

## AHA/ASA GUIDELINE

# 2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage: A Guideline From the American Heart Association/American Stroke Association

*The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.*

*The American Association of Neurological Surgeons/Congress of Neurological Surgeons Cerebrovascular Section affirms the educational benefit of this document.*

*Endorsed by the Neurocritical Care Society, Society of Neurointerventional Surgery, and Society of Vascular and Interventional Neurology*

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**AIM:** The “2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage” replaces the 2012 “Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage.” The 2023 guideline is intended to provide patient-centric recommendations for clinicians to prevent, diagnose, and manage patients with aneurysmal subarachnoid hemorrhage.

**METHODS:** A comprehensive search for literature published since the 2012 guideline, derived from research principally involving human subjects, published in English, and indexed in MEDLINE, PubMed, Cochrane Library, and other selected databases relevant to this guideline, was conducted between March 2022 and June 2022. In addition, the guideline writing group reviewed documents on related subject matter previously published by the American Heart Association. Newer studies published between July 2022 and November 2022 that affected recommendation content, Class of Recommendation, or Level of Evidence were included if appropriate.

**STRUCTURE:** Aneurysmal subarachnoid hemorrhage is a significant global public health threat and a severely morbid and often deadly condition. The 2023 aneurysmal subarachnoid hemorrhage guideline provides recommendations based on current evidence for the treatment of these patients. The recommendations present an evidence-based approach to preventing, diagnosing, and managing patients with aneurysmal subarachnoid hemorrhage, with the intent to improve quality of care and align with patients' and their families' and caregivers' interests. Many recommendations from the previous aneurysmal subarachnoid hemorrhage guidelines have been updated with new evidence, and new recommendations have been created when supported by published data.

**Key Words:** AHA Scientific Statements ■ hematoma ■ intracranial aneurysm ■ intracranial hemorrhages  
■ subarachnoid hemorrhage, aneurysmal ■ vasospasm

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## TOP 10 TAKE-HOME MESSAGES

1. Improving timely and equitable access to health care system resources such as comprehensive stroke centers is important to improve overall patient outcomes. Management of aneurysmal subarachnoid hemorrhage (aSAH) in centers with dedicated neurocritical care units, experience with higher case volumes, physician expertise in

- aneurysm treatment, expert nursing care, and multidisciplinary teams is associated with lower mortality and increased likelihood of good functional outcomes. Timely transfer to centers with expertise in aSAH is recommended.
2. Acute rebleeding after initial aSAH is associated with increased mortality and poor clinical outcomes. Prompt evaluation, identification of aneurysmal source, and treatment of the ruptured aneurysm are recommended, preferably within 24 hours. The goal of treatment should be complete obliteration whenever feasible to reduce the risk of rebleeding and retreatment.
3. Balancing the goal of securing the ruptured aneurysm with risk of intervention is based on patient and aneurysm characteristics and should be determined by specialists with expertise in endovascular and surgical treatments. Use of established grading scales can assist in prognostication and shared decision-making with patients, families, and surrogates.
4. Medical complications in multiple organ systems are associated with worse outcomes after aSAH. Standard intensive care unit bundles of care for mechanically ventilated patients and venous thromboembolism prophylaxis are recommended. Close hemodynamic monitoring and blood pressure management to minimize blood pressure variability are beneficial. Goal-directed treatment of intravascular volume status to maintain euvolemia and avoid excess morbidity associated with hypervolemia is also important in improving overall outcomes. Routine use of antifibrinolytic therapy did not improve functional outcomes.
5. For new-onset seizures after aSAH, treatment with antiseizure medication for 7 days is recommended. Prophylactic antiseizure medication should not be routinely used but can be considered in high-risk patients (with ruptured middle cerebral artery aneurysm, intraparenchymal hemorrhage, high-grade aSAH, hydrocephalus, or cortical infarction). Phenytoin use is associated with excess morbidity and should be avoided. Monitoring with continuous electroencephalography can detect nonconvulsive seizures, especially in patients with depressed consciousness or fluctuating neurological examination.
6. Delayed cerebral ischemia remains a significant complication and is associated with worse outcomes after aSAH. Monitoring of clinical deterioration requires trained nurses with expertise to rapidly detect neurological examination changes. Diagnostic modalities, including transcranial Doppler, computed tomography angiography, and computed tomography perfusion, when performed by trained expert interpreters, can be useful to detect cerebral vasospasm and predict delayed cerebral ischemia. Continuous electroencephalography and

invasive monitoring may also be useful in patients with high-grade aSAH with limited neurological examination.

7. Early initiation of enteral nimodipine is beneficial in preventing delayed cerebral ischemia and improving functional outcomes after aSAH. Routine use of statin therapy and intravenous magnesium is not recommended.
8. Elevating blood pressure and maintaining euvolemia in patients with symptomatic delayed cerebral ischemia can be beneficial in reducing the progression and severity of delayed cerebral ischemia. However, prophylactic hemodynamic augmentation and hypervolemia should not be performed to minimize iatrogenic patient risks.
9. Cerebrovascular imaging after treatment and subsequent imaging monitoring are important in treatment planning for remnants, recurrence, or regrowth of the treated aneurysm and to identify changes in other known aneurysms. Although the risk of rerupture is low, the use of imaging to guide treatment decisions that may reduce the risk of future aSAH among survivors is recommended, especially in patients with residual aneurysm. Imaging monitoring for the development of de novo aneurysms is also important in younger patients with multiple aneurysms or with  $\geq 2$  first-degree relatives with aSAH.
10. A multidisciplinary team approach to identify discharge needs and design rehabilitation treatment is recommended. Among aSAH survivors, physical, cognitive, behavioral, and quality of life deficits are common and can persist. Early identification with validated screening tools can identify deficits, especially in behavioral and cognitive domains. Interventions for mood disorders can improve long-term outcomes, and counseling on the higher risk for long-term cognitive dysfunction may be beneficial.

## PREAMBLE

Since 1990, the American Heart Association (AHA)/American Stroke Association (ASA) has translated scientific evidence into clinical practice guidelines with recommendations to improve cerebrovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cerebrovascular care. AHA/ASA sponsors the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts.

Clinical practice guidelines for stroke provide recommendations applicable to patients with or at risk of developing cerebrovascular disease. The focus is on medical practice in the United States, but many aspects are relevant to patients throughout the world. Although it

must be acknowledged that guidelines may be used to inform regulatory or payer decisions, the core intent is to improve quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment; furthermore, the recommendations set forth should be considered in the context of individual patient values, preferences, and associated conditions.

AHA/ASA strives to ensure that guideline writing groups contain requisite expertise and are representative of the broader medical community by selecting experts from a broad array of backgrounds, representing different sexes, races, ethnicities, intellectual perspectives, geographic regions, and scopes of clinical practice and by inviting organizations and professional societies with related interests and expertise to participate as endorsers. AHA/ASA has rigorous policies and methods for development of guidelines that limit bias and prevent improper influence. The complete policy on relationships with industry and other entities can be found at <https://professional.heart.org/-/media/phd-files/guidelines-and-statements/policies-development/aha-asa-disclosure-rwi-policy-5118.pdf?la=en>.

Beginning in 2017, numerous modifications to AHA/ASA guidelines have been implemented to make guidelines shorter and enhance user friendliness. Guidelines are written and presented in a modular knowledge chunk format, in which each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text, and, when appropriate, flow diagrams or additional tables. Hyperlinked references are provided for each modular knowledge chunk to facilitate quick access and review. Other modifications to the guidelines include the addition of Knowledge Gaps and Future Research segments in some sections and a web guideline supplement ([Data Supplement](#)) for useful but noncritical tables and figures.

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## 1. INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a significant global public health threat. The overall worldwide incidence of aSAH is  $\approx 6.1$  per 100 000 person-years,<sup>1</sup> with a global prevalence of 8.09 million (95% uncertainty interval, 7.02–9.72 million) cases.<sup>2</sup> However, the incidence of aSAH is highly variable by region, with the highest incidence in Japan and Finland at 28 and 16.6 per 100 000 person-years, respectively,<sup>1</sup> and the highest age-standardized prevalence in Japan and Andean Latin America.<sup>2</sup> In addition, there seems to be wide regional heterogeneity among incidence trends over time, with an overall downward trend in the incidence of aSAH

between 1955 and 2014 by 1.7% annually worldwide and by 0.7% annually in North America.<sup>1,3,4</sup> There was a decrease of 0.81% (95% uncertainty interval, −1.91% to 0.26%) in the age-standardized global prevalence rate of aSAH from 2010 to 2020. In contrast, between 2007 and 2017, the incidence in the United States increased to 11.4 per 100 000 person-years.<sup>5</sup>

aSAH is a severely morbid and often deadly condition. Prehospital mortality rates from aSAH have been reported to be 22% to 26%.<sup>6</sup> Although hospital inpatient mortality rates from aSAH have shown no improvement (13.7% in 2006 to 13.1% in 2018 [United States]<sup>7</sup> and 19%–20% in 2021 [global]<sup>8</sup>), population-based studies report a decline in overall case-fatality rates (−1.5%/y between 1980 and 2020) with substantial between-country variation.<sup>9,10</sup> Age-standardized mortality rates estimated for subarachnoid hemorrhage (SAH) were highest in Oceania, Andean Latin America, and Central Asia in 2020.<sup>2</sup> As our population ages, aSAH may be an even more significant public health burden. The incidence of aSAH increases with age, particularly in women >55 years of age.<sup>1</sup> There is a reported sex-specific predilection of aSAH in women, with a 1.3 relative risk (RR) for women compared with men.<sup>1,11</sup> In the United States, the incidence of aSAH was also disproportionately higher and increasing in Black patients compared with people of other races and ethnicities.<sup>5</sup>

Despite a seemingly downward trend in overall aSAH incidence and prevalence, there are populations at increased risk. The persistently high in-hospital and prehospital mortality rates and increased incidence in the aging population necessitate improved therapies and practice standards in the management of patients with aSAH. These mortality rates are likely underestimated and do not account for the additional burden of loss of productivity and long-term morbidity among survivors. The previous AHA/ASA guideline for the management of aSAH was published in 2012.<sup>12</sup> Since that guideline, there have been important advances in knowledge of the treatment of aSAH based on evidence and data. This 2023 guideline seeks to provide evidence-based practical recommendations for clinical practice.

### 1.1. Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based and supported by extensive evidence review. A search for literature published since the 2012 guideline, derived from research involving principally human subjects, published in English, and indexed in MEDLINE, PubMed, Cochrane Library, and other selected databases relevant to this guideline, was conducted between March 2022 and June 2022. In addition, the guideline writing group (GWG) reviewed documents on related subject matter previously published by AHA. Newer studies published between July 2022 and January 2023 that affected recommendation

content, Class of Recommendation (COR), or Level of Evidence (LOE) were included if appropriate.

The study data that support recommendations in this guideline (see recommendation tables in each section) can be found in the guideline's [Data Supplement](#). The supplement comprises evidence tables summarizing the specific evidence used by the GWG to formulate recommendations listed in tables, as well as a list of search terms. Please note that AHA/ASA methodology discourages the inclusion of citations in Knowledge Gaps and Future Research subsections so that the focus remains on information that is lacking and questions remaining in the field rather than on research that has been completed.

Each section was assigned a primary author and a primary reviewer. (Some topics also had secondary authors and secondary reviewers.) Author assignments were based on the areas of expertise of the members of the GWG and their lack of any relationships with industry related to the section material. All recommendations were reviewed and discussed by the full writing group to include a diverse range of perspectives. Recommendations were then voted on, and a modified Delphi process was used to reach consensus. GWG members who had relationships with industry relevant to certain topics were recused from voting on those particular recommendations. (These instances are listed in Appendix 1, the relevant relationships with industry table.) All recommendations in this guideline were agreed to by between 80.9% and 100% of the voting GWG members.

### 1.2. Organization of the GWG

The aSAH GWG consisted of neurocritical care specialists, vascular neurologists, vascular neurosurgeons, neurointerventionalists with a variety of backgrounds (radiology, neurology, and neurosurgery), an anesthesiologist, physiatrists/stroke recovery physicians, an acute care nurse practitioner, a fellow in training, and a lay/patient representative. The GWG included representatives from AHA/ASA, the American Association of Neurological Surgeons/Congress of Neurological Surgeons, the American Academy of Neurology, the Neurocritical Care Society, the Society of Neurointerventional Surgery, and the Society of Vascular and Interventional Neurology. Appendix 1 of this document lists GWG members' relevant relationships with industry and other entities. For purposes of full transparency, the GWG members' comprehensive disclosure information is available online.

### 1.3. Document Review and Approval

This document was reviewed by AHA Stroke Council Scientific Statement Oversight Committee; AHA Science Advisory and Coordinating Committee; AHA's Executive Committee; reviewers from the American Association of Neurological Surgeons/Congress of Neurological

Surgeons, American Academy of Neurology, Neurocritical Care Society, Society of Neurointerventional Surgery, Society of Vascular and Interventional Neurology, and 39 individual content reviewers. Appendix 2 lists the reviewers' comprehensive disclosure information.

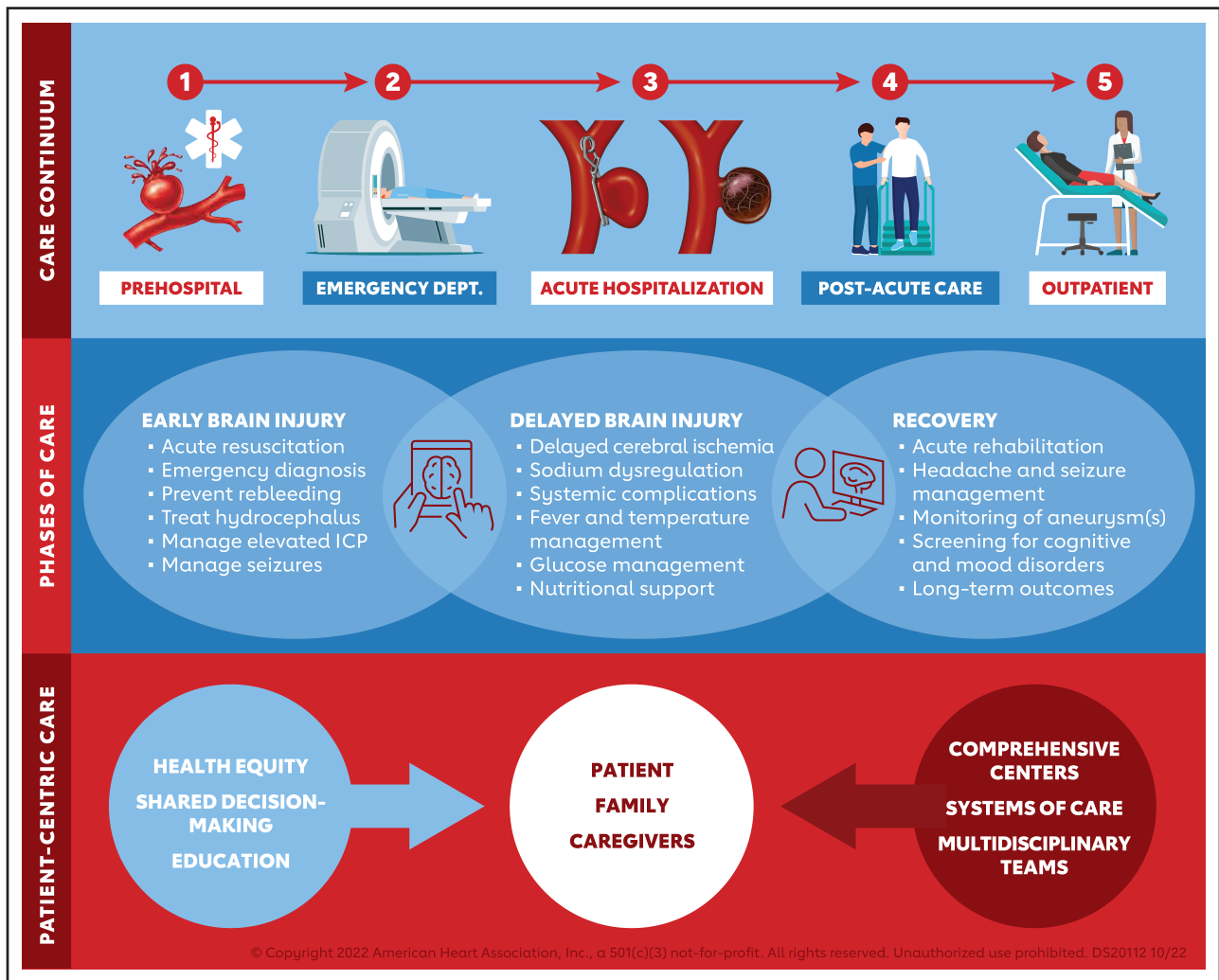
### 1.4. Scope of the Guideline

This guideline addresses the diagnosis and treatment of aSAH in adults and is intended to update and replace the AHA/ASA 2012 aSAH guideline.<sup>12</sup> This 2023 guideline is limited explicitly to aSAH and does not address other types of SAH such as those caused by trauma, vascular malformation, or hemorrhage-prone neoplasm. Furthermore, this guideline does not overlap with AHA/ASA guidelines or scientific statements on the treatment of intracerebral hemorrhage (ICH),<sup>13</sup> arteriovenous malformations,<sup>14</sup> and unruptured intracranial aneurysms.<sup>15</sup>

This guideline aims to cover the full course of aSAH (Figure 1), from initial diagnosis (Section 4), systems of

care (Section 5), and acute interventions (Sections 6, 7, and 7.1) to further inpatient care of post-aSAH complications (Sections 8–8.5). New sections in this 2023 aSAH guideline include nursing care (Section 8.1) and recovery (Section 9). Risk factors for recurrent aSAH are also addressed (Section 10); however, risk factors for aneurysm development and rupture and management of unruptured aneurysms are not included in this guideline because these topics are addressed in a separate guideline for management of unruptured intracranial aneurysms.<sup>15</sup> The new, important emphases in this guideline are shared decision-making, health equity, and systems of care.

