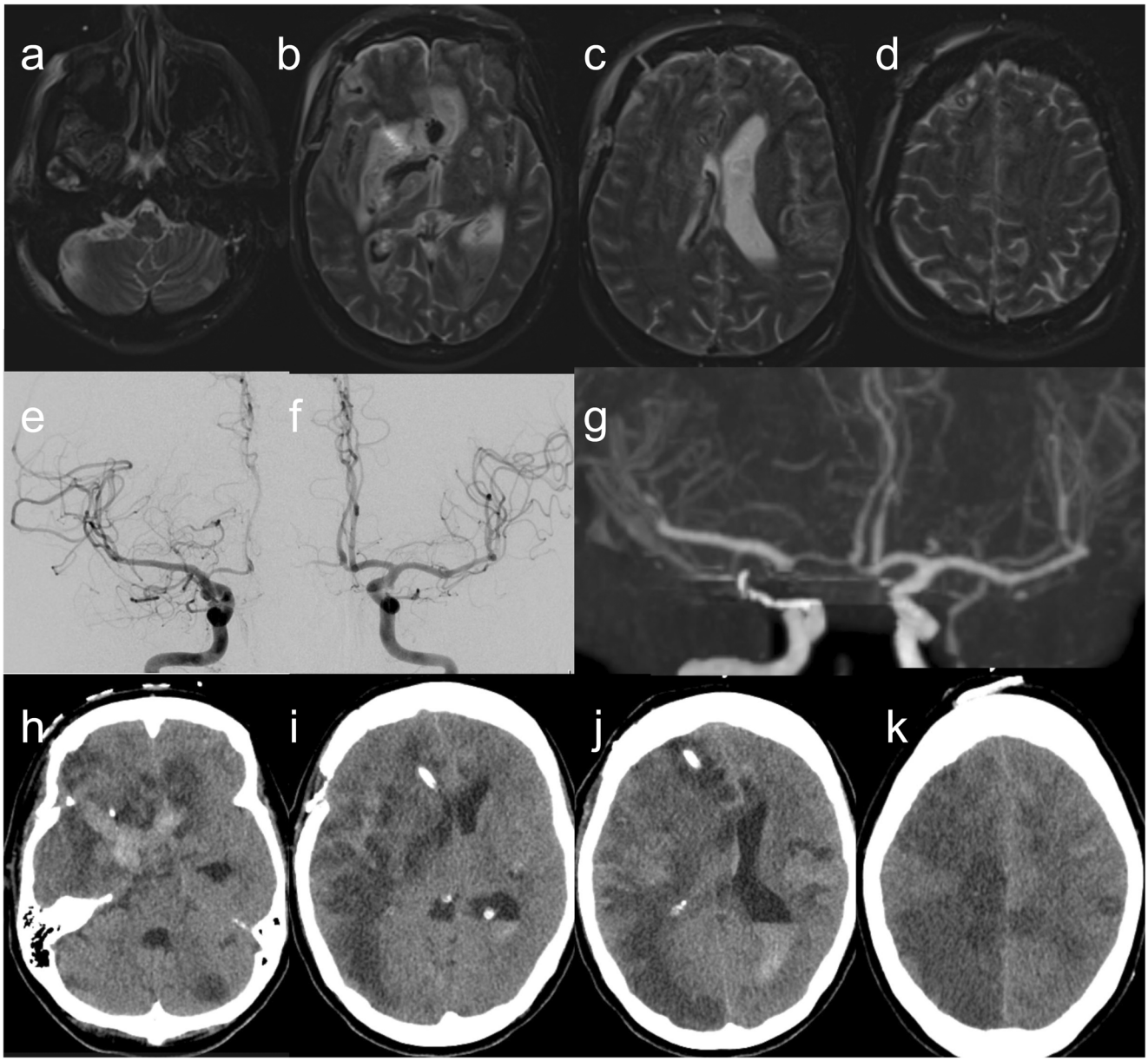

Fig. 5 This patient had withdrawal of her right extremities to pain and a Glasgow coma score of 7 after surgery. T2 weighted axial MRI 3 days after surgery showed SAH and hemorrhage extending up into the basal ganglia with surrounding hyperintensity (**a**–**d**). There was a hyperintensity in the left cerebellum (**a**) but no other regions of ischemia. Comparison of the admission catheter angiography (anteroposterior right [**e**] and left [**f**] internal carotid angiograms) with MR angiography 3 days (**g**) and CT angiography 6 days post-SAH did not show angiographic vasospasm and transcranial Doppler flow velocities were never elevated. The patient developed worsening respiratory function and increased intracranial pressure. A CT scan 12 days after the SAH showed multiple cerebral and cerebellar infarctions (**h**–**k**). Care was withdrawn and the patient died

