

# Critical Care Management of Patients Following Aneurysmal Subarachnoid Hemorrhage: Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference

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**Abstract** Subarachnoid hemorrhage (SAH) is an acute cerebrovascular event which can have devastating effects on the central nervous system as well as a profound impact on several other organs. SAH patients are routinely admitted to an intensive care unit and are cared for by a multidisciplinary team. A lack of high quality data has led to numerous

approaches to management and limited guidance on choosing among them. Existing guidelines emphasize risk factors, prevention, natural history, and prevention of rebleeding, but provide limited discussion of the complex critical care issues involved in the care of SAH patients. The Neurocritical Care Society organized an international, multidisciplinary consensus conference on the critical care management of SAH to address this need. Experts from neurocritical care, neurosurgery, neurology, interventional neuroradiology, and neuroanesthesiology from Europe and North America were recruited based on their publications and expertise. A jury of four experienced neurointensivists was selected for their experience in clinical investigations and development of practice guidelines. Recommendations were developed based on literature review using the GRADE system, discussion integrating the literature with the collective experience of the participants and critical review by an impartial jury. Recommendations were developed using the GRADE system. Emphasis was placed on the principle that

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**Disclaimer** This statement is provided as an educational service of the Neurocritical Care Society. It is based on an assessment of current literature and the consensus of the opinions of the attendees and jury of the conference. It is not intended to include all possible proper methods of care for SAH patients. Neither is it intended to exclude any reasonable alternative methodologies. The Neurocritical Care Society recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. No formal practice recommendations should be inferred.

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The Organizer, Members of the Jury, and Conference participants in the International Multi-disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage are listed in Appendix.

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recommendations should be based not only on the quality of the data but also tradeoffs and translation into practice. Strong consideration was given to providing guidance and recommendations for all issues faced in the daily management of SAH patients, even in the absence of high quality data.

**Keywords** Subarachnoid hemorrhage · Critical care · Aneurysm · Vasospasm · Anticonvulsants · Hyponatremia · Endovascular · Fever

## Introduction

Subarachnoid hemorrhage (SAH) is an acute cerebrovascular event which can have devastating effects on the central nervous system as well as a profound impact on several other organs. The course of the disease can be prolonged, with considerable secondary brain injury due to delayed cerebral ischemia (DCI). Systemic manifestations affecting cardiovascular, pulmonary, and renal function are common, and complicate the management of DCI.

Due to the profound effects of the hemorrhage itself and the risk of early rebleeding and hydrocephalus, SAH patients are routinely admitted to an intensive care unit and are cared for by a multidisciplinary team including neurosurgeons, (neuro) intensivists, (neuro) anesthesiologists and interventional neuroradiologists. The ICU course of SAH patients ranges from a few days to a few weeks and is frequently accompanied by multiple medical complications.

Despite considerable effort, only one intervention—the use of nimodipine—for this complex multifaceted disorder

has been proven to improve outcome in prospective randomized controlled trials [1]. This lack of high quality definitive data has led to numerous approaches to management and provides limited guidance on choosing among them.

There have been relatively few guidelines developed for SAH management. They emphasize risk factors, prevention, natural history, and prevention of rebleeding, but provide limited discussion of the critical care issues involved in the care of SAH patients. In order to provide a comprehensive review of those issues the Neurocritical Care Society organized a multidisciplinary consensus conference on the critical care management of SAH. Topics were chosen based on their relevance to the critical care management of patients with aneurysmal SAH. Procedures used to repair aneurysms were not addressed.

## Statement of Purpose

The purpose of the consensus conference was to develop recommendations for the critical care management of patients following acute SAH. The complex multi-organ pathophysiology of SAH presents a multitude of clinical challenges which demand attention. For each situation decisions must be made about if, when, and how to intervene. Ideally, each decision would be made based on high quality data; yet the reality is that such data rarely exist. Still, decisions about management must be made. Recommendations were developed based on the literature, a robust discussion regarding the interpretation of the literature, the collective experience of the members of the group and review by an impartial jury.

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## Process

Topics were identified based on clinical decision points in the critical care management of SAH patients. Experts drawn from Europe and North America from the fields of neurosurgery, neurocritical care, neurology, interventional neuroradiology, and neuroanesthesiology were recruited based on their expertise related to each topic. A jury of four experienced neurointensivists was selected for their expertise in clinical investigation and development of practice guidelines.

Each participant performed a critical literature review. The findings were summarized in tables and a summary was prepared which reviewed the data and provided specific management recommendations. These were submitted in draft form before the conference and distributed to all participants.

The quality of the data was assessed and recommendations developed using the GRADE system [2]. The quality of the evidence was graded as:

- High = Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low = Any estimate of effect is very uncertain.

The GRADE system classifies recommendations as strong or weak, according to the balance among benefits, risks, burden, and cost, and according to the quality of evidence. Keeping those components explicitly separate constitutes a crucial and defining feature of this grading system. An advantage of the GRADE system is that it allows for strong recommendations in the setting of lower quality evidence and thus it is well suited to this situation. Recommendations were either strong or weak and based on the following:

- The trade-offs, taking into account the estimated size of the effect for the main outcomes, the confidence limits around those estimates, and the relative value placed on each outcome
- The quality of the evidence
- Translation of the evidence into practice in a specific setting, taking into consideration important factors that could be expected to modify the size of the expected effects

The conference took place on October 22–23, 2010. Each participant presented a summary of the data and recommendations to the jury and other participants. Presentations were followed by discussion focused on refining the proposed management recommendations. Approximately 1/3 of the conference time was utilized for discussion.

The jury met for 2 days after the conference and again at a subsequent 2-day meeting and held several conference calls. They reviewed selected key studies, the recommendations made by the primary reviewers and the discussion that took place at the conference. Strong consideration was given to providing guidance and recommendations for all issues faced in the daily management of SAH patients, even in the absence of high quality data.

## Medical Measures to Prevent Rebleeding

### Questions Addressed

- Do any medical interventions reduce the incidence of rebleeding in patients awaiting definitive management of their ruptured aneurysm?
- Do alterations in investigative approaches reduce the incidence of rebleeding in patients awaiting definitive management of their ruptured aneurysm?
- Does stringent blood pressure reduction reduce the incidence of rebleeding in patients awaiting definitive management of their ruptured aneurysm?

### Summary of the Literature

Rebleeding following aneurysmal SAH is common. Its incidence is highest immediately following the initial hemorrhage (5–10% over the first 72 h) [3], is higher in patients with poor-grade SAH, larger aneurysms, sentinel bleeds, and those who undergo catheter angiography within 3 h of the ictus. Immediate repair of the ruptured aneurysm by either coil embolization or microsurgical clip ligation markedly reduces the risk of rebleeding, with microsurgical exclusion being slightly more efficacious [4]. Nevertheless, some patients are either too sick for immediate repair or require transport to a center where repair can be performed. Repair procedures have significant risks and require experienced teams to minimize the serious procedural side effects of repair. This fact can lead to further delay in repair, and increase the risk of rebleeding. We considered three interventions that might modulate this risk: antifibrinolytic therapy, catheter vs. CT angiography, and blood pressure control.

Nine studies of antifibrinolytic therapy prior to 2002 involving 1399 patients showed no benefit on poor outcome or death despite a marked significant reduction in rebleeding, probably due to a significantly higher incidence of cerebral ischemia in the treated patients [5]. It is noteworthy that all of these studies continued therapy for weeks (into the period when the risk of vasospasm was high), and at least one of these studies initiated therapy as late as 4 days post-ictus, when the risk of rebleeding was

substantially reduced. More recently, one randomized trial (involving 505 patients) [6] and two case control studies (involving 428 patients) [7, 8] examined whether an early short course of antifibrinolytic therapy can reduce the risk of rebleeding while early, safe repair is being arranged. A third study also found a reduction in rebleeding but noted an increased incidence of DVTs [8]. These studies suggest a uniform reduction in rebleeding rates from ~11 to ~2.5%, but the studies were not adequately powered to determine the effect of antifibrinolytic therapy on overall patient outcome.

Several case reports or case series report aneurysmal rebleeding when catheter angiography is undertaken very early (less than 3–6 h) following aneurysmal SAH. Specific rebleeding rates are difficult to compute, as many of these are individual case reports, and the denominator in case series (i.e., the total number of patients undergoing early angiography) is poorly defined. However, rates as high as 20–38.5% have been quoted [9–13]. It seems unwarranted to conclude this is a specific risk attributable to DSA for several reasons. First, where a clear denominator is provided to assess the incidence of rebleeding, figures are much lower (~5%) [11]. Second, it is unclear whether these instances of rebleeding with DSA actually reflect a risk of the procedure, or are simply a manifestation of the high rebleeding rates known to occur after initial aneurysm rupture. Third, there is no satisfactory direct comparison of rebleeding with and without DSA or to CTA within the first 6 h post-SAH; the one case series that does report a twofold risk with DSA included only a small number of patients [12]. Intriguingly, reports of contrast extravasation during ultra-early CTA [14, 15] have heretofore been interpreted as the investigation being able to image the process of early rebleeding [13], rather than being a cause of such rebleeding.

There are no systematic data that address blood pressure levels in patients with unsecured aneurysms in relation to the risk of rebleeding. Some early studies of hypervolemic-hypertensive therapy reported aneurysmal rebleeding or hemorrhagic transformation of hypodense lesions with elevation of systolic blood pressure to 160–200 mmHg. However, more recent series do not report rebleeding at systolic blood pressure in this range, and the clear consensus of the participants at the workshop was that modest blood pressure elevation (mean arterial pressure <110 mmHg; systolic blood pressure <160 mmHg) was not associated with rebleeding.

## Discussion

Further definitive evidence of benefit from antifibrinolytic agents will require a trial with very early identification of patients and early administration of tranexamic acid or aminocaproic acid, a large sample size and sufficient power

to detect an effect on functional outcome. Patients in good neurological condition with evidence of sentinel hemorrhage, loss of consciousness at ictus and who harbor larger aneurysms on initial CTA are likely to be the best population for study. There appears to be sufficient equipoise in the USA for such a trial to be conducted, and we would underline the fact that our recommendations in this area would need to be revised when data from such a study were available. Given the less-than-definitive evidence on which we have based our recommendation for early antifibrinolytic therapy, we have explicitly stated several cautionary recommendations that would mitigate against side effects of the intervention.