Some aspects of inpatient aSAH medical care and post-aSAH rehabilitation and recovery are likely to be similar between patients with aSAH and patients with other types of stroke. Readers are therefore referred to relevant AHA/ASA guidelines and scientific statements in these overlapping areas. Table 1 lists associated AHA/ASA guidelines and scientific statements that may be of interest to the reader.



**Figure 1. Care continuum of the patient with aSAH.**

aSAH indicates aneurysmal subarachnoid hemorrhage; and ICP, intracranial pressure.

**Table 1. Associated AHA/ASA Guidelines and Statements**

Title	Organization	Publication year
AHA/ASA guidelines		
2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association	AHA/ASA	2022 <sup>13</sup>
Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association	AHA/ASA	2015 <sup>15</sup>
Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association	AHA/ASA	2012 <sup>12</sup>
Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Statement for Healthcare Professionals From a Special Writing Group of the Stroke Council, American Heart Association	AHA/ASA	2009 <sup>16</sup>
AHA/ASA scientific statement		
Management of Brain Arteriovenous Malformations: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association	AHA/ASA	2017 <sup>14</sup>

AHA/ASA indicates American Heart Association/American Stroke Association.

### 1.5. CORs and LOEs

Recommendations are designated with both a COR and an LOE. The COR indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The LOE rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (see Table 2 for the COR/LOE schema).

### 1.6. Abbreviations

Abbreviation	Meaning
AHA	American Heart Association
ALISAH	Albumin in Subarachnoid Hemorrhage
ARDS	acute respiratory distress syndrome
ASA	American Stroke Association
aSAH	aneurysmal subarachnoid hemorrhage
AVERT	A Very Early Rehabilitation Trial
BP	blood pressure
BRAT	Barrow Ruptured Aneurysm Trial
CBF	cerebral blood flow
cEEG	continuous electroencephalography
CLOTS	Clots in Legs or Stockings After Stroke
COR	Class of Recommendation
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
CT	computed tomography
CTA	computed tomography angiography
CTP	computed tomography perfusion
DCI	delayed cerebral ischemia
DSA	digital subtraction angiography
EEG	electroencephalography
EVD	external ventricular drain
GCS	Glasgow Coma Scale
GWG	guideline writing group
HH	Hunt and Hess

Abbreviation	Meaning
HIMALAIA	Hypertension Induction in the Management of Aneurysmal Subarachnoid Haemorrhage With Secondary Ischaemia
ICH	intracerebral hemorrhage
ICP	intracranial pressure
ICU	intensive care unit
IHAST	Intraoperative Hypothermia for Aneurysm Surgery Trial
ISAT	International Subarachnoid Aneurysm Trial
LOE	Level of Evidence
LOS	length of stay
LP	lumbar puncture
MCA	middle cerebral artery
MMSE	Mini-Mental Status Examination
MoCA	Montreal Cognitive Assessment
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PRINCE	Point Prevalence in Neurocritical Care
QASC	Quality in Acute Stroke Care
QOL	quality of life
RCT	randomized controlled trial
RR	relative risk
SAH	subarachnoid hemorrhage
SAHIT	Subarachnoid Hemorrhage International Trialists
TCD	transcranial Doppler
TTM	therapeutic temperature management
ULTRA	Ultra-Early Tranexamic Acid After Subarachnoid Hemorrhage
VTE	venous thromboembolism
WFNS	World Federation of Neurosurgical Societies

## 2. GENERAL CONCEPTS

### 2.1. Significance of Condition

aSAH is a devastating condition. Approximately 13% of patients will die in the hospital of aSAH,<sup>7</sup> and up to 26% will die before arriving at the hospital.<sup>6</sup> Unlike other stroke subtypes, aSAH affects individuals in their working years, with a mean age of 55 years.<sup>7</sup> Although

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**Table 2. Applying American College of Cardiology/American Heart Association Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care\* (Updated May 2019)**

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
<b>CLASS 1 (STRONG)</b> <span style="float: right;"><b>Benefit &gt;&gt;&gt; Risk</b></span> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• Is recommended</li> <li>• Is indicated/useful/effective/beneficial</li> <li>• Should be performed/administered/other</li> <li>• Comparative-Effectiveness Phrases†:                             <ul style="list-style-type: none"> <li>– Treatment/strategy A is recommended/indicated in preference to treatment B</li> <li>– Treatment A should be chosen over treatment B</li> </ul> </li> </ul>	<b>LEVEL A</b> <ul style="list-style-type: none"> <li>• High-quality evidence‡ from more than 1 RCT</li> <li>• Meta-analyses of high-quality RCTs</li> <li>• One or more RCTs corroborated by high-quality registry studies</li> </ul>
<b>CLASS 2a (MODERATE)</b> <span style="float: right;"><b>Benefit &gt;&gt; Risk</b></span> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• Is reasonable</li> <li>• Can be useful/effective/beneficial</li> <li>• Comparative-Effectiveness Phrases†:                             <ul style="list-style-type: none"> <li>– Treatment/strategy A is probably recommended/indicated in preference to treatment B</li> <li>– It is reasonable to choose treatment A over treatment B</li> </ul> </li> </ul>	<b>LEVEL B-R (Randomized)</b> <ul style="list-style-type: none"> <li>• Moderate-quality evidence‡ from 1 or more RCTs</li> <li>• Meta-analyses of moderate-quality RCTs</li> </ul>
<b>CLASS 2b (WEAK)</b> <span style="float: right;"><b>Benefit ≥ Risk</b></span> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• May/might be reasonable</li> <li>• May/might be considered</li> <li>• Usefulness/effectiveness is unknown/unclear/uncertain or not well-established</li> </ul>	<b>LEVEL B-NR (Nonrandomized)</b> <ul style="list-style-type: none"> <li>• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</li> <li>• Meta-analyses of such studies</li> </ul>
<b>CLASS 3: No Benefit (MODERATE)</b> <span style="float: right;"><b>Benefit = Risk</b></span> <b>(Generally, LOE C or B use only)</b> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• Is not recommended</li> <li>• Is not indicated/useful/effective/beneficial</li> <li>• Should not be performed/administered/other</li> </ul>	<b>LEVEL C-LD (Limited Data)</b> <ul style="list-style-type: none"> <li>• Randomized or nonrandomized observational or registry studies with limitations of design or execution</li> <li>• Meta-analyses of such studies</li> <li>• Physiological or mechanistic studies in human subjects</li> </ul>
<b>CLASS 3: Harm (STRONG)</b> <span style="float: right;"><b>Risk &gt; Benefit</b></span> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• Potentially harmful</li> <li>• Causes harm</li> <li>• Associated with excess morbidity/mortality</li> <li>• Should not be performed/administered/other</li> </ul>	<b>LEVEL C-EO (Expert Opinion)</b> <ul style="list-style-type: none"> <li>• Consensus of expert opinion based on clinical experience</li> </ul>

COR and LOE are determined independently (any COR may be paired with any LOE).  
 A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.  
 \* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).  
 † For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.  
 ‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.  
 COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

the cause for cerebral aneurysms and aSAH is likely multifactorial, hypertension and tobacco use are important modifiable risk factors.<sup>1</sup> Family history is a rare but important risk factor.<sup>17</sup> In individuals with ≥2 first-degree relatives with known cerebral aneurysms, there is a 12% prevalence of harboring a cerebral aneurysm.<sup>18</sup> Radiological screening for aneurysms is cost-effective when performed every 5 to 7 years for individuals 20 to 80 years of age with a family history of ≥2 first-degree relatives with known cerebral aneurysms.<sup>19,20</sup>

The socioeconomic costs of aSAH are significant. Inpatient hospital charges in the United States for patients with aSAH have been reported to be

\$373 353.94 and as much as \$530 544.77 in those patients with aSAH who develop delayed cerebral ischemia (DCI).<sup>21</sup> These costs do not include posthospitalization costs associated with long-term care and rehabilitation or the societal cost of loss of work and productivity of patients with aSAH.

## 2.2. Mechanisms of Injury After aSAH

Over the past decade, clinical and translational studies, including randomized clinical trials, have expanded our understanding of aSAH-associated brain injury as being multiphasic and multifactorial.<sup>22</sup> Pathophysiological

mechanisms in the first 72 hours after aSAH that drive early brain injury also influence secondary complications and overall outcomes.<sup>23</sup> DCI is now hypothesized to be caused by the combined effects of large-vessel cerebral vasospasm and multiple brain injury processes triggered by aneurysm rupture and early brain injury. Mechanisms involving arteriolar constriction and cerebral microthrombosis, cortical spreading depolarization/ischemia, blood-brain barrier breakdown, cerebral autoregulation impairment, and capillary transit time heterogeneity are hypothesized to play a role in the pathophysiology of DCI and DCI-related cerebral infarction.<sup>22,24,25</sup> Neuroinflammation, either independently or as a consequence of early brain injury, has been identified as a potential target for intervention.<sup>26,27</sup>

Early repair of the ruptured aneurysm by endovascular coiling or neurosurgical clipping to prevent rebleeding has reduced case fatality. In addition, management in specialized neurological intensive care units (ICUs) with multidisciplinary clinical groups focused on treatment of cerebral edema, hydrocephalus, elevated intracranial pressure (ICP), DCI, and medical complications has likely contributed to improved acute outcomes.<sup>24</sup> However, there is growing evidence for chronic morbidity in areas of cognitive recovery, mood disorders, and quality of life (QOL).<sup>22</sup>

This guideline identifies knowledge gaps and the need for future research on improving biomarkers for injury and outcome prediction, recognizing long-term follow-up needs for the delayed complications in aSAH survivors, and incorporating patient-centric outcomes with shared decision-making throughout the continuum of care.

### 2.3. Generalizability

It is important to note that much of the evidence throughout this guideline comes from high-resource countries and may represent relatively homogeneous ethnic, racial, and socioeconomic-level patient populations. The generalizability of this guideline may be limited when lower-resource settings are considered, highlighting the need for further studies in clinically underserved areas and within underrepresented groups.

## 3. NATURAL HISTORY AND OUTCOME OF aSAH

Recommendations for Natural History and Outcome of aSAH		
Referenced studies that support recommendations are summarized in online Data Supplement 1.		
COR	LOE	Recommendations
1	B-NR	1. In patients with aSAH, use of clinical scales (eg, the Hunt and Hess [HH] grade or World Federation of Neurosurgical Societies [WFNS] grade) is recommended to determine initial clinical severity and predict outcome. <sup>28,29</sup>

Recommendations for Natural History and Outcome of aSAH (Continued)		
COR	LOE	Recommendations
2a	B-NR	2. In patients with high-grade aSAH, aneurysm treatment is reasonable, after careful discussion of likely prognosis with family members, to optimize patient outcome. <sup>28,30</sup>
2a	B-NR	3. In patients with aSAH and advanced age, aneurysm treatment is reasonable, after careful discussion of prognosis with family members, to improve survival and outcome. <sup>31–33</sup>
3: No benefit	B-NR	4. In patients with aSAH who do not improve after correction of modifiable conditions and are deemed unsalvageable because of evidence of irreversible neurological injury, treatment of the aneurysm is not beneficial. <sup>34,35</sup>

### Synopsis

aSAH requires prompt clinical evaluation, aneurysm treatment, and management of associated complications to optimize patient outcomes (see also specific recommendations in Sections 6–8). The use of established grading scales serves as a clinical prognostic indicator. Patients with high-grade SAH may be candidates for aneurysm treatment as long as they do not have irrecoverable and devastating neurological injury. Patients of advanced age require careful consideration for treatment and the use of shared decision-making and prognosis discussion with the family or surrogate decision maker. Social determinants of health and their impact on aSAH outcomes are addressed in Section 5.

### Recommendation-Specific Supportive Text

- Several studies have established the efficacy of clinical grades to predict outcomes such as HH and WFNS grades.<sup>28,29</sup> Other classification systems such as the Yasargil grading, the Glasgow Coma Scale (GCS), and the Johns Hopkins GCS grading scale have been introduced.<sup>36</sup> Recent combination of radiographic (eg, Fisher) and clinical grades has led to composite scores such as the VASOGRADE, HAIR (HH grade, age, IVH, rebleed), SAHIT (Subarachnoid Hemorrhage International Trialists), and SAH scores.<sup>37–39</sup> These grading scales provide clinical outcome prediction and assist the medical team in standardizing the severity of the hemorrhage.<sup>37–39</sup>
- The management of patients with high-grade aSAH remains a great challenge. Most literature defines high-grade SAH as a clinical HH grade 4 and 5 or WFNS grade 4 and 5. Although aneurysm treatment may prevent rerupture, treatment needs to be individualized according to patient-specific factors such as medical comorbidities and prehemorrhage functional status and should incorporate shared decision-making with the family or surrogate decision makers. In a study by Mocco and colleagues,<sup>28</sup> 98 patients with HH grade 4 and 5 aSAH received treatment, of whom 40% had a



favorable outcome in 12 months. Similar results were reported in a meta-analysis by Zhao et al,<sup>40</sup> which included 85 studies with 4506 patients with poor-grade aSAH. Good outcomes were observed in 39% of treated patients.

3. When controlling for degree of neurological injury, older patients compared with younger patients with aSAH have less favorable outcomes.<sup>28,29,31–33</sup> In a post hoc analysis of the 405 patients included in BRAT (Barrow Ruptured Aneurysm Trial), 42% of patients >65 years of age reached functional independence at the 6-year follow-up. Although this number was significantly smaller than in the younger cohort (82%), it demonstrates that aneurysm treatment in this age group is reasonable and should be considered after discussion with the family and surrogates.<sup>31</sup>
4. Some patients with high-grade aSAH with irrecoverable brain injury have such a poor prognosis that aneurysm treatment provides no benefit.<sup>34,35</sup> These patients may have partially or completely absent brainstem reflexes, lack of purposeful responses to noxious stimuli, large completed ischemic infarct on admission computed tomography (CT), or presence of global cerebral edema consistent with anoxic brain injury.<sup>33–35,41,42</sup> Modifiable medical conditions should be identified early because their outcomes are significantly more favorable. Some of these conditions include seizures, hydrocephalus, electrolyte abnormalities such as hyponatremia, status epilepticus, and hypothermia. In addition, there are nuances to these parameters, including a time dimension. Absent brainstem responses at presentation mean less than absent brainstem responses at 12 or 24 hours. Brain edema may be difficult to identify on early CT imaging. Other nuances include high ICP without ventricular enlargement and response to management of cerebral edema and mass effect. Expert multidisciplinary medical and critical care management is of paramount importance.

**Knowledge Gaps and Future Research**

- *Medical comorbidities and parameters:* Several medical parameters have been associated with clinical outcomes in aSAH. Some of these are body mass index, hypertension, hyperglycemia, troponin levels, hyperthermia, peak white blood cell, C-reactive protein, and high neutrophil counts. However, additional investigation is required for the determination of their prognostic value and influence on treatment outcomes.
- *Novel biomarkers:* Biomarkers including imaging, serum, and cerebrospinal fluid (CSF) are an active area of research in aSAH. Further studies incorporating new methods of proteomics, genomics, and other biological markers with existing clinical, radiographic, and physiological monitoring data will be

important in determining their use in prognosis and interventions for improving outcomes.

