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NEUROCRITICAL CARE SOCIETY

NCS GUIDELINES

Guidelines for the Neurocritical Care Management of Aneurysmal Subarachnoid Hemorrhage

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Abstract

Background: The neurointensive care management of patients with aneurysmal subarachnoid hemorrhage (aSAH) is one of the most critical components contributing to short-term and long-term patient outcomes. Previous recommendations for the medical management of aSAH comprehensively summarized the evidence based on consensus conference held in 2011. In this report, we provide updated recommendations based on appraisal of the literature using the Grading of Recommendations Assessment, Development, and Evaluation methodology.

Methods: The Population/Intervention/Comparator/Outcome (PICO) questions relevant to the medical management of aSAH were prioritized by consensus from the panel members. The panel used a custom-designed survey instrument to prioritize clinically relevant outcomes specific to each PICO question. To be included, the study design qualifying criteria were as follows: prospective randomized controlled trials (RCTs), prospective or retrospective observational studies, case–control studies, case series with a sample larger than 20 patients, meta-analyses, restricted to human study participants. Panel members first screened titles and abstracts, and subsequently full text review of selected reports. Data were abstracted in duplicate from reports meeting inclusion criteria. Panelists used the Grading of Recommendations Assessment, Development, and Evaluation Risk of Bias tool for assessment of RCTs and the "Risk of Bias In Nonrandomized Studies – of Interventions" tool for assessment of observational studies. The summary of the evidence for each PICO was presented to the full panel, and then the panel voted on the recommendations.

Results: The initial search retrieved 15,107 unique publications, and 74 were included for data abstraction. Several RCTs were conducted to test pharmacological interventions, and we found that the quality of evidence for non-pharmacological questions was consistently poor. Five PICO questions were supported by strong recommendations, one PICO question was supported by conditional recommendations, and six PICO questions did not have sufficient evidence to provide a recommendation.

Conclusions: These guidelines provide recommendations for or against interventions proven to be effective, ineffective, or harmful in the medical management of patients with aSAH based on a rigorous review of the available literature. They also serve to highlight gaps in knowledge that should guide future research priorities. Despite improvements in the outcomes of patients with aSAH over time, many important clinical questions remain unanswered.

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Introduction

The neurointensive care management of patients with aneurysmal subarachnoid hemorrhage (aSAH) is one of the most critical components contributing to short-term and long-term patient outcomes. Guidelines for the medical management of aSAH resulting from a comprehensive review of the literature and discussion among an international panel of experts in the field were issued a decade ago [1]. The consensus conference recommendations summarized the most up to date approach to the medical management of aSAH, facilitated delivery of increasingly consistent care, and provided guidance in decision making by the multidisciplinary and interprofessional teams involved in the care of these patients.

Recent reports suggest a meaningful improvement in functional outcome observed even in patients presenting with poor grade aSAH. This improvement is likely rooted in a variety of contributing factors, including improved endovascular and surgical techniques, but also in the overall improvement of the critical care management of these patients [2–6].

As the body of literature has been rapidly growing, the Neurocritical Care Society assembled a committee to review the evidence and update the recommendations. In addition to considering more recently published studies, another difference between the previous and the current guidelines is the methodological approach, as the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system has also evolved in recent years [7]. This updated GRADE guidance was used by the committee for these new guidelines for the selection of publications eligible for inclusion, literature review and data abstraction, and formulation of the recommendations. A total of nine specific topics were selected to be addressed in these guidelines including: Blood pressure management for the prevention of rebleeding; Use of antifibrinolytics for the prevention of rebleeding; Pharmacological interventions including calcium channel blockers, endothelin antagonists, statins, and high dose magnesium; Fluid administration; Hemodynamic management; Triggers for intervention in patients with delayed cerebral ischemia (DCI); Management of hyponatremia; Management of anemia; and Management of hydrocephalus. These guidelines do not apply to pediatric populations or to patients with nonaneurysmal SAH.

Methods

This guideline was developed using the GRADE approach for evidence assessment [8].

Panel Composition

The initial guideline panel assembled in March 2019 was composed of 12 neurocritical care experts with diverse background in neurology, anesthesiology, critical care, neurosurgery, and pharmacology. The panel also included methodological experts with extensive experience in guideline development and had international representation. The Neurocritical Care Society provided technical support for the literature search and reference management and methodologists for the development of this guideline.

Disclosure and Management of Potential Conflicts of Interest

During the committee selection process and prior to confirming the panel membership, all members of the expert panel complied with the conflicts of interest process for reviewing and managing conflicts of interest, which requires disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict. The chairs and all members of the panel have been determined to have no conflicts in the preparation of this work.

Question Generation

Clinical questions included in this guideline were developed into a Population, Intervention, Comparison, Outcomes (PICO) format and prioritized by consensus from the panel members. These guidelines are not intended to be comprehensive. It was decided a priori—prior to the inception of the literature search—that up to ten PICO questions relevant to the medical management of aSAH would be prioritized from a more comprehensive list of pertinent topics. The topics included focused on frequently considered interventions in the critical care treatment of patients with aSAH, especially those for which new data are available. During this process, all topics addressed in the original guidelines were considered. The panel selected nine PICO questions relevant to the management of aSAH in the immediate postbleeding phase prior to aneurysm securing and to the management after the aneurysm is secured. It was decided that topics pertaining to general neurocritical care, although part of the treatment of patients with aSAH, would not be covered. Once the PICO questions were developed, two members of the panel were assigned to review each topic. Ultimately, nine PICO questions were selected, however, the

topic of pharmacological interventions for the treatment of DCI was divided into four subtopics (calcium channel blockers, endothelin antagonists, statins, and magnesium; Supplementary Material Table 1).

Determination of Relevant Outcomes

The panel members extensively discussed a strategy to prioritize clinically relevant and long-term outcomes beyond mortality. The strategy to achieve a consensus on which end points should be considered relevant for each PICO question used a custom-designed survey instrument listing a broad array of relevant outcomes specific to each PICO question. Survey answers ranged from "Critically Important" (score 9) to "Not Important" (score 1), and they were obtained for each outcome on each PICO question. Results of the survey were discussed in a panel meeting, and outcomes with a median score higher than 5 or agreed upon discussion were confirmed for each PICO question (Supplementary Material Table 1).

Search Strategy

Once the PICO questions were defined, the two panelists assigned to each PICO question were tasked with scoping the literature to finalize PICO details, identifying the search terms for the PICO question, and selecting two to three key publications considered to be highly relevant to the topic. The search terms and relevant publications selected were then provided to the librarian who performed the search using the following databases: Medline/PubMed; CINAHL, COCHRANE, and Embase. The search, which included publications since 1946, was conducted on September 25, 2019, and it was subsequently updated on April 1, 2021 (Supplementary Material Table 2). The initial search retrieved a total of 15,107 unique publications (Fig. 1).

Screening and Study Selection

The panel used the DistillerSR software (DistillerSR; Evidence Partners. https://www.evidencepartners.com) to screen the publications for the level 1, level 2, and level 3 review. Level 1 review included screening of the titles and abstract for inclusion, and level 2 involved full text review. Inclusion criteria were adult population (>age 18) and English language only. The study design qualifying criteria were the following: prospective randomized controlled trials (RCTs), prospective or retrospective observational studies, case–control studies, case series with a sample larger than 20 patients, meta-analyses, and studies restricted to human study participants. There were no date restrictions, but a minimum acceptable criterion was that the publications be peer reviewed. Case-reports or reports published in abstract form or supplement only were excluded. Prior to initiating the level 3 review, which consisted of data abstraction, all full publications were downloaded and assigned to the individual PICO topics. It was possible for publications to be listed under more than one PICO question.

Data Abstraction

The panel used a standardized database for data abstraction and critical appraisal of bias. Two panel members reviewed each study. Panelists used the GRADE risk of bias tool for assessment of RCTs and the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS I) tool for assessment of observational studies. The results of the data abstraction were reviewed in a series of full panel meetings, and any discrepancies or uncertainties were discussed to reach a majority consensus. Data abstraction also included the summary of findings, incorporating potential confounders of observed associations.

Risk of Bias and Quality of the Evidence

The overall quality of evidence was determined based on overall risk of bias and the presence of inconsistencies, indirectness, imprecision, possible publication bias, and any additional limitations. These qualifiers were used for upgrades or downgrades of the evidence according to the GRADE methodology [8–39].

Panel Discussion and Evidence to Recommendation Process

Following the completion of data abstraction conducted in duplicate manner by two members of the panel as outlined above, the evidence for each PICO was presented to the full panel, the data reviewed and discussed until all questions were addressed and resolved, and a preliminary recommendation was proposed. The panel then proceeded to vote on the recommendations; an agreement of greater than 80% of panel members was required for a recommendation to be approved. Only for one PICO question, regarding pharmacological intervention with calcium channel blockers, the panel was unable to reach a majority consensus due to divergence in the interpretation of some of the data. The topic was rediscussed with a decision to divide the recommendation into its individual components based on the type of pharmacological agent and route of administration, and a consensus was eventually reached. All evidence reviewed was then summarized in evidence tables presented in this article.