We did not feel that the data available provided a clear basis for attributing an increased rebleeding risk to ultra-early DSA. Formal assessment of catheter vs. CT angiography in the hyperacute phase would require further collection of epidemiological data in the first instance, and a large trial comparing the two would be needed to provide definitive recommendations. Given that CTA is now well established, it seems unlikely that a large RCT comparing DSA and CTA will ever materialize. However, pending the continued collection of epidemiological data, it was felt that choosing CTA over DSA for ultra-early angiography was a reasonable option where both options are available, the technical quality of CTA was good, and an endovascular intervention was not planned at the time of angiography. However, in the setting of SAH, the overwhelming aim is to detect and secure a culprit aneurysm, and there is no case for delaying investigation (either CTA or DSA) to reduce any theoretical risk of rebleeding.

There appears to be little concern that rebleeding with modest blood pressure elevation is a significant clinical issue, and there was no enthusiasm for a study addressing this issue.

## Recommendations

- Early aneurysm repair should be undertaken, when possible and reasonable, to prevent rebleeding (High Quality Evidence; Strong Recommendation).
- An early, short course of antifibrinolytic therapy prior to early aneurysm repair (begun at diagnosis; continued up to the point at which the aneurysm is secured or at 72 h post-ictus, whichever is shorter) should be considered (Low Quality Evidence; Weak Recommendation).
- Delayed (>48 h after the ictus) or prolonged (>3 days) antifibrinolytic therapy exposes patients to side effects of therapy when the risk of rebleeding is sharply reduced and should be avoided (High Quality Evidence; Strong Recommendation).
- Antifibrinolytic therapy is relatively contraindicated in patients with risk factors for thromboembolic

complications (Moderate Quality Evidence; Strong Recommendation).

- Patients treated with antifibrinolytic therapy should have close screening for deep venous thrombosis (Moderate Quality Evidence; Strong Recommendation).
- Antifibrinolytic therapy should be discontinued 2 h before planned endovascular ablation of an aneurysm (Very Low Quality Evidence; Weak Recommendation).
- When CTA and DSA are both available and CTA is of high technical quality, CTA should be performed preferentially if endovascular intervention is not planned at the time of angiography (Very Low Quality Evidence; Weak Recommendation).
- Treat extreme hypertension in patients with an unsecured, recently ruptured aneurysm. Modest elevations in blood pressure (mean blood pressure <110 mmHg) do not require therapy. Pre-morbid baseline blood pressures should be used to refine targets; hypotension should be avoided (Low Quality Evidence; Strong Recommendation).

### Seizures and Prophylactic Anticonvulsant Use

#### Questions Addressed

- What is the incidence and impact of convulsive and non-convulsive seizures after SAH?
- Does anticonvulsant prophylaxis influence this incidence?

#### Summary of the Literature

Abnormal movements that may appear seizure-like are common at the onset of SAH, but it is usually unclear whether this is a true seizure or represents posturing at the time of aneurysm rupture [16, 17]. Clinical seizures are uncommon after the initial aneurysm rupture (occurring in 1–7% of patients) and when they occur in patients with an unsecured aneurysm, they are often the manifestation of aneurysmal re-rupture [4, 18]. Risk factors for the development of seizures in SAH are surgical aneurysm repair in patients >65 years of age, thick subarachnoid clot, and possibly intraparenchymal hematoma or infarction [16, 17]. Prophylactic treatment with anticonvulsants in SAH patients without seizures has previously been commonplace, although no randomized trials specifically addressing this issue have been performed. Recent studies have suggested that anticonvulsant use is associated with worsened long-term outcome after SAH, although most of the patients in these studies were treated with phenytoin

[19, 20]. Thus, prophylactic anticonvulsant therapy with phenytoin may worsen outcome, although the impact of other anticonvulsant medications is less clear. Also, in patients with no history of seizure, a short course (72 h) of anticonvulsant prophylaxis seems as effective as a more prolonged course in preventing seizures [21]. In comatose (poor-grade) SAH patients, non-convulsive seizures may be detected on continuous EEG (cEEG) in 10–20% of cases [22–24]. While patients with non-convulsive seizures have a worsened outcome, the impact of successful treatment of these non-convulsive seizures has not been studied. Also, the influence of anticonvulsant prophylaxis on the occurrence of non-convulsive seizures has not been studied.

#### Discussion

There was general agreement among the participants that current evidence raises concern that anticonvulsants, specifically phenytoin, may worsen outcome after SAH. Therefore, there was consensus that routine prophylactic phenytoin use should not be undertaken after SAH. There was, however, controversy regarding use of other anticonvulsant medications and the unknown potential for anticonvulsants to lessen the impact of non-convulsive seizures. Also, the possibility that certain subgroups, such as elderly patients undergoing craniotomy, may have a higher seizure risk led the group to consider that a short course (3–7 days) of anticonvulsant prophylaxis might still be considered in certain situations, especially if an agent other than phenytoin was used. There was also agreement that patients who suffer a clear clinical seizure after the period of aneurysmal rupture should be treated with anticonvulsants, but that if seizures do not recur, these anticonvulsants should be discontinued after 3–6 months. There was disagreement about whether an EEG should be performed at that time and, if so, whether seizure-free patients with an epileptic focus should be continued on anticonvulsants. There was consensus that cEEG is probably underutilized in poor-grade SAH patients and that non-convulsive seizures are common. However, there was concern regarding whether these non-convulsive seizures represented markers of disease severity or a target for treatment. Thus, there was modest disagreement on the aggressiveness with which to pursue treatment of non-convulsive seizures. There was a general agreement that one or perhaps two anticonvulsants should be used to attempt to treat non-convulsive seizures identified on cEEG, but disagreement about whether to pursue more aggressive means such as benzodiazepine or barbiturate infusions if initial measures were unsuccessful.

## Recommendations

- Routine use of anticonvulsant prophylaxis with phenytoin is not recommended after SAH (low quality evidence—strong recommendation).
- Routine use of other anticonvulsants for prophylaxis may be considered (very low quality evidence—weak recommendation).
- If anticonvulsant prophylaxis is used, a short course (3–7 days) is recommended (low quality evidence—weak recommendation).
- In patients who suffer a seizure after presentation, anticonvulsants should be continued for a duration defined by local practice (low quality evidence—weak recommendation).
- Continuous EEG monitoring should be considered in patients with poor-grade SAH who fail to improve or who have neurological deterioration of undetermined etiology (low quality evidence—strong recommendation).

## Cardiopulmonary Complications

### Questions Addressed

- What monitoring should be utilized in SAH patients with cardiovascular instability?
- Are there recommendations regarding managing cardiopulmonary complications in patients with SAH?

### Summary of the Literature

Myocardial injury occurs following SAH and is thought to be related to sympathetic stimulation and catecholamine discharge. Elevations of troponin I levels occur in approximately 35% [25, 26], arrhythmias in 35% [27], and wall motion abnormalities on echocardiography in about 25% of patients with SAH [28]. Echocardiographic abnormalities are more frequent in patients with elevated troponin levels. The terms “Neurogenic Stress Cardiomyopathy” and “Stunned Myocardium” have been applied to the clinical syndrome of chest pain; dyspnea; hypoxemia, and cardiogenic shock with pulmonary edema and elevated cardiac markers that occurs within hours of SAH. This syndrome has a wide spectrum of severity, and it may contribute to sudden death in 12% of patients. The manifestations are usually transient lasting 1–3 days after which myocardial function returns to normal. Management should focus on supportive care that balances cardiac needs with the neurological goals [29].

In general, cardiac abnormalities are more common in patients who later develop DCI and have worse outcomes

[30]. Although several mechanisms have been proposed to explain the cardiac abnormalities, the evidence seems strongest for a catecholamine induced process [29]. Monitoring of cardiac function may be beneficial in the setting of hemodynamic instability or myocardial dysfunction, but there is no evidence that it improves outcome. Management of cardiac complications is heterogeneous, and interventions should reflect current best medical practices.

Symptomatic pulmonary complications occur in over 20% of patients after SAH [31, 32], although evidence of impaired oxygenation occurs in up to 80% [33]. These complications are associated with worse clinical grade SAH and higher mortality [34–36]. Patients may develop pulmonary edema (cardiac or neurogenic), acute lung injury or acute respiratory distress syndrome. The mechanism of pulmonary injury may also be related to sympathetic hyperactivity or cardiac failure. Management of pulmonary issues follows general principles of pulmonary management, however, with careful attention to avoid hypovolemia.

### Discussion

The participants all agreed that cardiopulmonary complications are common after SAH, and have a significant impact on clinical care. They frequently complicate management by increasing procedural risk and exacerbate brain oxygen delivery by lowering perfusion pressure and arterial oxygenation saturation. It was generally agreed that a baseline assessment of cardiac function with echocardiography may be beneficial, especially if there are any signs of myocardial dysfunction. Although there is limited evidence, the panel strongly felt that cardiac output should be monitored (invasively or non-invasively) in those patients with myocardial dysfunction or hemodynamic instability.

The participants voiced the opinion that management of these complications may vary based on the patient’s clinical status and in the setting of vasospasm. There was strong agreement that cardiopulmonary issues are worsened in the event of hypervolemia, thus the goal of therapy should be euvolemia. The panel also strongly recommended that management of cardiopulmonary issues should reflect current best medical practice, while balancing the needs of the underlying neurological condition.

### Recommendations

#### Monitoring

- Baseline cardiac assessment with serial enzymes, electrocardiography, and echocardiography is recommended, especially in patients with evidence of

myocardial dysfunction (Low quality evidence; Strong Recommendation).

- Monitoring of cardiac output may be useful in patients with evidence of hemodynamic instability or myocardial dysfunction. (Low quality evidence; Strong Recommendation).

#### Treatment

- In case of pulmonary edema or evidence of lung injury, the goal of therapy should include avoiding excessive fluid intake and judicious use of diuretics targeting euvolemia (Moderate quality evidence; Strong recommendation).
- Standard management of heart failure is indicated with the exception that CPP/MAP should be maintained as appropriate for the neurological condition. (Moderate quality evidence; Strong recommendation).

