Management of raised intracranial pressure in aneurysmal subarachnoid hemorrhage: time for a consensus?

Naif M. Alotaibi, MD,1–3 Justin Z. Wang, MD,2 Christopher R. Pasarikovski, MD,2 Daipayan Guha, MD,1,2 Fawaz Al-Mufti, MD,2 Muhammad Mamdani, PharmD, MPH, MA,5 Gustavo Saposnik, MD, MSc,6,7 Tom A. Schweizer, PhD,1,2,6 and R. Loch Macdonald, MD, PhD1,2,6

1Institute of Medical Science, Faculty of Medicine, University of Toronto, and 2Division of Neurosurgery, Department of Surgery, St Michael’s Hospital, University of Toronto, Ontario, Canada; 3Department of Neurosurgery, National Neuroscience Institute, King Fahad Medical City, Riyadh, Saudi Arabia; 4Department of Neurology and Critical Care, Robert Wood Johnson University Hospital, New Brunswick, New Jersey; and 5Li Ka Shing Centre for Healthcare Analytics Research and Training, Institute for Clinical Evaluative Sciences; 6Neuroscience Research Program, Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael’s Hospital; and 6Stroke Outcomes and Decision Neuroscience Research Unit, St. Michael’s Hospital, University of Toronto, Ontario, Canada

Elevated intracranial pressure (ICP) is a well-recognized phenomenon in aneurysmal subarachnoid hemorrhage (aSAH) that has been demonstrated to lead to poor outcomes. Despite significant advances in clinical research into aSAH, there are no consensus guidelines devoted specifically to the management of elevated ICP in the setting of aSAH. To treat high ICP in aSAH, most centers extrapolate their treatment algorithms from studies and published guidelines for traumatic brain injury. Herein, the authors review the current management strategies for treating raised ICP within the aSAH population, emphasize key differences from the traumatic brain injury population, and highlight potential directions for future research in this controversial topic.

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KEY WORDS aneurysm; subarachnoid hemorrhage; aSAH; intracranial pressure; ICP; management
and multifactorial contributors associated with elevated ICP following aSAH make it unique when compared with other causative pathologies associated with intracranial hypertension such as TBI or ischemic stroke.

It has been estimated that more than 50% of aSAH patients will have an ICP > 20 mm Hg at some point during their hospital stay. This percentage is even higher among aSAH patients who present in poor clinical status (60%–70%). Although these numbers are still commonly quoted and have been reported in previous reviews, it should be noted that they were initially obtained from a retrospective case series of aSAH patients who underwent craniotomy following aneurysm rupture. In this series of 433 patients, all aSAH patients underwent postoperative ICP monitoring but only 33% were monitored preoperatively. A recent prospective study, however, showed similarly high rates of elevated ICP following aSAH. Zoerle et al. recorded episodes of ICP > 20 mm Hg lasting at least 5 minutes and the mean ICP value during every 12-hour interval in 116 patients with aSAH. More than 80% of patients had at least one episode of elevated ICP, and 36% of those patients had a mean ICP > 20 mm Hg during their hospital stay.

The most common cause of elevated ICP in aSAH is hydrocephalus—either communicating hydrocephalus, due to impaired cerebrospinal fluid (CSF) absorption from arachnoid villi/granulations as a result of blood in the subarachnoid space, or obstructive hydrocephalus, due to direct blockage of CSF pathways via intraventricular hemorrhage (IVH), which is seen in up to 50% of aSAH cases. The second most common cause is intracerebral hemorrhage (ICH), which occurs in approximately 30% of patients; ICH and IVH are most frequently seen after initial rupture, but they can occur during rebleeding or as intra- or postoperative complications during aneurysm securing procedures.

Another common cause of raised ICP in aSAH is global cerebral edema, which is diagnosed on CT scans based on effacement of the hemispheric sulci and basal cisterns, with loss of hemispheric gray-white matter differentiation. It can be seen on initial CT scans after aneurysm rupture in 8% of patients but may also be found in delayed fashion in 10%–12% of patients. The pathophysiology of global cerebral edema is complex and the postulated mechanisms involved include intracranial circulatory arrest and sudden increase in ICP.