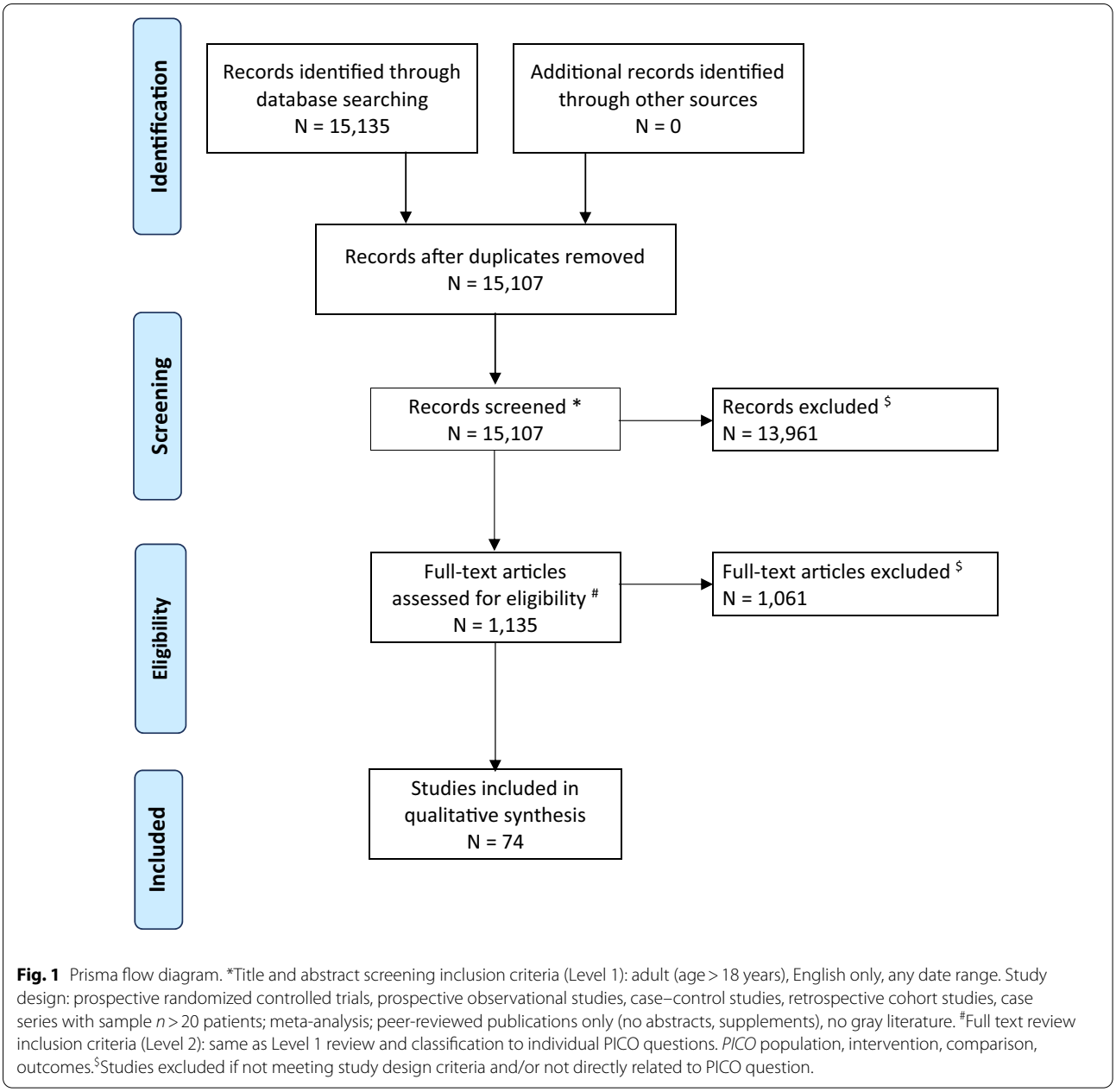

Fig. 1 Prisma flow diagram. *Title and abstract screening inclusion criteria (Level 1): adult (age > 18 years), English only, any date range. Study design: prospective randomized controlled trials, prospective observational studies, case–control studies, retrospective cohort studies, case series with sample *n* > 20 patients; meta-analysis; peer-reviewed publications only (no abstracts, supplements), no gray literature. #Full text review inclusion criteria (Level 2): same as Level 1 review and classification to individual PICO questions. *PICO* population, intervention, comparison, outcomes.$Studies excluded if not meeting study design criteria and/or not directly related to PICO question.

In addition to evaluating the quality of the evidence when determining the strength of the recommendation, the panel also carefully reviewed the certainty of evidence and balance between desirable and undesirable effects of each intervention on the a priori defined PICO-specific outcomes and considered the confidence regarding these effects [9]. As per GRADE methodology, recommendations are labeled as "strong" or "conditional" or "insufficient evidence." The statement "we recommend" or "we recommend against" indicate strong recommendations, and "we suggest" indicate conditional recommendations. The panel discussed at length whether to incorporate good practice statements based on very limited or no evidence and agreed not to include them [40, 41]. Consequently, these guidelines are strictly evidence-based, and none of the recommendations are based solely on personal opinions.

Summary of Recommendations

A summary of the PICO topics and their recommendations is shown in the executive summary table (Table 1).

Table 1 Summary of recommendations

Recommendation	Reasoning
Blood pressure targets for the prevention of rebleeding of ruptured aneurysm	There is insufficient evidence to recommend a blood pressure reduction goal for the treatment of hypertension before aneurysm treatment in aSAH. Lack of evidence to recommend a specific blood pressure reduction goal does not necessarily imply that blood pressure reduction is not helpful before aneurysm treatment*
Antifibrinolytics for the prevention of rebleeding of ruptured aneurysm	We recommend against the administration of antifibrinolytic therapy to prevent rebleeding of ruptured aneurysms in patients with aSAH (strong recommendation, high-moderate quality of evidence)*
Calcium channel blockers	We recommend the administration of oral nimodipine in patients with aSAH to reduce DCI and cerebral infarction, and to improve functional outcome (strong recommendation, moderate quality of evidence)
	We recommend against the administration of intravenous (IV) nicardipine for the prevention of DCI because of increased risk of adverse effects (strong recommendation, moderate quality of evidence)#
	There is insufficient evidence to recommend for or against the administration of calcium channel blocker other than nicardipine by intravenous or intraventricular routes#
Endothelin antagonists	We recommend against endothelin receptor antagonist administration because of lack of benefit on mortality and functional outcomes and an increased risk of adverse events (strong recommendation—high quality of evidence)#
Statins	We recommend against starting statin treatment to reduce DCI or improve functional outcomes in aSAH because of lack of benefit (strong recommendation, high quality of evidence)*
Magnesium/therapeutic hypermagnesemia	We recommend against the use of targeted hypermagnesemia to improve outcomes in aSAH due to lack of benefit (strong recommendation, moderate quality evidence)
Hemodynamic management—fluid administration	We suggest against liberal fluid administration because of an increased risk of pulmonary edema (Conditional recommendation—low quality of evidence)
	We suggest using targeted fluid administration to achieve euvolemia, which may include goal directed hemodynamic therapy, to reduce the risk of pulmonary edema, prevent DCI, and improve functional outcome (Conditional recommendation, very low quality of evidence)
Hemodynamic management—blood pressure and cardiac output augmentation	There are insufficient quality data to recommend for or against blood pressure or cardiac output augmentation for the prevention and treatment of DCI. Due to the associated risks, use of these interventions should be judicious and tailored to the patient's individual hemodynamic profile*
DCI management—triggers for interventional procedures for treatment of DCI	There is insufficient evidence to provide a recommendation on the optimal trigger (change in neurological exam plus findings on advanced neuroimaging versus change in exam alone) for interventional procedures for the treatment of DCI*
Mineralocorticoid therapy	There is insufficient evidence to support mineralocorticoid administration to maintain normal serum sodium concentrations and/or even fluid balance or to improve functional outcome*
Management of anemia	There is insufficient evidence to provide a recommendation for using a transfusion threshold higher than a hemoglobin of > 7 g/dL in patients with aSAH*
Management of hydrocephalus	There is insufficient evidence to provide a recommendation on direct clamping versus gradual weaning strategy for EVD removal for the management of hydrocephalus in patients with aSAH#

aSAH aneurysmal subarachnoid hemorrhage, *DCI* delayed cerebral ischemia, *EVD* external ventricular drain

* Change from the 2011 Recommendations

\# Not addressed in the 2011 Recommendations

Table 2 GRADE evidence profile, PICO 1: in patients with aSAH, what is the impact of blood pressure reduction compared with no blood pressure reduction before aneurysm treatment on mortality, modified Rankin scale (mRS) score, Glasgow outcome scale (GOS) score, rebleeding, new cerebral infarction, and delayed cerebral ischemia (DCI)?

Certainty assessment					Quality of evidence
N of studies	Overall ROB	Inconsistency	Indirectness	Imprecision	
Mortality					
0 RCT	NA	NA	NA	NA	NA
3 Cohort	Serious	0	−2	−2	⊕○○○ VERY LOW
Functional outcome (mRS, GOS)					
0 RCT	NA	NA	NA	NA	NA
0 Cohort	NA	NA	NA	NA	NA
Rebleeding					
0 RCT	NA	NA	NA	NA	NA
3 Cohort	Serious	0	−2	−2	⊕○○○ VERY LOW
DCI or new cerebral infarction					
0 RCT	NA	NA	NA	NA	NA
3 Cohort	Serious	0	−2	−2	⊕○○○ VERY LOW

GRADE Working Group grades of evidence:

⊕⊕⊕⊕: *High certainty* (very confident that the true effect lies close to that of the estimate of the effect)

⊕⊕⊕○: *Moderate certainty* (moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)

⊕⊕○○: *Low certainty* (limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect)

⊕○○○: *Very low certainty* (very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect)

Risk of bias:

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

DCI delayed cerebral ischemia, *GOS* Glasgow Outcome Scale, *mRS* modified Rankin Scale

Blood Pressure Targets for the Prevention of Rebleeding of Ruptured Aneurysm

PICO Question

In patients with aSAH, what is the impact of blood pressure reduction compared with no blood pressure reduction before aneurysm treatment on mortality, modified Rankin scale (mRS) score, Glasgow outcome scale (GOS) score, new cerebral infarction, rebleeding, and DCI?