### Monitoring Intravascular Volume Status

#### Questions Addressed

- What is the role of monitoring fluid balance and central venous pressure (CVP)?
- What measurements should be used to assess blood volume?
- Is there a role for non-invasive hemodynamic monitoring?
- Is there a role for pulmonary artery catheters (PACs)?

#### Summary of the Literature

SAH patients frequently develop hypovolemia and hyponatremia. Retrospective studies have identified a relationship between hypovolemia and an increased incidence of cerebral infarcts and worse outcome [37, 38]; especially when fluid administration is restricted. For this reason, assessment of intravascular volume in patients after SAH is essential to daily management. Therefore, guidance is needed regarding the mechanism and impact of alterations in fluid balance, and the methods for monitoring volume status. Available literature describes multiple factors that may contribute to changes in volume status [39, 40].

Fluid balance may not accurately reflect intravascular volume [41–44], therefore invasive and non-invasive methods have been used as possible alternatives to monitor volume status. Although all methods provide information to guide patient management, none have demonstrated superiority over vigilant fluid management [45–47]. In fact,

CVP appears to be an unreliable indicator of intravascular volume [45, 46], and, although PACs may have a role in hemodynamically unstable patients, the complications associated with their routine use appear to outweigh any potential benefit [48–50].

#### Discussion

The participants generally agreed that volume status of patients should be monitored after SAH even though it may not accurately reflect intravascular volume, nor is there evidence that close monitoring has a beneficial impact on outcome.

The panel discussed multiples methods to monitor volume status, and weighed the evidence regarding potential risk versus benefit of each. It was generally felt that both physical findings and clinical data must be integrated into assessment of volume status. Although there was not a preferred method of monitoring volume status, a hierarchical approach is often used. The primary assessment should be close monitoring of fluid input and output. Other invasive and non-invasive modalities may be used to provide supplemental information based on the clinical scenario, but no one tool should be used in isolation. The panel did voice strong agreement against the routine use of invasive PACs or dependence on CVP targets.

#### Recommendations

- Monitoring of volume status may be beneficial (Moderate quality evidence; weak recommendation).
- Vigilant fluid balance management should be the foundation for monitoring intravascular volume status. While both non-invasive and invasive monitoring technologies are available, no specific modality can be recommended over clinical assessment (Moderate quality evidence; weak recommendation).
- Central venous lines should not be placed solely to obtain CVP measures and fluid management based solely on CVP measurements is not recommended (Moderate quality evidence; strong recommendation).
- Use of PACs incurs risk and lacks evidence of benefit. Routine use of PACs is not recommended (Moderate quality evidence; strong recommendation).

### Managing Intravascular Volume Status

#### Questions Addressed

- Should prophylactic hypervolemia be employed in the management of SAH patients?

## Summary of the Literature

There appears to be a defect in regulation of intravascular volume following SAH which can result in hypovolemia in a significant number of patients and is associated with worse outcome [39, 51, 52]. Early reports suggested that prophylactic hypervolemia and augmentation of blood pressure could raise cerebral blood flow in SAH patients [53]. These observations raised the possibility that a management strategy of aggressive fluid administration targeted to achieve hypervolemia might be beneficial.

Two prospective randomized controlled trials investigated the use of prophylactic hypervolemic therapy after surgical repair of the ruptured aneurysm [54, 55]. Central venous or pulmonary capillary wedge pressure targets were used to guide therapy. Neither study found any benefit in terms of CBF, TCD defined vasospasm or clinical outcome. These studies and others [56, 57], however, identified an increased incidence of complications, primarily pulmonary edema, associated with hypervolemic therapy.

In a prospective observational study a rise in regional CBF and brain oxygen tension were seen with prophylactic hemodynamic augmentation [56]; the beneficial effect was attributed entirely to induced hypertension rather than hypervolemia.

Although primarily targeted at the correction of hyponatremia, a number of small randomized trials provide information about the impact of fludrocortisone and hydrocortisone on volume status. They indicate that these agents appear to reduce the volume of fluids needed to maintain euvolemia [58–62].

## Discussion

There was broad agreement among the participants that hypovolemia was to be avoided following SAH. The prospective studies comparing prophylactic hypervolemia and euvolemia were regarded as convincing evidence for lack of benefit for prophylactic hypervolemia. There was general agreement that there were significant cardiopulmonary complications associated with prophylactic hypervolemia.

Discussion turned to the potential use of mineralo- or gluco-corticoids to prevent the development of hypovolemia. Prospective randomized controlled trials of hydrocortisone and fludrocortisone to prevent hyponatremia in SAH suggest that those agents may reduce the amount of fluid required to maintain euvolemia. There was support for their use in patients with excessive diuresis; however, this was tempered by concern about the impact on glucose control from the high dose of hydrocortisone employed in the studies.

## Recommendations

- Intravascular volume management should target euvolemia and avoid prophylactic hypervolemic therapy. In contrast, there is evidence for harm from aggressive administration of fluid aimed at achieving hypervolemia (high quality evidence; strong recommendation).
- Isotonic crystalloid is the preferred agent for volume replacement (Moderate quality evidence; weak recommendation).
- In patients with a persistent negative fluid balance, use of fludrocortisone or hydrocortisone may be considered (moderate quality evidence; weak recommendation).

## Glucose Management

### Questions Addressed

- Is there an optimal serum glucose concentration range after SAH that avoids secondary brain injury?
- Does maintenance of that range with insulin infusions improve outcome over liberal glucose management?
- Does cerebral glucose concentration on microdialysis provide better information than serum glucose regarding optimal management?

## Summary of the Literature

Hyperglycemia is commonly identified during initial evaluation of patients with SAH [63]. Numerous retrospective observational studies have found that admission hyperglycemia is associated with poorer clinical grade and worsened outcome [64–66]. However, in some studies, this effect was not significant when adjusting for clinical condition and amount of subarachnoid blood. Although there have not been any randomized controlled clinical trials of tight versus liberal glucose management in SAH, several observational studies have reported on SAH patients who were managed clinically according to various target glucose regimens, including several which used insulin infusions [67–69]. Liberal glucose management (>220 mg/dl) is associated with increased infection risk, although patients in the main study with this finding received dexamethasone as part of clinical care [68]. One study found improved outcomes in patients successfully treated to a target glucose range of 80–140 mg/dl [70]. Hyperglycemia has been associated with occurrence of vasospasm [71]. A study of SAH patients treated with insulin infusions to maintain tight glucose control (80–110 mg/dl) found an increase in episodes of hypoglycemia, and this was associated with more vasospasm and less favorable 3-month outcome [72]. There have also



been reports of cerebral microdialysis findings of cerebral metabolic crisis and low cerebral glucose in SAH patients being treated with insulin infusions, even in the absence of systemic hypoglycemia [73, 74]. Current methods for assessing serum (or cerebral) glucose are intermittent and do not provide continuous measurements.

## Discussion

There was general agreement that extreme systemic hyperglycemia is both a marker of severity of SAH as well as a risk factor for infection. There was concern that aggressive control of serum glucose using insulin infusions could result in inappropriately low cerebral glucose levels, and that in most situations, this would go undetected because microdialysis is not widely available as a clinical management tool. There was also concern that low cerebral glucose levels may occur even in the setting of low-normal serum glucose levels. There was also recognition that systemic hypoglycemic events are more common with insulin infusions, especially with a tight target glucose range, and that the NICE-SUGAR trial found worsened outcome in patients treated with this regimen (although not specific to SAH) [75]. Thus, the group felt that hyperglycemia was a common occurrence and a significant concern, but that a specific target serum glucose range to minimize secondary brain injury after SAH was not known and current methods of intermittent assessment of serum glucose were probably insufficient for adequate glucose control management.

## Recommendations

- Hypoglycemia (serum glucose <80 mg/dl) should be avoided (High quality evidence-strong recommendation).
- Serum glucose should be maintained below 200 mg/dl (Moderate quality evidence-strong recommendation).
- If microdialysis is being used, serum glucose may be adjusted to avoid low cerebral glucose (Very low quality evidence-weak recommendation).

## Management of Pyrexia

### Questions Addressed

- Should measures be used to suppress fever in SAH patients? During what time period?
- What methods are available?
- How should shivering be managed?

## Summary of the Literature

Fever is reported to occur in 41–72% of patients following SAH and is more common in patients who are poor-grade [76–78], have more subarachnoid blood and have intraventricular blood. In experimental models of cerebral ischemia higher temperature is associated with larger infarcts and worse outcome. Retrospective studies in SAH patients have consistently found that fever is independently associated with poor outcome [76, 79–81]. Infarcts are more common in febrile patients. Temperature elevation appears to be part of a systemic inflammatory reaction that is frequently not infectious in origin. The strongest predictors of fever are poor Hunt–Hess grade and intraventricular hemorrhage (IVH) [82, 83]. Febrile episodes may be associated with microdialysis values that suggest metabolic stress which reverse with reduction in temperature [84].

Suppression of infectious fever, however, has risk. Fever is an adaptive host response to infection. In a number of different clinical settings treatment of fever results in a prolonged course of illness [85, 86]. No study has prospectively addressed the impact of fever control on neurologic injury, infection or outcome in SAH patients [87].

The efficacy of different methods of treating fever has been assessed in a number of studies. Acetaminophen and ibuprofen are not very effective, as they normalize temperature in only a minority of patients [88, 89]. Continuous infusions of NSAIDs may be more effective [90]. Use of fanning, evaporative cooling, sponging, ice packs, cooling blanket are often ineffective.

Newer surface and intravascular devices to treat fever have also been introduced [91]. In prospective randomized controlled trials intravascular devices were more effective at controlling fever than conventional means in SAH patients [92]. A similar degree of efficacy has been demonstrated for surface devices [93]. In a small study intravascular methods maintained a more stable temperature when compared to water circulating gel-coated pads [94].

Aggressive means to control fever can cause shivering. The metabolic consequences include a marked increase in resting energy expenditure, carbon dioxide production, systemic oxygen consumption [95] and a decrease in brain tissue oxygen tension [84]. A number of measures have been employed to reduce shivering including counterwarming of extremities and the use of medications such as buspirone, magnesium, meperidine, propofol as well as other sedatives. The absolute and relative efficacy of these different measures is unknown.