Despite results showing acceptable safety and tolerability in patients, the study was ultimately halted after an interim analysis revealed that the experimental formulation was unlikely to reach its primary endpoint of superior clinical outcome profile relative to oral nimodipine (risk ratio, 1.01 [95% CI, 0.83–1.22], $p = 0.95$). Further work remains to better understand the mechanisms of neurological deterioration following SAH and identify mechanistically inspired targets for the development of next-generation therapeutics for the prevention and treatment of DCI.

Rescue Therapies

Rescue therapies to treat DCI include induced hypertension and superselective intra-arterial procedures such as balloon angioplasty or vasodilator drug infusion. Currently, the

combination of hypervolemia, induced hypertension, and hemodilution, referred to as "triple H therapy," is not indicated. Although induced hypertension is recommended by most guidelines as the preferred rescue therapy option, the evidence for this recommendation is only of moderate or low quality [12, 37–39, 85, 86]. One recent RCT examined the efficacy of induced hypertension in treating DCI; however, it was stopped after 41 patients were randomized [100]. The reported adjusted risk ratio for poor clinical outcome was 1.0 (95% CI 0.6–1.8), but for serious adverse events, it was 2.1 (95% CI 0.9–5.0). This does not engender enthusiasm for such treatments. Among the explanations are that DCI is a somewhat vague diagnosis of exclusion with a high degree of interobserver variability [101]. Therefore, it is probably applied in patients who have no regions of brain hypoperfusion or ischemia and therefore can only suffer adverse events with no chance of benefit. Hence, more accurate patient selection of those who actually have regions of brain ischemia may clarify the role of rescue therapies.

No RCT has been published for the use of endovascular treatment by balloon angioplasty or vasodilator drug infusion as rescue therapies. Current guidelines note that the evidence for either of these interventions in the post-SAH setting is moderate to low quality. Procedures incorporating balloon angioplasty and vasodilator infusion vary widely depending on the combination of interventions used, as well as the types, doses, and dose regimens of the intra-arterial vasodilators (nimodipine, nicardipine, verapamil, milrinone, fasudil to name a few). Recently, Venkatraman et al. conducted a meta-analysis of 55 studies that used various permutations of balloon angioplasty and intra-arterial vasodilators, and found that there was evidence that these interventions reduced aVSP but did not improve clinical outcome [102]. One potential reason for these findings is that both of these rescue therapy interventions mechanistically aim to reverse aVSP, despite the fact that DCI, the more important prognostic indicator, does not require aVSP to occur.

Other Neurologic Complications

Hydrocephalus, cerebral edema, and brain swelling secondary to SAH may produce increased intracranial pressure. Whereas edema is characterized by increased fluid in the intra- or extracellular spaces, the term "brain swelling" is more used to describe elevated intravascular blood volume in the brain. As such, edema can be inferred from CT imaging, often manifesting as reduced gray–white differentiation and loss of sulci [103].

Typically, hydrocephalus will occur in approximately 18–36% of cases within 3 days of SAH [104]. Despite the potential risks associated with EVD placement, such as infection (7.9%, 95% CI 6.3–9.4%) and symptomatic hemorrhage (0.7%, 95% CI 0.4–1.1%) [105], one must have a low threshold for EVD insertion given its life-saving potential. About a quarter of patients with SAH will require permanent CSF diversion [106]. A recent meta-analysis of 21 publications found that high Fisher grade (odds ratio [OR] 7.7, 95% CI 4.5–13.4), acute hydrocephalus (OR 5.7, 95% CI 4.0–8.1), in-hospital complications (OR 4.9, 95% CI 2.8–8.6), IVH (OR 3.9, 95% CI 2.8–5.5), high Hunt and Hess grade (OR 3.3, 95% CI 2.5–4.2), rebleeding (OR 2.2, 95% CI 1.2–4.0), posterior circulation aneurysm (OR 1.9, 95% CI 1.4–2.5), and age ≥ 60 years (OR 1.8, 95% CI 1.5–2.2) were among the biggest risk factors for permanent CSF diversion requirements [106]. An added benefit of EVD placement is the ability to monitor intracranial pressure. In the presence of a poor baseline neurological exam, EVDs or other ICP monitoring devices may then be important for detecting and treating hydrocephalus, cerebral edema, and intracranial hemorrhage.