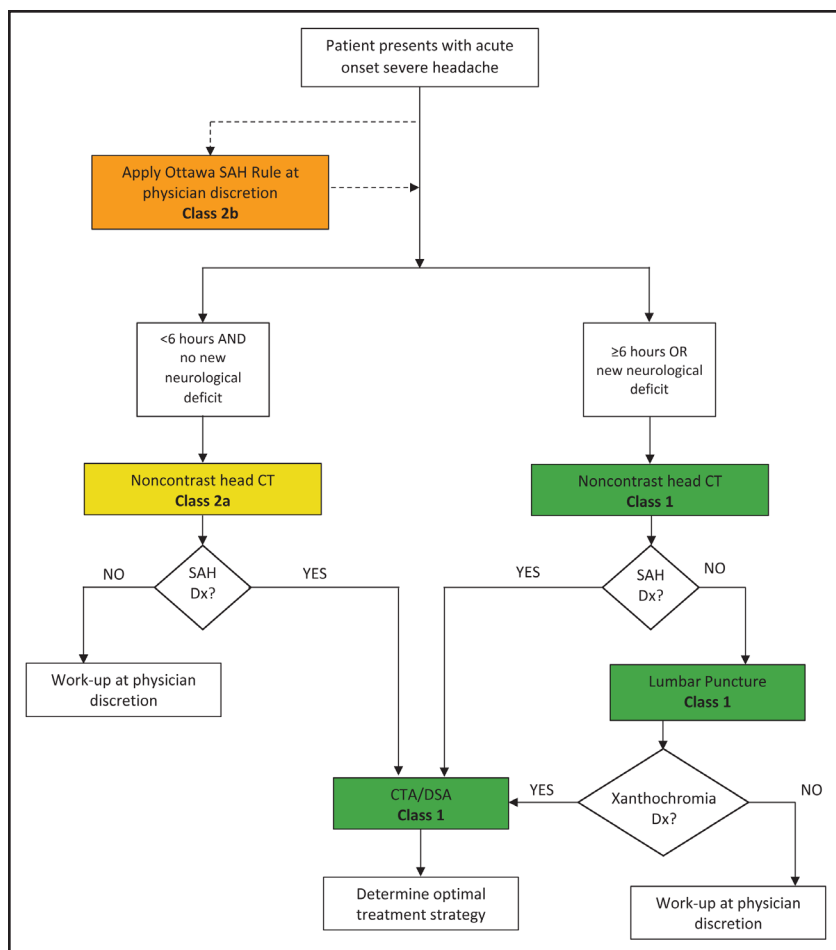
- *Advanced age:* Advanced age constitutes an additional risk factor for poor clinical outcome. However, a specific threshold is yet to be determined and will likely vary between individuals.
- *Acute resuscitation and early do-not-resuscitate order:* Impact of an early do-not-resuscitate order versus acute resuscitation on outcomes has not been specifically studied in aSAH. Acute resuscitation and delaying the do-not-resuscitate order for up to 72 hours have been advocated in other stroke populations to prevent therapeutic nihilism.
- *Irrecoverable early brain injury:* The factors cited previously as evidence of early and irrecoverable brain injury are incompletely defined, particularly in terms of time course and severity.

**4. CLINICAL MANIFESTATIONS AND DIAGNOSIS OF aSAH**

**Recommendations for Clinical Manifestations and Diagnosis of aSAH**  
 Referenced studies that support recommendations are summarized in online Data Supplement 2.

COR	LOE	Recommendations
Evaluation for aSAH		
1	B-NR	1. In patients with acute onset of severe headache, prompt diagnostic workup and evaluation are recommended to diagnose/exclude aSAH and minimize morbidity and mortality. <sup>43–46</sup>
1	B-NR	2. In patients with acute onset of severe headache who present >6 hours from symptom onset or who have a new neurological deficit, a noncontrast head CT and, if negative for aSAH, lumbar puncture (LP) should be performed to diagnose/exclude aSAH. <sup>47,48</sup>
2a	B-NR	3. In patients with acute onset of severe headache who present <6 hours from symptom onset and without new neurological deficit, a noncontrast head CT performed on a high-quality scanner and interpreted by a board-certified neuroradiologist is reasonable to diagnose/exclude aSAH. <sup>49–53</sup>
2b	B-NR	4. In patients with acute onset of severe headache without a new neurological deficit, application of the Ottawa SAH Rule may be reasonable to identify those at high risk for aSAH. <sup>45,54,55</sup>
Evaluation for cause of aSAH		
1	B-NR	5. In patients with spontaneous SAH with high level of concern for aneurysmal source and a negative or inconclusive CT angiography (CTA), digital subtraction angiography (DSA) is indicated to diagnose/exclude cerebral aneurysm(s). <sup>56–59</sup>
2a	B-NR	6. In patients with SAH from confirmed cerebral aneurysm(s), DSA can be useful to determine the optimal strategy for aneurysm intervention. <sup>60,61</sup>

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**Figure 2. Workflow for patients with symptoms concerning for aSAH.**

Colors correspond to Class of Recommendation in Table 2. CT indicates computed tomography; CTA, computed tomography angiography; DSA, digital subtraction angiography; Dx, diagnosis; and SAH, subarachnoid hemorrhage.

**Synopsis**

The classic clinical presentation of aSAH in an awake and alert patient is a headache that is sudden in onset and immediately reaches maximal intensity. A warning or sentinel headache that precedes the aSAH-associated presentation occurs in 10% to 43% of cases.<sup>46</sup> Misdiagnosis or delayed diagnosis can have grave consequences, including death and severe disability. Noncontrast head CT remains the mainstay of SAH diagnosis, but the specific workup required depends on the time of presentation from symptom onset and the patient's neurological status. Figure 2 outlines a suggested workflow for patients presenting to medical attention with a severe headache or other symptoms concerning for aSAH. Treating physicians will need to exercise judgment on the likelihood that a certain test will alter their clinical management.

**Recommendation-Specific Supportive Text**

1. Effective management of aSAH and its possible associated complications requires prompt identification and initial management. aSAH is a life-threatening condition, and the failure to identify aSAH when present is associated with significant morbidity and mortality.<sup>46</sup> Physicians must maintain a high level of awareness and concern for this diagnosis and pursue appropriate workup, when

- necessary, because diagnosis of a sentinel bleed before a catastrophic rupture can be lifesaving.<sup>43,44</sup>
2. In patients who do not meet criteria for application of the Ottawa SAH Rule (Table 3), additional workup with head CT and, if necessary, LP for xanthochromia evaluation is necessary.<sup>47</sup> LP is often performed >6 to 12 hours after symptom onset. Walton et al<sup>48</sup> reported 1235 patients from 3 studies in which CSF obtained by LP after a negative or nondiagnostic head CT was examined by spectrophotometric analysis for xanthochromia and reported a sensitivity of 100% and specificity of 95.2%. The American College of Emergency Physicians provided an LOE C recommendation for CTA or LP as the next diagnostic study if noncontrast head CT is inconclusive in a patient with a high suspicion for SAH.<sup>62</sup> No study has evaluated CTA versus LP as the next step in the workup in a patient with a high suspicion of aSAH and a normal or nondiagnostic head CT. CTA does not directly evaluate for SAH, only cerebrovascular pathology, and its sensitivity is ≈97.2%. Another analysis estimated the sensitivity of CTA for ruptured aneurysms <3 mm at 61%.<sup>64</sup> Given the severe morbidity and potential mortality associated with a missed aSAH

**Table 3. Ottawa SAH Rule**

For alert patients >15 y of age with new severe nontraumatic headache reaching maximum intensity within 1 h. Patients require additional investigation for SAH if they meet any of the following criteria:	
1	Age ≥40 y
2	Neck pain or stiffness
3	Witnessed loss of consciousness
4	Onset during exertion
5	Thunderclap headache (instantly peaking pain)
6	Limited neck flexion on examination

SAH indicates subarachnoid hemorrhage.

diagnosis, these small differences are critical. LP for xanthochromia evaluation should be performed in patients presenting >6 hours from ictus in whom there is high suspicion for SAH.

- High-quality CT scanners can detect SAH with a high sensitivity, especially when the images are interpreted by fellowship-trained, board-certified neuroradiologists. (Equipment specifications for a high-quality CT scanner have been published by the American College of Radiology.<sup>65</sup>) For patients presenting within 6 hours of headache onset who have no new neurological deficits, the lack of SAH on a noncontrast head CT is likely sufficient to exclude aSAH.<sup>50–53</sup> This question was evaluated in a 2016 meta-analysis in which 8907 patients were studied. Thirteen patients had a missed SAH on head CT performed within 6 hours, leading to a sensitivity of 98.7% and specificity of 99.9%. Therefore, when performed within 6 hours of symptom onset, a negative head CT was likely to miss <1.5 in 1000 SAHs.<sup>51</sup> It is important to note that many of these analyses do not apply to patients with atypical presentations such as primary neck pain, syncope, seizure, or new focal neurological deficit. Therefore, the lack of a classic presentation should still prompt appropriate imaging and workup.
- The Ottawa SAH Rule serves as a method to screen out individuals with a low likelihood of aSAH.<sup>45</sup> Application of the rule requires that patients who present with a severe headache and meet any of the criteria outlined in Table 3 may need to undergo additional testing, as directed by the treating physician. The initial study by Perry et al<sup>45</sup> enrolled 2131 patients, of whom 132 (6.2%) had SAH. Application of the rule was 100% sensitive but only 15.3% specific. The rule was later validated by the study authors at 6 medical centers in a prospective manner, with 1153 patients enrolled and 67 SAHs, and was found to be 100% sensitive and 13.6% specific.<sup>55</sup> The rule was externally validated by Bellolio et al<sup>54</sup> in 454 patients, of whom 9 had SAH, and it was 100% sensitive

but only 7.6% specific. Use of the Ottawa SAH Rule can therefore identify a subset of patients (albeit small) who are unlikely to have aSAH and thereby avoid additional imaging and workup that use resources and expose patients to unnecessary risk.

- CTA is widely available and often is the next diagnostic test performed when SAH is diagnosed with noncontrast CT. Certain hemorrhage patterns likely reflect a greater risk for the presence of an underlying aneurysm than others (eg, diffuse basal cistern and sylvian fissure SAH versus small-volume focal cortical SAH). For diffuse SAH, DSA is indicated for evaluation regardless of CTA results because small aneurysms or other vascular lesions may not be fully appreciated or defined on CTA imaging owing to limitations in spatial resolution.<sup>56–59,66</sup>
- DSA is considered the gold-standard modality for the evaluation of cerebrovascular anatomy and aneurysm geometry and can aid in decision-making on the choice of optimal treatment modality. CTA alone may, in certain clinical settings, be used for treatment decision-making.<sup>60,61</sup>

**Knowledge Gaps and Future Research**

- Utility of magnetic resonance imaging:* Diagnostic accuracy studies of various established and emerging magnetic resonance imaging sequences for the detection and characterization of aSAH are needed.
- Perimesencephalic SAH:* There is currently equipoise concerning the appropriate diagnostic pathway for a perimesencephalic distribution of SAH with CTA alone versus catheter-based DSA.
- Emerging technologies:* Dual-energy CT and single-photon counting CT represent novel imaging techniques that may be helpful for SAH and aneurysm detection.

**5. HOSPITAL CHARACTERISTICS AND SYSTEMS OF CARE**

Recommendations for Hospital Characteristics and Systems of Care Referenced studies that support recommendations are summarized in online Data Supplement 3.		
COR	LOE	Recommendations
1	B-NR	1. For patients with aSAH, timely transfer from hospitals with low case volume to higher-volume centers with multidisciplinary neurointensive care services, comprehensive stroke center capabilities, and experienced cerebrovascular surgeons/neuroendovascular interventionalists is recommended to improve outcomes. <sup>67–77</sup>
1	B-NR	2. For patients with aSAH, care should be provided in a dedicated neurocritical care unit by a multidisciplinary team. <sup>78–80</sup>

## Synopsis

Hospital resources and case volumes are important considerations in systems of care. Lower mortality rates have been demonstrated in some nonrandomized studies when patients with aSAH are treated by experienced cerebrovascular surgeons and neuroendovascular interventionists in hospitals with larger volumes of aSAH cases (eg, >35 aSAH cases per year, used in the 2012 aSAH guideline) compared with smaller volumes of aSAH cases (eg, <10 aSAH cases per year, used in the 2012 aSAH guideline) and when care is provided in dedicated neurocritical care units. Delays in transfer to facilities with such capabilities may be associated with worse outcomes.

## Recommendation-Specific Supportive Text

1. The effect of hospital characteristics and health systems of care—including physician expertise, case volumes, and care provision in dedicated neurocritical care units—on outcomes for patients with aSAH has been described in large nonrandomized studies.<sup>67–69,71,75–77</sup> Specifying exact case volumes for what should constitute a high-volume center versus a low-volume center is particularly challenging given the heterogeneity of studies. Thus, specific case numbers are not included in Recommendation 1; instead, the case numbers used in the 2012 aSAH guideline are included in the Synopsis for historical reference. The US Nationwide Inpatient Sample and international studies suggest that treatment in a high-volume center was associated with a lower risk of in-hospital death and higher odds of good functional outcome.<sup>72,75</sup> Stroke center designation has been associated with reduced in-hospital mortality for patients with aSAH.<sup>71</sup> Timely arrival of patients with aSAH in hospitals where they can receive both aneurysm treatment and neurocritical care is relevant given the risks for aneurysm rerupture and DCI.<sup>70,73,74</sup> According to US Nationwide Inpatient Samples, factors associated with treatment delay in aSAH were older age, non-White race, Medicaid payer status, surgical clipping, and admission to low-surgical-volume hospitals.<sup>80,81</sup>
2. Outcomes have been reported primarily as in-hospital and short-term posthospitalization mortality, although some studies have offered more granular details such as rates of DCI during hospitalization for aSAH<sup>82</sup> or the time to transfer patients from referring hospitals to large-volume aSAH centers.<sup>83</sup> Case-fatality rates in aSAH have declined over the past 2 decades, attributed to improved medical and surgical care and the emergence of neurocritical care units.<sup>74</sup> In the PRINCE study (Point Prevalence in Neurocritical Care) of 257 centers in 47 countries, variability in the delivery of neurocritical care to patients with various

neurological emergencies is present worldwide; severity of illness and absence of a dedicated neurocritical care unit were independent predictors of mortality.<sup>78,79</sup> Although some studies describe superior outcomes at hospitals that take care of more patients with aSAH, other studies do not find this relationship. One explanation offered for noninferior outcomes at lower-volume centers has been the expertise of individual health care professionals.<sup>68,82</sup> Teaching status of a hospital was associated with improved outcomes in aSAH in an analysis of the US Nationwide Inpatient Sample from 2001 to 2010.<sup>84</sup>

## Knowledge Gaps and Future Research

- *Annual monitoring:* Much remains uncertain in terms of systems of care for the treatment of patients with aSAH. Quality improvement programs are a pillar of modern hospital care. Therefore, annual monitoring for complication rates for surgical and interventional procedures performed on patients with aSAH may reasonably be assumed to be standard practice. However, there are scant data on whether the institution of such programs affects mortality and morbidity. In addition, individual hospital case numbers remain controversial and should continue to be examined in terms of relevance to patient outcomes.
- *Patient characteristics and health inequities:* For patients with aSAH, there is significant variability in outcome in different hospital resource settings that may relate to race, baseline medical comorbidities, socioeconomic factors, insurance status, impact of do-not-resuscitate orders, and access to treatment. Payer status, type of health insurance, race, ethnicity, local health care system organization, and transfer status versus presentation at the hospital where definitive therapy can be performed are areas that warrant further examination. Recognition of inequities and variable access to care at the health system level is essential so that interventions can be directed at ameliorating inequities and thereby improving outcomes. Underresourced populations can be disproportionately affected by disasters, further compounding adverse health outcomes. As in other areas of health care, recognition of implicit bias and trainings to mitigate that bias may contribute to amelioration of health inequities in stroke care and should be investigated.
- *Guideline adherence:* Guideline adherence and the impact on patient outcomes for aSAH has not been systematically studied. Data available for traumatic brain injury and for ischemic stroke suggest that guideline adherence is positively correlated with improved outcomes.

## 6. MEDICAL MEASURES TO PREVENT REBLEEDING AFTER aSAH

Recommendations for Medical Measures to Prevent Rebleeding After aSAH		
Referenced studies that support recommendations are summarized in online Data Supplement 4.		
COR	LOE	Recommendations
1	C-EO	1. In patients with aSAH and unsecured aneurysm, frequent blood pressure (BP) monitoring and BP control with short-acting medication(s) is recommended to avoid severe hypotension, hypertension, and BP variability.
1	C-EO	2. In patients with aSAH who are receiving anticoagulants, emergency anticoagulation reversal with appropriate reversal agents should be performed to prevent rebleeding.
3: No benefit	A	3. In patients with aSAH, routine use of antifibrinolytic therapy is not useful to improve functional outcome. <sup>85–87</sup>

### Synopsis

Prompt obliteration of the ruptured aneurysm is the only treatment proven to be effective to reduce the likelihood of rebleeding.<sup>88,89</sup> Ultraearly administration of antifibrinolytic therapy might reduce the risk of rebleeding, but this effect has not been consistent across trials.<sup>85–87</sup> Furthermore, treatment with antifibrinolytics does not improve functional outcomes.<sup>85–87</sup> Therefore, the routine use of antifibrinolytic therapy is not recommended because of a lack of benefit. Treatment of hypertension is commonly pursued in practice until the ruptured aneurysm is treated, but the effect of early hypertension control on the risk of rebleeding is not well established.<sup>90–92</sup> Although it is reasonable to treat severe hypertension on presentation, there is insufficient evidence to recommend a particular BP target. Sudden, profound reduction of BP should be avoided.<sup>93</sup> For patients taking anticoagulants, clinical judgment supports emergency reversal of anticoagulation, even if the value of this intervention has not been studied in patients presenting with aSAH.