## Discussion

There was wide agreement among the participants that suppression of fever was appropriate in SAH patients at risk for or with active DCI. Although only effective in a minority of patients, all agreed that first step in fever control was the administration of antipyretics. Concern was raised regarding the antiplatelet effects of ibuprofen and other NSAIDs in patients who had undergone craniotomies. In the discussion that followed it became evident that the majority of those present were comfortable administering NSAIDs for fever control following craniotomy. The use of intravenous infusion of NSAIDs was discussed as potentially being more effective than intermittent doses.

Many of the participants reported routine use of surface and intravascular devices to control fever. All agreed they were more effective in eliminating fever and maintained the target temperature more consistently. There was considerable discussion regarding the shivering they induce. Concern was raised regarding the catecholamine release, rise in oxygen consumption and metabolic stress caused by shivering. Most centers using cooling devices routinely employed measures to minimize shivering, starting with surface counter-warming. Additional pharmacologic measures were often required using a variety of agents. Because of their modest impact on level of consciousness, buspirone and magnesium were preferred by some, others routinely used meperidine.

The use of surface as opposed to intravascular devices varied across centers. Intravascular devices appear to maintain a more stable temperature but there are insufficient data to compare the two approaches in terms of shivering and complications. A comparison of the methods in another clinical condition, coma after cardiac arrest, found no important differences in their performance, shivering and other complications [96]. There were some reports of thrombosis formation associated with intravascular devices but other frequent users had not noted any association.

## Recommendations

- Temperature should be monitored frequently; infectious causes of fever should always be sought and treated (High quality evidence—strong recommendation).
- During the period of risk for DCI control of fever is desirable; intensity should reflect the individual patient's relative risk of ischemia (Low quality evidence—strong recommendation).
- While the efficacy of most antipyretic agents (acetaminophen, ibuprofen) is low, they should be used as the

first line of therapy (Moderate quality evidence—strong recommendation).

- Surface cooling or intravascular devices are more effective and should be employed when antipyretics fail in cases where fever control is highly desirable (High quality evidence—strong recommendation).
- Use of these devices should be accompanied by monitoring for skin injury and venous thrombosis (Weak quality evidence—strong recommendation).
- Patients should be monitored and treated for shivering (High quality evidence—strong recommendation).

## Deep Venous Thrombosis Prophylaxis

### Questions Addressed

- Should prophylaxis for deep venous thrombosis be performed after aneurysmal SAH?
- What is the best agent?
- What is the optimal timing?

### Summary of the Literature

SAH induces a prothrombotic state that may lead to the development of deep venous thrombosis (DVT) and pulmonary embolism. The incidence of DVT in SAH ranges from 1.5 to 18%, with the higher incidence being demonstrated using prospective lower extremity ultrasound screening in a large cohort [97, 98]. Poor-grade SAH patients appear to have the highest rates of DVT. The conventional methods for DVT prophylaxis in SAH patients include the use of mechanical methods such as sequential compression devices (SCDs), and medical treatments including unfractionated heparin, low molecular weight heparin, or non-heparinoid anticoagulant agents. In a meta-analysis, SCDs, unfractionated heparin and low molecular weight heparin were similarly effective in preventing DVTs [99]. There was a trend toward higher rates of intracerebral hemorrhage and non-cerebral minor hemorrhage with low molecular weight heparin as compared with SCDs or unfractionated heparin [99]. The timing of DVT prophylaxis in relationship with aneurysm occlusion is controversial, but typically prophylactic medications are withheld until the aneurysm has been either clipped or coiled.

The risk of brain hemorrhage appears to be dependent on the agent used. The highest risk of hemorrhage appears to be with low molecular weight heparin, and the lowest risk with SCDs [99]. The duration of DVT prophylaxis has not been studied. The period of greatest risk for developing DVT is not presently known.

## Discussion

The discussion centered on the relative risks of hemorrhagic complications associated with heparin agents in the setting of unprotected aneurysms. The consensus was that SCDs be initiated immediately upon admission but that anticoagulation be withheld until after the aneurysm was secured, due to the risks of re-rupture. The use of low molecular weight heparin was thought by some participants to be too risky to be recommended routine use, whereas as others routinely used them.

## Recommendations

- Measures to prevent deep venous thrombosis should be employed in all SAH patients (high quality evidence—strong recommendation).
- Sequential compression devices, should be routinely used in all patients (high quality evidence—strong recommendation).
- The use of low molecular weight heparin or unfractionated heparin for prophylaxis should be withheld in patients with unprotected aneurysms and expected to undergo surgery (low quality evidence—strong recommendation)
- The use of unfractionated heparin for prophylaxis could be started 24 h after undergoing surgery (moderate quality evidence—strong recommendation).
- Unfractionated heparin and low molecular weighted heparin should be withheld 24 h before and after intracranial procedures (moderate quality evidence—strong recommendation).
- The duration of DVT prophylaxis is presently uncertain but maybe based on patient mobility (low quality evidence—weak recommendation).

## Statins

### Questions Addressed

Does acute statin therapy, initiated immediately after aneurysmal SAH:

- Reduce the incidence and/or severity of cerebral vasospasm?
- Reduce the occurrence of DCI?
- Reduce early (in-hospital) mortality?
- Improve late functional outcome?

### Summary of the Literature

Statins have pleiotropic biological properties, providing a plausible basis for potential benefit in the context of

vasospasm and DCI following aneurysmal SAH. Clinical evidence suggesting benefit comes from six RCTs (two of which have only been published as non-peer-reviewed abstracts) [100–105] five cohort studies [106–109] and one case control study [110] involving a cumulative total of 1851 patients. However, only 309 of these patients participated in RCTs (none of which enrolled more than 100 patients). A recent meta-analysis of the RCT data [111] suggested that statins may reduce DCI, but urged caution, since there was at least some heterogeneity in study results, with two of the four higher quality RCTs showing no benefit. Further, the definitions of DCI were inconsistent, and patients treated without statins in this collected population had an unusually high rate of DCI (48% vs. 20–30% in the literature). Finally, the increase in statistical power afforded by the addition of ~1500 patients from observational studies did not result in statistically detectable benefit in DCI reduction. Limiting analysis to the four peer-reviewed RCTs showed a marginal benefit of statins on mortality, but this was lost when the two non-peer-reviewed studies were included, and statin use in the observational studies was associated with a non-significant increase in mortality. Data provided on vasospasm and outcome was variable across studies, and there was no consistent impact of statins on mortality or functional outcome. Another meta-analysis that included only four high quality RCTs showed no benefit in regard to TCD vasospasm, DCI, functional outcome, and mortality [112]. There are no data that directly address the impact of statin continuation or withdrawal in patients who present with an aneurysmal SAH after having been on these agents. However, data from ischemic stroke patients [113] and myocardial ischemia [114, 115] suggest that acute statin withdrawal may worsen outcome, and provide reason for caution.

## Discussion

Some of the participants felt that, given the relative safety of these agents, there was already adequate evidence to make a recommendation for statin therapy in this setting. However, the majority did not, and the overall consensus was that we should wait for definitive evidence before recommending routine statin use, although the acute initiation of statin therapy could arguably be considered a treatment option. It was noted that an ongoing multicenter study of statin use in aneurysmal SAH (the STASH study; <http://www.stashtrial.com/home.html>) had recently been reactivated following a hiatus; it was hoped that, when completed, this might provide more definitive evidence that could underpin future recommendations. Evidence of cardiovascular morbidity from withdrawal of chronic statin therapy, albeit outside the setting of SAH, was considered relevant. However, the setting of SAH provided a context

in which the heart was arguably more vulnerable, and it was felt appropriate to extrapolate the evidence from non-SAH settings, and support the continuation of chronic statin therapy for patients already on statins at the time of aneurysmal rupture.

#### Recommendations

- Patients on statins prior to presentation with aneurysmal SAH should have their medication continued in the acute phase (Low Quality Evidence, Strong Recommendation).
- Acute statin therapy in statin-naïve patients may be considered for reducing DCI following aneurysmal SAH, pending the outcome of ongoing trials (Moderate Quality Evidence, Weak Recommendation).

### Magnesium

#### Questions Addressed

Should magnesium be routinely administered for the prevention of cerebral vasospasm and DCI after SAH?

#### Summary of the Literature

Magnesium is a non-competitive calcium antagonist with several important vascular and potentially neuroprotective effects [116, 117]. It promotes vasodilatation by blocking the voltage-dependent calcium channel, decreases glutamate release and reduces calcium entry into cells [118]. In addition, magnesium can also attenuate the effect of potent vasoconstrictors including endothelin 1, and blocks the formation of reactive oxygen species.

Six phase II studies have been conducted using a variety of doses and different endpoints ranging from dichotomized outcome defined using the Glasgow Outcome Scale (GOS), frequency of symptomatic vasospasm or DCI, and the occurrence of adverse events [119–124]. The largest trial [125] administered 64 mmol/l/day for 14 days and, while the intervention did not show a difference on the primary endpoint (risk of hypodense lesion on CT), it did reduce DCI by one-third. Most studies found magnesium to be safe, although in one study hypotension was identified as a problem [122].

The only phase III trial enrolled 327 patients within 48 h of SAH; the primary outcome was an extended GOS (GOSE) of 5–8 at 6 month [125]. This outcome was achieved in 64% of the patients in the magnesium group and 63% in the placebo group. There was no effect on secondary outcome measures or in any predefined subgroup, and the incidence of hypotension was similar in both groups.

#### Discussion

There was considerable interest in a potential role for magnesium in the treatment of SAH patients. The low cost and relative safety were appealing, although the results from the only phase III trial significantly dampened interest in its routine use. There was discussion regarding the penetration of magnesium into the CNS and whether CSF levels might be a more appropriate target. Most participants felt it was appropriate to not routinely use magnesium until the results of a second phase III study (MASH-II) were available.

#### Recommendations

1. Inducing hypermagnesemia is not recommended pending the conclusion of current randomized trials (moderate quality evidence, strong recommendation).
2. Hypomagnesemia should be avoided (Moderate quality evidence, strong recommendation).

### Definitions: Delayed Neurological Deterioration, Delayed Cerebral Ischemia and Vasospasm

#### Questions Addressed

- What is the etiology of delayed neurological deterioration (DND)?
- What is vasospasm?
- What is DCI?
- Which outcome measure should be used for SAH clinical research trials?