Severe refractory vasospasm is not uncommon following aSAH and may require aggressive treatment with intraarterial vasodilator therapy using nicardipine, papaverine, milrinone, verapamil, or a combination of those. High ICP in aSAH can occur following vasodilator therapy, especially with papaverine. The mechanism of this complication is not well understood, but a sudden increase in cerebral blood volume secondary to vasodilation is probably the cause. A multicenter randomized study (ClinicalTrials.gov identifier NCT01996436) is currently being conducted to compare different intraarterial agents, which is expected to provide a higher level of evidence on the effect of these medications on ICP in the aSAH population.

Other less common causes of elevated ICP in aSAH include subdural hematoma (5%), massive cerebral infarction secondary to vasospasm (2%–3%), and extracranial causes such as raised intrathoracic pressure from neurogenic pulmonary edema, central fever, severe hyponatremia, or overcorrection of hyponatremia.

Monitoring Strategies

Patients with good neurological status who are responsive to instruction are usually monitored through serial clinical examinations. Since the majority of patients with aSAH either present with hydrocephalus or develop it at some point during their hospital stay, external ventricular drains (EVDs) are most commonly used both to monitor and manage elevated ICP via CSF drainage if needed. It is for the latter reason that parenchymal pressure monitors are rarely used in aSAH as they do not allow therapeutic CSF drainage. EVDs can also assist in determining if there is a need for permanent CSF diversion such as via insertion of a ventriculoperitoneal shunt. The main disadvantage of using EVDs for ICP monitoring is that ICP values are unreliable when the EVD is open and CSF is being continuously drained. EVDs must be closed for several minutes to accurately assess the true ICP value.

The use of other invasive monitoring, such as microdialysis, tissue oxygenation probes, and radioac
tric tracers, to predict secondary ischemia/hypoxia in aSAH has not yet gained broad clinical acceptance, and the current evidence is insufficient to support its routine use. Similarly, noninvasive methods of ICP monitoring, including near-infrared spectroscopy, optic nerve sheath diameter monitoring, pulsatility index on transcranial Doppler ultrasonography, and electroencephalogram power spectrum analysis, are evolving technologies that have tremendous potential but currently remain in the experimental phase.

In 2014, researchers and clinical experts from the Neurocritical Care Society and the European Society of Intensive Care Medicine organized the International Multidisciplinary Consensus Conference on Multimodal Monitoring Strategies. Results of the meeting provided several important recommendations (e.g., continuous monitoring for ICP in poor-grade aSAH patients) based on a rigorous systematic review, in an effort to unify ICP monitoring strategies among high-volume tertiary centers.

Impact of Raised ICP on aSAH Outcomes

Despite the variation between studies of the type of ICP monitoring used and the precise cut-off values for elevated ICP, patients with high ICP during their hospital course following aSAH have consistently trended toward higher mortality rates and worse functional outcomes. Elevated ICP and its etiologies (ICH, IVH, global edema, and so on) have all been found to be independent predictors of death. While this association has been identified in large retrospective series, the impact of high ICP on aSAH outcomes has not yet been evaluated in large prospective multicenter series. However, a recent systematic review that examined 26 studies focusing on elevated ICP and aSAH outcomes also concluded that higher ICP following aSAH was associated with a higher mortality.
TABLE 1. Recommendations from the Brain Trauma Foundation for TBI-associated raised ICP and the limitations and implications of applying them to aSAH patients

<table>
<thead>
<tr>
<th>Recommendation*</th>
<th>Limitations/Considerations in aSAH Patients</th>
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<tbody>
<tr>
<td>&quot;Bifrontal DC is not recommended to improve outcomes in severe TBI patients with diffuse injury (without mass lesions)&quot;</td>
<td>Diffuse injury/edema (without mass lesions) occurs in less than 10% of aSAH patients and is not a common indication for DC in aSAH.15,20</td>
</tr>
<tr>
<td>&quot;Mannitol is effective for control of raised ICP at doses of 0.25 to 1 g/kg body weight&quot;</td>
<td>Mannitol can lead to serious hypotension and hypovolemia that is against the recommendation of aSAH guidelines.52,67 Hypertonic saline could be superior to mannitol since most aSAH patients are hyponatremic.</td>
</tr>
<tr>
<td>&quot;An EVD system zeroed at the midbrain with continuous drainage of CSF may be considered to lower ICP burden more effectively than intermittent use&quot;</td>
<td>Continuous drainage has been shown to be associated with worse adverse events in aSAH.57</td>
</tr>
<tr>
<td>&quot;High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment&quot;</td>
<td>High-dose barbiturate will interfere with neurological monitoring for DCI.20</td>
</tr>
<tr>
<td>&quot;The use of steroids is not recommended for improving outcome or reducing ICP&quot;</td>
<td>Recent studies have linked corticosteroids in SAH patients with favorable outcomes,17,21,24 but it has not been evaluated for aSAH patients with raised ICP.</td>
</tr>
</tbody>
</table>

DC = decompressive craniectomy.