Recommendation

There is insufficient evidence to recommend a blood pressure reduction goal for the treatment of hypertension before aneurysm treatment in aSAH. Lack of evidence to recommend a specific blood pressure reduction goal does not necessarily imply that blood pressure reduction is not helpful before aneurysm treatment.

Rationale

After assessing the available literature on the topic of the impact of blood pressure reduction aiming to prevent rebleeding from a ruptured aneurysm, the panel univocally agreed that the quality of available evidence was too low to support the recommendation of a target for blood pressure reduction versus no blood pressure reduction. All studies on this topic included some degree of treatment of severe hypertension. Thus, although the committee was unable to provide a statement supporting a specific blood pressure reduction goal in patients with unsecured aneurysms, the absence of evidence for more aggressive blood pressure reduction from comparative studies does not necessarily imply the lack of role of blood pressure reduction in the prevention of rebleeding, as highlighted in the summary of evidence.

Summary of the Evidence

Investigations regarding blood pressure targets for prevention of rebleeding and their impact on functional outcomes are limited to retrospective and observational data (Table 2; Supplementary Table 3). Elevated systolic blood pressure, particularly above 160 mm Hg, has been associated with aneurysm rebleeding [42–45]. Lowering elevated blood pressure—as part of a treatment protocol—has been

associated with lower odds of rebleeding [46], although this finding is not unequivocal [47]. The concern that blood pressure reduction may compromise cerebral perfusion and cause cerebral ischemia was not corroborated in a mixed cohort study of neurocritically ill patients [48]. There is some evidence that increased blood pressure variability may be associated with risk of rebleeding and worse outcomes in aSAH [49, 50] and, therefore, blood pressure variability may need to be studied in future investigations.

Conclusions

Acute hypertension is usually treated after aSAH until aneurysm securement has occurred, but there is currently no sufficient evidence to recommend any specific blood pressure targets to prevent rebleeding or improve mortality or functional outcomes. Early blood pressure variability (i.e., degree of blood pressure reduction over a period of time) may affect functional outcomes, but it is unknown whether reduction of blood pressure variability can improve outcomes in aSAH. Further research is needed to define the optimal therapeutic strategy for the management of hypertension in patients with aSAH before the ruptured aneurysm is secured.

Antifibrinolytics for the Prevention of Rebleeding of Ruptured Aneurysm

PICO Question

In patients with aSAH, what is the impact of administering antifibrinolytics prior to aneurysm treatment compared with no antifibrinolytics on mortality, mRS, GOS, new cerebral infarction, rebleeding, DCI, and thrombotic events?

Recommendation

We recommend against the administration of antifibrinolytic therapy to prevent rebleeding of ruptured aneurysms in patients with aSAH (strong recommendation, high-moderate quality of evidence).

Rationale

Rebleeding increases the risk of poor clinical outcome and mortality in patients with aSAH. Yet, well-designed clinical trials did not show benefit on long-term clinical outcome from the use of antifibrinolytics for the prevention of rebleeding from a ruptured aneurysm. Although preliminary evidence informed the prior edition of the guidelines based on the suggestion of a protective effect of antifibrinolytics on the prevention of rebleeding, these findings were not confirmed in subsequent RCTs of early postadmission administration of antifibrinolytics, leading to the change in this updated recommendation.

Summary of the Evidence

The panel evaluated whether the use of antifibrinolytics improves mortality, mRS, GOS, new cerebral infarction, rebleeding, DCI, or thrombotic events in patients with aSAH. The panel identified six RCTs and six observational studies with 47 different outcome analyses. All RCTs compared tranexamic acid (TXA) to placebo [51–56]. Of the non-RCTs, four compared ε-aminocaproic acid (EACA) with no EACA [57–60], one compared TXA with no TXA [56], and one compared EACA or TXA with no antifibrinolytic therapy [61]. The overall quality of the evidence was high-moderate (Table 3; Supplementary Table 4).

Earlier studies investigated long-term administration (i.e., throughout the hospital admission and for up to 4 weeks) of antifibrinolytics in aSAH, whereas more recent publications reported on the shorter duration of administration (less than 72 h). Four older RCTs evaluated the long-term administration of TXA [51–54]. Three of these found a significant reduction in rebleeding rates associated with TXA [51, 52, 62], and one reported no difference in rebleeding rates between the treatment arms [53]. However, they all showed no difference in functional outcomes. In addition, most of these RCTs showed increased rates of cerebral ischemic complications and mortality with TXA [52, 53]. Two non-RCTs evaluated the long-term administration of EACA [57, 61]. Both of these reported that patients treated with antifibrinolytic therapy had lower rebleeding rate but a higher rate of cerebral ischemic deficits.

Four more recent observational studies evaluated a shorter course of antifibrinolytic therapy [56, 58–60]. Two studies [58, 59] reported that EACA administration was associated with decreased rebleeding and increased thromboembolic complications, whereas another [60] did not find any association. The most recent observational study [56] suggested that early and short-term treatment with TXA was not associated with improved functional outcome but was associated with a decrease in mortality.

Two RCTs evaluated the shorter duration of TXA administration (less than 72 h) [55, 56]. One of them [55] showed that TXA administration reduced ultra-early rebleeding rates. However, this RCT was not adequately powered to show any effect on clinical outcome. The most recent and largest RCT to date evaluating antifibrinolytic therapy in aSAH was the Ultra-early tranexamic acid after subarachnoid haemorrhage (ULTRA) trial, which concluded that the ultra-early, short-term TXA treatment did not improve functional outcome at 6 months [56]. Likewise, this RCT showed no differences in the risk of rebleeding, mortality, cerebral ischemia, and thromboembolic complication rates

Table 3 GRADE evidence profile, PICO 2: in patients with aSAH, what is the impact of administering antifibrinolytics prior to aneurysm treatment compared with no antifibrinolytics on mortality, mRS, GOS, rebleeding, new cerebral infarction, DCI, and thrombotic events?

Certainty assessment					Quality of evidence
N of studies	Overall ROB	Inconsistency	Indirectness	Imprecision	
Mortality					
5 RCT	Some concern	0	0	−2	⊕⊕⊕◯ MODERATE
3 Cohort	Serious	0	−1	−1	⊕⊕◯◯ LOW
Functional outcome (mRS, GOS)					
5 RCT	Low	0	0	0	⊕⊕⊕⊕ HIGH
0 Cohort	Serious	0	−1	−1	⊕⊕◯◯ LOW
Rebleeding					
6 RCT	Low	0	0	0	⊕⊕⊕⊕ HIGH
5 Cohort	Serious	−1	−1	−1	⊕⊕◯◯ LOW
DCI or new cerebral infarction					
6 RCT	Some concern	0	0	−2	⊕⊕⊕◯ MODERATE
3 Cohort	Serious	−1	−1	−1	⊕⊕◯◯ LOW
Thrombotic events					
2 RCT	Some concern	0	0	−2	⊕⊕◯◯ LOW
5 Cohort	Serious	−1	−1	−2	⊕◯◯◯ VERY LOW

GRADE Working Group grades of evidence:

⊕⊕⊕⊕: *High certainty* (very confident that the true effect lies close to that of the estimate of the effect)

⊕⊕⊕◯: *Moderate certainty* (moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)

⊕⊕◯◯: *Low certainty* (limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect)

⊕◯◯◯: *Very low certainty* (very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect)

Risk of bias:

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

DCI delayed cerebral ischemia, *GOS* Glasgow Outcome Scale, *mRS* modified Rankin Scale

between patients treated with TXA or placebo. Probability of excellent functional outcome was actually lower in the TXA arm.

Conclusions

The panel recognized that the most recent evidence from the largest RCT evaluating antifibrinolytic therapy in aSAH [56] should change the prior recommendations from the 2011 Multidisciplinary Consensus Conference [1]. The Multidisciplinary Consensus Conference recommended, based on the available data at the time, albeit with a weak recommendation, that an early and short course of antifibrinolytic therapy be considered. Instead, based on entire body of current evidence, including an additional well-designed phase III clinical trial, the panel unanimously concluded that the administration of antifibrinolytic therapy to prevent rebleeding of ruptured aneurysm in patients with aSAH should not be recommended.

Calcium Channel Blockers

PICO Question

In patients with aSAH, what is the impact of administering calcium channel blockers compared with no calcium channel blockers on mortality, mRS, GOS, new cerebral infarction, and prevention of DCI?

Recommendation

1. We recommend the administration of oral nimodipine in patients with aSAH to reduce DCI and cerebral infarction, and to improve functional outcome (strong recommendation, moderate quality of evidence).

Rationale

Oral nimodipine is the only agent that has been shown to improve outcomes in patients with aSAH with a high quality of evidence.

Table 4 GRADE evidence profile, PICO 3a: in patients with aSAH, what is the impact of administering calcium channel blockers compared with no calcium channel blockers on mortality, mRS, GOS, new cerebral infarction, and prevention of DCI?

Certainty assessment					Quality of evidence
N of studies	Overall ROB	Inconsistency	Indirectness	Imprecision	
Mortality					
7 RCT	Some concern	0	−1	−1	⊕⊕⊕◯ MODERATE
5 Cohort	Critical	0	−2	−2	⊕◯◯◯ VERY LOW
Functional outcome (mRS, GOS)					
4 RCT	Low	−1	−1	−1	⊕⊕⊕◯ MODERATE
3 Cohort	Critical	0	−2	−2	⊕◯◯◯ VERY LOW
New cerebral infarction					
5 RCT	Some concern	0	−1	−1	⊕⊕⊕◯MODERATE
3 Cohort	Critical	0	−2	−2	⊕◯◯◯ VERY LOW
DCI					
5 RCT	Some concern	0	−1	−1	⊕⊕⊕◯MODERATE
4 Cohort	Serious	0	−2	−2	⊕◯◯◯ VERY LOW

GRADE Working Group grades of evidence:

⊕⊕⊕⊕: *High certainty* (very confident that the true effect lies close to that of the estimate of the effect)

⊕⊕⊕◯: *Moderate certainty* (moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)

⊕⊕◯◯: *Low certainty* (limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect)

⊕◯◯◯: *Very low certainty* (very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect)

Risk of bias:

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

DCI delayed cerebral ischemia, *GOS* Glasgow Outcome Scale, *mRS* modified Rankin Scale

Recommendation

2. We recommend against the administration of intravenous (IV) nicardipine for the prevention of DCI because of increased risk of adverse effects (strong recommendation, moderate quality of evidence).