#### Summary of the Literature

Delayed neurological deterioration (DND) occurs frequently after SAH. For the purposes of this document, DND encompasses clinically detectable neurological deterioration in a SAH patient following initial stabilization, but excludes further SAH due to new bleeding from the ruptured aneurysm. Some of the common causes of DND include: DCI, hydrocephalus, cerebral edema, fevers, seizures, and electrolyte abnormalities. Although it is frequently difficult to determine which of these mechanisms is the most important in a given patient at a given point in time, the burden of these potentially adverse events may have substantial impact on mortality and long-term outcome.

Although vasospasm and DCI are the most frequently discussed causes of DND, the definitions used to describe these interconnected but distinct processes are numerous and not standardized. This inconsistency makes it difficult

to compare results between treatment or intervention trials, and interferes with the development of evidence based guidelines. One of the major contributors to this problem is the inappropriate tendency to combine radiographic evidence of vascular narrowing and clinical findings into a single definition.

Vasospasm is a term applied to arterial narrowing after SAH demonstrated by radiographic images or sonography [126]. This narrowing can result in decreased cerebral blood flow and oxygen delivery, which may produce cerebral ischemia or infarction. DCI is a term applied to any neurological deterioration (e.g., hemiparesis, aphasia, altered consciousness) presumed related to ischemia that persists for more than an hour and cannot be explained by other physiological abnormalities noted on standard radiographic, electrophysiologic, or laboratory findings [126]. Additionally, DCI may occur but the neurological deterioration not be recognized due to the poor clinical condition of the patients and/or administration of sedatives. In both situations it can result in cerebral infarction. Thus, while both vasospasm and DCI have been associated with clinical deterioration and worse outcomes, either one may also be asymptomatic. Unfortunately, they are often used as surrogate markers of each other even though they can occur independently.

Recent studies provided evidence that cerebral infarction on neuro-imaging had the strongest association to functional outcomes [127–129]. Recently a multidisciplinary research group recommended that SAH clinical trials should only use cerebral infarction and functional outcome as the primary outcome measures. Clinical deterioration due to DCI and vasospasm on angiography or TCD should only be secondary outcome measures. In addition, the term vasospasm should only be used as a descriptor of radiographic findings [126].

## Discussion

The panelists voiced general agreement that inconsistencies in the use of the terms vasospasm and DCI should be avoided and that standardized definitions are needed. It was agreed that ‘vasospasm’ is primarily a descriptor of findings on diagnostic studies, and ‘clinical deterioration due to DCI’ should be used to describe a clinical finding. The panel also agreed that neither of these should be used as primary outcome measures for clinical research.

## Recommendations

SAH clinical trials should use only radiographic evidence of cerebral infarction and functional outcome as the primary outcome measures (Moderate quality evidence; strong recommendation).

## Monitoring for DCI and Triggers for Intervention

### Questions Addressed

- Are there medications which should be routinely administered to prevent DCI?
- How should patients be monitored for the detection of reversible causes of neurological deterioration?
- In what setting should patients be monitored?
- What should trigger an increase in monitoring or a clinical intervention?

### Summary of the Literature

#### Monitoring

The purpose of monitoring patients with SAH is to detect treatable and reversible causes of neurological deterioration. There are numerous causes of neurological deterioration including DCI, hypoxia, electrolyte disturbances, infection, fever, hydrocephalus, convulsive, and non-convulsive seizures. Frequent neurological examinations, and the availability of urgent neuroimaging (usually with CT), and EEG are standards in the management of patients with SAH. Nimodipine has been shown in multiple randomized clinical trials to improve outcome after aneurysmal SAH, presumably by limiting DCI, and it is considered a standard part of aneurysmal SAH management [1, 130, 131]. Even so, DCI is common after SAH, and once a ruptured aneurysm is secured, it is the major cause of secondary morbidity. Because interventions intended to improve cerebral perfusion, such as induced systemic hypertension or endovascular angioplasty, might potentially rescue ischemic, but not yet infarcted, regions of brain, early detection of impaired cerebral perfusion is the goal of monitoring for DCI after SAH. The highest risk period for DCI occurs 3–14 days after SAH. Higher risk patients are those with larger amounts of SAH and poorer clinical grade. Monitoring strategies and tools for DCI in SAH are divided into three basic categories: clinical, radiographic, and physiological.

Clinical monitoring for DCI consists of repeated neurological assessments to identify new neurological deficits that are attributable to ischemia or infarction. Not all ischemic events, however, are detected on clinical examination. Two studies found that CT scans identified asymptomatic infarction in 10–20% of patients, with clinically unrecognized infarcts more common in patients in coma [132, 133]. A study using MRI found clinically unrecognized infarcts in 23% of patients [134]. The utility of clinical examination in detecting reversible ischemia is generally thought to be good in good-grade patients, but less reliable in poor-grade patients who are obtunded or comatose.

Radiographic monitoring modalities include conventional digital subtraction angiography (DSA), CT (with CTA and CTP), and MRI. DSA is considered the gold standard for detection of arterial narrowing and thus is commonly used to define vasospasm. However, it does not assess the adequacy of perfusion to meet metabolic demands of the tissue. Several studies have assessed CTA and found it highly correlated with DSA findings of large artery narrowing [135, 136]. CTA has been found to be 87–95% specific for angiographic vasospasm (compared with DSA) but tends to overestimate the degree of stenosis. CTA has a high specificity and a negative predictive value of 95–99%, suggesting that it could be used as a screening tool to limit the use of DSA. CT perfusion imaging (CTP) does provide some measure of tissue perfusion which may enhance the predictive value of multi-modality CT (non-contrast + CTA + CTP) for DCI monitoring. CTP finding of delayed mean transit time (MTT) > 6.4 s in conjunction with arterial narrowing on CTA was more accurate in predicting the need for endovascular intervention for vasospasm [137, 138]. However, all published CTP studies are small (less than 100 patients) and CTP does not currently evaluate the posterior fossa well. There were too few reports of MR perfusion to consider this as a reasonable DCI monitoring tool at this time.

Physiological monitoring modalities include transcranial Doppler ultrasonography (TCD), electroencephalography (EEG), brain tissue oxygen monitoring, cerebral microdialysis, thermal diffusion cerebral blood flow (TD-CBF) monitoring, and near-infrared spectroscopy. TCD bridges the gap between physiological and radiological monitors and has most often been studied in comparison with DSA. TCD has long been used for monitoring patients with SAH, but studies of diagnostic accuracy for detection of vasospasm and DCI vary widely with regard to sensitivity and specificity of TCD [139, 140]. Overall, TCD is generally considered to have fairly high specificity but only moderate sensitivity compared with DSA. Flow velocities below 120 cm/s (absence), >200 cm/s (presence), MCA/ICA ratio >6 (presence), or rapidly increasing velocities over several days (high risk) are commonly considered thresholds [140, 141]. Brain tissue oxygen (PbtO<sub>2</sub>) monitoring and cerebral microdialysis (CMD) for patients with SAH have both been described in numerous observational studies [142–146]. These physiological parameters are directly measuring tissue oxygen delivery and metabolism, and thus may provide complementary information to that from radiographic studies rather than direct correlation. One study found that impaired autoregulation of PbtO<sub>2</sub> was predictive of delayed infarction [147]. However, no studies have examined the effectiveness of interventions based on

these monitoring tools in preventing or reversing DCI. Likewise, findings on EEG of reduced alpha variability have been indicative of DCI. A small study found intracortical EEG superior to surface EEG in the detection of DCI [148]. As with PbtO<sub>2</sub> and CMD monitoring, no interventional trials have examined EEG-directed DCI treatment. While TD-CBF and NIRS monitoring have been described, these reports involve a small number of patients and serve only to indicate feasibility of the techniques.

#### *Triggers for Intervention*

This section seeks to identify quantitative thresholds that should trigger additional investigations or a change in management. In most instances clinical suspicion triggers both confirmatory investigations and therapy in parallel, although the more invasive forms of therapy (such as endovascular therapy) include, by definition, the confirmatory investigation of angiography before the therapy is delivered. The literature in this area is sparse, and hard data are not easily accessible. However, we have provided recommendations based on the best information available and consensus of the panel and jury, grouped under the following headings.

*Triggers for Confirmatory Investigation for Vasospasm or DCI in Low Risk Good-Grade SAH Patients* The primary monitoring tool in this setting is repeated clinical evaluation, supplemented by monitoring with regular (i.e., daily) TCD. The development of a new focal deficit, a change in the level of consciousness not clearly attributable to another cause, or an increase in TCD velocities/Lindgaard ratio should prompt additional investigations that seek to detect or monitor the evolution of arterial narrowing (CTA or DSA), and document the presence of perfusion deficits CTP that result from such narrowing. Where the selected investigation cannot be obtained emergently (within 1–2 h) it may be prudent, depending on the clinical situation, to initiate medical therapy for DCI while awaiting imaging.

*Triggers for Repeat CTA/CTP/DSA in Good-Grade Patients at High Risk of Vasospasm and/or DCI* Patients with a high Fisher grade and/or arterial narrowing demonstrated with DSA/CTA at the time of initial presentation may benefit from monitoring with these techniques in the absence of detectable clinical consequences. In such patients, the development of new deficits and/or changes in sensorium will often directly trigger therapeutic interventions (e.g., blood pressure elevation, red cell transfusion, endovascular interventions). However, there may be a case for repeating CTA + CTP in this setting when:

- There is substantial clinical uncertainty whether the change in clinical status is actually due to DCI
- An endovascular intervention is being considered, and/or
- The risks of therapy are particularly high (e.g., blood pressure elevation in a patient with significant ischemic heart disease).

Concerns regarding radiation burden and renal impairment limit the number of occasions on which CTA/CTP can be performed to screen for vasospasm or DCI. However in the context of monitoring established vasospasm and DCI, the risk/benefit ratio is more favorable.

*Triggers for Detection/Confirmation of Vasospasm in Sedated or Poor-Grade Patients* Clinical examination may be less useful as a monitoring tool in this setting, but should still be regularly undertaken, since a change from baseline provides an indication for further investigation or treatment. In many such instances, however, a clinical suspicion of vasospasm or DCI will be triggered by a change in TCD parameters, EEG, invasive cerebral monitoring (PbtO<sub>2</sub> or microdialysis), or by the detection of vasospasm or perfusion deficits on routine screening CTA/CTP or DSA. Where the clinical suspicion of DCI is based on a non-imaging tool, it is prudent to confirm the diagnosis using CTA + CTP or DSA. In patients where screening using CTA or DSA has already established the presence of vasospasm, and the clinical picture is consistent, it is reasonable to initiate therapy without further investigation. In poor-grade patients where a perfusion deficit has been demonstrated on a screening CTP, it is reasonable to initiate therapy for DCI unless the deficit coincides with an established infarction.