It has previously been suggested that fenestrating the lamina terminalis during the clipping of an aneurysm may reduce future need for permanent CSF diversion, accelerate clot clearance, and ultimately prevent aVSP [107]. It is important to note, however, that these benefits have not been proven and this practice is not formally recommended at this time [12, 37–39, 85, 86]. Currently, administering anticonvulsant drugs prophylactically is not recommended in SAH patients. Patients who have documented seizures should be treated, but there is controversy as to whether patients at high risk of developing seizures should be treated. Observational studies have suggested that phenytoin is associated with poor outcomes. Currently, no RCT has been conducted to assess the efficacy of secondary seizure prevention following SAH [108].

Systemic Complications

Medical complications are a common occurrence after SAH, with some reports suggesting that all patients will experience at least one complication [109]. Medical complications among 580 patients with SAH included fever (54%, > 38.3 °C), anemia treated with transfusion (36%), hyperglycemia (30%, > 11.1 mmol/L), treated hypertension (27%, > 160 mmHg systolic), hypernatremia (22%, > 150 mmol/L), pneumonia (20%), hypotension treated with vasopressors (18%, < 90 mmHg systolic), pulmonary edema (14%), and hyponatremia (14%, < 130 mmol/L) [110]. A systemic inflammatory response syndrome occurs in about 50% of SAH patients [111]. Fever, anemia, and hyperglycemia were associated with poor functional outcomes, and these findings have been confirmed by subsequent reports [112, 113]. However, there is nuance to some of these associations, as subfebrile high temperatures do not necessarily require intervention, and the number of days of fever appeared to be the driver of poor prognosis in a large cohort of SAH patients [111]. An RCT assessed the value of adding intravascular

cooling devices to the standard fever treatment of acetaminophen and cooling blankets, and although only 41% of the 296 patients had SAH, fever burden was reduced without increases in complications [114]. Nevertheless, in the absence of clear efficacy data, invasive cooling devices are used infrequently for mitigating fever after SAH.

Strict (80–120 mg/dL) versus conventional (80–220 mg/dL) blood glucose control has also been assessed in an RCT of 78 patients with SAH, and while stricter glucose management reduced infection risk, there was no difference in clinical outcomes [115]. Furthermore, hypoglycemia occurred in 11% of patients and may be as harmful to the brain as hyperglycemia [115, 116]. Current recommendations range from none to treating glucose > 10 mmol/L (180 mg/dL) or 200 mg/dL or conventional levels (80–200 mg/dL) [12, 37–39, 85, 86].

Anemia (hemoglobin < 10 g/dL) develops in half of SAH patients within 4 days of admission, and almost all patients will develop anemia during the DCI risk period [117]. Although anemia is associated with poor outcome [113], red blood cell transfusion is associated with risks, including nosocomial infection, multiorgan failure, and lung injury and has not consistently been associated with benefit in anemic patients with SAH [118]. Transfusing when the hemoglobin fell below 7 g/dL led to fewer complications but similar mortality compared to a transfusion threshold of 10 g/dL, but this study included few patients with neurologic injuries and thresholds may differ in SAH patients. Dhar et al. studied the effects of transfusing SAH patients across a range of hemoglobin concentrations (7 to 13 g/dL) with one unit of erythrocytes on oxygen delivery to the brain as measured by positron emission tomography. They showed that hemoglobin increased by 12% (9.6 ± 1.4 to 10.8 ± 1.4 g/dL) and oxygen delivery increased 10% (5.0 [interquartile range 4.4–6.6] to 5.5 [4.8–7.0] mL/100 g/min) [119]. Notably, these increases were of greater magnitude than those occurring with induced hypertension or hypervolemia. There is no consensus on transfusion thresholds, and reports vary in their suggestion from 7 to 12 g/dL [120]. The ongoing SAHaRA trial will assess the benefit of transfusion in an RCT [121]. Until definitive results are available, decreasing anemia by minimizing blood tests and iatrogenic blood loss and mobilizing the patient should be a priority in SAH care. Erythropoietin (EPO) has been studied in SAH in one small RCT, reducing delayed ischemic deficits and rates of poor outcomes at discharge [122]. However, EPO increases mortality after ischemic stroke and thromboembolic events in critical care patients and therefore is not recommended.