Rationale

Adequately powered trials of IV nicardipine have shown marginal improvement in intermediate end points but no effect on clinically relevant outcomes. Additionally, these trials showed a significant increase in the risk of adverse effects including hypotension, pulmonary edema, and acute renal insufficiency.

Recommendation

3. There is insufficient evidence to recommend for or against the administration of calcium channel blocker other than nicardipine by IV or intraventricular routes.

Rationale

Other calcium channel blockers and other routes for their administration are not supported by sufficient evidence. Agents administered intravenously may place patients at higher risk for adverse effects, such as hypotension and pulmonary edema.

Summary of the Evidence

Eight RCTs and nine observational studies were evaluated, including five studies of oral nimodipine [63–67], four studies of continuous IV nimodipine only [68–71], three studies of nicardipine prolonged-release implants [72–74], two studies of continuous IV nimodipine followed by oral nimodipine [75, 76], one study of continuous IV nicardipine [77], one study of intraventricular nicardipine [78], and one study of oral flunarizine [79] (Table 4; Supplementary Table 5). Only studies evaluating the prophylactic administration of calcium channel blockers, rather than for treatment of established DCI or angiographic vasospasm, were included.

Five studies comparing oral nimodipine to placebo were evaluated. Two studies [63, 64] demonstrated improvement in functional outcome as assessed by the 3-month GOS as well as a reduced rate of infarction in one study [63] and a reduced rate of DCI in the other [64]. One additional study demonstrated a significantly reduced risk of DCI with oral nimodipine [65]. These findings are also supported by a 2007 Cochrane Review [80]. It is notable that nimodipine appears to improve patient outcomes without significantly reducing the rate of angiographic vasospasm [64, 66].

Oral nimodipine at a dosage of 60 mg every 4 h for a duration of 21 days is the most commonly used administration regimen in practice [63, 66, 67]; however, two of the RCTs employed other dosages: 90 mg every 4 h [64], and 0.35 mg/kg every 4 h [65]. Hypotension is a well-known adverse effect of oral nimodipine (a dihydropyridine calcium channel blocker), which may lead to reduced cerebral perfusion that could negate its beneficial effect in patients with aSAH. In the studies mentioned above, patients who missed multiple doses of nimodipine were often excluded by protocol from the analyses, and hypotension was uncommonly reported as an adverse effect. However, in practice, hypotension associated with nimodipine may lead to dosage splitting (i.e., 30 mg every 2 h) or therapy discontinuation [81–85]. Several retrospective assessments of these practices have noted an association between modified nimodipine regimens and poor outcomes, but these analyses are highly confounded by selection bias because nimodipine was often withheld upon diagnosis of DCI or vasospasm and frequently along with initiation of vasopressors for blood pressure augmentation. It is not known whether reducing the dose or discontinuing therapy when hypotension occurs, or while blood pressure augmentation is employed, will impact patient outcomes as compared with continuing standard dose nimodipine for a complete course of therapy.

All RCTs of oral nimodipine used a treatment duration of 21 days [63–67]. Some small retrospective studies have suggested that an abbreviated nimodipine course, such as discontinuing use after 14 days or on discharge from hospital if occurring earlier than day 21, may not adversely impact patient outcomes; yet, there is no conclusive evidence to support that a shorter course of oral nimodipine is as effective as the standard course of 21 days [81, 86, 87].

Continuous IV nicardipine at a dosage of 0.15 mg/kg/hr for up to 14 days was compared with a placebo in 906 patients with aSAH [77]. This study found reduced occurrence of symptomatic vasospasm among patients treated with IV nicardipine, but without a change in overall functional outcome. Additionally, IV nicardipine group was associated with increased risk of adverse events. In this study, 34.5% of patients in the IV nicardipine group compared with 17.5% in the placebo group had at least one episode of hypotension, although the occurrence of severe life-threatening hypotension was not different between groups (3% in each arm). Pulmonary edema and azotemia occurred in 6.0% of patients in the IV nicardipine group compared with 2.4% of placebo-treated patients ($p < 0.001$). More patients in the IV nicardipine group had treatment terminated due to adverse events (14.1% vs. 5.9%, $p < 0.001$). Lack of benefit and increased risk of adverse effects are the basis of our recommendation against the use of continuous IV nicardipine in patients with aSAH.

Ten additional studies evaluated the use of IV or intraventricular calcium channel blockers other than continuous IV nicardipine, which included continuous IV nimodipine alone [68–71], continuous IV nimodipine followed by oral nimodipine [75, 76], intraventricular nicardipine [78], and nicardipine prolonged-release implants [72–74]. Each of these studies were rated as low to very low quality of evidence and showed conflicting results for the outcomes of interest. Because of the insufficient quality of these studies, the panel decided not to make a recommendation for or against the use of IV or intraventricular routes of calcium channel blockers other than continuous IV nicardipine.

Of note, one recently published RCT evaluated the use of single-dose intraventricular sustained-release nimodipine microparticles in patients with aSAH; the trial was terminated early for futility [88]. This RCT was reviewed by the panel but was not included because it did not meet our PICO inclusion criteria due to the use of a calcium channel blocker (oral nimodipine), rather than placebo, as comparator.

Conclusions

Oral nimodipine is recommended for all patients with aSAH to improve outcomes. Other calcium channel blockers and routes for prophylactic use have insufficient evidence at this time or are not recommended due to adverse effects. Optimal management of nimodipine therapy (dose splitting, reduction, or withholding) in patients unable to tolerate the hemodynamic side effects or who are receiving vasopressors for blood pressure augmentation for treatment of DCI remains unknown. Whether abbreviated courses of oral nimodipine can be similarly effective to the typical 21-day course also remains unresolved.

Table 5 GRADE evidence profile, PICO 3b: in patients with aSAH, what is the impact of endothelin antagonists compared with no endothelin antagonists on mortality, mRS, GOS, new cerebral infarction, and prevention of DCI?

Certainty assessment					Quality of evidence
N of studies	Overall ROB	Inconsistency	Indirectness	Imprecision	
Mortality					
2 RCT	Low	0	0	−2	⊕⊕⊕◯ MODERATE
0 Cohort	NA	NA	NA	NA	NA
Functional outcome (mRS, GOS)					
5 RCT	Low	0	0	−2	⊕⊕⊕◯ MODERATE
0 Cohort	NA	NA	NA	NA	NA
New cerebral infarction					
5 RCT	Low	−1	0	−1	⊕⊕⊕⊕HIGH
0 Cohort	NA	NA	NA	NA	NA
DCI					
4 RCT	Low	0	−1	0	⊕⊕⊕⊕HIGH
0 Cohort	NA	NA	NA	NA	NA

GRADE Working Group grades of evidence:

⊕⊕⊕⊕: *High certainty* (very confident that the true effect lies close to that of the estimate of the effect)

⊕⊕⊕◯: *Moderate certainty* (moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)

⊕⊕◯◯: *Low certainty* (limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect)

⊕◯◯◯: *Very low certainty* (very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect)

Risk of bias:

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

DCI delayed cerebral ischemia, *GOS* Glasgow Outcome Scale, *mRS* modified Rankin Scale

Endothelin Antagonists

PICO Question

In patients with aSAH, what is the impact of endothelin antagonists compared with no endothelin antagonists on mortality, mRS, GOS, new cerebral infarction, and prevention of DCI?

Recommendation

We recommend against endothelin receptor antagonist administration because of lack of benefit on mortality and functional outcomes and an increased risk of adverse events (strong recommendation, high quality of evidence).

Rationale

Despite very promising data from translational studies and a phase IIb RCT, the phase III RCTs evaluating endothelin receptor antagonist administration in patients with aSAH showed no improvement in functional outcomes. In addition, there were notable adverse effects associated with this therapy. Consequently, the panel recommends against the use of endothelin receptor antagonist administration at this time.

Summary of the Evidence

Six studies, four of which were dose-finding/phase II trials, were included in the analysis. The phase II trials were not powered to show efficacy; although they demonstrated a signal of improvement in their primary end points (Table 5; Supplementary Table 6), these were not statistically significant [89–92].

In the two phase-III trials, patients receiving endothelin receptor antagonist (clasozentan) did not have significant improvement in mortality, mRS, GOS, new cerebral infarction, or prevention of DCI [93, 94]. In the second Clazosentan to Overcome Neurological Ischemia and Infarct Occurring After Subarachnoid Hemorrhage (CONSCIOUS-2) trial, a phase III study of patients with aSAH undergoing surgical clipping, the relative risk reduction was 17% (95% confidence interval [CI] −4 to 33; $p = 0.10$) for the primary end point of vasospasm-related morbidity and all-cause mortality, which was not statistically significant [93]. These results led to the early termination of CONSCIOUS-3, which enrolled patients undergoing endovascular coiling. Use of the higher dosage of clasozentan (15 mg/hr) in CONSCIOUS-3 was associated with a significant reduction in all-cause mortality and vasospasm-related

Table 6 GRADE evidence profile, PICO 3c: in patients with aSAH, what is the impact of statin treatment compared with no statins on mortality, mRS, GOS, new cerebral infarction, and prevention of DCI?