*Thresholds for Cessation of Therapy for DCI* In good-grade patients clinical assessment combined with cautious staged de-escalation of therapy provides the best basis for management decisions. It is important to recognize that the consequences of a reduction in mean arterial pressure may be delayed for several hours. In poor-grade patients, this approach has a role, but may need to be supplemented by investigations. Options include TCD trends of vasospasm, continuous EEG monitoring, PbtO<sub>2</sub> and/or microdialysis.

In some instances, it may be appropriate to withdraw therapy because it has been unsuccessful, and DCI has resulted in established infarction. Where there is doubt, it may be reasonable to use CTP while lowering blood pressure to determine if it results in significant perfusion deficits.

*Modality Specific Thresholds for Initiation, Titration, or Withdrawal of Therapy* With the exception of clear clinical deterioration, the panel felt that it was unwise to base treatment decisions on an individual measurement provided by any single monitoring modality or monitoring device. All of the individual devices and techniques used are subject to technical artifact, and inter-center variability in their use and calibration results in large variations in the absolute values measured. In many cases, critical thresholds for individual techniques are derived from conditions other than SAH, typically traumatic brain injury and ischemic stroke. Further, while some physiological thresholds may be associated with outcome, there is no clear evidence that correction of monitored variable to (or towards) “normality” actually improves outcome.

Given these caveats, some literature thresholds are available for the techniques discussed above, and are discussed in the accompanying article. It is most useful to integrate the data from all available sources with the clinical picture to help make management decisions. Trends in measured variables, rather than isolated values, provide a more secure basis for inferences regarding abnormal physiology and treatment decisions.

Where a new neurological deficit develops, and has a strong likelihood of being due to ischemia, most centers would initiate medical therapy, especially when other potential causes were unlikely or had been excluded. The threshold values from TCD and other monitoring devices discussed above provide additional information that underpins initiation of such therapy. Some therapies, including hypertension and optimization of hemoglobin levels, may be initiated while awaiting confirmatory investigations. Other interventions used in DCI, such as endovascular therapy, require angiography for initiation and in these instances confirmation of a diagnosis of vasospasm as a cause of DCI will automatically precede therapy.

## Discussion

This was considered a high-priority topic by the group because of the major impact of neurological deterioration, especially from DCI, on SAH outcome, the importance of early intervention to detect and reverse ischemia before the occurrence of permanent infarction, and because the choice of monitoring strongly influences the specific triggers used for further hemodynamic or endovascular intervention to treat vasospasm and DCI. There was strong consensus that the clinical examination is an important first assessment point in patients with SAH and that triggers for further monitoring and intervention may differ depending on the clinical status of the patient. However, there was general

agreement and great concern that clinical examination alone was an insufficient monitoring paradigm for detection of DCI, especially in poor-grade patients. There was general consensus that additional radiographic and/or physiological monitoring should be routinely employed in the monitoring of SAH patients for DCI and that this monitoring should be performed during the DCI “at risk” time period even in the absence of clinical evidence of DCI, or prior to its occurrence. Also, because of the challenges in monitoring for DCI, this should take place in a location (hospital and intensive care unit) with adequate expertise to implement and interpret these monitoring tools.

However, it was recognized that the specific choice of radiographic and physiological monitoring tools which were used in routine clinical care varied substantially among the various consensus group members. Some of this variability reflected differences in resource allocation and preferences between European and US participants and some represented specific expertise and interest across group members. Specifically, the timing and use of routinely repeated TCD, CTA, and DSA studies during the DCI “at risk” period varied widely across consensus group members. Even so, all recommended the use of some form of monitoring beyond just repeat clinical assessment. Additionally, the jury emphasized the difference between screening for vasospasm in patients at risk for DCI and confirmation of DCI. TCD, PbtO<sub>2</sub>, and CMD allow frequently repeatable or continuous measures, but confirmation by DSA or CTP may be needed. Because of emerging concerns regarding radiation toxicity, an institutional protocol that balances DCI detection with attempts to minimize radiation exposure is encouraged.

#### Recommendations

- Monitoring for neurological deterioration, and specifically DCI, should take place in an environment with substantial multidisciplinary expertise in the management of SAH (Moderate quality evidence—strong recommendation).
- Patients at high risk for DCI should be closely monitored throughout the at risk period. This is best accomplished in an ICU setting where additional monitoring and treatment can be rapidly implemented (Very low quality evidence—strong recommendation).
- Oral nimodipine (60 mg every 4 h) should be administered after SAH for a period of 21 days (High quality evidence—strong recommendation).
- Imaging of vascular anatomy and/or perfusion can be used to confirm a diagnosis of DCI in monitored good-grade patients who show a change in neurologic exam or TCD variables (Strong quality evidence—strong recommendation).
- A strategy for detection and confirmation of DCI should be employed. This should first and foremost involve frequent repeat neurological assessment by qualified providers. Intermittent screening or more continuous monitoring methods may additionally be used.
  - TCD may be used for monitoring and detection of large artery vasospasm with variable sensitivity. Thresholds of mean blood flow velocities <120 cm/s for absence and >200 cm/s and/or MCA/ICA ratio >6 for presence are reasonable (Moderate quality evidence—strong recommendation).
  - DSA is the gold standard for detection of large artery vasospasm (High quality evidence—strong recommendation).
  - High quality CTA can be used for screening for vasospasm, and due to its high specificity may reduce the need for DSA studies (Low quality evidence—weak recommendation).
  - CTP findings of elevated MTT > 6.4 s may be additive to CTA findings in predicting DCI (Low quality evidence—weak recommendation).
  - EEG, PbtO<sub>2</sub> monitoring, and CMD may all be useful physiological monitors for DCI detection. Data from probes should be interpreted in light of its limited field of view and location in relation to pathology. The relative value of these monitors individually versus as part of a multi-modality monitoring strategy is not known (Low quality evidence—weak recommendation).
- In high risk patients who have a clinical picture strongly suggestive of DCI, and in whom elective screening CTA/CTP or DSA has already demonstrated vasospasm/DCI, it is reasonable to initiate medical therapy without further investigations (Moderate quality evidence—strong recommendation).
- In patients where there is clinical uncertainty regarding the cause of neurological deterioration, DSA is indicated if an endovascular intervention is planned (Moderate quality evidence—strong recommendation).
- In sedated or poor-grade SAH patients, clinical deterioration may be difficult to assess, and TCD, continuous EEG, PbtO<sub>2</sub> monitoring, and/or CMD are options for monitoring for vasospasm and DCI (Low quality evidence—weak recommendation).
- Elective screening with CTP/CTA or DSA on may provide additional information (Low quality evidence—weak recommendation).



## Hemodynamic Management of DCI

### Questions Addressed

- Do attempts to increase intravascular volume aid in the management of DCI?
- What effects does induced hypertension have on patients with DCI?
- Are inotropic agents useful for patients with DCI?
- Is hemodilution a useful approach to improving cerebral oxygen delivery?
- Are there special concerns regarding hemodynamic management in patients with unsecured aneurysms?

### Summary of the Literature

Hemodynamic augmentation, initially described as triple-H therapy, has been a mainstay in the management of DCI for decades. Despite its widespread use, the evidence supporting it is only of moderate quality. Much of the literature consists of small case series or retrospective reviews. The only two randomized trials addressed prophylactic use and are discussed earlier in this document.

Early case series reported that the combined treatment including volume expansion, hemodilution and induced hypertension along with a variety of ancillary measures lead to clinical improvement in about two-thirds of patients [53, 149]. More recent studies utilized physiological outcome measures (CBF, PbtO<sub>2</sub>) and attempted to assess the effects of the components of hemodynamic augmentation: volume expansion, induced hypertension, hemodilution and inotropic enhancement of cardiac output.

Consistent with the discussion above on routine intravascular volume management, hypervolemia does not appear to offer any benefit over euvolemia when treating DCI. In prospective observational studies, induced hypertension increased CBF independent of the patient's volume status [56, 150]. When hypervolemia resulted in hemodilution CBF rose but since arterial oxygen content falls, overall oxygen delivery to the brain is reduced [151]. In addition, hypervolemia is associated with a higher rate of complication [55, 150].

Case series have linked induced hypertension with neurologic improvement in the majority of patients treated [53, 152–154]. Induced hypertension has been shown to increase CBF in a number of observational studies, and this effect may be greater in patients with angiographic vasospasm or in brain regions that are hypoperfused [155–157]. In a prospective case series, use of high doses of phenylephrine appeared to have a favorable safety profile and was not associated with heightened risk of cardiac complications [158].

Two case series suggest that the use of inotropic agents were also an effective means of improving CBF and reversing neurological deficits in patients who did not respond to vasopressors [47, 159]. Recently the use of combined intra-arterial and intravenous milrinone has been reported to produce cerebral vasodilation, but also systemic hypotension [160, 161]. Case reports suggest potential benefit from use of intra-aortic balloon pump counterpulsation [162].

Retrospective case series report no occurrence of rebleeding during induced hypertension in the presence of unsecured unruptured aneurysms after repair of the aneurysm which bled [163, 164]. There are no studies investigating blood pressure targets for relief of DCI.

### Discussion

All participants utilized some form of hemodynamic augmentation to treat DCI, usually in conjunction with endovascular interventions, but would like to have better quality data to support its use. Yet, most felt that, due to its widespread use, it was unlikely that randomized outcome studies of hemodynamic augmentation with untreated control groups would be feasible.

Most participants targeted euvolemia, although a large fluid bolus was considered reasonable while initiating vasopressor therapy. A minority of the participants preferred the use of colloid whereas most favored crystalloid fluids. There was considerable discussion about how to assess volume status; no single index (CVP, fluid balance, renal function, etc.) was considered adequate and integration of multiple indices was encouraged.