### Recommendation-Specific Supportive Text

1. Increased BP variability has been associated with worse outcomes in aSAH,<sup>93</sup> and excessive BP reduction may compromise cerebral perfusion and induce ischemia, especially in patients with elevated ICP. Hence, this writing group recommends gradual reduction of BP when patients are severely hypertensive (>180–200 mmHg) but ensuring strict avoidance of hypotension (mean arterial pressure <65 mmHg) and closely monitoring the neurological examination while lowering the BP. A meta-analysis of factors predictive of early rebleeding in aSAH suggested higher rates of rebleeding with systolic BP >160 mmHg but not with systolic BP <140 mmHg but also highlighted the heterogeneity of results across the few available

2. The benefit of emergency reversal of anticoagulation has not been tested in patients presenting with aSAH. Yet, the value of immediate anticoagulation reversal has been demonstrated in other forms of intracranial hemorrhage.<sup>13,96</sup> Consequently, immediate anticoagulation reversal in any patient presenting with aSAH is strongly recommended. Reversal strategies should follow current published standards for life-threatening bleeding.<sup>13,97</sup>
3. The largest, high-quality randomized controlled trial (RCT) evaluating ultraearly, short-term antifibrinolytic therapy in patients with aSAH, ULTRA (Ultra-Early Tranexamic Acid After Subarachnoid Hemorrhage), did not show a significant reduction in the rate of rebleeding and demonstrated no improvement in functional outcomes among patients treated with tranexamic acid compared with patients who did not receive antifibrinolytic therapy.<sup>85</sup> Patients assigned to receive tranexamic acid were started on the medication after a median time of 185 minutes from symptom onset, and the medication was continued until the aneurysm was secured, up to 24 hours. A good functional outcome at 6 months (modified Rankin Scale [mRS] score 0–3) was observed in 287 of 475 patients (60%) in the tranexamic acid group and 300 of 470 patients (64%) in the control group. Moreover, the rate of excellent outcome (mRS score 0–2) was lower in the tranexamic acid group. Rates of rebleeding were 10% in the tranexamic acid group and 14% in the control group.<sup>85</sup> Older studies showed conflicting results on reduction of rebleeding and absence of significant improvement in functional outcomes among patients treated with antifibrinolytic therapy.<sup>86,87</sup> Consequently, current evidence indicates that antifibrinolytic therapy is not indicated for the routine management of patients with aSAH.

### Knowledge Gaps and Future Research

- *Antifibrinolytic therapy:* Although the ULTRA trial provides convincing evidence that the use of tranexamic acid does not significantly decrease the rate of rebleeding and is not effective to improve functional outcomes in patients with aSAH whose ruptured aneurysm is obliterated early (median time was 14 hours from symptom onset in the trial), there is a possibility that a short course of antifibrinolytic therapy could have a role in the management of patients in

whom aneurysm treatment will be delayed because of logistic or medical reasons.

- *BP treatment:* Research needs to be conducted to determine the optimal management of BP between presentation and aneurysm obliteration. Whether the therapeutic targets to be tested should be cut-offs of systolic BP, use of mean arterial pressure, or proportions of BP reduction (to minimize BP variability) is an issue that deserves careful consideration during the planning of a future trial to answer this question. The value of individualizing the monitoring (invasive versus noninvasive) and treatment of acute hypertension to minimize BP variability (bolus versus continuous infusion) and optimizing cerebral perfusion pressure (when ICP is known) also merits investigation.
- *Effect of antithrombotics:* There is some evidence that aspirin use could be associated with an increased risk of rebleeding. Consequently, it might be reasonable to investigate whether a treatment aimed at improving platelet function in patients who have aSAH while taking antiplatelet agents could be beneficial. There is currently limited evidence on the risks and benefits of platelet transfusion in patients with aSAH, either in general or for patients who require an open surgical intervention. Safety concerns in patients with ICH should be considered if a trial on platelet transfusion in aSAH were to be conducted.
- *Effect of CSF diversion:* It is uncertain whether CSF diversion may increase the risk of rebleeding before treatment of the ruptured aneurysm, with conflicting reports in the literature. Further investigation should be performed on optimal external ventricular drain (EVD) management strategies when CSF diversion is required.

## 7. SURGICAL AND ENDOVASCULAR METHODS FOR TREATMENT OF RUPTURED CEREBRAL ANEURYSMS

Recommendations for Surgical and Endovascular Methods for Treatment of Ruptured Cerebral Aneurysms		
Referenced studies that support recommendations are summarized in online Data Supplement 5.		
COR	LOE	Recommendations
Timing		
1	B-NR	1. For patients with aSAH, surgical or endovascular treatment of the ruptured aneurysm should be performed as early as feasible after presentation, preferably within 24 hours of onset, to improve outcome. <sup>40,98–104</sup>
Treatment goal		
1	B-NR	2. For patients with aSAH, complete obliteration of the ruptured aneurysm is indicated whenever feasible to reduce the risk of rebleeding and retreatment. <sup>105–107</sup>

Recommendations for Surgical and Endovascular Methods for Treatment of Ruptured Cerebral Aneurysms (Continued)		
COR	LOE	Recommendations
2a	C-EO	3. For patients with aSAH in whom complete obliteration of the ruptured aneurysm by either clipping or primary coiling treatment is not feasible in the acute phase, partial obliteration to secure the rupture site and retreatment in a delayed fashion in those with functional recovery are reasonable to prevent rebleeding.
Modality of treatment: general		
1	B-R	4. For patients with aSAH from ruptured aneurysms of the posterior circulation that are amenable to coiling, coiling is indicated in preference to clipping to improve outcome. <sup>108–110</sup>
1	B-R	5. For patients with aSAH deemed salvageable and with depressed level of consciousness due to large intraparenchymal hematoma, emergency clot evacuation should be performed to reduce mortality. <sup>111,112</sup>
1	C-EO	6. For patients with aSAH, the ruptured aneurysm should be evaluated by specialist(s) with endovascular and surgical expertise to determine the relative risks and benefits of surgical or endovascular treatment according to patient and aneurysm characteristics.
2b	B-R	7. For patients >70 years of age with aSAH, the superiority of coiling or clipping to improve outcome is not well established. <sup>113,114</sup>
2b	C-LD	8. For patients <40 years of age with aSAH, clipping of the ruptured aneurysm might be considered the preferred mode of treatment to improve durability of the treatment and outcome. <sup>113,115</sup>
Modality of treatment: for aneurysms equally suitable for clipping and coiling		
1	A	9. For patients with good-grade aSAH from ruptured aneurysms of the anterior circulation equally suitable for both primary coiling and clipping, primary coiling is recommended in preference to clipping to improve 1-year functional outcome. <sup>110,116</sup>
2a	B-R	10. For patients with good-grade aSAH from ruptured aneurysms of the anterior circulation equally suitable for both primary coiling and clipping, both treatment options are reasonable to achieve favorable long-term outcome. <sup>108,109,117</sup>
Endovascular adjuncts		
2a	C-LD	11. For patients with aSAH from ruptured wide-neck aneurysms not amenable to surgical clipping or primary coiling, endovascular treatment with stent-assisted coiling or flow diverters is reasonable to reduce the risk of rebleed. <sup>118,119</sup>
2a	C-LD	12. For patients with aSAH from ruptured fusiform/blister aneurysms, the use of flow diverters is reasonable to reduce mortality. <sup>120,121</sup>
3: Harm	B-NR	13. For patients with aSAH from ruptured saccular aneurysms amenable to either primary coiling or clipping, stents or flow diverters should not be used to avoid higher risk of complications. <sup>122,123</sup>

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### Synopsis

Patients with aSAH should undergo repair of their aneurysm as soon as it is feasible to reduce the risk of aneurysm rerupture, an event that is frequently fatal. However, the choice of treatment modality is highly nuanced. The goal of securing the aneurysm must be balanced with the risks of the procedure. Open surgical options and endovascular techniques have different advantages and disadvantages that need to be carefully weighed for each individual patient because many patient-specific factors (including patient age, aneurysm geometry and location, and presence of intraparenchymal hemorrhage) must be considered. Sometimes complete obliteration is not feasible, either technically or because procedural risks outweigh the benefits. The best outcomes for patients with SAH will be achieved when both endovascular and open surgical options are available. The quality of the evidence supporting recommendations for treatment modality is relatively limited, with a particular paucity of data on comparison of different endovascular techniques with surgical techniques or with each other. Further studies for many of these questions are necessary, and several of these are listed under "Knowledge Gaps and Future Research."

### Recommendation-Specific Supportive Text

1. Early treatment of ruptured aneurysms reduces the risk of rebleeding and facilitates treatment of DCI. Timing of ruptured aneurysm treatment has been directly examined in only 1 small randomized prospective trial of patients with good-grade aSAH in the precoiling era; this study of 159 patients demonstrated that early surgery (0–3 days from SAH) resulted in lower death and dependence at 3 months compared with intermediate surgery (4–7 days) or late surgery ( $\geq 8$  days).<sup>103</sup> Subsequent retrospective and prospective observational studies of both clipping and coiling, including post hoc analyses of the randomized ISAT trial (International Subarachnoid Aneurysm Trial), have defined early treatment variably as within 24, 48, or 72 hours from onset of SAH (rather than from time of presentation). Meta-analyses of these studies and individual series support the outcome benefit of early treatment,<sup>99,102,104</sup> including in patients with high-grade aSAH.<sup>40,98</sup> The data demonstrate a beneficial effect of treatment  $< 24$  hours versus  $> 24$  hours from ictus but have not been able to similarly demonstrate significant beneficial difference between  $< 24$  hours and 24 to 72 hours.<sup>100,104</sup> Studies also support the benefit of treatment in the intermediate time frame (4–7 days) rather than delaying beyond 7 to 10 days, indicating that treatment should not be postponed beyond the typical DCI period in patients presenting during that time frame.<sup>99,102,103</sup>
2. The risks of both rebleeding and retreatment are substantially higher in patients with incomplete obliteration of a ruptured aneurysm.<sup>105–107,124</sup> Therefore, the goal of initial treatment is complete obliteration whenever feasible.
3. For patients in whom, after multidisciplinary discussion, complete obliteration is not feasible by clipping or primary coiling during the initial treatment, partial treatment aimed at securing the putative rupture site during the acute phase is reasonable to reduce the risk of early rebleeding. Retreatment, typically within 1 to 3 months,<sup>105</sup> as allowed by the patient's functional status and recovery is advisable to prevent future rebleeding.
4. Subgroup analysis of posterior circulation aneurysms, derived from 2 RCTs included in a Cochrane review, is limited by small numbers (69 participants) but supports the benefit of coiling over clipping with an RR of 0.41 (95% CI, 0.19–0.92) for death or dependency.<sup>110</sup> Similarly, in the prospective controlled BRAT study, the outcomes of posterior circulation aneurysms were significantly better in the coil than the clip group at both 1 year and longer-term follow-up.<sup>108,109</sup>
5. One small RCT of 30 patients published in the precoiling era examined emergency surgery versus conservative management for patients with ruptured aneurysm with large intracerebral hematoma resulting in severely decreased level of consciousness/serious neurological deficit but with spontaneous respiration and reaction to pain.<sup>111</sup> The study demonstrated a large mortality benefit (27% versus 80%) in favor of clot evacuation/clipping and a higher rate of independent outcome (53% versus 20%). Rapid intervention is supported by observational data indicating significantly shorter time to treatment in patients with large ( $> 50$  cm<sup>3</sup>) intracerebral hematoma and favorable outcome compared with those with unfavorable outcome.<sup>112</sup> Although small retrospective studies have reported the feasibility of coiling to secure the aneurysm before clot evacuation,<sup>125,126</sup> these include smaller intracerebral hematoma volumes (eg,  $> 30$  cm<sup>3</sup>) and are subject to selection bias. The desire for rapid clot evacuation generally favors surgery without delay and concomitant aneurysm clipping.
6. Studies that inform recommendations for the modality of aneurysm treatment have routinely required the involvement of treating specialists with endovascular and surgical expertise. ISAT, the largest RCT examining clipping and coiling for ruptured aneurysms,<sup>116</sup> relied on judgment concerning the suitability for both coiling and clipping by individuals with expertise in endovascular and surgical techniques. Similarly, the prospective controlled BRAT study relied on the presence of individuals with expertise in each technique.<sup>127</sup> In patients with aSAH, evaluation of the ruptured aneurysm for endovascular and

surgical treatment options by specialists with expertise, individually or as a team, in both modalities is necessary to optimally evaluate the relative risks and benefits of each treatment strategy.

7. Although older patients (>70 years of age) are often preferentially treated with coiling, in practice, there are insufficient data to support a clear benefit of coiling in this population. In the largest available RCT, ISAT, subgroup analysis by age demonstrated no benefit of coiling in the group >70 years of age, with an RR of death dependency of 1.15 (95% CI, 0.82–1.61) for coiling.<sup>113</sup> Within the cohort of patients >65 years of age in ISAT, outcome was dependent on aneurysm location, with coiling superior in those with internal carotid and posterior communicating artery aneurysms but clipping superior for those with ruptured middle cerebral artery (MCA) aneurysms.<sup>114</sup> Nonrandomized registry and observational data have also failed to demonstrate an effect of treatment modality on outcomes in the elderly (>75 years of age).<sup>128,129</sup>
8. Longer life expectancy and better long-term protection from rerupture related to clipping favor consideration of clipping in young patients. Subgroup analysis from the largest available RCT, ISAT, indicates less benefit of coiling in those <50 years of age,<sup>113</sup> and calculations based on ISAT data suggest that clip placement may be more advantageous for patients <40 years of age.<sup>115</sup>
9. The Cochrane review and meta-analysis of 4 RCTs of clipping versus coiling indicates that primary coiling provides higher odds of functional independence (mRS score 0–2) at 1 year, with an RR 0.77 (95% CI, 0.67–0.87) for death/dependency.<sup>110</sup> The meta-analysis results are driven primarily by the largest RCT, ISAT,<sup>116</sup> and did not include BRAT, a single-center, prospective, controlled but nonrandomized trial with alternating-day treatment allocation.<sup>127</sup> In the ISAT trial, of the selected patients who were judged suitable for both coiling and clipping, 97% had anterior circulation aneurysms, and the majority were WFNS grades 1 to 3.
10. Collectively, data do not demonstrate a significant difference in long-term functional outcome between patients treated with primary coiling and those treated with clipping. In a post hoc analysis of the largest RCT, ISAT, excluding pretreatment deaths (which were higher in the clipping cohort because of a longer mean interval between randomization and treatment), the RR for death or dependency at 1 year was still significantly in favor of coiling (RR, 0.77 [95% CI, 0.67–0.89]), but the RR for death was 0.88 (95% CI, 0.66–1.19). At 5 years, the difference between coiling and clipping was not significant for either death or dependency (RR, 0.88 [95% CI, 0.77–1.02]) or death alone (RR, 0.82 [95% CI, 0.64–1.05]).<sup>117</sup> In the prospective controlled BRAT study, which also favored coiling at 1 year, no significant benefit of coiling versus clipping was evident at the 3- and 6-year follow-up in the original cohort of all patients with SAH<sup>108,109</sup> or in analysis limited to saccular aneurysms.<sup>130</sup> Long-term data also indicate a small but higher incidence of rebleeding with coiling and a higher incidence of seizures with clipping.<sup>110,113,131,132</sup>
11. Although stent-assisted coiling and flow diverters are associated with higher reported risks of complications<sup>123</sup> and rebleeding<sup>133</sup> than primary coiling (including balloon-assisted techniques) or clipping, their use can be effective in achieving aneurysm occlusion or reducing rebleeding when other options for aneurysm treatment are not feasible.<sup>118,119</sup> Performing ventriculostomy before the endovascular procedure and initiating antiplatelet administration in this setting may reduce ventriculostomy-related hemorrhage.<sup>123</sup>
12. Blister aneurysms, also referred to as blood-blister-like aneurysms arising as pseudoaneurysms from defects in the arterial wall, represent a challenging subgroup of aneurysms associated with high rupture risk and attendant morbidity and mortality. Such lesions are not amenable to primary coiling or standard clipping, requiring more complex surgical wrapping or extracranial-intracranial bypass strategies.<sup>134</sup> Meta-analyses of small retrospective case series indicate that morbidity and mortality with flow diverters are comparable to those reported with surgical strategies.<sup>120,121</sup>
13. The use of stent-assisted coiling and flow diverters has a higher risk of thrombogenicity than primary coiling, necessitating dual antiplatelet therapy. Their use in ruptured aneurysms is associated with a higher risk of hemorrhagic complications,<sup>122</sup> particularly ventriculostomy-related hemorrhage.<sup>123</sup> Consequently, the use of stents or flow diverters should be avoided in the acute phase whenever a ruptured aneurysm can be treated (even partially to secure the rupture site) by primary coiling (including use of balloon-assisted techniques) or clipping.

### Knowledge Gaps and Future Research

- *Ultra-early treatment:* Although data strongly support early aneurysm treatment, the timing of treatment generally has not been prospectively assigned, and studies have used various definitions. There are no data to support emergency (eg, ≤6 hours) or 24/7 treatment, including nighttime, which may create suboptimal logistic conditions or dissuade transfer to comprehensive centers, with subsequent potential for detrimental outcome.
- *QOL/cognitive outcomes:* Data on differential QOL and neurocognitive outcomes after clipping versus



coiling are limited, and further studies focused on these outcomes are needed.

