Critical care management of aneurysmal subarachnoid haemorrhage in Australia and New Zealand: what are we doing, and where to from here?

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ABSTRACT

- Patients with an aneurysmal subarachnoid haemorrhage (SAH) frequently require admission to the intensive care unit. There, a variety of therapeutic strategies are initiated, in addition to definitive procedures aimed at securing the aneurysm.
- Despite a substantial investment in caring for these patients, outcomes for this group remain poor. Although the severity of the initial bleed is crucial in this context, many patients undergo further deterioration in the ICU. Delayed cerebral ischaemia is a significant cause of long-term morbidity and mortality after SAH.
- There are limited data supporting much of the critical care provided to patients with SAH in the ICU, leading to substantial institutional and practitioner variation in treatment. Whether this influences patient outcomes is unknown, although it represents a major knowledge gap in neurocritical practice in Australia and New Zealand.

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Subarachnoid haemorrhage (SAH) is a devastating form of stroke, associated with high rates of morbidity and mortality. SAH can occur spontaneously or as a result of trauma, but the greatest clinical ambiguity relates to the management of spontaneous, aneurysmal SAH. Optimal treatment in the intensive care unit is uncertain, leading to substantial variation in the care provided.[1] The nature and extent of this variation and its impact on patient-centred outcomes represent a major knowledge gap in Australian and New Zealand neurocritical care practice. We aim to highlight these issues and identify a series of key questions that might inform future research.

What is known about the care of critically ill patients with SAH?

Epidemiology and outcomes

SAH accounts for about 5% of all strokes[2] and has an estimated incidence of 10.3 per 100 000 person-years in Australia and New Zealand. It affects women more often than men and its incidence peaks in the age range of 45–64 years.[3] Globally, outcomes remain poor,[4] with 25%–35% of patients dying within the first month after occurrence in high-income countries.[2] In Australia and New Zealand, the overall in-hospital mortality rate was 29.2% in patients with SAH receiving treatment in the ICU between 2000 and 2015.[5] SAH mortality was twice that of traumatic brain injury (TBI), and ICU and hospital lengths of stay were significantly longer.[5]

Abbreviations

CSF	cerebrospinal fluid
CT	computed tomography
DCI	delayed cerebral ischaemia
DND	delayed neurological deterioration
ICP	intracranial pressure
ICU	intensive care unit
RCT	randomised controlled trial
SAH	subarachnoid haemorrhage
SMR	standardised mortality ratio
TBI	traumatic brain injury
TCD	transcranial Doppler
VS	vasospasm

Persistent neurocognitive changes, including deficits in memory, executive functioning and language, fatigue, depression and post-traumatic stress, have been reported in survivors of SAH.[6] A 2011 New Zealand study identified significant cognitive deficits in SAH survivors,[7] and a similar survey in Australia reported a substantial reduction in health-related quality of life, which was most pronounced in younger patients.[8] The average patient with SAH is young, stays in the ICU and hospital for a protracted period, and has a high risk of premature death or long-term cognitive and physical disability.[9]

The overall financial burden of SAH includes in-hospital and ongoing rehabilitation costs. Reports have estimated the total first-year treatment costs to be between US$41 000 and US$65 900 per patient.[10,11] This is substantially higher than the estimated cost associated with ischaemic stroke,

Table 1. Terminology relating to delayed cerebral ischaemia

Term	Note
Delayed neurological deterioration (DND)	Refers to any neurological deterioration after initial aneurysmal SAH stabilisation and can result from multiple aetiologies, including hydrocephalus, seizures, cerebral oedema, metabolic causes, infection and delayed cerebral ischaemia.
Vasospasm (VS)	Purely a radiological entity. It describes cerebral arterial narrowing detected by angiography or TCD. It occurs in 50%–70% of patients after aneurysmal SAH,22 but only half these patients develop DCI.23 VS typically develops between Days 4 and 10 post-ictus, peaks at Day 7, and may persist for up to 3 weeks.
Delayed cerebral ischaemia (DCI)	Defined as a new focal neurological deficit and/or deterioration in level of consciousness, lasting for more than 1 hour, when other causes of DND have been excluded; or the appearance of new infarctions on CT or MRI scans.22,23 It is therefore possible to have DCI without neurological signs, but this is rare.

SAH = subarachnoid haemorrhage. TCD = transcranial Doppler. CT = computed tomography. MRI = magnetic resonance imaging.

mostly due to higher inpatient care costs as a consequence of extended ICU and hospital lengths of stay. Importantly, these data quantify direct costs only, and do not account for loss of work-related income for the patient or family members.