The most common agents used to induce hypertension were phenylephrine and norepinephrine; dopamine was used by a minority. There were two different approaches to defining blood pressure targets. About half used predefined targets whereas the others targeted a percent increase from baseline blood pressure. All agreed that blood pressure targets should be adjusted further based on each patient's response to initial elevation of blood pressure. Vasopressin was considered useful in situations where achieving blood pressure targets required very high doses of vasopressors. Concern was expressed regarding the hypotensive effects of nimodipine.

Augmentation of cardiac output with inotropes was considered by some as an alternative to induced hypertension, but more participants utilized it if the response to hypertension was inadequate. A few participants avoided use of inotropes because of the concern that they often lowered blood pressure. Some centers tend to favor milrinone over dobutamine, primarily because of the ability to infuse milrinone intra-arterially into vasospastic vessels,

and follow this with an intravenous infusion to maintain vasodilation and augment cardiac output.

The use of induced hypertension in patients in whom the ruptured aneurysm had been repaired, but an additional unprotected (but unruptured) aneurysm was present, was considered reasonable by most participants. No one was aware of cases where a secondary unruptured aneurysm had ruptured during induced hypertension for treatment of DCI. Some use more modest blood pressure goals in this situation.

## Recommendations

### *Intravascular Volume*

- The goal should be maintaining euvolemia, rather than attempting to induce hypervolemia (moderate quality evidence, strong recommendation).
- Consider a saline bolus to increase CBF in areas of ischemia as a prelude to other interventions (moderate quality evidence, weak recommendation).

### *Blood Pressure*

- Patients clinically suspected of DCI should undergo a trial of induced hypertension (moderate quality evidence, strong recommendation).
- The choice of vasopressor should be based on the other pharmacologic properties of the agents (e.g., inotropy, tachycardia) (moderate quality evidence, strong recommendation).
- Blood pressure augmentation should progress in a stepwise fashion with assessment of neurologic function at each MAP level to determine if a higher blood pressure target is appropriate (poor quality evidence, strong recommendation).
- If nimodipine administration results in hypotension, then dosing intervals should be changed to more frequent lower doses. If hypotension continues to occur, then nimodipine may be discontinued (low quality, strong recommendation).

### *Inotropy*

- If patients with DCI do not improve with blood pressure augmentation, a trial of inotropic therapy may be considered (low quality evidence, strong recommendation).
- Inotropes with prominent  $\beta$ -2 agonist properties (e.g., dobutamine) may lower MAP and require increases in vasopressor dosage (high quality evidence, strong recommendation).

- Mechanical augmentation of cardiac output and arterial blood flow (e.g., intra-aortic balloon counter-pulsation) may be useful (low quality evidence, weak recommendation).

### *Hemodilution*

- Hemodilution in an attempt to improve rheology should not be undertaken except in cases of erythrocythemia (moderate quality evidence, strong recommendation).

### *Patients with DCI Who Have Unsecured Aneurysms*

- If the aneurysm thought to have ruptured is unsecured when a patient develops DCI, cautious blood pressure elevation to improve perfusion might be attempted, weighing potential risks and benefits (weak quality evidence, strong recommendation).
- Unsecured aneurysms which are not thought to be responsible for the acute SAH should not influence hemodynamic management (moderate quality evidence, strong recommendation).

## **Endovascular Management of DCI**

### Questions Addressed

- What is the role of endovascular rescue treatments (with intra-arterial vasodilators and balloon angioplasty) in managing DCI, and when should they be employed?

### Summary of the Literature

Defining the optimum timing and method of endovascular rescue therapy is complex. Ideally, endovascular treatment would be done before the development of permanent ischemic damage, only in those patients at risk for vasospasm-related ischemia, and use the least invasive and lowest risk treatment. The available endovascular rescue treatments vary considerably across studies in terms of the timing of intervention, the need for re-treatment, the duration of treatment overall, and the clinical or biomarker indications used to trigger the treatment. Interpretation of this summary statement should be made in close consideration of the summary of triggers. Most studies are retrospective case series or comparison studies, with few prospective studies. Hence, the literature has demonstrated the feasibility, durability, and safety profile of intra-arterial

vasodilator therapy and angioplasty, and the combination of the two, but has not demonstrated this for newer methods. The literature has not provided sufficient information regarding timing of the endovascular rescue therapy nor the optimum number of repeat treatments necessary. However, the single randomized controlled trial of prophylactic angioplasty, done early after SAH without the presence of angiographic arterial narrowing, suggested a lower risk of DCI, albeit at a risk of vessel rupture and death from the procedure and ultimately no difference in outcome [165]. There are presently insufficient data to determine if intra-arterial vasodilator therapy alone, or angioplasty alone, or a combination of treatments is superior to one another or superior to medical treatment alone. High volume centers offering endovascular treatment have superior overall outcomes as compared with low volume centers devoid of the endovascular option, yet they differ in a number of other important aspects as well [166].

## Discussion

There was wide international variation in the use of endovascular therapies with some groups strongly recommending their use and other not utilizing them at all. For those that recommend use, discussion centered on practicalities of their use and defining triggers. There was wide variability concerning the triggers, types of endovascular treatments, and number of treatments rendered across centers. Triggers that were utilized included high Fisher grade, asymptomatic vasospasm, DCI, deterioration in physiological monitoring, and failure to respond to medical therapy. It was emphasized that the relative benefit to risk ratio was very dependent on the expertise of the endovascular team, and insufficient standards exist at present to determine who should be performing these interventions. The discussion emphasized the risks of prophylactic angioplasty, and concluded it should not be utilized due to unacceptably high risk of procedural deaths. These discussions noted the inherent conflict of performing randomized trials given the ethical concerns of withholding treatment.

## Recommendations

- Endovascular treatment using intra-arterial vasodilators and/or angioplasty may be considered for vasospasm-related DCI (moderate quality evidence—strong recommendation).
- The timing and triggers of endovascular treatment of vasospasm remains unclear, but generally rescue therapy for ischemic symptoms that remain refractory to medical treatment should be considered. The exact timing is a complex decision which should consider the aggressiveness of the hemodynamic intervention, the patients'

ability to tolerate it, prior evidence of large artery narrowing, and the availability of and the willingness to perform angioplasty or infusion of intra-arterial agents (moderate quality evidence—strong recommendation).

- The use of routine prophylactic cerebral angioplasty is not recommended (High quality Evidence—Strong Recommendation).

## Anemia and Transfusion

### Questions Addressed

- How common is anemia in SAH?
- Is there an optimal hemoglobin concentration range for patients suffering from acute SAH?
- Should transfusion be used to maintain an optimal hemoglobin concentration in patients suffering from acute SAH?

### Summary of the Literature

Anemia is very common after SAH. It develops in about half of patients and hemoglobin concentration drops below 11 g/dl in over 80% of patients [167–169]. On average, hemoglobin concentration falls 3 g/dl after SAH; anemia usually develops in 3–4 days after hemorrhage [167].

Under normal conditions cerebral oxygen delivery exceeds metabolic needs. This provides reserve, so that when CBF falls the brain can increase oxygen extraction. Cerebral oxygen delivery, however, is determined by the product of CBF and arterial oxygen content, which is linearly related to hemoglobin concentration. Thus, CBF must rise considerably in anemia to maintain oxygen delivery; this makes SAH patients particularly vulnerable to anemia.

The appropriate target hemoglobin concentration in SAH patients is unknown. In two large retrospective cohort studies, higher hemoglobin concentration was independently associated with good functional outcome [170, 171]. PET studies in SAH patients indicate that raising hemoglobin concentration with red blood cell transfusion from 8 to 10 g/dl improves cerebral oxygen delivery [172]; similarly, transfusion improves brain oxygen tension [173]. There are no data that address whether higher hemoglobin levels further improve oxygen delivery.

Still, even if a higher hemoglobin concentration is desirable it is not clear that transfusion is an appropriate means to do so. In general critical care patients, red blood cell transfusion is associated with complications, such as immunosuppression, postoperative infections, and pneumonia. In a randomized controlled trial comparing a “liberal (10 g/dl)” and “restricted (7 g/dl)” transfusion

trigger there was lower mortality in the restrictive group among younger (<55 years), and less ill patients (TRICC trial) [174]. It is notable that the sample in this trial included very few neurosurgical patients. However, even in SAH patients, transfusion has also been associated with medical complications and infection [168, 175]. Thus, while higher targets may be desirable in SAH patients, the increased risk of transfusion must be considered.

## Discussion

There was wide agreement that anemia was common in SAH patients, and that there is considerable uncertainty regarding its management. There was wide agreement on two issues: First, measures to minimize blood loss should be routine, and second, that data supporting restrictive transfusion in medical patients do not apply to SAH. There was less agreement as to what the transfusion trigger should be. There was considerable support for the concept that higher hemoglobin levels might be appropriate for patients at high risk for, or who have, DCI. There was strong sentiment that controlled trials of different transfusion triggers are critically needed.

## Recommendations

- Measures should be taken to minimize blood loss from blood drawing (low quality evidence, strong recommendation).
- Transfusion criteria for general medical patients should not be applied to decisions in SAH patients.
- Patients should receive packed RBC transfusions to maintain hemoglobin concentration above 8–10 g/dl (moderate quality evidence, strong recommendation).
- Higher hemoglobin concentrations may be appropriate for patients at risk for DCI, but whether transfusion is useful cannot be determined from the available data (no evidence, strong recommendation).

## Management of Hyponatremia

### Questions Addressed

- What are the complications from hyponatremia?
- Is prophylactic treatment to prevent hyponatremia effective?
- What are the best treatment alternatives?
- What are the complications from treatment?

### Summary of the Literature

Hyponatremia is the most common electrolyte imbalance in patients with aneurysmal SAH, occurring in 30–50% of

cases [176, 177]. Cerebral salt wasting (CSW) first described in 1950 [178] was considered the cause of hyponatremia, but after the recognition of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in 1959, many clinicians assumed that SAH patients were suffering from the latter syndrome. More recent work emphasizes that the diagnosis of CSW requires hypovolemia, whereas SIADH usually results in euvoolemia or modest hypervolemia [40, 177, 179–181]. It appears that in SAH both entities may coexist in the same patient [40, 177] being manifest by excessive urine output with simultaneous excessive free water retention.