Certainty assessment					Quality of evidence
N of studies	Overall ROB	Inconsistency	Indirectness	Imprecision	
Mortality					
4 RCT	Low	0	0	−2	⊕⊕⊕◯ MODERATE
6 Cohort	Critical	0	−1	−1	⊕◯◯◯ VERY LOW
Functional outcome (mRS, GOS)					
5 RCT	Low	−1	−1	−2	⊕⊕⊕◯ MODERATE
6 Cohort	Critical	−1	−1	−1	⊕◯◯◯ VERY LOW
New cerebral infarction					
2 RCT	Low	0	0	0	⊕⊕⊕⊕ HIGH
6 Cohort	Critical	−1	−1	−1	⊕◯◯◯ VERY LOW
DCI					
7 RCT	Low	0	−1	0	⊕⊕⊕⊕ HIGH
6 Cohort	Critical	−1	−1	−2	⊕◯◯◯ VERY LOW

GRADE Working Group grades of evidence:

⊕⊕⊕⊕: *High certainty* (very confident that the true effect lies close to that of the estimate of the effect)

⊕⊕⊕◯: *Moderate certainty* (moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)

⊕⊕◯◯: *Low certainty* (limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect)

⊕◯◯◯: *Very low certainty* (very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect)

Risk of bias:

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

DCI delayed cerebral ischemia, *GOS* Glasgow Outcome Scale, *mRS* modified Rankin Scale

morbidity at 6 weeks, with an odds ratio (OR) of 0.474 (95% CI 0.275–0.818; $p = 0.0075$), but the scores on the extended GOS were not improved (OR 1.337; 95% CI 0.802–2.22; $p = 0.266$) [94].

The use of the endothelin receptor antagonist was associated with increased risk of adverse events in the phase III trials. The most common side effects included pulmonary complications related to fluid retention, hypotension, and anemia.

Conclusions

Based on current data, the committee recommends against the use of endothelin receptor antagonists for aSAH. Because of the positive effects on surrogate end points, future trials may be justified.

Statins

PICO Question

In patients with aSAH, what is the impact of statin treatment compared with no statins on mortality, mRS, GOS, new cerebral infarction, and prevention of DCI?

Recommendation

We recommend against starting statin treatment to reduce DCI or improve functional outcomes in aSAH because of lack of benefit (strong recommendation, high quality of evidence).

Rationale

Despite preliminary studies suggesting a beneficial effect of treatment with statin in reducing the risk of vasospasm in aSAH, a well-designed, large, phase III RCT conclusively demonstrated the lack of benefit from statin administration to statin-naïve patients on short-term or long-term outcomes. This recommendation pertains to new initiation of a statin and does not address the decision about continuing statin for patients taking them prior to admission.

Summary of the Evidence

Eight RCTs [95–102] and six observational studies relevant to this question were identified (Table 6; Supplementary Table 7) [103–108].

Early small RCTs with high Risk of Bias (ROB) suggested that pravastatin or simvastatin started within 48–72 h of aSAH onset was associated with lower risk

of vasospasm [96, 97, 109]. However, these findings were not confirmed in another phase II trial [98] and retrospective studies of routine statin use found no differences in outcomes as compared with historical controls [103–108].

Simvastatin in aneurysmal subarachnoid haemorrhage (STASH) was a large, multicenter, double-blind, RCT that randomly assigned 803 patients presenting within 96 h of aSAH to receive simvastatin 40 mg/day or placebo for up to 21 days [99]. Ordinal analysis of 6-month mRS scores adjusted for age and admission World Federation of Neurosurgical Societies (WFNS) grading scale (primary end point) showed no differences between the two groups (OR 0.97; 95% CIs 0.75–1.25). Secondary end points, including in-hospital mortality, DCI, DCI requiring rescue therapy, radiological infarction, length of hospital stay, and quality of life, were also similar between the two groups [99].

Subsequently, a smaller RCT showed no differences in risk of DCI or 3-month functional outcome between patients receiving a lower (40 mg/day) versus a higher (80 mg/day) dosage of simvastatin [100]. Another placebo-controlled randomized trial found that pitavastatin 4 mg daily was associated with lower risk of severe angiographic vasospasm but without a significant reduction in the risk of DCI or any improvement in functional outcomes at 3 months [102].

Conclusions

The available body of evidence, including a well-designed and adequately powered phase III RCT, indicates that the use of statin therapy does not improve DCI or functional outcomes in patients with aSAH.

Magnesium/Therapeutic Hypermagnesemia

PICO Question

In patients with aSAH, what is the impact of targeted therapeutic hypermagnesemia compared with no targeted hypermagnesemia on mortality, mRS, GOS, new cerebral infarction, and prevention of DCI?

Recommendation

We recommend against the use of targeted hypermagnesemia to improve outcomes in aSAH due to lack of benefit (strong recommendation, moderate quality evidence).

Rationale

In making this recommendation, the panel agreed that the available evidence made available over time allowed for issuing a strong recommendation. Although early pilot trials suggested potential benefits from utilization of magnesium and therapeutic hypermagnesemia with doses ranging from fixed amounts, weight-based dosing or targeted serum concentrations varying from high-normal (2.0–2.5 mmol/L) to supratherapeutic (twice baseline or goal magnesium concentration of 4–5.5 mg/dL), subsequent larger RCTs did not corroborate such benefit.

Summary of the Evidence

Between 2002 and 2010, six phase II RCTs evaluating the use of magnesium in aSAH were conducted, employing variable dosing regimens and different end points (GOS, symptomatic vasospasm or DCI, and the occurrence of adverse events; Table 7; Supplementary Table 8) [110–115]. Those trials suggested improved outcomes with magnesium administration, while several observational studies during the same time period—albeit limited by methodological issues—found inconsistent results associated with the treatment [116–120]. These early, preliminary studies were followed by two large randomized, saline-controlled phase III trials (Intravenous Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage and Magnesium in Aneurysmal Subarachnoid Hemorrhage 2) including 327 and 1203 patients, respectively [121, 122]. Neither of these RCTs found any benefit of IV magnesium sulfate infusion over placebo in functional outcomes or death. A post hoc subanalysis of the Magnesium in Aneurysmal Subarachnoid Hemorrhage 2 data evaluated magnesium and glucose levels and also found no benefit from magnesium administration [123]. Three additional smaller (all $\leq$ 120 study participants) studies that evaluated IV magnesium in different dosing, with different comparators, or in combination with additional medications offered mixed results, but were significantly limited by risk of bias and methodological concerns.

Conclusions

Despite early results from phase II trials suggesting a beneficial effect, phase III RCTs have shown that magnesium does not improve mortality, functional outcomes, DCI, or cerebral infarction in patients with aSAH.

Hemodynamic Management: Fluid Administration

PICO Question

In patients with aSAH at risk for DCI, what is the impact of high volume (liberal, targeting hypervolemia) fluid administration compared with conventional fluid management, targeting euvolemia, on mortality, mRS, GOS, new cerebral infarction, DCI, and pulmonary edema?

Table 7 GRADE evidence profile, PICO 3d: in patients with aSAH, what is the impact of targeted therapeutic hypermagnesemia compared with no targeted hypermagnesemia on mortality, mRS, GOS, new cerebral infarction, and prevention of DCI?

N of studies	Overall ROB	Inconsistency	Indirectness	Imprecision	
Mortality					
5 RCT	Some concern	0	0	−2	⊕⊕◯◯ LOW
2 Cohort	Serious	0	−1	−2	⊕◯◯◯ VERY LOW
Functional outcome (mRS, GOS)					
11 RCT	Low	−1	0	0	⊕⊕⊕⊕ HIGH
1 Cohort	Serious	0	0	−2	⊕◯◯◯ VERY LOW
New cerebral infarction					
4 RCT	Some concern	−2	0	−2	⊕⊕◯◯ LOW
0 Cohort	NA	NA	NA	NA	NA
DCI					
11 RCT	Low	−1	0	−1	⊕⊕⊕◯ MODERATE
4 Cohort	Critical	0	0	−2	⊕◯◯◯ VERY LOW

GRADE Working Group grades of evidence:

⊕⊕⊕⊕: *High certainty* (very confident that the true effect lies close to that of the estimate of the effect)

⊕⊕⊕◯: *Moderate certainty* (moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)

⊕⊕◯◯: *Low certainty* (limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect)

⊕◯◯◯: *Very low certainty* (very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect)

Risk of bias:

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

DCI delayed cerebral ischemia, *GOS* Glasgow Outcome Scale, *mRS* modified Rankin Scale

Recommendation

1. We suggest against liberal fluid administration because of an increased risk of pulmonary edema (Conditional recommendation, low quality of evidence).

Rationale

In making this recommendation, the panel considered that the quality of evidence was low overall. The literature does not support a benefit of liberal fluid administration on DCI, cerebral infarction, mortality, or functional outcomes for liberal fluid administration in aSAH. However, there was a consistent signal that liberal fluid administration targeting hypervolemia is associated with a higher risk of pulmonary edema than conventional fluid management targeting euvolemia. Thus, the panel suggests against liberal fluid administration given these safety concerns.

Recommendation

2. We suggest using targeted fluid administration to achieve euvolemia, which may include goal-directed hemodynamic therapy, to reduce the risk of pulmonary edema, prevent DCI, and improve functional outcome (conditional recommendation, very low quality of evidence).

Rationale

In making this recommendation, the panel considered that the quality of evidence was very low. Limited literature suggests that protocolized fluid management, including goal-directed hemodynamic therapy, may provide a means of achieving a target of euvolemia and may lead to a reduction in DCI and improved functional outcomes while reducing the risk of pulmonary edema.