Management of Raised ICP in aSAH

General Principles

There are no specific guidelines from the American Heart Association14 or the Neurocritical Care Society20 dedicated to the management of high ICP in patients with aSAH. Most reviews and recommendations are based on TBI guidelines by the Brain Trauma Foundation, which recommend ICP monitoring in those with Glasgow Coma Scale scores ≤ 8 to maintain ICP < 22 mm Hg and cerebral perfusion pressure (CPP) between 60–70 mm Hg.10 Applying the same management algorithm to aSAH has gained traction without any strong supporting evidence of efficacy. Table 1 presents some of the current Brain Trauma Foundation recommendations for elevated ICP and several theoretical limitations to consider when applying them to aSAH.

The initial management of aSAH is highly dependent on initial neuroimaging.20 If signs of acute hydrocephalus are present, urgent EVD insertion is a potentially life-saving procedure. The clinical response to EVDs in patients with initially poor neurological status has been shown to be a good predictor of outcome.60 However, the ideal rate and duration of CSF drainage following EVD insertion is controversial. A recent randomized controlled trial (RCT) compared continuous CSF drainage to intermittent drainage in 60 patients following aSAH. The investigators found that the overall rate of complications (EVD blockage, infection, CSF leak, hemorrhage) was higher in the continuous drainage group, but there were no significant differences in ICP control, rates of delayed cerebral ischemia (DCI), or functional outcomes.57 The optimal duration of CSF diversion, and the techniques for EVD weaning, were not explored in this study and remain the target of future investigation.

Hyposmolar Agents

The use of osmotically active agents, such as mannitol and hypertonic saline, to manage elevated ICP is common practice in the setting of trauma and aSAH. Hyperosmolar agents create a gradient across the blood-brain barrier, causing a shift in fluid from the interstitial and intracellular space into the bloodstream.68 This decreases the overall fluid volume within the brain and, through the principles of the Monro-Kellie hypothesis, results in a decrease in ICP.

Important differences between mannitol and hypertonic saline exist. Mannitol is a strong diuretic that can cause intravascular volume contraction and alter blood rheology.68 Hypertonic saline has minimal diuretic effect and can increase blood pressure and serum sodium. In the setting of aSAH, parameters such as fluid balance, blood pressure, serum sodium, and serum osmolality must be managed carefully to prevent secondary injury and reduce the risk of vasospasm/DCI.18 Furthermore, current guidelines recommend euvolume and hypertensive therapy in the setting of DCI.14

The optimal hyposmolar agent to lower raised ICP in aSAH is contentious. A recent publication surveyed members of the Neurocritical Care Society and found that while 90% of members used hyposmolar agents for refractory elevated ICP, 55% preferred hypertonic saline to mannitol.31 Our recent systematic review59 on hyposmolar agents in aSAH revealed 2 randomized studies examining the effect of hypertonic saline on ICP in aSAH. Huang and Yang59 found no difference between mannitol and hypertonic saline in controlling refractory raised ICP ≥ 20 mm Hg. Hypertonic saline decreased ICP by a mean of 9.9 mm Hg (p < 0.01). The population was composed of poor-grade patients. A second study by Bentsen et al.3 in
2006 was a single-blind RCT comparing hypertonic saline to normal saline. The patients were hemodynamically stable, with ICP between 10 and 20 mm Hg. The study was not conducted on patients with refractory raised ICP, as it would be unethical to give normal saline in this scenario. The authors found that hypertonic saline decreased ICP by 3 mm Hg (p = 0.04) compared with normal saline. There is no consensus within the literature with respect to hypertonic saline dose concentration, volume of infusion, or timing of repeat dosing. The most commonly reported hypertonic saline concentrations were between 3% and 23.5%. Both concentrations appeared effective at decreasing ICP. Most centers used serum sodium of 155–160 and serum osmolality of 320 mEq as the upper limit for safe repeat dosing.59