Older studies reported an association between hyponatremia and higher risk of cerebral infarctions, especially in the setting of fluid restriction [37–39]. Subsequent studies performed during the era of aggressive fluid administration to SAH patients have found no conclusive evidence that hyponatremia influences prognosis [27, 176].

Controlled studies have been performed on the use of the corticosteroids fludrocortisone [58–60] and hydrocortisone [61, 62] to prevent hyponatremia. Overall, both corticosteroids were consistently effective in limiting excessive natriuresis and hyponatremia when started early after SAH onset. Use of corticosteroids was associated with increased incidence of hyperglycemia and hypokalemia, both of which were treatable. The incidence of congestive heart failure or pulmonary edema did not appear to be significantly increased. Data suggest that 3% saline may be safe [182] but are too scant to assess its value in the management of hyponatremia.

Vasopressin-receptor antagonists, such as conivaptan, are effective for the treatment of hyponatremia associated with euvolemic or hypervolemic conditions [183, 184] and in hyponatremic SAH patients [185]. They can, however, produce a significant rise in urine output raising concern about intravascular volume contraction, especially in the setting of DCI.

## Discussion

The participants agreed that they all monitor sodium concentration carefully and take measures to avoid or treat hyponatremia. Generally the trigger used for treatment is a sodium concentration of <135 mEq/l or if neurological deterioration is attributed to falling sodium concentration. There was little discussion regarding the potential consequences of hyponatremia. Current practice varied somewhat with free water restriction, hypertonic saline solutions and fludrocortisone being most commonly used. Several participants reported anecdotally, that mildly hypertonic solutions (1.25–2.0% saline) were effective in managing mild hyponatremia when it occurred. Others routinely administered fludrocortisone. Concern was

expressed regarding the high doses of hydrocortisone used in prior studies and their impact on glucose management.

#### Recommendations

- Fluid restriction should not be used to treat hyponatremia (weak quality evidence; strong recommendation).
- Early treatment with hydrocortisone or fludrocortisone may be used to limit natriuresis and hyponatremia (moderate quality evidence; weak recommendation).
- Mild hypertonic saline solutions can be used to correct hyponatremia (very low quality evidence; strong recommendation).
- Extreme caution to avoid hypovolemia is needed if vasopressin-receptor antagonists are used for treatment of hyponatremia (weak quality evidence; strong recommendation).
- Free water intake via intravenous and enteral routes should be limited (very low quality evidence; strong recommendation).

### Endocrine Function

#### Questions Addressed

- Does hypothalamic–pituitary–adrenal (HPA) axis dysfunction occur in the acute period after SAH?
- How can adrenal insufficiency be identified in SAH patients?
- Should glucocorticoids be supplemented to improve outcome after SAH?
- Should mineralocorticoids be supplemented to improve outcome after SAH?

#### Summary of the Literature

In the acute setting, the preponderance of data suggest that cortisol levels range from normal to supranormal in the hyperacute period, and then tend to fall to normal values later during the ICU course [186–190]. The data from long-term studies on SAH are not useful for the acute management of SAH. There are few studies regarding hormonal replacement for either mineralocorticoids or corticosteroids. Overall, the use of fludrocortisone appears to be safe but minimally effective at improving outcome [58, 59]. While the case for moderate doses of hydrocortisone is not proven, there is some suggestion that the intervention may facilitate the maintenance of euvolemia

and eunatremia. Two studies of moderate doses of steroids suggest a trend toward improved outcome [191, 192]. A single study suggests that during the treatment of vasospasm, patients may be unresponsive to vasopressors due to relative adrenal insufficiency [193].

#### Discussion

Hypothalamic dysfunction appears to occur acutely in a minority of patients with SAH. The diagnosis of HPA axis dysfunction, especially adrenal insufficiency, is troublesome in intensive care, and there is wide variability of practice in making the diagnosis. Basal levels of cortisol, ACTH stimulation test, and empiric administration of stress-dose steroids are all reasonable approaches. The use of stress-dose steroids in patients unresponsive to vasopressors may have merit based on the presented data. In contrast, the use of high dose steroids in patients with neurocritical care illness has a substantial track record of causing serious adverse side effects, increased mortality, and no benefit. This is tempered by literature in sepsis suggesting that stress-dose corticosteroids, lower than the high doses used in the CRASH and NASCIS trials, may improve outcome, especially in septic shock patients who are unresponsive to vasopressors. The preponderance of evidence presented to the panel suggests that high dose steroids have a harmful effect or no effect at all in patients with SAH. There is potential for hormonal replacement to improve outcome in the chronic setting (months to years) after SAH, but, there is, as yet, insufficient evidence that hormonal replacement in the acute setting improves neurological outcome.

#### Recommendations

- Hypothalamic dysfunction should be considered in patients who are unresponsive to vasopressors. The optimal method of diagnosis remains unclear (moderate quality evidence—weak recommendation).
- Administration of high dose corticosteroids is not recommended in acute SAH (high quality evidence—weak recommendation)
- Hormonal replacement with mineralocorticoids should be considered in acute SAH to prevent hypovolemia and hyponatremia (moderate quality evidence—weak recommendation).
- Hormonal replacement with stress-dose corticosteroids for patients with vasospasm and unresponsiveness to induced hypertension may be considered (weak quality evidence—weak recommendation).

## High Volume Centers

### Questions Addressed

- Should patients with SAH only be treated at high volume centers?

### Summary of the Literature

Most SAH patients are treated at small volume centers that treat fewer than 18 cases/year and large volume centers with the greatest expertise in treating SAH appear to be underutilized [194, 195]. Roughly 15% of patients are transferred from the lowest volume centers to any other center, and only 4.5% are sent to the highest volume centers [196]. Mortality is substantially higher (by 10–20%) at small volume centers as compared with high volume centers [197]. Correspondingly, the long-term good outcomes are substantially less common (by 18–29%) at small volume centers [195, 198]. Transfer of patients to high volume centers carries a low risk and is cost effective, even for poor-grade patients [196]. High volume centers have many features that may contribute to improved outcomes, such as vascular neurosurgeons, specialty neurointensive care units run by neurointensivists, and interventional neuroradiologists. Preliminary studies suggest that neurointensivist-directed neurocritical care units result in reduced mortality in patients with SAH at high volume centers [195].

### Discussion

SAH is a complex disease with a prolonged course punctuated by the need for expertise in multiple subspecialties including neurocritical care, interventional neuroradiology and vascular neurosurgery. Aneurysm repair, and the detection and timely treatment of DCI are critical features of the care for SAH and are best accomplished at high volume centers. The threshold number of cases/year necessary to be a high volume center was discussed and primary papers were carefully reviewed. The available data indicate that high volume centers (defined as >60 cases per year) had the best outcomes and low volume centers with <20 cases/year had the worst outcomes. The rate of transfer to high volume centers is too low given the complex nature of treatment that is required. Efforts to establish mechanisms to facilitate patient transfer and enhance the public awareness of the need for SAH patients to be treated at high volume centers are urgently needed.

### Recommendations

- Patients with SAH should be treated at high volume centers (Moderate quality evidence—strong recommendation).

- High volume centers should have appropriate specialty neurointensive care units, neurointensivists, vascular neurosurgeons and interventional neuroradiologists to provide the essential elements of care (Moderate quality evidence—strong recommendation)

## Conclusions

The International Consensus Conference on Critical Care Management of Patients Following Aneurysmal Subarachnoid Hemorrhage was designed to address a gap in currently available recommendations. Our goal was to provide carefully considered management recommendations for issues which routinely arise when caring for these patients. We knew that we would be constrained by the paucity of high quality data that could support recommendations; yet, the dilemma faced by all practitioners who care for SAH patients is that many clinical decisions must still be made. These constraints were addressed using a range of strategies.

The GRADE system was utilized because recommendations are based not only on to the quality of evidence, but also incorporate the balance among benefits, risks, burden and cost. Additionally, the consensus opinion of recognized experts in the field was considered. To insure a balanced approach, a jury reviewed data, the opinions of the primary reviewers, and the group's discussions to develop the final recommendations. While this approach allowed us to make strong recommendations in the setting of low quality data, the reader must recognize them for what they are: the advice one would receive from a group of experts with extensive experience and familiarity with the literature rather than a prescriptive statement.

The need for additional research to provide a rational basis for clinical management in this setting must be emphasized. Many of the participants identified specific research questions which need to be addressed in order to clarify optimal treatment of SAH patients. Results of ongoing clinical trials of statins and magnesium should significantly improve the understanding of the utility of these therapies and the strength of recommendations regarding their use. A pivotal randomized trial of early antifibrinolytic therapy is needed to assess the safety and efficacy of this intervention prior to definitive aneurysm treatment via clipping or coiling. Larger well-designed studies assessing the optimal temperature range and serum glucose targets are needed. Targets for hemoglobin management and thresholds for transfusion need to be defined. Multi-center studies of continuous EEG for ischemia monitoring and non-convulsive seizure management are necessary to confirm or refute the findings from initial single center studies. Finally, further studies of specific

clinical and neuromonitoring or neuroimaging triggers for acute intervention for DCI are needed, especially for poor-grade patients.

It is not realistic to expect that definitive clinical trials can be funded or performed to address many of the questions for which clinical decisions must currently be made based on limited data. In addition to utilizing clinical trials to assess interventions, the complexity of the condition and the wide range of research questions indicate the need to bring alternative research methodologies to bear. One approach that might be particularly helpful in developing pragmatic real world solutions would be the use of comparative effectiveness research methodology. [199] In particular, study of the heterogeneity of clinical care, both within and outside the USA could be of value in understanding its relationship to patient outcome and could potentially provide valuable insights into improving patient care.

One of the major strengths of this work was the multidisciplinary and international contribution, which provided a broad range of perspectives and resulted in well informed consensus views. Clinical problems do not respect professional or national boundaries, and we would recommend that future steps aimed at addressing this problem should continue to use the wide range of input.

This patient population presents many clinical challenges. Advances in our knowledge of pathophysiology and critical care management will continue to have substantial impact on patient care. Thus, the recommendations presented in this document should be reviewed on a regular basis to determine whether changes are warranted.

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**Appendix**

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**Disclosure of Relevant Financial Relationships**

Relevant financial relationships are those in which an individual (including the individual’s spouse/partner) in the last 12 months has had a personal financial (any amount) relationship with a commercial interest producing health care goods or services.

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