Cardiac and respiratory dysfunctions are common after SAH, and manifestations include cardiomyopathy, Takotsubo cardiomyopathy, electrocardiogram abnormalities, arrhythmias, pneumonia, pulmonary edema, and acute respiratory distress syndrome (ARDS) [123, 124]. Furthermore, cardiac arrest at the time of SAH is not uncommon and reports of good functional outcomes after cardiac arrest in SAH patients are rare [125]. Treating these complications follows standard recommendations, taking into account that after SAH, there are other risks, including rebleeding and DCI and that it is important to maintain euvolemia and eunatremia. Some combination of cerebral salt wasting and syndrome of inappropriate antidiuretic hormone secretion often causes hyponatremia after SAH [126]. Using isotonic saline as the intravenous fluid and minimizing free water administration are used as prophylaxis, while hypertonic saline and possibly mineralocorticoids are used as the treatment. Importantly, fluids should not be restricted, as hypovolemia increases risk for DCI.

Rehabilitation and Outcome

Rehabilitation

In critically ill patients with non-neurologic illnesses, physical therapy and early mobilization shorten intensive care unit (ICU) and hospital length of stay (LOS), reduce the duration of mechanical ventilation, and improve other short-term outcomes [127, 128]. In studies including predominately ischemic stroke patients, there was a positive correlation between early rehabilitation starting about 72 h after stroke and functional recovery [129]. However, an RCT comparing very early mobilization (within 24 h) of ischemic or hemorrhagic stroke to usual stroke care found reduced odds of favorable outcome at 3 months in the interventional group [130]. Ischemic stroke patients are usually relatively stable 24 h after the ictus whereas SAH patients are at the highest risk of DCI during post-hemorrhage days 3–14, so it is recommended that SAH patients be mobilized when they are deemed stable. However, there is no good evidence as to when to mobilize patients after SAH and RCT are needed [131].

The most common persisting morbidities after SAH are executive dysfunction, short-term memory impairment, impulsivity, difficulty with concentration and making decisions, anxiety, depression, and fatigue [132]. Studies of cognitive rehabilitation for these types of deficits in SAH patients are scarce, but the effect of rehabilitation on these outcomes in other neurological pathologies has been investigated. A Cochrane review found insufficient evidence to support cognitive compared to conventional or no rehabilitation for improving quality of life, return to work, independence in activities of daily living, and community integration in patients with traumatic brain injury [133]. Multiple other reviews reported limited evidence supporting the effectiveness of cognitive and occupational rehabilitation in stroke patients [134, 135].

Current guidelines for SAH patients generally recommend referral for cognitive, behavioral, and psychosocial

assessment. It should be noted that these problems are not well-assessed by either the modified Rankin (mRS) or Glasgow outcomes scales (GOS), the most commonly used measures of functional outcome in SAH RCT (Table 2). In patients with no symptoms according to the mRS, one-half have cognitive impairments on testing and one-sixth suffer from mood disorders. This led to calls for new scales of SAH outcome, and the SAH Outcomes Tool (SAHOT) score was invented to possibly more completely assess cognitive, psychological, and physical debilitations after SAH [136]. It consists of a 56-item questionnaire translating to a raw score with a range of 0–112 and an ordinal 9-point scale from 1 (best outcome) to 9 (death). Validation studies are needed, but this provides a valuable starting point for measuring both cognitive and physical disabilities after SAH.