- *Modality of treatment in patients with high-grade aSAH:* Although patients with high-grade aSAH are often preferentially treated with coiling in practice, there are insufficient robust randomized data on coiling versus clipping specifically in patients with high-grade aSAH to support clear evidence-based guidance in this population.
- *Anterior circulation aneurysms:* Ruptured MCA aneurysms, and anterior circulation bifurcation aneurysms in general, are typically considered more favorable for clipping, which is supported by limited data; however, there are insufficient data to provide definitive guidance, especially in the setting of emerging endovascular technologies.
- *Novel flow diversion technologies:* Endosaccular flow diverters and less thrombogenic intravascular flow diverters reduce the need for dual antiplatelets and attendant higher complications. Limited noncomparative data suggest protection against rebleeding and acceptable outcome with endosaccular devices, but there are insufficient comparative data and long-term outcomes to provide guidance on the use of these devices for ruptured aneurysms.
- *Evolving endovascular technologies:* In general, evolving endovascular technologies may provide additional treatment options for ruptured aneurysms, but their comparative efficacy cannot be extrapolated from prior data on other endovascular techniques such as primary coiling. New technologies should be studied prospectively relative to existing treatment options before widespread adoption.

### 7.1. Anesthetic Management of Surgical and Endovascular Treatment of aSAH

Recommendations for Anesthetic Management of Surgical and Endovascular Treatment of aSAH		
Referenced studies that support recommendations are summarized in online Data Supplement 6.		
COR	LOE	Recommendations
2a	B-R	1. In patients with aSAH, the intraoperative use of mannitol or hypertonic saline can be effective in reducing ICP and cerebral edema. <sup>135,136</sup>
2a	B-NR	2. In patients with aSAH, anesthetic goals should include minimizing postprocedural pain, nausea, and vomiting. <sup>137–140</sup>
2a	B-NR	3. In patients with aSAH, prevention of intraoperative hyperglycemia and hypoglycemia during aneurysm surgery is reasonable to improve outcomes. <sup>141–147</sup>
2a	C-LD	4. In patients with aSAH and an unsecured ruptured aneurysm, frequent intraoperative BP monitoring and BP control are reasonable to prevent ischemia and rerupture. <sup>148–153</sup>

Recommendations for Anesthetic Management of Surgical and Endovascular Treatment of aSAH (Continued)		
COR	LOE	Recommendations
2b	B-NR	5. In patients with aSAH, intraoperative neuromonitoring may be reasonable to guide anesthetic and operative management. <sup>154–159</sup>
2b	C-LD	6. In patients with aSAH and an uncontrolled intraoperative aneurysmal rupture, adenosine may be considered to facilitate aneurysm clip placement by inducing cardiac standstill and temporary profound pause. <sup>160,161</sup>
3: No benefit	B-R	7. In patients with good-grade aSAH, the routine use of induced mild hypothermia during aneurysm surgery is not beneficial. <sup>147,162–168</sup>

#### Synopsis

There are limited studies evaluating intraoperative anesthetic management of patients undergoing ruptured aneurysm repair. Intraoperative management paradigms may be gleaned from perioperative investigations, and the anesthetic principles that apply to open surgical treatment of aSAH may generally be applied to endovascular treatment.<sup>169</sup> In patients receiving a general anesthetic, a balanced technique using a combination of medications to provide hypnosis, analgesia, and amnesia while preventing patient movement is commonly used. Infusions of certain hypnotic and analgesic medications might best be administered through continuous infusion to maintain a stable anesthetic state. Goals include hemodynamic stability, favorable ventilatory strategies, and absolute lack of movement during exposure, clipping, or deployment of coils. Anesthetic medications should be titrated in a manner to facilitate acquisition of a neurological examination as soon as the procedure is complete, whenever possible. The neurointerventional treatment of cerebral aneurysms can be performed under local sedation or general anesthesia and has unique issues.<sup>170</sup> Sedation may be more advantageous for patients with significant systemic medical conditions; however, outcome data are lacking. Confusion or neurological impairment makes sedation challenging, whereas general endotracheal anesthesia ensures control of ventilation and immobility of the patient. Neuroanesthesiologists may limit the severity of complications by efficiently managing anticoagulation and maintaining systemic and cerebral hemodynamics.

#### Recommendation-Specific Supportive Text

1. Although there are no specific studies of hyperosmotic agents in the intraoperative management of patients with aSAH, use of these agents is described in the intraoperative setting, and they are used routinely in patients with aSAH. Hypoosmotic fluids are generally avoided, whereas isoosmotic and sometimes hyperosmotic fluids are favored.<sup>171</sup> Intraoperatively, hyperosmotic agents have been used to manage brain relaxation and intracerebral pressure in the face of vasogenic or

- cytotoxic edema, which greatly increase the risk of poor outcome if associated with local and global cerebral ischemia.<sup>135</sup> In addition, surgical exposure and the operative procedure become more difficult. Both mannitol and hypertonic saline have been used to decrease ICP and increase cerebral blood flow (CBF) and brain relaxation.<sup>136</sup> Mannitol is a potent diuretic and can cause hypovolemia and hypotension, whereas hypertonic saline increases blood sodium, has minimal effect on diuresis, and can increase BP. A clinical trial to evaluate the optimal intraoperative dose of mannitol in patients with aSAH is ongoing at the time of guideline publication (ClinicalTrials.gov identifier: NCT04135456). Currently, there is insufficient evidence to recommend one therapy over the other or to affirm whether outcomes are affected.
2. Postoperative nausea and vomiting can have a negative impact after aneurysm coiling and clipping by increasing the risk of aspiration of gastric contents.<sup>137</sup> Incidence after aSAH has not been studied, but postoperative nausea and vomiting after craniotomy occur in 22% to 70% of patients.<sup>140</sup> A multimodal regimen of medication targeting different chemoreceptors is recommended.<sup>172</sup> Although serotonin 5-HT<sub>3</sub> receptor antagonists (eg, ondansetron), steroids (eg, dexamethasone), and their combination are the most frequently used antiemetics, the addition of propofol, reduction of narcotics, and euvolemia are generally advocated. Medications that can cause confusion or sedation such as anticholinergics (eg, scopolamine) and phenothiazines (eg, promethazine) at higher doses may impair neurological examination. The use of volatile anesthetic medications for craniotomy has been associated with a higher incidence of postoperative nausea and vomiting compared with intravenous agents such as propofol,<sup>138,173</sup> and dexmedetomidine may offer an advantage compared with fentanyl as an analgesic.<sup>139</sup> Further clinical trials comparing different regimens that significantly reduce the incidence of postoperative nausea and vomiting after aSAH would provide relevant data in this patient population.
  3. Poor perioperative glycemic control in patients with aSAH has been associated with increased risk of poor clinical outcome. The management of intraoperative glucose concentrations has not been well studied; however, the prevention of intraoperative hyperglycemia and hypoglycemia during aneurysm surgery is probably indicated.<sup>141,142,144–146</sup> A post hoc analysis of IHASt (Intraoperative Hypothermia for Aneurysm Surgery Trial)<sup>147</sup> determined that commonly encountered hyperglycemia was associated with long-term changes in cognition and gross neurological function.<sup>143</sup>
  4. Intraoperative volume status and BP goals are not well defined in intraoperative aSAH management. Numerous pathophysiological states may be present after aneurysmal rupture such as cardiovascular dysfunction, systemic inflammation, autoregulatory failure, and spreading depolarizations that can be affected by intravascular volume.<sup>152</sup> During the intraoperative period, frequent BP monitoring and BP control are reasonable to prevent ischemia and rerupture. Hypovolemic states often necessitate additional pressor support, especially when clinical management necessitates hypertensive therapy. There are suggestions that hypovolemia (in the perioperative period) may contribute to the incidence of DCI,<sup>152</sup> whereas hypervolemia lacks benefit<sup>148,149,151,153</sup> and the rapid reduction of BP is potentially harmful.<sup>150</sup> Careful BP management needs to occur throughout the perioperative period, including transportation.
  5. Intraoperative neuromonitoring can be used to evaluate functional brain integrity in a timely manner during aneurysm surgery. Common intraoperative neuromonitoring modalities used are spontaneous electroencephalography (EEG) and somatosensory aSAH evoked and motor evoked potentials.<sup>155</sup> Although neuromonitoring has traditionally been used for open craniotomies, some centers also use intraoperative neuromonitoring for endovascular coiling. Anesthetic protocols to optimize neurophysiological recordings are recommended.<sup>157,159</sup> Although no prospective studies have validated the efficacy of intraoperative neuromonitoring on outcome and a recent retrospective study questioned its utility with respect to overall outcomes in elective aneurysm management,<sup>156</sup> a growing body of evidence supports its use.<sup>154,158</sup> In addition, pharmacologically induced EEG burst suppression may be reasonable during temporary clipping if hypotension can be avoided.<sup>174</sup>
  6. The use of adenosine for temporary profound hypotension may be considered to facilitate exposure and aneurysm clip placement in selected situations, particularly in the setting of uncontrolled intraoperative rupture. It has been used for both ruptured and unruptured aneurysms in both the anterior and posterior cerebral circulation. The pharmacological properties of rapid onset and offset of adenosine and its predictable action make it a valuable tool in cerebrovascular surgery. Its clinical onset of action is within seconds, providing a brief period of profound systemic hypotension with a low side-effect profile. In 2017, Desai et al<sup>161</sup> compiled 19 case series and retrospective reviews illustrating the benefit of adenosine. Initial doses have been described to obtain a predictable and transient period of cardiac pause for

≈45 seconds.<sup>160</sup> Adenosine is contraindicated in patients with sinus node disease, second- or third-degree atrioventricular block, and pulmonary issues such as bronchoconstrictive or bronchospastic lung disease. Caution should be used in patients with first-degree atrioventricular block, bundle-branch block, or history of heart transplantation. Its administration to patients with coronary artery disease may result in cardiac arrest, sustained ventricular tachycardia, or myocardial infarction.

7. Systemic hypothermia has been studied to attenuate ischemic injury during aneurysm surgery. Although early studies suggested a neurological benefit,<sup>165,166,168,175,176</sup> a multicenter, prospective, randomized trial that evaluated 1000 patients with good-grade SAH (WFNS grade 1, 2, or 3) found no improvement in 3-month neurological outcome after surgery.<sup>147</sup> A post hoc analysis demonstrated no difference between temporary clipping in the hypothermic and normothermic groups (target temperatures, 33°C and 36.5°C, respectively) in the incidence of cognitive impairment and 24-hour and 3-month outcomes.<sup>164</sup> Because this study evaluated only patients with good-grade SAH, the conclusions may not extrapolate to the high-grade SAH population, and it should be noted that rewarming strategies were not standardized. A comparison of mild hypothermia and normothermia was performed in limited studies,<sup>162,163</sup> suggesting that further investigations with larger populations are warranted to evaluate this patient cohort. Although the effects of intraoperative hyperthermia after an aSAH have not been investigated, it has been associated with worse outcomes in the perioperative period.<sup>167</sup>

**Knowledge Gaps and Future Research**

*BP and volume management:*

- The usefulness of the routine placement of an arterial line for continuous BP monitoring before induction of anesthesia and during anesthesia for craniotomy or endovascular intervention is not well established.
- There are limited data to indicate appropriate BP target ranges in patients with aSAH in the perioperative period, particularly during elevated ICP and acute rupture.
- There are no studies defining optimal intraoperative volume status in the management of patients with aSAH.
- There are limited human data on the role of albumin in fluid management in aSAH and its ability to impart any cerebral neuroprotection and improve clinical outcomes. However, the ALISAH multicenter pilot trial (Albumin in Subarachnoid Hemorrhage) identified a dose-dependent increase in cardiac complications.

*Anesthetics:*

- There is insufficient evidence on optimal anesthetic management in aSAH, which is generally institutionally driven. Within institutions, variability may occur during the perioperative period. The long-term impact of anesthetic medications on neurological outcomes during aSAH is not known, and although neuroprotection and conditioning by anesthetics have been studied extensively for >60 years, there is limited evidence for them occurring. The potential for anesthetics to cause conditioning effects to protect against angiographic vasospasm and DCI in humans has recently been presented and may deserve validation.
- Although ketamine may influence neurological examination of the patient, its role in aSAH intraoperative management may merit re-evaluation because it influences the occurrence of cerebral infarctions associated with DCI and may attenuate spreading depolarizations after an aSAH. Further studies are needed to evaluate the significance of this with respect to both immediate and long-term effects.
- There is insufficient evidence on the effects of reducing sympathetic activation during the management of aSAH by either β-adrenergic blockade or narcotic administration and the impact on mortality.
- *Ventilation:* There is limited information to guide ventilatory management to control arterial carbon dioxide tension or arterial carbon dioxide tension goal in patients with aSAH in the intraoperative period.
- *Glucose and electrolytes:* Additional data are needed on the intraoperative management of glucose and electrolytes such as sodium during aSAH management and whether treatment affects clinical outcomes.
- *Subspecialty training:* There is insufficient information on outcomes of patients managed by anesthesiologists with subspecialty training in neuroanesthesiology compared with general training.

**8. MANAGEMENT OF MEDICAL COMPLICATIONS ASSOCIATED WITH aSAH**

Recommendations for Management of Medical Complications Associated With aSAH		
Referenced studies that support recommendations are summarized in online Data Supplement 7.		
COR	LOE	Recommendations
Pulmonary management		
1	B-NR	1. In patients with aSAH who require mechanical ventilation for >24 hours, implementation of a standardized ICU care bundle is recommended to reduce the duration of mechanical ventilation and hospital-acquired pneumonia. <sup>177,178</sup>

Recommendations for Management of Medical Complications Associated With aSAH (Continued)		
COR	LOE	Recommendations
2b	B-NR	2. In patients with aSAH who develop severe acute respiratory distress syndrome (ARDS) and life-threatening hypoxemia, rescue maneuvers such as prone positioning and alveolar recruitment maneuvers with ICP monitoring may be reasonable to improve oxygenation. <sup>179–182</sup>
Intravascular volume and electrolyte management		
2a	B-R	3. In patients with aSAH, close monitoring and goal-directed treatment of volume status are reasonable to maintain euvolemia. <sup>183–185</sup>
2a	B-R	4. In patients with aSAH, use of mineralocorticoids is reasonable to treat natriuresis and hyponatremia. <sup>186,187</sup>
3: Harm	B-R	5. In patients with aSAH, induction of hypervolemia is potentially harmful because of the association with excess morbidity. <sup>188–190</sup>
Other		
1	C-LD	6. In patients with aSAH whose ruptured aneurysm has been secured, pharmacological or mechanical venous thromboembolism (VTE) prophylaxis is recommended to reduce the risk for VTE. <sup>191–193</sup>
2a	B-NR	7. In patients with aSAH, effective glycemic control, strict hyperglycemia management, and avoidance of hypoglycemia are reasonable to improve outcome. <sup>141,142,194,195</sup>
2b	C-LD	8. In patients with aSAH with fever refractory to antipyretic medications, the effectiveness of therapeutic temperature management (TTM) during the acute phase of aSAH is uncertain. <sup>196–198</sup>

**Synopsis**

A significant number of patients with aSAH develop multisystem medical complications, including fever resulting from infectious and noninfectious causes such as central fever; systemic inflammatory syndrome; hyponatremia attributable to cerebral salt wasting or syndrome of inappropriate antidiuretic hormone; infectious complications such as pneumonia and sepsis; VTE complications; cardiac complications, including neurogenic stunned myocardium; and respiratory failure requiring mechanical ventilatory support, including ARDS.<sup>177,199</sup> (Readers are directed to Section 8.3 for discussion of DCI and induced hypertension and to Section 6 for discussion of initial BP management.) Patients with aSAH with medical complications have worse outcomes compared with those without complications.<sup>178,200</sup> Prevention, timely diagnosis, treatment of medical complications, and high-quality critical care support are important in improving overall outcomes for patients with aSAH.