Summary of the Evidence

Fourteen studies that assessed various fluid administration strategies in treating patients with aSAH were evaluated (Table 8; Supplementary Table 9). Three early studies compared the effects of fluid restriction or diuresis with more liberal fluid administration; in one small randomized trial aneurysm surgery was delayed for 7–10 days [124]. In the other two observational studies, the timing of aneurysm surgery was not specified [125, 126]. These three studies reported better outcomes with more liberal fluid administration compared to fluid restriction and/or diuresis but change in practice pattern over time made the findings of these studies no longer applicable. Four additional RCTs [127–130] and two observational studies [131, 132], ranging in quality from very low to

Table 8 GRADE evidence profile, PICO 4: in patients with aSAH at risk for DCI, what is the impact of high volume (liberal) fluid administration compared with conventional fluid management on mortality, mRS, GOS, new cerebral infarction, DCI, and pulmonary edema?

Certainty assessment					Quality of evidence
N of studies	Overall ROB	Inconsistency	Indirectness	Imprecision	
Mortality					
5 RCT	Some concern	0	0	−2	⊕⊕◯◯ LOW
5 Cohort	Serious	−1	0	−1	⊕◯◯◯ VERY LOW
New cerebral infarction					
5 RCT	Low	0	0	−1	⊕⊕◯◯ LOW
6 Cohort	Serious	−1	0	−2	⊕◯◯◯ VERY LOW
Functional outcome (mRS, GOS)					
2 RCT	Low	0	−1	−2	⊕⊕◯◯ LOW
1 Cohort	Serious	0	−2	−2	⊕◯◯◯ VERY LOW
DCI					
7 RCT	Some concern	−1	−1	−2	⊕⊕◯◯ LOW
5 Cohort	Serious	−1	−1	−2	⊕◯◯◯ VERY LOW
Pulmonary edema					
6 RCT	Low	0	−2	−2	⊕⊕◯◯ LOW
2 Cohort	Serious	0	−2	−2	⊕◯◯◯ VERY LOW

GRADE Working Group grades of evidence:

⊕⊕⊕⊕: *High certainty* (very confident that the true effect lies close to that of the estimate of the effect)

⊕⊕⊕◯: *Moderate certainty* (moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)

⊕⊕◯◯: *Low certainty* (limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect)

⊕◯◯◯: *Very low certainty* (very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect)

Risk of bias:

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

DCI delayed cerebral ischemia, *GOS* Glasgow Outcome Scale, *mRS* modified Rankin Scale

high (Table 8; Supplementary Table 9), compared hypervolemic fluid management with normovolemia or moderate hypervolemia. None of these studies demonstrated improved neurological outcomes with hypervolemic fluid management compared with normovolemia. In addition, pulmonary edema was reported more frequently in the hypervolemic arms of all four RCTs. Pulmonary edema was reported as an outcome in one of the observational studies [131] and occurred more frequently in the group treated with hypervolemia. The increased frequency of pulmonary edema associated with hypervolemia did not reach statistical significance in any individual study.

Several studies investigated various approaches to protocolized fluid and/or hemodynamic management in patients with aSAH. Hoff et all used pulse dye densitometry-derived blood volume measurement to guide fluid management in a cohort of 54 patients with aSAH, and compared this strategy with another cohort of 48 patients who underwent "conventional" fluid management corresponding to a target of clinical normovolemia aiming at 750 mL positive daily fluid balance [133]. There were no differences in the risk of DCI or other outcomes between groups, and the risk of bias for this study was judged to be critical. When a computerized prescribing routine and hemodynamic assessment using pulse pressure variation or central venous pressure to limit fluid administration was compared with an historical cohort treated with conventional fluid management, a reduction in hypoxemic patients was found in the cohort treated with protocolized/limited fluid administration but no differences in other outcomes. Shikata et al. compared a protocol for optimized and restricted fluid and sodium administration to conventional fluid management in consecutive series of patients with aSAH [134]. Optimized fluid and sodium administration were associated with an increased likelihood of a favorable mRS score at discharge.

Two RCTs utilized transpulmonary thermodilution as part of goal-directed hemodynamic therapy protocols to guide fluid and cardiovascular treatment of patients with aSAH [135, 136]. Mutoh et al. randomized 160 patients

with aSAH to conventional fluid management guided by fluid balance and central venous pressure or to management using "early goal-directed fluid therapy" (EGDT) using a transpulmonary thermodilution-based algorithm [135]. There were no significant differences in pulmonary edema, DCI, or other outcomes (Table 8; Supplementary Table 9).

Anetsberger et al. randomized 108 patients with aSAH to standard therapy versus a goal-directed hemodynamic therapy algorithm that incorporated transpulmonary thermodilution for hemodynamic assessment [136]. Daily fluid intake and balance were similar between groups. The goal-directed hemodynamic therapy group had a reduced incidence of DCI and an increased number of patients with favorable neurologic outcome at 3 months.

Conclusions

Although not statistically significant in any single study, the safety end point of pulmonary edema was consistently more common in patients receiving liberal or hypervolemic fluid strategies. Thus, the panel suggests avoiding liberal fluid administration to reduce the risk of pulmonary edema. Although several studies reported improved outcomes with protocolized fluid management, the overall quality of evidence was judged to be low to very low; thus, there is insufficient evidence to recommend a specific fluid management or hemodynamic protocol at this time. The panel recommends targeting euvolemia in patients with aSAH, although the technique for assessing or achieving this goal remains undefined at present.

Further investigation of protocolized fluid management after aSAH is needed, including investigation of techniques for assessment and attainment of euvolemia, and exploration of noninvasive techniques for the implementation of goal-directed hemodynamic therapy.

Hemodynamic Management: Blood Pressure and Cardiac Output Augmentation

PICO Question

In patients with aSAH at risk for DCI or diagnosed with DCI, what is the impact of blood pressure and/or cardiac output augmentation compared with no blood pressure or cardiac output augmentation on mortality, mRS, GOS, new cerebral infarction, DCI prevention, pulmonary edema, myocardial infarction, and arrhythmia?

Recommendation

There are insufficient quality data to recommend for or against blood pressure or cardiac output augmentation for the prevention and treatment of DCI. Due to the associated risks, use of these interventions should be judicious and tailored to the patient's individual hemodynamic profile.

Rationale

Although blood pressure augmentation has been a mainstay of DCI management for decades, the paucity of supportive quality data precludes recommending any particular strategy of hemodynamic augmentation. In making this recommendation, the panel emphasized that the management of hemodynamic augmentation should be tailored to the patient's individual hemodynamic profile. The recommendation on blood pressure and cardiac augmentation does not specifically address the use of individual pharmacological agents because of the lack of high-quality evidence.

Summary of the Evidence

Eight RCTs and four observational, comparative studies were reviewed (Table 9; Supplementary Table 10). The overall body of literature was limited by small sample size and heterogeneity in inclusion and exclusion criteria, definition of DCI, complications, and outcome assessment. Although some studies could not be interpreted for the PICO due to study design [131, 137–141], a majority of the remaining studies showed no benefit from blood pressure or cardiac output augmentation, and several found such treatment was associated with harm. Egge et al. studied prophylactic hypertensive hemodilution compared with normovolemia in Hunt and Hess grade I to III patients and found no difference in DCI or GOS [129]. Rondeau et al. compared norepinephrine-induced hypertension with dobutamine-induced augmentation in cardiac index and found no difference in angiographic vasospasm between the groups [142]. In a small study, Togashi et al. used a two-by-two design to evaluate hypervolemia and induced hypertension to prevent DCI and found no difference in mRS between treatment groups [130]. However, patients receiving induced hypertension had worse neurobehavioral scores and several experienced significant adverse events including pulmonary edema. Gathier et al., conducted a multicenter RCT comparing induced hypertension to normotension in patients with symptomatic DCI [143]. The intervention group was treated with fluids and norepinephrine until neurologic deficits improved, a maximum systolic/mean arterial pressure of 230/130 mm Hg was reached, or the patient experienced a complication. The trial was stopped prematurely due to slow recruitment; the authors noted a higher rate of poor outcome in the induced hypertension group.

Two RCTs evaluated EGDT protocols using a central line and noninvasive or invasive cardiac output monitoring to guide care before and after development of DCI

Table 9 GRADE evidence profile, PICO 5: in patients with aSAH at risk for DCI or diagnosed DCI, what is the impact of blood pressure and/or cardiac output augmentation compared with no blood pressure or cardiac output augmentation on mortality, mRS, GOS, new cerebral infarction, DCI prevention, pulmonary edema, myocardial infarction, and arrhythmia?

Certainty assessment					Quality of evidence
N of studies	Overall ROB	Inconsistency	Indirectness	Imprecision	
Mortality					
0 RCT	NA	NA	NA	NA	NA
0 Cohort	NA	NA	NA	NA	NA
Functional outcome (mRS, GOS)					
5 RCT	Low	−1	−1	−2	⊕⊕◯◯ LOW
4 Cohort	Moderate	−1	−1	−2	⊕◯◯◯ VERY LOW
New cerebral infarction					
2 RCT	High	0	−2	−2	⊕◯◯◯ VERY LOW
2 Cohort	Critical	0	−2	−2	⊕◯◯◯ VERY LOW
DCI					
4 RCT	High	0	−2	−2	⊕◯◯◯ VERY LOW
0 Cohort	NA	NA	NA	NA	NA
Adverse events					
5 RCT	Some concern	0	−2	−2	⊕⊕◯◯ LOW
1 Cohort	Serious	0	−2	−2	⊕◯◯◯ VERY LOW

GRADE Working Group grades of evidence:

⊕⊕⊕⊕: *High certainty* (very confident that the true effect lies close to that of the estimate of the effect)

⊕⊕⊕◯: *Moderate certainty* (moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)

⊕⊕◯◯: *Low certainty* (limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect)

⊕◯◯◯: *Very low certainty* (very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect)

Risk of bias:

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

DCI delayed cerebral ischemia, *GOS* Glasgow Outcome Scale, *mRS* modified Rankin Scale

symptoms [135]. One study found no significant difference in incidence of DCI or mRS using EGDT [135]. The second, a single-center RCT, found that use of protocol-driven invasive hemodynamic monitoring was associated with reduced incidence of DCI and improved 3-month GOS, but no difference in mortality [136].