Initial neurosurgical and intensive care management

Patients with SAH should be transferred to a neurosurgical centre as soon as feasible,[12] where the aim is to promptly secure the aneurysm, given that the risk of rebleeding is highest 2–12 hours after the onset of symptoms.[13-15] Before aneurysm repair, the risk of rebleeding can be reduced through avoiding hypertension and through administration of antifibrinolytic agents. There is no single consistent blood pressure target, although many authors recommend a systolic blood pressure level of < 160 mmHg.[13,16]

Antifibrinolytic therapy (to prevent the breakdown of the initial clot) has been recommended for short-term use (< 3 days) or until the aneurysm has been secured.[13-15,17] Antiepileptic drugs are also often prescribed for SAH, but prospective observational data suggest a strong association between higher phenytoin exposure and inferior functional and cognitive outcomes.[18] Phenytoin prophylaxis should therefore probably not be routinely provided,[14] although other agents can be considered.

Definitive aneurysm repair involves two principal treatment options: endovascular coiling and surgical clipping. A large randomised controlled trial (RCT) of these therapies, principally in patients with favourable clinical characteristics, showed improved outcomes after endovascular treatment.[19] Most aneurysms were located in the anterior cerebral circulation (middle cerebral artery aneurysms are traditionally clipped, and posterior circulation aneurysms coiled), with a diameter of < 10 mm. A larger clot burden was present in patients undergoing surgical clipping, which may have contributed to the inferior outcomes in this group,[20] and endovascular therapy is associated with a greater need for subsequent retreatment.[21] In the absence of an identifiable aneurysm, the pattern of blood on computed tomography (CT) imaging of the brain can help guide the need for further investigation. Patients who have a perimesencephalic pattern of SAH that is not due to a basilar artery aneurysm typically have a good prognosis and may need no further imaging, but other distributions of unexplained subarachnoid blood often require repeat angiography.

Delayed cerebral ischaemia

Delayed cerebral ischaemia (DCI) is a common complication of aneurysmal SAH and, except for rebleeding, has the greatest impact on morbidity and mortality. The terminology relating to DCI is confusing but important, and is summarised in Table 1.

DCI typically occurs in conjunction with vasospasm (VS), but the causal relationship has been questioned. Regions with low blood flow do not always correlate with narrowing seen on angiographic imaging,[24] and infarction can occur in patients without VS.[25] Additionally, large, multicentre RCTs of endothelin antagonists have shown a reduction in VS, but do not confer outcome benefits.[26] Other factors implicated include hypercoagulability-related microthrombosis, impaired distal vascular autoregulation, intravascular volume contraction[27] and spreading cortical depolarisation.[28]

DCI is diagnosed clinically or radiologically using CT or magnetic resonance imaging.[22,23] Digital subtraction angiography is the gold standard for diagnosing VS, although CT angiography is often used. Transcranial Doppler (TCD) measurement is a non-invasive way to measure linear blood flow velocity in large conducting vessels. Threshold measurements and trends can be used to diagnose VS. CT perfusion may also be used to predict impending DCI. Early identification of interhemispheric perfusion asymmetry is associated with later development of DCI, especially when combined with other risk factors such as age, clinical presentation and blood load.[29]

Routinely employed strategies to reduce the risk of DCI include the use of nimodipine, prevention of hypovolaemia and hypotension, and removal of subarachnoid blood. Nimodipine is a centrally acting calcium channel antagonist that has been shown to reduce the incidence of DCI and improve functional outcomes.[30] It is usually administered enterally at a dose of 60 mg every 4 hours for 21 days.[13] The mechanism of action is unclear, as it does not appear to decrease VS.

Prophylactic therapy including hypervolaemia, hypertension and haemodilution (triple-H therapy) has previously been employed in attempts to prevent DCI. There are no convincing trial data to support this intervention, and the potential complications are significant. Specifically, there are concerns that triple-H therapy may aggravate vasogenic oedema, increase intracranial pressure and lead to haemorrhagic transformation of established infarcts. One case series estimated an intracranial complication rate of 28% attributable to triple-H therapy.[31] Extracranial complications include pulmonary oedema, myocardial infarction, coagulopathy and electrolyte disorders.[15]

The volume of subarachnoid blood is an important predictor of DCI, and various methods to enhance blood clearance have been investigated. Intracisternal administration of thrombolytics appears to decrease DCI[32,33] and, in small RCTs, there was no increase in haemorrhagic complications.[34] Lumbar cerebrospinal fluid (CSF) drainage may also be beneficial.[35] Other therapies trialled in preventing DCI include HMG-CoA reductase inhibitors[36] and hypermagnesaemia.[37] Neither can be recommended, although statins should not be discontinued and hypomagnesaemia should be avoided.