**Recommendation-Specific Supportive Text**

1. Respiratory failure requiring mechanical ventilation, health care-associated pneumonia, and ARDS are important medical complications that may develop

- during the course of acute aSAH and affect outcomes. ARDS is independently associated with worse SAH outcomes. Recent multicenter observational studies report an ARDS incidence up to 3.6% within the first 7 days of aSAH.<sup>191,201</sup> Large cohort studies demonstrated that adaptation of bundled care for mechanically ventilated patients with brain injury (including patients with aSAH) accelerated extubation readiness, reduced duration of mechanical ventilation, and increased ventilator-free days and ICU-free days.<sup>177,178</sup> Such bundled care included lung-protective, low tidal volume ventilation, moderate positive end-expiratory pressure, early enteral nutrition, standardization of antibiotic therapy for hospital-acquired pneumonia, and a systematic approach to extubation.
2. Acute lung injury is prevalent (up to 27%) in aSAH and is associated with higher treatment intensity, longer ICU stay, and unfavorable overall outcome.<sup>191,201–203</sup> ARDS is a life-threatening condition occurring in 3.6% to 27% of aSAH cases before the COVID-19 pandemic.<sup>191,196,201,204</sup> Whether the COVID-19 pandemic has increased the incidence of ARDS complicating aSAH is not known at this time. Maneuvers to treat refractory hypoxemia in severe ARDS such as alveolar recruitment, higher positive end-expiratory pressure use, and prone positioning are controversial in patients with severe brain injury because of the concern that they may worsen ICP elevation. Small RCTs now demonstrate that alveolar recruitment and prone positioning can be performed in patients with aSAH with ICP monitors to effectively increase arterial oxygen partial pressure while not leading to pathological ICP and cerebral perfusion pressure values.<sup>179–182,197,205–209</sup> Although no studies compared the safety of these maneuvers in patients with or those without ICP monitors, given the overall critical condition of these patients and the available safety data, it is advisable to monitor ICP in patients who may require these maneuvers.
  3. The optimal method to assess and continuously monitor intravascular volume status and fluid responsiveness in critically ill patients, including patients with aSAH, remains controversial.<sup>204,210</sup> Extensive evidence suggests that central venous pressure correlates poorly with circulating blood volume and is not able to predict hemodynamic response to a fluid challenge in critically ill patients. Therefore, central venous pressure is not an adequate surrogate measure for intravascular volume status.<sup>208,211–213</sup> Intravascular volume depletion in SAH can occur as a result of natriuresis and may be associated with DCI and poor outcome, leading many experts to recommend continuous monitoring and optimization of adequate circulating blood volume in aSAH. Early

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- goal-directed treatment using continuous monitoring and optimization of hemodynamic parameters, including cardiac output, preload, and stroke volume variability to guide fluid and hemodynamic management in aSAH during endovascular/surgical therapy and ICU care, can increase the detection and treatment of dehydration/intravascular volume depletion compared with conventional methods. However, this may not affect the incidence of vasospasm, DCI, death, or functional outcome.<sup>183,184,190,203</sup> One RCT suggested that in patients with high-grade aSAH, early goal-directed treatment within 24 hours of aSAH onset for hemodynamic monitoring is associated with reduced rates of subsequent DCI, ICU length of stay (LOS), and unfavorable outcome (mRS score 4–6).<sup>183,203</sup>
4. Hyponatremia, with or without polyuria or natriuresis, is a prominent clinical feature in aSAH but has been inconsistently associated with DCI and poor outcome in cohort studies.<sup>186,214–230</sup> Clinically significant hyponatremia and uncontrolled natriuresis resulting in potential intravascular volume depletion can lead to significant additional neurological and systemic deteriorations that require high-intensity interventions in the ICU.<sup>196,231</sup> Several moderately sized RCTs found fludrocortisone to be effective in reducing excess sodium excretion, urine volume, hyponatremia, and intravenous fluid use during acute aSAH, but fludrocortisone did not consistently reduce DCI or affect outcome.<sup>143,187,219,232–237</sup> These RCTs did not find significant morbidity with fludrocortisone use for reducing hyponatremia or natriuresis other than hypokalemia and the need for potassium supplementation. Other agents, including high-dose hydrocortisone, have been studied in RCTs and demonstrated similar effects on serum sodium, urinary sodium excretion, and natriuresis but reported more medical complications such as hyperglycemia, hypokalemia, gastrointestinal hemorrhage, and congestive heart failure.<sup>187,198,217,218,237,238</sup> The majority of these RCTs used fludrocortisone or hydrocortisone in combination with either delayed aneurysm treatment<sup>186,239</sup> or induced hypervolemic hypertensive hemodilution therapy, which may have confounded the relationship between study drug and overall outcome.
  5. Prophylactic induced hypervolemia, often administered as part of hypervolemic hypertensive hemodilution therapy using crystalloids or colloid fluids such as human albumin or blood transfusion, had historically been used in clinical practice with the goal of preventing or reducing DCI. The RCTs to date demonstrate that volume expansion increases the rate of medical complications without improving overall outcome or reducing DCI.<sup>141,142,188–190,194,195,211</sup> One study demonstrated a reduction of perioperative secondary ischemia with no impact on overall outcome.<sup>199,240</sup>
  6. In patients with acute aSAH, 4% to 24% will develop VTE.<sup>179–182,189–191,221</sup> Routine asymptomatic screening may increase occult deep vein thrombosis detection rates but with an unclear impact on outcome.<sup>180,188,192,221</sup> CLOTS (Clots in Legs or Stockings After Stroke) 3 was the largest RCT examining physical VTE prophylaxis (intermittent pneumatic compression) in ischemic (84.2%) and hemorrhagic (13%) strokes but excluded aSAH.<sup>179,191</sup> The safety of pharmacological VTE prophylaxis in aSAH can be derived from clinical trials of pharmacological agents typically used for VTE prophylaxis. A small RCT of enoxaparin 40 mg SC injection once daily in aSAH after aneurysm treatment found that enoxaparin did not increase bleeding and may have decreased the VTE rate but had no overall effect on outcome.<sup>184</sup> Retrospective cohort studies of low-molecular-weight heparin in aSAH after aneurysm occlusion did not find significant hemorrhages.<sup>183,185,236</sup> The optimal timing of pharmacological VTE prophylaxis in aSAH relative to aneurysm occlusion and neurosurgical procedures remains unclear. A case-control study<sup>187,193</sup> comparing early ( $\leq 24$  hours after aneurysm occlusion) with delayed ( $> 24$  hours) pharmacological prophylaxis ( $> 40\%$  had an EVD) found no intracranial hemorrhagic complications in the early group. Three patients in the delayed group who received concomitant dual antiplatelet therapy developed severe intracranial hemorrhages.
  7. Hyperglycemia on admission, during aneurysm surgery, or within 72 hours of aSAH presentation has been associated with vasospasm, DCI, unfavorable short-term and long-term functional outcomes, and risk of death in both patients with diabetes and those without diabetes in multiple studies.<sup>142,143,195,241</sup> Although the data are fairly consistent in the association between hyperglycemia and aSAH outcome, data are conflicting on what glycemic threshold should be targeted, what monitoring and treatment intensities should be used, and whether all these affect outcome. Acute hyperglycemia on SAH presentation may reflect the severity of the initial brain injury and therefore may not be a modifiable factor in preventing secondary brain injury. Several small RCTs comparing intensive with conventional glycemic control in aSAH did not demonstrate any outcome benefit.<sup>141,194</sup> However, 1 study found that patients who received intensive insulin therapy targeting a glucose level of 80 to 120 mg/dL had significantly lower infection rates but had no effect on overall outcome.<sup>194</sup> A key consideration with such inconsistent data is whether tight glycemic control

can lead to systemic or cerebral hypoglycemia and metabolic crisis in the acutely injured brain and potentially worsen brain injury and outcome, which remains to be determined.<sup>232,233,239</sup>

8. Fever is common in acute aSAH, often refractory to conventional antipyretics, and associated with worse outcomes in multiple studies.<sup>198,202,238</sup> Data remain heterogeneous on how fever is defined and whether treatment of fever or TTM improves outcomes in aSAH.<sup>196,197</sup> Available fever control/TTM modalities include pharmacological treatment, surface cooling devices with or without a feedback loop, and endovascular cooling devices.<sup>205,209</sup> To date, none of these modalities, alone or in combination, have improved outcome, although many are effective in temperature control. TTM can be associated with complications such as shivering requiring pharmacological control, increased duration of sedation, longer days on mechanical ventilation, longer ICU stay, hypotension, and catheter-related complications if endovascular devices are used.<sup>205-207</sup> Furthermore, the use of mild hypothermia in aSAH has been studied in small RCTs, suggesting clinical feasibility,<sup>163</sup> but different modalities may not have the same impact on reducing inflammatory biomarkers.<sup>242</sup>

**Knowledge Gaps and Future Research**

- *Transfusion targets in aSAH:* Anemia is common and associated with poor aSAH outcome. Red blood cell transfusion can increase cerebral oxygen but causes medical complications and worsens outcome. Optimal hemoglobin thresholds and the indications for transfusion remain unknown. Multicenter clinical trials are underway to address these key questions.
- *Systemic inflammation and infection:* Systemic inflammatory response syndrome is prevalent and complicates the course of patients with aSAH, worsening outcome. There are inconsistent data on how to distinguish infectious from noninfectious causes of systemic inflammatory response syndrome in aSAH. Infectious complications, including pneumonia and sepsis, are prevalent and worsen outcome, but whether treatment of infection improves outcome is unknown. Furthermore, evidence suggests that inflammation contributes to brain injury after aSAH; however, medications targeting inflammation such as glucocorticoid steroids have not been sufficiently studied in aSAH to assess their safety and efficacy.
- *Cardiopulmonary arrest:* About 4% of patients with aSAH suffer early cardiac arrest, and about one-quarter of survivors can have good outcomes, although data are inconsistent. Currently, there are insufficient data to inform optimal treatment and prognostication in aSAH-associated cardiac arrest.

- *Cardiac complications:* Cardiac arrhythmias, biomarkers of myocardial injury and cardiomyopathy, have frequently been described after aSAH. The limited amount of evidence focuses mainly on the predictive value of aSAH-associated cardiac injury on outcomes. However, there is no specific evidence on the management of cardiac complications.
- *Protein malnutrition:* Protein malnutrition is common in aSAH. Nutrition support with high-protein supplementation may improve outcome in select patients with aSAH such as those who develop infection, but the impact and optimal treatment of protein malnutrition in aSAH remain unknown.
- *Circulatory volume:* Whether the goal is hypervolemia or euvolemia, a key area of insufficient evidence is how circulatory volume should best be determined in aSAH. Conventional methods for circulating volume estimation such as fluid balance or central venous pressure are associated with more instances of hypovolemia. There is no gold standard, and no studies have compared different modes of circulatory volume measure in aSAH and the impact on overall outcome. Studies looking at total fluid administration in aSAH found that higher fluid intake was associated with DCI. Small RCTs suggest that goal-directed therapy with advanced circulatory volume monitoring devices may reduce the instances of hypovolemia, and goal-directed therapy in patients with high-grade aSAH may be associated with a reduced incidence of DCI.
- *Fever and TTM:* Key questions and research priorities remain in TTM delivery in aSAH, including the optimal target temperature, duration of TTM, optimal TTM modalities to use, and how side effects of TTM affect outcomes.

**8.1. Nursing Interventions and Activities**

Recommendations for Nursing Interventions and Activities		
Referenced studies that support recommendations are summarized in online Data Supplement 8.		
COR	LOE	Recommendations
1	B-R	1. In patients with aSAH, use of evidence-based protocols and order sets is recommended to improve standardization of care. <sup>243-250</sup>
1	B-NR	2. In patients with aSAH, frequent neurological assessment with a neurological assessment tool such as the GCS or National Institutes of Health Stroke Scale (NIHSS) is recommended to monitor DCI and other secondary complications. <sup>246,251-254</sup>
1	B-NR	3. In patients with aSAH, frequent vital sign and neurological monitoring is recommended for detection of neurological change and prevention of secondary cerebral insults and poor outcomes. <sup>244,246,250,255-257</sup>

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Recommendations for Nursing Interventions and Activities (Continued)		
COR	LOE	Recommendations
1	B-NR	4. In patients with aSAH, a validated dysphagia screening protocol should be implemented before initiation of oral intake to reduce the incidence of pneumonia. <sup>244,246,258–261</sup>
2a	C-LD	5. In patients with aSAH, specialized nursing stroke competencies and certification can be effective to positively affect outcomes, timeliness of care, and adherence to stroke protocols. <sup>248,262–264</sup>
2a	C-LD	6. In patients with aSAH and a secured aneurysm, an early, evidence-based mobility algorithm is reasonable to improve level of function at discharge and global functional outcome at 12 months. <sup>249,265–268</sup>

### Synopsis

Nursing care activities, assessments, and interventions for patients with aSAH are initiated at the time of arrival and continue throughout the patient's hospital stay and recovery. Expert nursing care is the backbone and pillar of critical care interventions in preventing medical complications and maximizing the chance for a good functional outcome. The focus of care is reduction of medical complications and secondary insults, including maintaining euvolemia and avoiding BP variability. Prevention includes rapid recognition and treatment of neurological deterioration related to DCI, cerebral edema, hydrocephalus, fevers, hyperglycemia, and pneumonia.<sup>244,246,251,253–256,258</sup> The literature identifies frequent assessments by nurses as a key component in prevention strategies.<sup>244,246,255–257</sup> The use of validated tools such as the NIHSS or GCS and validated dysphagia screening scales is shown to positively affect earlier intervention for vasospasm and DCI and decrease rates of pneumonia.<sup>246,251,254,256–258</sup> Furthermore, nursing activities provided by certified and competent stroke-trained nurses are suggested to have a positive impact on patient outcomes.<sup>262–264</sup> Use of and adherence to aSAH order sets and protocols help to improve standardization of care and reduce mortality.<sup>243,245,248,250</sup>

### Recommendation-Specific Supportive Text

1. Uniform and standardized care for stroke patients has been shown to reduce LOS, decrease rate of DCI, and positively affect patient functional outcomes at 90 days.<sup>243,244,246,247,249,250</sup> Nursing interventions are often driven by stepwise algorithms and protocols that clearly define the activities. The QASC trial (Quality in Acute Stroke Care), a large observational study, found that patients in a nurse-initiated intervention group using a fevers, sugars, and swallowing protocol had a 16% absolute improvement in death and dependency at 90 days compared with patients in the control group.<sup>244,246</sup> Follow-up of the QASC study found that establishing and hardwiring this nursing protocol led to an 80% increase in patient receipt of all protocol

interventions 4 years after the bundle introduction, with ongoing reduced dependency at 90 days.<sup>249</sup> Current studies of patients with stroke suggest that the use of stroke-specific order sets provides the foundation for standardized care. Compliance with current guidelines and a review of individual indicators such as treatment of hypertension, administration of nimodipine, and timely treatment of aneurysms have shown a positive association with reduced 1-year mortality rate.<sup>250</sup> Protocol-specific pathways and stroke order sets that guide nursing activities result in improved standardization of care and better 90-day outcomes.<sup>249,250</sup>

2. Although diagnostic and imaging tools aid in the monitoring and detection of DCI, a large body of evidence suggests that there may be other predictors of DCI risk, including aneurysm size, location, Fisher score, oxygen saturation, and changes in neurological examination as measured by neurological assessment scales.<sup>245,251–254,257</sup> The most common described scales used to predict neurological changes are the GCS and NIHSS. One large subgroup analysis looking at significant independent predictors of DCI found that although a change in GCS score alone was not an independent predictor of DCI risk, a decrease in GCS by  $\geq 2$  points was associated with clinical DCI.<sup>254</sup> Multiple studies identified the NIHSS and GCS as the preferred assessment scales for neurological monitoring without identifying one scale as superior over another.<sup>251–253</sup> Other DCI-specific prediction scales such as VASOGRADE have shown the ability to significantly predict DCI using a stratification model.<sup>251</sup>
3. Early detection of neurological deterioration for patients with aSAH is crucial to prevent secondary insults related to DCI or other complications resulting from cerebral edema or hydrocephalus. The studies reviewed include both RCTs and non-RCTs with a consistent recommendation for nurses to provide frequent assessments in the acute phase.<sup>244–246,254–257</sup> Frequent assessments ranged from every 15 minutes to every 4 hours.<sup>246,251,255–257</sup> The duration of frequent assessments also varied, with a range of at least 48 hours to 7 days after the bleed.<sup>245,246,254–257</sup> One study observed neurological deterioration in 42.6% of patients after aneurysm clipping using the GCS and NIHSS as the frequent assessment tool every hour up to 72 hours.<sup>256</sup> There are a lack of consensus and wide variability in the timing and duration of frequent assessments, allowing more individualized care plans based on the complexity and needs of the patient.
4. It is estimated that up to 65% of patients with stroke will develop neurogenic dysphagia in the

acute phase, putting them at increased risk of developing pneumonia and leading to increased LOS and poor functional outcome and mortality at 90 days.<sup>258–261</sup> Nurses are in a unique position to evaluate for dysphagia before administering anything by mouth. A systematic review and subgroup analysis that included 4528 patients found that nurse-initiated dysphagia screening and the use of formal guidelines had a significant positive effect in the prevention of pneumonia and decreased mortality rates.<sup>261</sup> Another large systematic review and single-blinded cluster RCT that included both patients with hemorrhagic stroke and patients with ischemic stroke reported various dysphagia screening tools and recommended the use of a validated tool as best practice within 24 hours of admission.<sup>246</sup>

5. Implementing stroke care protocols and order sets and providing specialized assessments to the patient with stroke require expert nursing care. A pre-/posttest-designed study found that nurses who participated in stroke competency training had improved knowledge of and adherence to stroke guidelines with a positive association with decreased LOS.<sup>263</sup> Nurse-specific competencies described in the literature include NIHSS assessment, dysphagia screening, patient and family stroke education, monitoring for increased ICP, and EVD management.<sup>248,262–264</sup> In a retrospective, comparative review, stroke-certified nurses were found to deliver more timely care and have a higher adherence rate to stroke protocols than noncertified nurses.<sup>264</sup> Additional studies are needed to better understand the impact that specialized nurse training and competencies have on long-term patient outcomes.<sup>248,262–264</sup>
6. Immobility is a common problem for patients with stroke that contributes to many secondary problems, including thromboembolism, pressure sores, pneumonia, and poor functional outcomes.<sup>247,266–268</sup> Initiation of rehabilitation therapies with early mobilization has a positive impact, without a negative effect on the frequency or severity of DCI events, and is associated with positive global functional outcome 1 year after hemorrhage.<sup>267,268</sup> A prospective, interventional study compared a nurse-driven early mobilization group with a standard treatment group and found that with each step of mobilization achieved in the early intervention group in the first 4 days after aneurysm repair, there was a 30% reduction of risk of severe vasospasm.<sup>267</sup> Implementation of a nurse-driven evidence-based mobility program found a 2.3-fold increase in the level of function at 90 days for patients participating in the mobility program

compared with nonparticipants.<sup>266</sup> Evidence suggests that certain patients may benefit from an early mobilization intervention.