A randomized trial and an observational study of the use of IV milrinone were included, one comparing IV versus IV + IA milrinone [140], and the other comparing IV milrinone versus continuous magnesium infusion for 21 days [138]. These studies suffered from moderate to serious bias and were found to be inconclusive.

The panel discussed at length the discordance between clinical practice and the study results. Most panel members thought that the selection criteria, design, and size of the studies to date did not allow them to adequately address the PICO question. Most studies were conducted in a single center with a small sample size and were heavily influenced by local protocols and standards. Confounding concomitant interventions including surgical and intensive care management likely influenced the outcomes. Therefore, based on the available evidence, recommendation for or against blood pressure and/or cardiac output augmentation cannot be made.

Conclusions

This recommendation was based on the lack of solid evidence to support the practice rather than the existence of appropriate studies that failed to show benefit. Available evidence does not support or refute a role for augmentation of blood pressure and/or cardiac outcome. Blood pressure and cardiac output augmentation are not without risk. Excessive vasopressor and inotrope use are associated with increased mortality and end-organ damage in patients with cardiogenic shock [144]. Several studies reviewed for this PICO reported an association between blood pressure or cardiac augmentation and cardiovascular adverse events [130, 145]. For instance, Gathier et al. found patients treated

Table 10 GRADE evidence profile, PICO 6: in patients with aSAH, is treatment triggered by change in exam plus advanced neuroimaging (CTA, CTP, TCD) versus examination alone superior in improving mortality, mRS, GOS, and preventing new cerebral infarction?

Certainty assessment					Quality of evidence
N of studies	Overall ROB	Inconsistency	Indirectness	Imprecision	
Mortality					
0 RCT	NA	NA	NA	NA	NA
0 Cohort	NA	NA	NA	NA	NA
Functional outcome (mRS, GOS)					
0 RCT	NA	NA	NA	NA	NA
0 Cohort	NA	NA	NA	NA	NA
New cerebral infarction					
0 RCT	NA	NA	NA	NA	NA
0 Cohort	NA	NA	NA	NA	NA

GRADE Working Group grades of evidence:

⊕⊕⊕⊕: *High certainty* (very confident that the true effect lies close to that of the estimate of the effect)

⊕⊕⊕◯: *Moderate certainty* (moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)

⊕⊕◯◯: *Low certainty* (limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect)

⊕◯◯◯: *Very low certainty* (very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect)

Risk of bias:

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

DCI delayed cerebral ischemia, *GOS* Glasgow Outcome Scale, *mRS* modified Rankin Scale

with induced hypertension had more severe adverse events (11% vs. 5%, Relative risk 2.1; 95% CI 0.9–5.0) including death, pneumothorax, atrial fibrillation, and myocardial infarction [145]. Therefore, the panel felt a statement in response to this PICO should include a note of caution to the practitioner employing these therapies, emphasizing the importance of tailoring therapy to individual patients and closely monitoring for complications.

More research is necessary to determine whether blood pressure and/or cardiac augmentation can be effective to reduce ischemic brain damage and improve functional outcomes in patients with aSAH who develop DCI.

DCI Management: Triggers for Interventional Procedures for Treatment of DCI

PICO Question

In patients with aSAH, is treatment triggered by change in examination plus advanced neuroimaging (Computed Tomography (CT) Angiography, CT Perfusion, transcranial Doppler) versus examination alone superior in improving mortality, mRS, GOS, and preventing new cerebral infarction?

Recommendation

There is insufficient evidence to provide a recommendation on the optimal trigger (change in neurological examination plus findings on advanced neuroimaging vs. change in examination alone) for interventional procedures for the treatment of DCI.

Rationale

In making this recommendation, the panel considered that there were no available studies to answer this common clinical question. Most clinical centers employ a formal or informal protocol to trigger interventional procedures; however, there have been no formal studies comparing change in neurological examination plus findings on advanced neuroimaging versus change in clinical examination alone as the trigger for intervention. Consequently, the panel can only state that there is insufficient evidence regarding superiority of one approach over the other.

Summary of the Evidence

While there is abundant literature demonstrating the association of various clinical and imaging factors associated with the development of DCI, radiological infarction and clinical outcome, there have been no studies specifically evaluating triggers for endovascular intervention, especially evaluating whether adding neuroimaging findings to the changes in neurological examination serves to improve the decision making for the intervention. For example, one study identified clinical and imaging predictors of

vasospasm from baseline assessments but did not compare different ways of selecting patients for endovascular intervention as DCI developed (Table 10; Supplementary Table 11) [146]. Another study identified quantitative electroencephalogram parameters that were sensitive and specific for DCI in aSAH [147]. However, neuroimaging was used in both arms being compared and the population was limited to patients with severe aSAH. Although these analyses were critical to furthering our understanding of the disease course, they do not directly address the specific question hereby considered.

Conclusions

Given the absence of formal comparisons between approaches to trigger endovascular intervention in patients with neurological deterioration (clinical vs. clinical and neuroimaging), we are unable to provide a recommendation in favor or against a particular strategy. Both the absence of formal research and perception of variance in practice identify clinical equipoise for future studies. Given that this question applies to many patients with aSAH, the panel believes there is an urgent need for research in this area. Hypothesis-generating studies across centers that use or do not use neuroimaging as part of the protocolized triggering for intervention are needed. Initial descriptive studies can quantify practice variation, and between-center comparisons can provide initial observational data, although such comparisons are limited by high risk of bias. Thus, a direct comparison or cluster randomized clinical trial of at least two strategies, one of which would incorporate neuroimaging evaluation, is necessary to address this important clinical question.

Mineralocorticoid Therapy for the Management of Hyponatremia

PICO Question

In patients with aSAH, what is the impact of treatment with mineralocorticoids compared with no treatment with mineralocorticoids on mortality, mRS, GOS, new cerebral infarction, serum sodium levels, and fluid balance?

Recommendation

There is insufficient evidence to support mineralocorticoid administration to maintain normal serum sodium concentrations and/or even fluid balance or to improve functional outcome.

Rationale

Although mineralocorticoids are often prescribed to patients with aSAH to ameliorate hyponatremia and polyuria once these complications have developed, there are no studies testing mineralocorticoids for treatment of hyponatremia. Instead, the only available studies have evaluated mineralocorticoids for prevention of hyponatremia and volume contraction. These studies have insufficient quality to support the use of mineralocorticoids in aSAH. Mineralocorticoids can potentially be useful to correct hyponatremia, but the effect of hyponatremia correction with mineralocorticoids on the functional outcomes of patients with aSAH has not been formally investigated.

Summary of the Evidence

We identified four RCTs on this topic (Table 11; Supplementary Table 12) [125, 148–151]. All of these trials had a high risk of bias because of methodological limitations (especially lack of blinding) and imprecision related to their small size (between 28 and 91 patients). The studies tested fludrocortisone [125, 152] or hydrocortisone [149, 153] started within 48–72 h of aSAH onset and continued for 10–14 days as compared with no intervention or placebo. Primary end points varied, including incidence of hyponatremia generally defined as serum sodium concentrations lower than 135 mEq/L on at least 2 consecutive days, negative fluid balance and negative sodium balance. Functional outcomes and DCI were included as secondary end points. Overall, these trials suggested that mineralocorticoids can reduce the risk of hyponatremia and natriuresis without any effect on DCI or functional outcomes. Of note, hypokalemia was more common in patients treated with mineralocorticoids.

Conclusions

There is no evidence that mineralocorticoids improve functional outcomes in aSAH.

Mineralocorticoids might reduce the incidence of hyponatremia when started early after aSAH onset and continued for 10–14 days; however, available evidence is inconclusive. More rigorous and larger trials are necessary to define the use of mineralocorticoids for the prevention and treatment of hyponatremia in aSAH.

Management of Anemia

PICO Question

In patients with aSAH, is a more aggressive transfusion strategy (to keep a hemoglobin > 10 g/dL) more effective than a conservative transfusion strategy (to keep a hemoglobin > 7 g/dL) to improve mortality, mRS, GOS, new cerebral infarction, DCI prevention, and transfusion-related complications?

Recommendation

There is insufficient evidence to provide a recommendation for using a transfusion threshold higher than a hemoglobin of > 7 g/dL in patients with aSAH.

Table 11 GRADE evidence profile, PICO 7: in patients with aSAH, what is the impact of treatment with mineralocorticoids compared with no treatment with mineralocorticoids on mortality, mRS, GOS, new cerebral infarction, serum sodium levels, and fluid balance?