The mainstay of medical treatment for DCI is induced hypertension using vasopressor administration. Ideally, this should take into account the patient's blood pressure and response to augmentation.[14] It is important to note that targeted hypervolaemia does not improve cerebral perfusion and has associated complications.[38] Endovascular treatment options include balloon angioplasty for large proximal vessel VS and intra-arterial vasodilators for distal VS. Angioplasty can dramatically improve proximal angiographic blood flow and vessel patency.[39] Intra-arterial vasodilating agents that have been employed include verapamil, nicardipine, nimodipine, milrinone and papaverine.

What is not known about the care of critically ill patients with SAH in Australia and New Zealand?

Endovascular treatment and outcomes

The availability, utility and outcomes of primary endovascular aneurysm repair in Australia and New Zealand are not known, although it is likely that "clinical creep" has seen this intervention become the standard in many centres. The increasing application of these techniques significantly confounds the interpretation of older outcome literature, and a substantial learning curve also exists. Even more advanced endovascular techniques, such as the use of flow-diverting stents and periprocedural antiplatelet therapy, are rapidly entering clinical practice.[40,41] Therefore, a binational registry may be required to accurately capture outcome statistics with such rapidly evolving technology.

Basic ICU interventions

The day-to-day management of critically ill patients with SAH involves numerous considerations, including (but not limited to) haemodynamic support, temperature regulation, infection control, blood product administration, electrolyte and fluid balance, antifibrinolytic therapy, and venous thromboembolism and seizure prophylaxis. There are few high-quality data to guide clinicians, even for the most basic interventions. For example, the optimal haemoglobin and plasma sodium concentrations in patients with SAH are not known,[42] nor is the ideal duration of seizure prophylaxis, which may not be routinely required after aneurysm repair. Current guidelines provide a useful summary of the complexities involved but offer recommendations largely based on poor-quality evidence.[13,14]

Raised intracranial pressure (ICP) is common after SAH and is associated with increased mortality.[43] There is a paucity of data to guide clinicians on the optimal subset of patients who should be monitored, the threshold (if any) at which ICP should be treated, and the best method to achieve this.[44] The simple extrapolation of existing data from research into TBI seems grossly flawed.

Prevention, identification and treatment of DCI

The principal evidence supporting the use of nimodipine in patients with aneurysmal SAH is from a single RCT[45] that was conducted at a time when management practices were significantly different (eg, surgical intervention occurred for most patients with SAH). This has led to uncertainty in contemporary practice, particularly about the role of intravenous nimodipine, and the optimal timing and dose in patients with unfavourable clinical features and established infarction.[30] Moreover, the utility of nimodipine therapy in patients for whom high-dose vasopressors are required is unclear, and the use of other agents (such as milrinone) requires substantial further investigation.[46] Similarly, the use of lumbar CSF drainage requires further large-scale evaluation, particularly in terms of any procedural or infective complications.[47]

The optimal clinical approach to VS (routine monitoring or targeted investigation) is not known. There are obvious benefits in using TCD to screen for VS, but it does have some important limitations. The device requires training and is operator dependent; incorrectly positioning the probe can

Table 2. Key research questions relating to the critical care of patients with aneurysmal subarachnoid haemorrhage (SAH) in Australia and New Zealand

Physiological targets

- What haemodynamic targets are being employed before and after aneurysm repair? Is SBP or MAP targeted, and are they read from an arterial line or a non-invasive BP cuff?
- What temperature targets are being employed, and by what means are these achieved?
- What serum sodium level targets are being employed, and by what means are these achieved?
- How is fluid balance managed, and does this matter?
- What haemoglobin level threshold is used for blood transfusion in this cohort of patients?
- Are cerebral perfusion pressure targets and intracranial pressure targets being used and, if so, what are they?

Therapeutic interventions

- Which strategies are being employed to detect, prevent and treat delayed cerebral ischaemia? Which endovascular therapies are being used, how is this decided, and do they affect outcomes?
- How is nimodipine being administered in Australia and New Zealand, and does this matter?
- Are antiepileptic medications being routinely prescribed and, if so, which ones and how?
- Is supranormal magnesium therapy being used in Australia and New Zealand?
- Is antifibrinolytic therapy being used to prevent rebleeding and, if so, how?
- Is lumbar CSF drainage or intraventricular thrombolysis being employed in Australia and New Zealand?