### Knowledge Gaps and Future Research

- *Bundling of nursing activities:* Limited literature focuses on how nursing activities affect the prevention or detection of complications. Although it is believed that nurses should bundle activities and consider timing of interventions, no large RCTs or meta-analyses to date have addressed this patient population and long-term outcomes as they relate to nursing tasks.
- *Vital sign and neurological assessment frequency:* The impact of the frequency of vital sign and neurological assessments on identification of neurological deterioration, prevention of complications, and long-term functional outcomes is not well understood.
- *Multimodal monitoring:* The nursing burden of multimodal monitoring is unknown in the aSAH population. The volume of nurses required and the ongoing education and training needed are not established.
- *Stroke education impact:* Patient and family education is a common intervention provided by nurses. However, there are no specific studies evaluating the impact of education provided during the acute phase on the prevention of complications or long-term outcomes. A nurse-driven study evaluating this common patient care intervention may better guide nurses on the impact of education.
- *Negative impact of nursing activities:* Nursing care activities are intended to have a positive impact. For some patients, these activities may be minimally tolerated because they may exacerbate acute issues such as increased ICP, decreased perfusion pressures, pain, sleep, or hemodynamic fluctuations. Future studies evaluating the impact of clustered nursing interventions and risk/benefit review may be beneficial.
- *Sleep disruption tool:* There is no validated tool to evaluate the impact of frequent assessments of vital signs and neurological checks on sleep disruption. Frequent monitoring may have a potential negative impact on patient outcomes. Future studies and the development of a scale for this measure may be beneficial.
- *Nursing competencies:* There is little understanding of how nurse competency or certification contributes to positive outcomes. A study evaluating uniformity, timing, and validation of type of nurse competency and certifications may be helpful. In addition, a better understanding of appropriate expertise and standards for nurse staffing ratios are needed.



## 8.2. Monitoring and Detection of Cerebral Vasospasm and DCI

Recommendations for Monitoring and Detection of Cerebral Vasospasm and DCI		
Referenced studies that support recommendations are summarized in online Data Supplement 9.		
COR	LOE	Recommendations
2a	B-NR	1. In patients with aSAH with suspected vasospasm or limited neurological examination, CTA or CT perfusion (CTP) can be useful to detect vasospasm and predict DCI. <sup>270–275</sup>
2a	B-NR	2. In patients with aSAH, transcranial Doppler (TCD) ultrasound monitoring is reasonable to detect vasospasm and predict DCI. <sup>253,276–280</sup>
2a	B-NR	3. In patients with high-grade aSAH, continuous EEG (cEEG) monitoring can be useful to predict DCI. <sup>276,280–292</sup>
2b	B-NR	4. In patients with high-grade aSAH, invasive monitoring of brain tissue oxygenation, lactate/pyruvate ratio, and glutamate may be considered to predict DCI. <sup>293–305</sup>

### Synopsis

Narrowing of the cerebral arteries (cerebral vasospasm) occurs frequently in patients with aSAH and is associated with DCI and infarction. DCI occurs in ≈30% of patients, mostly between days 4 and 14 after aSAH. Clinical deterioration due to DCI has been defined as the occurrence of focal neurological impairment or a decrease of at least 2 points on the GCS.<sup>306–308</sup> This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes. New cerebral infarction has been defined as the presence of cerebral infarction on CT or magnetic resonance imaging scan of the brain within 6 weeks after aSAH not attributable to other causes.<sup>306–308</sup> Diagnosis of DCI can be challenging, and although serial neurological examinations are important (see Section 8.1), they are of limited value in patients with high-grade aSAH. Several diagnostic tools have been used to identify arterial narrowing and cerebral perfusion abnormalities that may help predict DCI. The most commonly available techniques include TCD ultrasound,<sup>253,276–280</sup> CTA and CTP,<sup>270–275</sup> and cEEG.<sup>276,280–292</sup> Other invasive methods include partial pressure of brain tissue oxygen (Pbto<sub>2</sub>), and cerebral microdialysis.<sup>293–305</sup>

### Recommendation-Specific Supportive Text

1. CTA and CTP can provide valuable assessment for vasospasm after aSAH and guide treatment decisions.<sup>309</sup> CTA has high sensitivity (91%) for detecting central vasospasm when symptoms develop.<sup>275</sup> The accuracy diminishes in distal vascular territories.<sup>310</sup> CTA can also be useful when TCD readings become elevated and neurological examination is limited.<sup>311</sup> In a prospective cohort study, CTA has been shown to have a diagnostic accuracy of 90% and a false-positive rate of 5% compared with

DSA, making it a reasonable option for vasospasm detection in patients with high-grade aSAH.<sup>270</sup> When severe vasospasm is detected on CTA, patients can be triaged for intervention in the angiography suite because of the risk for DCI.<sup>274</sup> CTA vasospasm scores are direct predictors of DCI and poor neurological outcome,<sup>312</sup> and CTP allows early prediction of perfusion abnormalities.<sup>313,314</sup> CTP can therefore aid in the detection of alterations to the microcirculation, in addition to the macroscopic vasospasm that can be detected with CTA.<sup>273</sup> CTP has a positive predictive value of 0.67 for DCI.<sup>271</sup> In addition, CTP can be performed on day 3 after aSAH to assess patients at risk for DCI entering the vasospasm window, thus limiting the need for repeat studies, contrast, and radiation exposure.<sup>272</sup>

2. TCD is a noninvasive, safe bedside neuromonitoring technique that allows repetitive and dynamic assessment of vasospasm after aSAH.<sup>253,276–280</sup> Most of the published studies have focused on MCA vasospasm, usually defined as mean CBF velocity  $\geq 120$  cm/s and Lindegaard ratio  $\geq 3$  (mean blood flow velocities in MCA/ipsilateral extracranial internal carotid artery). The most recent systematic review and meta-analysis included 17 studies ( $n=2870$  patients).<sup>277</sup> TCD evidence of vasospasm was found to be highly predictive of DCI. The pooled estimates for TCD diagnosis of vasospasm (for DCI) were a sensitivity of 90% (95% CI, 77%–96%), specificity of 71% (95% CI, 51%–84%), positive predictive value of 57% (95% CI, 38%–71%), and negative predictive value of 92% (95% CI, 83%–96%). Retrospective observational studies suggest that the combination of TCD and other neuromonitoring modalities (such as cEEG,<sup>307</sup> CTP,<sup>253</sup> and Pbto<sub>2</sub><sup>278</sup>) may increase the prediction of DCI. These findings are of significance because TCD is performed intermittently (at best 1–2 times per day), is operator dependent, can be limited by patient anatomy (poor temporal bone window), and can be affected by other physiological measures (such as heart rate and BP).<sup>276,279</sup>
3. Recent technical advances and broader availability have made cEEG feasible for more patients with aSAH. cEEG provides a continuous measure of cerebral function with predictable responses to ischemia.<sup>284,286</sup> In addition, quantitative EEG software programs allow the expeditious review of condensed raw EEG data. This has made the real-time detection of adverse events such as seizures and DCI possible. Published criteria for predicting DCI are based on changes in cEEG spectral features, including decreasing alpha-to-delta power ratio, relative alpha power variability, epileptiform discharges, rhythmic and periodic ictal-interictal continuum patterns, and isolated alpha suppression.<sup>281–292</sup> A prospective observational study<sup>284</sup> assessed the

diagnostic accuracy of cEEG for DCI in patients with high-grade aSAH following the Standards for Reporting of Diagnostic Accuracy Studies.<sup>315</sup> The study protocol consisted of clinical neurophysiologists prospectively reporting prespecified EEG alarms: (1) decreasing relative alpha power variability, (2) decreasing alpha-to-delta power ratio, (3) worsening focal slowing, or (4) late-appearing epileptiform abnormalities. The diagnostic reference standard was DCI. EEG alarms occurred in 96.2% of patients with and 19.6% without subsequent DCI (1.9-day median latency; interquartile range, 0.9–4.1). Among alarm subtypes, late-onset epileptiform abnormalities had the highest predictive value.

4. Invasive neuromonitoring techniques have increasingly been used to detect DCI in patients with high-grade aSAH.<sup>293–305</sup> Pbt<sub>o2</sub> provides a surrogate measure of regional CBF and represents the balance among oxygen supply, diffusion, and consumption. Pbt<sub>o2</sub> has been found to help in the early detection of DCI and brain hypoxia.<sup>278,295,300</sup> Pbt<sub>o2</sub> probes can be inserted safely.<sup>299</sup> Cerebral microdialysis monitoring may detect metabolic changes in the extracellular fluid associated with ischemia.<sup>297,302,304</sup> The lactate/pyruvate ratio is a metabolic measure of cerebral oxygen supply and may serve as a biochemical marker of impending hypoxia/ischemia. Lactate/pyruvate ratio and glutamate concentrations have been correlated with DCI in patients with high-grade aSAH. A recent systematic review of 47 studies investigating invasive neuromonitoring (Pbt<sub>o2</sub>, n=21; cerebral microdialysis, n=22) found evidence that these techniques identify patients at risk for DCI.<sup>295</sup> A major disadvantage is that they provide information of the regional brain milieu; thus, placement in the highest-risk area for DCI may be important. Some evidence supports the safety and utility of bihemispheric cerebral microdialysis to enhance DCI detection.<sup>293</sup>

**Knowledge Gaps and Future Research**

- *TCD monitoring:* Insufficient evidence exists to determine whether TCD monitoring affects long-term clinical outcome. Further studies of the role of TCD in the management of aSAH are needed, in particular standardized interpretation parameters and how they influence treatment decisions.
- *cEEG monitoring:* Some, but not all, cEEG features such as evidence of new or worsening epileptiform abnormalities are associated with a sustained impairment in functional outcome. Insufficient evidence exists to determine whether treatment decisions based on cEEG monitoring affect long-term clinical outcome.
- *Invasive multimodal neuromonitoring:* Studies investigating invasive multimodal neuromonitoring suffer from

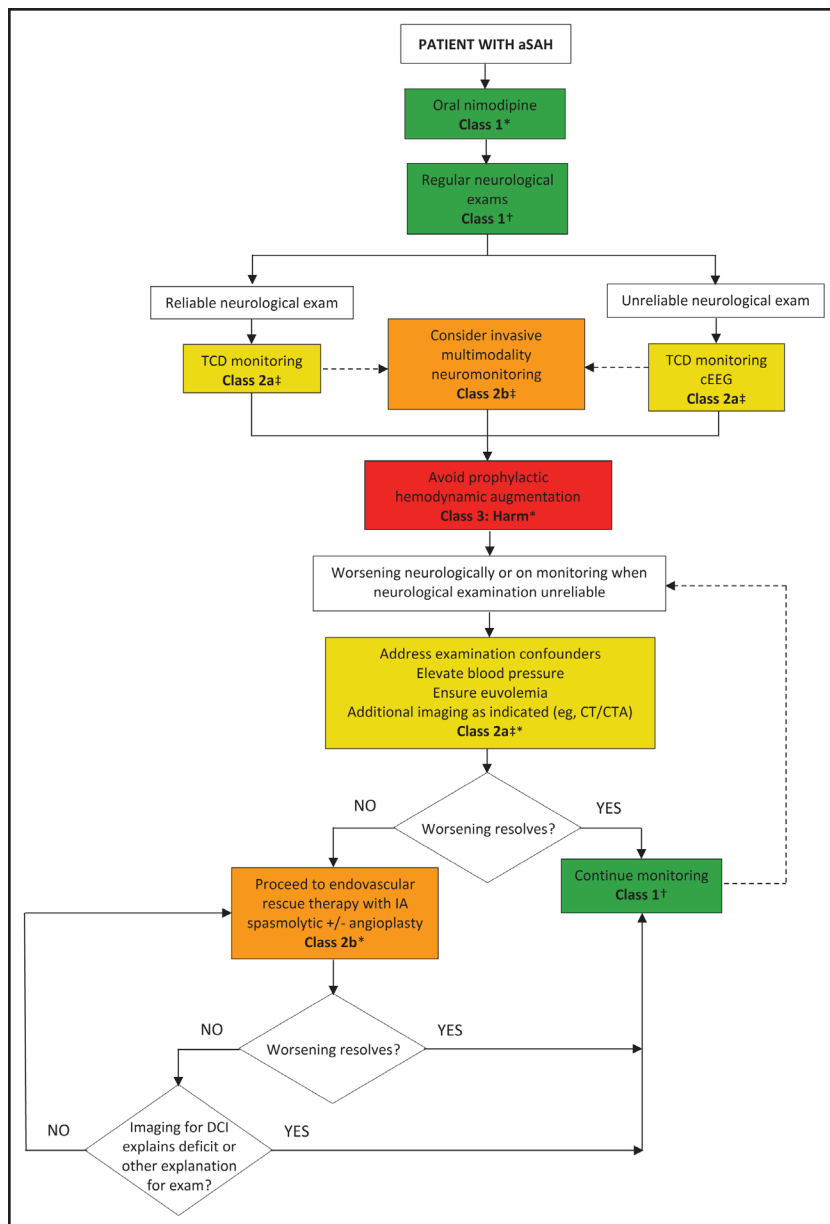
various sources of bias, including patient selection, lack of standardized timing of initiation of monitoring, and outcome ascertainment. In addition, insufficient evidence exists to determine whether invasive multimodal neuromonitoring affects long-term clinical outcome in patients with high-grade aSAH.

- *Electrocorticography:* Electrocorticography is a promising neuromonitoring technique to predict DCI but requires further validation and automatization.
- *Cerebral autoregulation:* Abnormal cerebral autoregulation has been associated with DCI. However, further validation of available algorithms and their real-time application are needed.
- *Blood flow monitoring:* Further studies are needed to determine whether CBF monitoring changes capture DCI (when TCDs become elevated or neurological examination changes) in a reliable manner to guide treatment decisions.
- *CTP:* Further validation of CTP thresholds to guide more invasive angiographic evaluation or medical therapy is needed.

**8.3. Management of Cerebral Vasospasm and DCI After aSAH**

Recommendations for Management of Cerebral Vasospasm and DCI After aSAH		
Referenced studies that support recommendations are summarized in online Data Supplement 10.		
COR	LOE	Recommendations
1	A	1. In patients with aSAH, early initiation of enteral nimodipine is beneficial in preventing DCI and improving functional outcomes. <sup>316–319</sup>
2a	B-NR	2. In patients with aSAH, maintaining euvolemia can be beneficial in preventing DCI and improving functional outcomes. <sup>320,321</sup>
2b	B-NR	3. In patients with aSAH and symptomatic vasospasm, elevating systolic BP values may be reasonable to reduce the progression and severity of DCI. <sup>322–325</sup>
2b	B-NR	4. In patients with aSAH and severe vasospasm, use of intra-arterial vasodilator therapy may be reasonable to reverse cerebral vasospasm and reduce the progression and severity of DCI. <sup>326–335</sup>
2b	B-NR	5. In patients with aSAH and severe vasospasm, cerebral angioplasty may be reasonable to reverse cerebral vasospasm and reduce the progression and severity of DCI. <sup>336–344</sup>
3: No benefit	A	6. In patients with aSAH, routine use of statin therapy to improve outcomes is not recommended. <sup>345,346</sup>
3: No benefit	A	7. In patients with aSAH, routine use of intravenous magnesium to improve neurological outcomes is not recommended. <sup>347,348</sup>
3: Harm	B-R	8. For patients with aSAH at risk of DCI, prophylactic hemodynamic augmentation should not be performed to reduce iatrogenic patient harm. <sup>189,211,349,350</sup>

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**Figure 3. A practical and evidence-guided approach to the management of patients with cerebral vasospasm and DCI after aSAH.**

Colors correspond to Class of Recommendation in Table 2. aSAH indicates aneurysmal subarachnoid hemorrhage; cEEG, continuous electroencephalography; CT/CTA, computed tomography/computed tomography angiography; DCI, delayed cerebral ischemia; IA, intra-arterial; and TCD, transcranial Doppler. \*Recommendation from Section 8.3, Management of Cerebral Vasospasm and DCI After aSAH. †Recommendation from Section 8.1, Nursing Interventions and Activities. ‡Recommendation from Section 8.2, Monitoring and Detection of Cerebral Vasospasm.

### Synopsis

For patients who survive initial aneurysmal rupture, DCI represents a major concern.<sup>306</sup> The angiographic presence of cerebral vasospasm as a cause of DCI is a major predictor of morbidity and mortality.<sup>89</sup> Undiagnosed and insufficiently treated cerebral arterial vasospasm was historically implicated as a major cause of death at autopsy after aSAH.<sup>351</sup> However, the mechanisms that lead to loss of brain tissue viability secondary to DCI are more complex than vasospasm alone. Proposed mechanisms for DCI include blood-brain barrier disruption, microthrombosis, cortical spreading depolarization/ischemia, and failure of cerebral autoregulation.<sup>352</sup> Therapy directed at vasospasm alone has had limited impact on DCI or mortality in patients with aSAH. Clearly, effective risk stratification, prophylaxis, detection, and treatment of DCI (Figure 3) represent an important frontier

in the management of aSAH. (See Section 8 for discussion of volume management and recommendation for hypervolemia.)