**Hypothermia and Barbiturate Coma**

Experimental animal studies have shown that mild hypothermia may reduce cerebral swelling secondary to aSAH and improve outcomes, although this effect failed to translate to clinical studies in humans.51 Hypothermia during aneurysm surgery as a method for neuroprotection did not improve patient outcomes in the Intraoperative Hypothermia for Aneurysm Surgery Trial (also known as IHAST), which included 1001 patients.69 Furthermore, a large single-center, observational study of 100 aSAH patients with raised ICP and/or refractory vasospasm showed an adverse event rate of 93% following the use of mild hypothermia.66 which could explain why targeted hypothermia has not been adopted for clinical practice in aSAH. Although cerebral metabolism and cerebral blood flow are often thought to be coupled and to change in a linear fashion, studies have shown that this relationship may in fact be uncoupled during hypothermia, whereby there may be a disproportionate decrease in cerebral blood flow relative to cerebral metabolism. In addition, carbon dioxide production is decreased in hypothermia. This contributes, in part, to the effect of decreased ICP, but it also may cause cerebral hyperperfusion and increase the affinity of hemoglobin for oxygen, thereby further hindering the delivery of oxygen to brain tissue. On the other hand, fever, which is common after aSAH, is an independent predictor of poor outcome.63 Higher temperatures induce an acute-phase reaction that leads to an increased cerebral metabolic distress (e.g., release of excitatory amino acids such as glutamate, creation of free radicals, and elevated lactate/pyruvate ratio).48,54,65 Therefore, it appears there must be a middle ground whereby the adverse effects of both temperature extremes can be balanced.

The role of hypothermia in poor-grade aSAH was never evaluated in “pre-hospital arrival” settings or “within the acute period after ictus.” This has been shown to be beneficial for post-cardiac arrest patients.8,64 and given the similarity between poor-grade aSAH and cardiac arrest patients in terms of pathophysiology for early brain injury (e.g., global transient circulatory arrest, hypoxic ischemic mechanisms), early or ultra-early hypothermia is still a potential treatment to be investigated for poor-grade patients.20 Barbiturates are usually one of the last interventions to be considered for treating refractory elevated ICP in TBI due their relatively high rate of adverse events, which include prolonged sedation, metabolic derangements, respiratory suppression, and cardiovascular events.20 Barbiturate coma alone has never been evaluated in a dedicated cohort for elevated ICP associated with aSAH. Most centers have reported their experience with a mixed patient sample of many intracranial pathologies.19,41 The main drawback of inducing a barbiturate coma in aSAH patients is the loss of the neurological status for DCI monitoring. Symptomatic DCI will be difficult to recognize even during neurological wake-up because the effects of high-dose barbiturates tend to persist after their cessation due to their long biological half-life.55 Therefore, using short-acting paralytic agents in combination with sedation could be superior to inducing a full barbiturate coma in aSAH patients. Table 2 shows the studies that were conducted for hypothermia and barbiturates in aSAH patients and demonstrates the heterogeneity among studies in terms of patient selection, outcome measures, and indications for treatment.

**Decompressive Craniectomy**

Decompressive craniectomy is frequently used as a life-saving surgical technique for elevated ICP or mass effect secondary to ischemic infarction or TBI.36 Multiple studies have found that decompressive craniectomy is very effective in reducing ICP and increasing CPP. However, the effects of decompressive craniectomy on functional outcomes are still controversial.45 In the aSAH population, decompressive craniectomy is usually performed to treat poor-grade patients with associated ICH or cerebral infarction and significant mass effect, although these indications are highly variable and are not well studied in the literature.51 Our recent meta-analysis3 of previous studies examining decompressive craniectomy in patients with poor-grade aSAH showed high pooled event rates of poor outcomes (60%) (defined as severe disability, vegetative state, or death) and mortality (29%) among craniectomy patients; these are not different from the natural history reported for poor-grade patients.6,8 This raises concerns about the current practice and indications for decompressive craniectomy in aSAH.