Outcome assessment

- What are the outcomes (mortality, morbidity and functional disability) for patients with aneurysmal SAH?
- What factors (physiological, therapeutic or other) determine neurological outcome after SAH?

Processes of care

- What resources (including ICU and hospital length of stay) are used in caring for these patients?
- Is there a relationship between the number of patients admitted to the hospital (or ICU) and outcome?
- Is there a relationship between variability of care (intra-institution) and outcome?

SBP = systolic blood pressure. MAP = mean arterial pressure. BP = blood pressure. CSF = cerebrospinal fluid. ICU = intensive care unit.

generate misleading results.[48] Analysis is also limited by the availability of acoustic windows, restricting the number of vessels that can be examined. The negative predictive value of TCD is also such that it cannot rule out VS.[49]

A more invasive approach is that of cerebral microdialysis. This technique provides continuous bedside measurement of markers of neuronal cell metabolism and injury. It is highly specialised and provides information on only a small area of cerebral tissue;[50] however, it has been successfully used to detect VS after SAH.[51] Overall, the utility of TCD or cerebral microdialysis in terms of patient-centred outcomes has not been established, and their use in Australia and New Zealand is unknown.

Although induced hypertension is commonly used in the treatment of DCI, the optimal blood pressure target, duration of treatment and monitoring technique are unclear. Trying to achieve a specific value without correlating it to clinical features may expose the patient to risk. Although neurological assessment is often significantly confounded in this setting, titrating hypertensive therapy to symptom resolution, while monitoring closely for end-organ complications (such as myocardial ischaemia), would be prudent.

There are also considerable risks associated with endovascular treatments, including intracranial arterial rupture, dissection and occlusion, and haemorrhagic infarction. The intra-arterial vasodilators, particularly papaverine, may cause hypotension, seizures and elevated ICP. It is important to note that surrogate (typically radiological) endpoints are often used to evaluate endovascular rescue therapies, and any impact on patient-centred outcomes is uncertain. The ideal modality, dose and frequency of these interventions remain unknown, as does their relative availability and clinical application in Australia and New Zealand.

Variation in care and the need for future research

Despite significant advances in SAH care, there continues to be substantial heterogeneity in clinical practice.[52-54] Current data suggest that there is significant variation in the use of prophylactic antiepileptic agents, endovascular

interventions, the application of triple-H therapy, and monitoring and treatment of ICP.[1,55]

Several studies have shown an association between a higher hospital SAH caseload and improved outcomes.[56-58] In a 2009 survey, lower-volume centres appeared to have a greater time to definitive aneurysm treatment and higher use of triple-H therapy.[52] A recent retrospective cohort study using data from the Australian and New Zealand Intensive Care Society Adult Patient Database examined the SAH standardised mortality ratio (SMR) in 91 facilities, representing 4320 patients.[5] Three sites had SMRs that were higher, and four (including the two largest centres) had significantly lower SMRs than the remainder of the group.

As with many multifaceted treatment strategies, it is currently uncertain which aspects of the "bundle" of care provided to patients in higher-volume centres are associated with the greatest benefit. The application of strict clinical protocols, regular endovascular intervention, or established, well developed neurosurgical and radiological expertise are all potential candidates. This is a key area for future research and may greatly inform future standards for neurovascular centres in Australia and New Zealand.

The wide variability in management practices reveals significant uncertainty about how best to manage many aspects of this disorder, despite the observation that aneurysmal SAH routinely affects younger patients, who consume significant resources during their hospital stay and are likely to die or be left disabled. Optimal blood pressure targets, haemodynamic augmentation strategies, fluid and electrolyte balance, and the use of neuroradiological interventions are a few of the potential areas for future investigation (see Table 2). A crucial first step is to understand the variation in practice among centres in Australia and New Zealand and to describe the current patterns of morbidity and mortality for patients with SAH.

Conclusions

Clinical outcomes for critically ill patients with aneurysmal SAH in Australia and New Zealand remain poor. About 30% of patients die in hospital and an unknown number are left with significant disability. These patients receive a wide range of therapies in the ICU, but high-quality evidence supporting many of these interventions is generally lacking. A strong rationale exists to pursue a systematic program of SAH research in Australia and New Zealand to identify therapies or processes of care that will lead to improved patient outcomes.

Competing interests

None declared.

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