Outcome

Outcome after SAH is commonly measured using scoring scales, including the mRS, a 7-point scale ranging from 0 (no symptoms at all) to 6 (death); the GOS, a 5-point scale from 1 (death) to 5 (good recovery); and the Extended-GOS (GOSE), which expands the GOS to an 8-point scale. While variable, patients are usually followed for 3 months after their inciting hemorrhage, although there is little evidence and no consensus on the appropriate length of follow-up. These scales are regularly dichotomized into favorable and unfavorable outcomes, with good recovery to moderate disability considered favorable and severe disability, vegetative state, or death considered unfavorable. This results in loss of information and has implications for statistical analysis of SAH RCT [137].

A meta-analysis of 33 studies including 8739 patients found that mortality in SAH varied from 8.3 to 66.7%. Three studies suggest SAH mortality has declined since 1965 [4, 46, 138–140]. Factors hypothesized to contribute to the reduction in mortality include better diagnosis of minor cases of SAH, early repair of the ruptured aneurysm to prevent rebleeding, and improved medical management. In terms of morbidity, six studies comprising 2424 patients found that 55% of patients were independent, as measured on a variety of different scales, after a follow-up of 1–12 months [4]. However, data on trends over time in morbidity are currently lacking.

Meanwhile, up to 33% of patients who survive SAH are unable to return to work or their previous level of employment [141], and the time course of recovery has been reported infrequently. One study reported that 83% of 52 patients with SAH improved between discharge and 6 months [142]. Over 50% of patients with poor functional outcomes on the mRS at discharge improved to good outcome within 6 months in two studies [142, 143]. Regardless, many studies on this topic are in relatively small cohorts and further information is needed.

Prognostic Factors

Jaja et al. developed a prognostic model for outcome based on 10,936 patients and validated it on 3355 patients [45]. This model predicted the risk of mortality or likelihood of functional outcome for SAH patients 3 months after the event according to the GOS, and was externally validated on data from a cohort within the Barrow Ruptured Aneurysm Trial (BRAT) [144]. Age, premorbid hypertension, and neurologic grade on admission were the key factors that predicted outcome. Clot thickness on CT, aneurysm size and location, and method of aneurysm repair added marginally to the predictive models. Their included variables were identified by a previously published systematic review which found these variables were associated with SAH outcomes (Table 3) [145]. A major strength of this model is the availability of its variables for consideration at the time of admission, so it can inform the treatment plan of patients from the beginning of their hospital course. Additionally, the model included patients from several RCT and prospective hospital observational registries, and was externally validated against several other RCT and registries. Complications in SAH, such as DCI, vasospasm, and rebleeding, can have negative impacts on patient outcomes but were not assessed by Jaja et al., due to variations in definitions and lack of information about these events in some of the studies. Similarly, while female sex is a risk factor for higher SAH incidence and mortality, its effect on functional outcomes remains somewhat unclear, leading to its exclusion from the model [146].

Future Directions

Given the complex management required for optimizing outcomes after SAH, future directions for research are myriad. Currently, management of SAH draws from a variety of practices for other conditions and is supported by varying levels of evidence [147], and an important issue moving forward will be the prioritization of time and resources towards studies that are most likely to successfully improve outcomes. While classical methods rely on translating preclinical studies to human trials, these methods have infrequently led to reliable interventions in SAH patients. For example, magnesium and hypothermia are effective preclinically but showed no outcome improvements in human RCT.

For questions relevant to all SAH patients, such as whether to repair aneurysms by surgical clipping or endovascular coiling, attaining a large sample is not a concern. However, for rarer events, the lower event frequency and potentially small effect sizes for interventions in question can lead to unattainably high sample sizes. These raise the option of new methods for studying treatments, because although pharmacological treatments must be studied in RCTs, other