Our meta-analysis results must be carefully interpreted since the quality of evidence is based on observational studies and considered “low-quality” as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading clinical evidence.30 Furthermore, we were unable to conclude if decompressive craniectomy is superior to medical management for high ICP because a control group was absent in most studies. RCTs are the gold standard in this setting, and there is no doubt that carrying out an RCT of decompressive craniectomy in poor-grade aSAH presents challenges greater than the already known limitations of doing such trials in the overall aSAH population. These new challenges will be related to the heterogeneity of high ICP in aSAH—i.e., the timing, pathology, and severity/cutoff values of high ICP and other factors that may influence imbalances between baseline characteristics, which include clinical herniation signs, ICH volume, and degree of midline shift. Furthermore, the body of evidence on all preoperative
management options for high ICP in aSAH is limited, and several important questions need to be answered prior to conducting RCT for decompressive craniectomy in poor-grade aSAH.

**Discussion**

Intracranial hypertension is a well-recognized phenomenon in aSAH that has been demonstrated to lead to poor outcomes. In fact, elevated ICP is known to be a significant contributor to secondary brain injury following aneurysm rupture and is an independent predictor of poor functional outcome and increased mortality. In addition, surgical securing of ruptured aneurysms has been shown to be more complicated when cerebral edema is present. However, elevated ICP has also long been thought to play a role in the arrest of the hemorrhage such that lowering the ICP may contribute to a greater risk of rebleeding. There is the notion that a “sweet spot” exists within a certain range of ICP values that will decrease the risk of secondary brain injury and lead to improved outcomes. Several studies on ICP monitoring in TBI have shown that increased monitoring and subsequent control of elevated ICP leads to better outcomes. These same principles have been translated to patients with aSAH despite significant differences in the pathophysiology of the conditions and without the same type of supporting evidence. The relative paucity of well-designed, large-scale randomized trials evaluating the optimal management of elevated ICP following aSAH has led to a lack of consensus to guide clinical management, even for strategies that have been shown to potentially beneficial such as hyperosmolar therapy and decompressive craniectomy.

Some of the complexity of designing studies for intracranial hypertension arise from the ethical obligation to not withhold potentially beneficial treatment from patients. For example, it would be unethical to use a placebo control group for patients with refractory intracranial hypertension. Therefore, in some instances, efforts to resolve the uncertainties in the management of elevated ICP in aSAH may benefit from the utilization of formal consensus methods. Consensus methods have been shown to be beneficial in instances where published data are scarce and where a wider and more heterogeneous range of information must be taken into consideration. In the past, consensus methods have been used to resolve a number of critical medical issues, including intraocular lens implantation, coronary artery bypass surgery, and breast cancer treatment. They are still currently used when there is a lack of published data and/or there are contradictory studies which obfuscate proper interpretation of the available data.

In 2016, the World Health Organization used a 3-day consensus conference involving experts from around the world to develop a set of new classification guidelines on central nervous system tumors that was a dramatic change from its 2007 counterpart. Consensus methods have been used to resolve a number of critical medical issues, including intraocular lens implantation, coronary artery bypass surgery, and breast cancer treatment. They are still currently used when there is a lack of published data and/or there are contradictory studies which obfuscate proper interpretation of the available data.