Certainty assessment					Quality of evidence
N of studies	Overall ROB	Inconsistency	Indirectness	Imprecision	
Mortality					
0 RCT	NA	NA	NA	NA	NA
0 Cohort	NA	NA	NA	NA	NA
Functional outcome (mRS, GOS)					
4 RCT	High	0	0	−2	⊕◯◯◯ VERY LOW
0 Cohort	NA	NA	NA	NA	NA
DCI					
4 RCT	High	0	0	−2	⊕◯◯◯ VERY LOW
0 Cohort	NA	NA	NA	NA	NA
Serum sodium					
4 RCT	High	−2	0	−2	⊕◯◯◯ VERY LOW
0 Cohort	NA	NA	NA	NA	NA
Fluid balance					
2 RCT	High	−1	0	−1	⊕◯◯◯ VERY LOW
0 Cohort	NA	NA	NA	NA	NA

GRADE Working Group grades of evidence:

⊕⊕⊕⊕: *High certainty* (very confident that the true effect lies close to that of the estimate of the effect)

⊕⊕⊕◯: *Moderate certainty* (moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)

⊕⊕◯◯: *Low certainty* (limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect)

⊕◯◯◯: *Very low certainty* (very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect)

Risk of bias:

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

DCI delayed cerebral ischemia, *GOS* Glasgow Outcome Scale, *mRS* modified Rankin Scale

Rationale

The panel acknowledged that anemia is common after aSAH and has been associated with poor functional outcome. In addition, the panel recognized that the role and optimal thresholds for red blood cell transfusion are of clinical relevance because anemia is a potentially modifiable factor influencing secondary brain injury. However, at present there is a paucity of quality data evaluating any transfusion strategy targeting a hemoglobin target higher than 7 g/dL specifically for patients with aSAH.

Summary of the Evidence

The panel evaluated whether any of two transfusion strategies (aggressive to maintain a hemoglobin > 10 g/dL and conservative to maintain a hemoglobin > 7 g/dL) improves mortality, mRS, GOS, new cerebral infarction, DCI prevention, or transfusion-related complications in patients with aSAH. The panel identified one RCT and one nonrandomized observational study with five different outcome analyses (Table 12; Supplementary Table 13).

Naidech et al. performed a small RCT evaluating the safety and feasibility of maintaining two goals of hemoglobin concentration (at least 10 g/dL or 11.5 g/dL) within 3 days of aSAH onset [154]. The authors reported no difference in new cerebral infarction, DCI prevention, or transfusion-related complications between the treatment arms. Ayling et al. performed a post hoc analysis of available data from the CONSCIOUS trial [91, 155]. The investigators used two propensity score matching algorithms stratified based on baseline hemoglobin level to study the effect of transfusions on outcome. No difference in mortality rates between the matched patients were found using either algorithm.

Conclusions

The panel agreed that specific optimal transfusion strategies and specific hemoglobin thresholds, along with

Table 12 GRADE evidence profile, PICO 8: in patients with aSAH, is a more aggressive transfusion strategy (to keep a hemoglobin > 10 g/dL) more effective than a conservative transfusion strategy (to keep a hemoglobin > 7 g/dL) to improve mortality, mRS, GOS, new cerebral infarction, DCI prevention, and transfusion-related complications?

Certainty assessment					Quality of evidence
N of studies	Overall ROB	Inconsistency	Indirectness	Imprecision	
Mortality					
0 RCT	NA	NA	NA	NA	NA
1 Cohort	Moderate	0	0	−2	⊕◯◯◯ VERY LOW
Functional outcome (mRS, GOS)					
0 RCT	NA	NA	NA	NA	NA
1 Cohort	Moderate	0	0	−2	⊕◯◯◯ VERY LOW
New cerebral infarction					
1 RCT	Some concern	0	0	−2	⊕◯◯◯ VERY LOW
0 Cohort	NA	NA	NA	NA	NA
DCI					
1 RCT	Some concern	0	0	−2	⊕◯◯◯ VERY LOW
0 Cohort	NA	NA	NA	NA	NA
Transfusion-related complications					
1 RCT	High	0	0	−2	⊕◯◯◯ VERY LOW
Cohort	NA	NA	NA	NA	NA

GRADE Working Group grades of evidence:

⊕⊕⊕⊕: *High certainty* (very confident that the true effect lies close to that of the estimate of the effect)

⊕⊕⊕◯: *Moderate certainty* (moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)

⊕⊕◯◯: *Low certainty* (limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect)

⊕◯◯◯: *Very low certainty* (very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect)

Risk of bias:

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

DCI delayed cerebral ischemia, *GOS* Glasgow Outcome Scale, *mRS* modified Rankin Scale

their impact on mortality, DCI prevention, functional outcome, and transfusion-related complications have not been established. All members of the panel agreed that the available evidence is insufficient to provide any recommendation supporting the treatment of patients with aSAH with a transfusion threshold higher than a hemoglobin of > 7 g/dL. In addition, the members of the panel concurred that further research is necessary to answer this question.

Management of Hydrocephalus

PICO Question

In patients with aSAH and an indwelling external ventricular drain (EVD), is a strategy based on direct clamping superior to gradual weaning on mortality, mRS, GOS, new cerebral infarction, incidence of ventriculoperitoneal (VP) shunt placement, rate of infection, and EVD complications?

Recommendation

There is insufficient evidence to provide a recommendation on direct clamping versus gradual weaning strategy for EVD removal for the management of hydrocephalus in patients with aSAH.

Rationale

Different centers favor either gradual weaning or direct clamping to decide whether an EVD can be safely removed or a VP shunt is necessary [156]. These two strategies have not been adequately compared. Therefore, the optimal strategy remains unknown.

Summary of the Evidence

One RCT, one cohort study with historical controls, and one multicenter observational study leveraging different EVD weaning protocols at different institutions addressed this question and were included (Table 13; Supplementary Table 14) [157–159].

Table 13 GRADE evidence profile, PICO 9: in patients with aSAH and an indwelling external ventricular drain (EVD), is a strategy based on direct clamping superior to gradual weaning on mortality, mRS, GOS, new cerebral infarction, incidence of ventriculoperitoneal (VP) shunt placement, rate of infection, and EVD complications?

Certainty assessment					Quality of evidence
N of studies	Overall ROB	Inconsistency	Indirectness	Imprecision	
Mortality					
0 RCT	NA	NA	NA	NA	NA
0 Cohort	NA	NA	NA	NA	NA
Functional outcome (mRS, GOS)					
0 RCT	NA	NA	NA	NA	NA
0 Cohort	NA	NA	NA	NA	NA
New cerebral infarction					
0 RCT	NA	NA	NA	NA	NA
1 Cohort	Serious	0	0	−2	⊕◯◯◯ VERY LOW
Incidence of ventriculoperitoneal (VP) shunt placement					
1 RCT	Some concern	0	0	−2	⊕◯◯◯ VERY LOW
2 Cohort	Serious	0	0	−2	⊕◯◯◯ VERY LOW
Rate of infection					
0 RCT	NA	NA	NA	NA	NA
1 Cohort	Serious	0	0	−2	⊕◯◯◯ VERY LOW
EVD complications					
0 RCT	NA	NA	NA	NA	NA
2 Cohort	Serious	0	0	−2	⊕◯◯◯ VERY LOW

GRADE Working Group grades of evidence:

⊕⊕⊕⊕: *High certainty* (very confident that the true effect lies close to that of the estimate of the effect)

⊕⊕⊕◯: *Moderate certainty* (moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)

⊕⊕◯◯: *Low certainty* (limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect)

⊕◯◯◯: *Very low certainty* (very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect)

Risk of bias:

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

DCI delayed cerebral ischemia, *GOS* Glasgow Outcome Scale, *mRS* modified Rankin Scale

The RCT was conducted in a single center and only included 81 patients who were randomly assigned to direct EVD clamping or gradual weaning (over 3 days) [157]. The proportion of patients undergoing VP shunting (primary end point) was similar in both groups (63.4% with direct clamping vs. 62.5% with gradual weaning). Patients randomly assigned to the direct clamping arm had shortened duration of EVD and intensive care unit stay (both secondary end points). Safety was comparable among both groups.

The observational, single-center study compared a series of consecutive patients treated with a strategy of intermittent cerebral spinal fluid (CSF) drainage and rapid EVD weaning versus a historical cohort treated with a strategy of continuous CSF drainage and gradual EVD weaning [160]. The analysis found a reduction in VP shunt placement with the intermittent CSF drainage/rapid EVD weaning strategy compared with the continuous CSF drainage/gradual EVD weaning strategy (13% vs. 35%). The intermittent CSF drainage/rapid EVD weaning strategy was also associated with shorter duration of EVD use, intensive care unit and hospital stays, and incidence of nonfunctioning EVD.

The prospective multicenter observational study that used a standardized weaning protocol in 139 patients showed similar results, except that there was a nonsignificant trend toward a reduction in rate of VP shunt placement comparing rapid versus gradual weaning in the adjusted analysis (OR 0.43; 95% CI 0.18–1.03). Rapid wean was associated with fewer EVD days, and fewer cases of nonfunctioning EVD [159].

It should be noted that the rates of VP shunt placement were markedly different between the two single-center studies, and this is a common problem when

evaluating the literature on EVD management and VP shunt requirements in general. The multicenter cohort study addressed this concern by standardizing the weaning protocols prior to study implementation.

Conclusions

Although the scant available evidence appears to support direct clamping over gradual weaning of the EVD, the optimal EVD weaning, and removal strategy can only be reliably determined through the conduction of a large, multicenter RCT comparing clearly defined protocols and adhering to well defined indications for VP shunt placement.

Summary

Despite improvements in the outcomes of patients with aSAH over time, many important clinical questions on various aspects of the treatment of these patients remain unanswered. These guidelines provide recommendations for or against interventions proven to be effective, ineffective, or harmful, but these guidelines also serve to highlight gaps in knowledge that should guide future research priorities.

The treatment of patients with aSAH is undoubtedly complex and demands clinical judgment. Yet, more and better-quality research is necessary to help guide it. Although several pharmacological interventions have been tested through RCTs, we found that the quality of evidence for nonpharmacological questions was consistently poor. This is in part intrinsic to the challenges of evaluating management approaches or algorithms that involve many facets and potential pathways. Therefore, the neurocritical care and neurosurgical communities as well as funding agencies must work together to improve the scientific basis for the management of aSAH in the future.

Supplementary Information

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Author contributions

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