Table 3 Prognostic factors for outcome after subarachnoid hemorrhage

	Factor
Demographic/medical history factors	Age, history of hypertension
Initial examination factors	Glasgow coma scale, WFNS Grade, Hunt–Hess Grade, mean arterial blood pressure, systolic blood pressure,
Radiographic/aneurysmal factors	Amount of subarachnoid blood (Fisher scale, modified Fisher scale, or Hjidra score), aneurysm location, aneurysm size, vasospasm upon admission, presence of intraventricular hemorrhage
Laboratory values	Serum glucose upon admission, arterio-alveolar gradient, serum bicarbonate, troponin
Treatment method factors	Method of treatment (clipping, coiling, neither, or both)

interventions could be studied observationally. The emerging field of artificial intelligence and causal inference are other techniques to apply to SAH [148]. Selection of interventions most suited to RCTs is an important issue overall and must be taken into account in future SAH studies [149]. A further complicating factor is the lack of valid short-term surrogate measures for functional outcomes, which would be extremely useful for detecting efficacy signals in phase two RCT. This is further complicated by the lack of SAH-specific outcome measures, although the previously discussed SAHOT score is an attempt to remedy this issue.

Finally, even in the face of strong clinical evidence, knowledge translation remains an issue. Gritti et al. reviewed guidelines and cross-sectional studies in SAH and found that, while nimodipine use, early aneurysm repair, and endovascular coiling were rapidly adopted, the cessation of triple H therapy and prophylactic anticonvulsant use was quite delayed [150]. Although well-meaning, the importance of following clinical guidelines cannot be understated, and strategies for implementing guidelines, particularly when they relate to the cessation of a treatment, rather than the adoption of a new treatment, will be needed to translate clinical evidence into meaning outcome improvements.

Search Strategy

In writing this narrative review, an extensive search of the literature was performed. MEDLINE was searched from inception to August 2020 with the keyword "subarachnoid hemorrhage." Reports that discussed non-aneurysmal causes of subarachnoid hemorrhage were excluded, and the final list was checked against a prior review written by the senior author [1]. Particular attention was paid to reports from the past 10 years, but older, highly cited, or otherwise important publications were included for historical context. Reference lists from included papers were also reviewed, and additional reports were added accordingly.

Table 2 Methods of outcome assessment used most commonly in subarachnoid hemorrhage trials

	Modified Rankin scale	Glasgow outcomes scale	Extended Glasgow outcomes scale
0	No symptoms or disability	N/A	N/A
1	No disability, symptoms do not prevent patient from carrying out ADLs	Death	Death
2	Slight disability, cannot carry out all ADLs, but can look after own affairs	Vegetative state	Vegetative State
3	Moderate disability, requires help with ADLs, but can walk unassisted	Severe disability	Severe disability
4	Moderate disability, unable to walk without assistance	Moderate disability	Moderate disability
5	Severely disabled, bedridden, incontinent, requiring constant nursing care	Good recovery	Lower moderate disability
6	Death	N/A	Upper moderate disability
7	N/A	N/A	Lower good recovery
8	N/A	N/A	Upper good recovery

ADLs, activities of daily living

Conclusions

SAH remains a highly morbid and fatal disease; yet, in recent years, improvements in outcomes have been observed. Diagnosing SAH and uncovering its etiology relies largely on CT scan with DSA for localization of aneurysms. Early repair of aneurysms and the rise of endovascular aneurysm repair have likely contributed to these improvements in outcomes, and providers treating SAH are now able to select patient-centered treatment strategies based on patient-level and aneurysmal factors to optimize outcomes for individual patients. Regardless, the most feared complication after the securing of the aneurysm is DCI, and the lack of effective therapies outside of nimodipine is a pressing issue in the field. Medical complications are also highly prevalent among those suffering from SAH. Despite improvements, there is a relative lack of data on functional outcomes, representing an important area for future research. Recent reports have suggested advances in prognostication and SAH-specific outcome assessment, although validation will be needed before widespread incorporation into SAH studies. Regardless, the treatment of SAH is an exciting area, and new technological and basic-science advances will hopefully lead to improved outcomes for this fragile patient population in the near future.

Compliance with Ethical Standards

Conflict of Interest RLM is a consultant for Grace Biotechnology and Idorsia Pharmaceuticals. EKO owns equity in MedAugur and Whiteboard Coordinator, receives consulting fees from Google, and is employed at Merck. JM reports receiving research support from Stryker, Penumbra, Medtronic, and Microvention and is a consultant for Imperative Care, Cerebrotech, Viseon, Endostream, Rebound Therapeutics, and Vastrax.

Ethics Approval Not applicable.

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