### Table 2: Studies with more than 10 patients that were conducted for hypothermia and barbiturates in aSAH

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Country</th>
<th>No. of Patients</th>
<th>Score</th>
<th>Study Design</th>
<th>Primary Indication</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypothermia</strong></td>
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<tr>
<td>Hindman et al., 1999</td>
<td>United States</td>
<td>52</td>
<td>WFNS I–III</td>
<td>Randomized trial (pilot)</td>
<td>Neuroprotection during aneurysm surgery</td>
<td>NIHSS</td>
</tr>
<tr>
<td>Kimme et al., 2004</td>
<td>Sweden</td>
<td>266</td>
<td>H&amp;H I–V</td>
<td>Prospective</td>
<td>Neuroprotection during aneurysm surgery</td>
<td>Adverse events</td>
</tr>
<tr>
<td>Todd et al., 2005</td>
<td>United States</td>
<td>1001</td>
<td>WFNS I–III</td>
<td>Randomized trial</td>
<td>Neuroprotection during aneurysm surgery</td>
<td>GOS, Barthel Index, NIHSS</td>
</tr>
<tr>
<td>Chouhan et al., 2006</td>
<td>India</td>
<td>47</td>
<td>WFNS I–V</td>
<td>Randomized trial (pilot)</td>
<td>Neuroprotection during aneurysm surgery</td>
<td>GOS</td>
</tr>
<tr>
<td>Anei et al., 2010</td>
<td>Japan</td>
<td>19</td>
<td>WFNS IV–V</td>
<td>Retrospective</td>
<td>Neuroprotection for poor-grade aSAH</td>
<td>mRS</td>
</tr>
<tr>
<td><strong>Barbiturates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Keller et al., 2005</td>
<td>Switzerland</td>
<td>23</td>
<td>H&amp;H I–V</td>
<td>Prospective</td>
<td>Refractory vasospasm</td>
<td>GOS</td>
</tr>
<tr>
<td>Seule et al., 2009</td>
<td>Switzerland</td>
<td>100</td>
<td>H&amp;H III–V</td>
<td>Prospective</td>
<td>Raised ICP &amp;/or refractory vasospasm</td>
<td>GOS, adverse events</td>
</tr>
<tr>
<td>Finfer et al., 1999</td>
<td>Australia</td>
<td>11</td>
<td>NA</td>
<td>Retrospective</td>
<td>Refractory vasospasm</td>
<td>GOS</td>
</tr>
<tr>
<td>Dereeper et al., 2002</td>
<td>Belgium</td>
<td>21</td>
<td>WFNS IV (mean)</td>
<td>Retrospective</td>
<td>Raised ICP</td>
<td>GOS</td>
</tr>
<tr>
<td>Heo et al., 2003</td>
<td>Korea</td>
<td>18</td>
<td>GCS 4–8</td>
<td>Prospective</td>
<td>Refractory vasospasm</td>
<td>GCS, GOS</td>
</tr>
</tbody>
</table>

GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; H&H = Hunt and Hess; mRS = modified Rankin Scale; NA = not available; NIHSS = National Institutes of Health Stroke Scale; WFNS = World Federation of Neurosurgical Societies.
Our review highlights many unanswered questions for the management of high ICP in aSAH, which require consensus methods and further research. These include the following: establishing ICP/CPP-targeted goals during initial resuscitation, determining optimum methods of CSF drainage and ICP recordings from EVDs, comparing hypertonic saline and mannitol as first-line therapies, examining the role of ultra-early or early hypothermia in poor-grade aSAH, identifying a subgroup that benefits from decompressive craniectomy in terms of functional outcomes, and, most importantly, developing a universal management algorithm that consider the unique hemodynamics and complications of aSAH.

In addition, whenever possible, future prospective trials should still be sought out. In their 2013 review on managing intracranial hypertension in aSAH, Mak et al. supported a future RCT involving decompressive craniectomy for medically refractory intracranial hypertension in aSAH. Matched case-control studies can be performed when randomized studies are not feasible to potentially identify whether ICP monitoring or strict ICP control leads to better functional outcomes in patients presenting with various grades of hemorrhages. Lastly, because the definitions of “normal” and “elevated” ICP in aSAH have traditionally been translated directly from studies on TBI, they may need to be adjusted considering the significant differences in pathophysiology. For example, a higher range of ICP levels may be more permissible in aSAH due to its hemostatic effect on preventing rebleeding compared with that in TBI and also because most aSAH patients presents with a high mean arterial blood pressure, which may allow for cerebral hyperperfusion to develop if ICP is rapidly lowered. However, currently no studies have been able to describe a well-defined and reliable range of what constitutes physiological and pathological ICP in aSAH. Identifying time-dependent ICP thresholds for aSAH patients may have important implications for guiding targeted therapy and predicting outcomes.

Conclusions
The roles of all current management interventions to treat high ICP in aSAH are not well studied. Accordingly, there is an urgent need to examine the best available evidence with systematic reviews and establish consensus methods. This will have important implications for guiding targeted therapy and predicting outcomes.

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Disclosures
Dr. Macdonald reports that he is an employee and the Chief Scientific Officer of Edge Therapeutics, Inc.

Author Contributions
Conception and design: Alotaibi. Acquisition of data: Alotaibi, Wang, Pasarikovski. Analysis and interpretation of data: all authors. Drafting the article: Alotaibi, Guha. Critical revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Alotaibi. Study supervision: Alotaibi, Macdonald.

Correspondence
Naif M. Alotaibi, Division of Neurosurgery, University of Toronto, 399 Bathurst St., WW 4-427, Toronto, ON M5T 2S8, Canada. email: naif.alotaibi@mail.utoronto.ca.