### Recommendation-Specific Supportive Text

1. Nimodipine is a dihydropyridine calcium channel blocker that was approved by the US Food and Drug Administration for clinical neurological improvement after aSAH. Continued enteral administration at a dose of 60 mg 6 times a day can be beneficial in preventing DCI and improving functional outcome, as originally published in the 1983 clinical trial<sup>353</sup> and confirmed in a meta-analysis of 16 trials involving 3361 patients.<sup>354</sup> Samseethong and colleagues<sup>318</sup> also found that continuous administration is valuable, but the ideal timing for when to begin nimodipine before the vasospasm window is debated.

Hernandez-Duran and colleagues<sup>317</sup> found that disruption of nimodipine was associated with a greater incidence of DCI ( $\rho=0.431$ ,  $P<0.001$ ); furthermore, an inverse correlation to DCI was shown if full dosing could be maintained ( $\rho=-0.273$ ,  $P<0.001$ ). Therefore, consistent administration is suggested even in the setting of nimodipine-induced hypotension that can be managed with standard medical interventions. However, if nimodipine causes significant BP variability, temporary stoppage may be necessary. Although nimodipine remains a therapeutic mainstay, it is important to acknowledge the age of the data guiding its use and limitations of repeating RCTs with the oral form of the medication now. Although studies of intravenous and intra-arterial nimodipine have been reported,<sup>355</sup> there are limited data to make any recommendation for these routes of nimodipine administration.

2. Maintenance of euvoolemia can be effective to prevent DCI and improve functional outcomes after SAH.<sup>356</sup> Gelder and colleagues<sup>321</sup> found that 58% of patients with documented volume depletion developed DCI. Hypervolemia is associated with worse outcomes and higher rates of complications (see Section 8).<sup>245,357–359</sup> Euvoolemia, not hypervolemia, should be targeted during intensive care and the vasospasm period.<sup>360</sup> Definitions of euvoolemia vary in the literature, and no clear standard exists. Use of central venous pressure alone is not reliable for assessing volume status.<sup>361</sup> Invasive measures of cardiac output have been used, including advanced hemodynamic monitoring with transpulmonary thermodilution.<sup>183,245</sup> The added importance of these monitoring techniques is uncertain. Euvoolemia is included as part of a goal-directed approach to therapy, as discussed previously (see Section 8). Crystalloid infusions to maintain euvoolemia have been supported in the literature.<sup>362</sup> With euvoolemia as part of goal-directed therapy, DCI was observed in 13% of the patients in the goal-directed therapy group and in 32% of the patients in the control group (odds ratio, 0.324 [95% CI, 0.11–0.86];  $P=0.021$ ) in 1 study.<sup>245</sup> Duangthongphon and colleagues<sup>320</sup> found that initiation of the euvolemic protocol reduced DCI from 44.2% to 7.7% (odds ratio, 0.10 [95% CI, 0.04–0.23];  $P<0.001$ ). Furthermore, mortality rates in patients with a good WFNS grade decreased from 16.3% to 8.8% (hazard ratio, 0.80 [95% CI, 0.28–2.28]). Maintenance of euvoolemia also reduces cardiac and pulmonary complications.<sup>363</sup>
3. BP variability is associated with less favorable neurological outcomes in SAH.<sup>364</sup> Clinically, hypotension can precede the development of focal neurological deficits in patients who are neurologically compensated otherwise. In the available

literature, the development of a focal deficit or a decrease in GCS is typically used to determine the presence of DCI, whereas criteria for patients with high-grade aSAH and limited clinical examinations are less certain. In a randomized trial of vasopressor administration, there was a trend toward maintained CBF during DCI in the treatment group. Serious adverse events (death, myocardial infarction, and cardiac arrhythmia) were higher but nonsignificant in the treatment group.<sup>323</sup> In a retrospective study, significantly more patients in the norepinephrine group exhibited neurological improvement compared with those in the phenylephrine group (94% versus 71%;  $P=0.01$ ) and were discharged to home or an acute rehabilitation facility (94% versus 73%;  $P=0.02$ ). The 2 groups experienced similar rates of complications.<sup>325</sup> The only RCT of induced hypertension in aSAH, HIMALAIA (Hypertension Induction in the Management of Aneurysmal Subarachnoid Haemorrhage With Secondary Ischaemia), was discontinued prematurely because of a lack of benefit for cerebral perfusion and poor enrollment, limiting the ability to interpret results. There was no difference in functional outcome, but the study was underpowered.<sup>322</sup> Observational data, including large, multiyear, multicenter retrospective data, indicate an improvement after induced hypertension in  $\approx 80\%$  of symptomatic patients.<sup>322,324</sup> Taken together, these data suggest that induced hypertension may be reasonable in patients with DCI.

4. A range of endovascular options exist for treating vasospasm.<sup>365,366</sup> Vasorelaxation/spasmolysis with intra-arterial vasodilators allows access to both proximal and distal cerebral vasculature. A range of agents, doses, and treatment durations exists. Each of these agents is further associated with side effects, including systemic hypotension, and no high-quality studies have compared them in a randomized fashion.<sup>367</sup> The benefit of these medications for DCI prevention/reversal and improved functional outcome and their comparative advantages or risks require future study. Papaverine, although a historically effective vasodilator, is generally avoided because of the risk of neurotoxicity.<sup>368</sup> Intra-arterial nimodipine is not available in all geographic regions.<sup>335</sup> Procedurally, systemic hypotension<sup>369</sup> and elevation of ICP due to vasodilation<sup>370</sup> are concerns during medication administration. Infusion through a cervical catheter seems reasonable, with intracranial microcatheter placement and infusion reserved for more severe cases.<sup>371</sup> Intermittent therapy is favored over continuous infusion of vasodilator, for both efficacy and complication profiles.<sup>372</sup> Intra-arterial infusions can be used in combination with angioplasty

techniques to target different levels of the cerebral vasculature.<sup>373</sup>

5. Angioplasty offers a mechanical option for improving perfusion in patients with severe vasospasm. Historically, angioplasty was performed with endovascular balloons and was confined to proximal vasculature. The choice between compliant and noncompliant balloons remains operator dependent.<sup>356</sup> A poor angiographic response to angioplasty is associated with recurrent vasospasm and risk of cerebral infarction.<sup>337</sup> Particular care must be taken with cerebral angioplasty given the high mortality associated with vessel rupture, although contemporary safety profiles are favorable. Limited direct comparisons exist between angioplasty and vasodilator therapy,<sup>360</sup> but data suggest greater durability in angiographic response after balloon angioplasty.<sup>336</sup> Combination therapy with intra-arterial vasodilator infusions allows access to the entire vasculature for diffuse spasm.
6. A recent meta-analysis by Shen and colleagues<sup>345</sup> found that among the 6 randomized aSAH trials for statin therapy, vasospasm was reduced but no significant benefit in DCI or mortality was observed. A proposed mechanism is the long-term dosing of statins predisposed to bacteremia in the aSAH population, thereby mitigating any potential benefit in vasospasm protection.<sup>374</sup> Thus, some groups are investigating shorter-duration therapy and combination therapies.<sup>375</sup> Current evidence indicates no benefit in outcomes based on prior dosing strategies; therefore, statins are not recommended as routine therapy in this population.<sup>376</sup>
7. Preclinical data suggested that magnesium sulfate could improve CBF and decrease vasospasm.<sup>377</sup> Clinical evidence found no benefit in terms of outcomes when intravenous magnesium sulfate was given.<sup>347</sup> Two meta-analyses of the available RCTs showed no benefit in terms of cerebral infarction or reduced mortality.<sup>378,379</sup> Some groups have argued that it is the concentration of magnesium in the CSF that is important compared with peripheral circulation, but this has yet to be validated. Current evidence therefore recommends against the routine use of magnesium sulfate to improve neurological outcomes for patients with aSAH.<sup>348</sup>
8. The peak risk for DCI and cerebral vasospasm is postbleed days 6 to 10 after aSAH. A prophylactic versus reactive approach to hemodynamic augmentation has been studied. Hemodynamic augmentation in the existing literature was achieved through various different methods, including intravenous colloids or various vasopressor medications (dobutamine, norepinephrine, milrinone, and phenylephrine). Patients treated with prophylactic hemodynamic augmentation had no difference in

neurological outcomes but a higher incidence of complications, including congestive cardiac failure. Permissive autoregulation seems a reasonable strategy given that in patients with aSAH developing DCI, there is a rise in BP values<sup>380,381</sup> that correlates with developing cerebral vasospasm. Recently, milrinone has been used for DCI prevention on the basis of limited and nonrandomized data. Available evidence suggests that the medication is well tolerated as an intravenous infusion through the period of peak DCI risk and may have a beneficial effect in preventing symptomatic vasospasm or DCI. Whether this effect is mediated through inotropy or cerebral vasodilation is unclear. The role of milrinone, although promising, requires further investigation.<sup>382,383</sup>

### Knowledge Gaps and Future Research

- *Risk stratification for DCI and evidence of functional improvement after DCI treatment:* The evidence for much of the therapy detailed previously is limited. A deeper understanding of DCI, accurate risk stratification, and the impact of current (and future) therapies are important needs.
- *Combination therapies:* Combination therapies may offer the best chance of success for DCI prevention, with ongoing investigation warranted. Platform and master protocol studies allow evaluation of multiple therapies simultaneously, and several effective examples exist. The role of this approach in aSAH is yet to be explored.
- *Utility of intra-arterial medication and devices:* High-quality, randomized data are required to understand the role of intra-arterial treatment for DCI, despite widespread use. Endovascular device evolution is expected, including the emergence of new angioplasty tools based on stent-retriever technology. Comparative research is an area of significant need.
- *Neural ganglia blocks:* Neural ganglia blocks with local anesthetic are being studied for symptom management in patients with aSAH. Given the potential for neural contributions to the neurovascular unit and vasospasm, the impact of such interventions on DCI requires additional study.
- *Antiplatelets and anticoagulation:* Antiplatelet and anticoagulation administration cannot be recommended for or against because of insufficient or conflicting evidence on use for the prevention of DCI.
- *Intrathecal medication delivery:* Intrathecal delivery of medications targeting heme degradation products (haptoglobin, deferoxamine, vitamin D) and various vasodilators (nimodipine, nicardipine, milrinone, cilostazol, magnesium sulfate, nitric oxide, and glyceryl trinitrate) has been evaluated to ameliorate DCI. Although preliminary data and animal studies

have shown promise, treatment in patients with aSAH requires further studies.

- *Drainage via lumbar drain or EVD:* Such drainage allows expedited removal of blood products from the CSF, with computational models showing effectiveness. Available trial data suggest that drainage through a lumbar drain reduces the incidence of DCI, despite trials being population and center limited. The role of a lumbar drain in aSAH is being actively investigated.
- *Cisternal fibrinolytic and spasmolytic medication:* These medications have recently been introduced to help clear subarachnoid blood in the CSF space. An ongoing double-blinded clinical trial is underway to detect effectiveness through administration by cisternal lavage.

### 8.4. Management of Hydrocephalus Associated With aSAH

Recommendations for Management of Hydrocephalus Associated With aSAH		
Referenced studies that support recommendations are summarized in online Data Supplement 11.		
COR	LOE	Recommendations
1	B-NR	1. In patients with aSAH and acute symptomatic hydrocephalus, urgent CSF diversion (EVD and/or lumbar drainage) should be performed to improve neurological outcome. <sup>236,384–387</sup>
1	B-NR	2. In patients with aSAH and hydrocephalus who require an EVD, implementation and adherence to an EVD bundled protocol that addresses insertion, management, education, and monitoring are recommended to reduce complication and infection rates. <sup>388–396</sup>
1	B-NR	3. In patients with aSAH and associated chronic symptomatic hydrocephalus, permanent CSF diversion is recommended to improve neurological outcome. <sup>397–400</sup>
3: No benefit	C-LD	4. In patients with aSAH, routine fenestration of the lamina terminalis is not indicated for reducing the rate of shunt dependency. <sup>401</sup>

#### Synopsis

Patients with aSAH are at risk of developing symptomatic acute or chronic hydrocephalus. The recommendations focus on interventions to improve neurological outcome after aSAH-associated acute or chronic hydrocephalus. In terms of the existing literature on the management of acute or chronic hydrocephalus, only 1 RCT<sup>402</sup> and 3 meta-analyses focus on risk factors.<sup>400,401,403</sup> The majority of the existing literature consists of nonrandomized case-control case series and case reports. The need for urgent EVD in the acute phase of hydrocephalus should be considered. The incidence and risk of ventriculostomy-associated infection range from <1% to 45%.<sup>389–391,393,395</sup>

Use of a targeted, bundled EVD management protocol has been identified as a best practice for prevention of ventriculostomy-associated infection and other associated complications.<sup>390–392,394</sup> Although the literature on the elements of a bundled protocol varies, the primary considerations should include a protocol that addresses insertion and technique, management, monitoring, and education.<sup>388–392,394,395</sup>

#### Recommendation-Specific Supportive Text

1. The risk of acute hydrocephalus after aSAH ranges from 15% to 87% in the acute stage.<sup>12,400</sup> aSAH with associated acute symptomatic hydrocephalus should be managed urgently by CSF diversion (EVD or lumbar drainage) to improve neurological condition.<sup>12,236,384–387</sup> Lumbar drainage of CSF after aSAH has been shown to reduce the prevalence of DCI and improve early clinical outcome.<sup>404</sup> (ICP monitoring may be considered in patients with suspected intracranial hypertension even in the absence of hydrocephalus.) The placement of an EVD or lumbar drain can be determined by hemorrhage or hydrocephalus CSF flow pattern. In terms of timing of EVD, no data exist; however, in centers without qualifications to perform aneurysm treatment, urgent stabilization of the patient, CSF diversion, and EVD placement, if needed, should be performed before transfer to a center with aSAH expertise.
2. The importance of developing and using an evidence-based EVD protocol for reduced complications is widely reported in the literature. A review of 10 bundled protocols from 1990 to 2013 evaluating the incidence of a protocol impact on infection rate before and after insertion found a significant reduction in ventriculostomy-associated infection with a preprotocol ventriculostomy-associated infection rate ranging between 6.1% and 37% to a postprotocol ventriculostomy-associated infection rate ranging from 0% to 9%.<sup>393</sup> This same review, along with others, summarized key practices for EVD insertion and maintenance bundles.<sup>390–394,396</sup> Aseptic technique and the use of antibiotic impregnated catheters are widely accepted as best practices to decrease CSF positive cultures and reduce rates of ventriculostomy-associated infection.<sup>390–396</sup> The place of insertion, inserting physician, type and size of catheter, and the antibiotic coating vary widely. Although the evidence suggests that reduced sampling and use of aseptic technique decrease rate of ventriculostomy-associated infection, there is not enough literature to support specific recommendations for this intervention.<sup>388–395</sup> EVD dressing management is also an important part of any bundle, but this is variable among organizations.<sup>390,393,394</sup> Table 4 outlines the

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**Table 4. Elements for an EVD Infection Control Bundled Protocol**<sup>388–395</sup>

Insertion and technique	Management	Monitoring and education
EVD setup	Type of dressing	Health care professional training (insertion and management)
Aseptic technique	Frequency of dressing change	Staff education and competency
Skin preparation	Flushing of EVD system	Monitoring number of EVD catheter days
EVD insertion location (ICU, OR, other)	CSF sampling frequency	Monitoring rates of infection
EVD insertion health care professional (neurosurgery, ICU, resident, APP)	CSF sampling technique	Uniform definition for ventriculostomy-associated infection
Catheter selection (size, antibiotic impregnated)	EVD manipulation	Use of EVD order panel
Procedure timeout	Catheter or system exchange	
	Nursing handoff	
	EVD clamping and weaning	
	Mobilization safety	

APP indicates advanced practice provider; CSF, cerebrospinal fluid; EVD, external ventricular drain; ICU, intensive care unit; and OR, operating room.

key components defined in the literature to be considered and included in a bundled EVD protocol.

3. According to the literature, aSAH-associated persistent or chronic shunt-dependent hydrocephalus occurs in 8.9% to 48% of patients with aSAH.<sup>400</sup> Significant predictors of shunt dependency include poor admission neurological grade, increased age, acute hydrocephalus, high Fisher grades, presence of intraventricular hemorrhage, rebleeding, ruptured posterior circulation artery aneurysm, anterior communicating artery aneurysm, surgical clipping, endovascular coiling, cerebral vasospasm, meningitis, and a prolonged period of EVD.<sup>12,397–400</sup> According to a large observational study, clipping and coiling of ruptured and unruptured cerebral aneurysms were associated with similar incidences of ventricular shunt placement for hydrocephalus.<sup>398</sup> Last, permanent CSF diversion was shown to improve neurological outcome after aSAH.<sup>12,397–400</sup>
4. A meta-analysis including 11 studies and 1973 patients revealed no significant association between lamina terminalis fenestration and a reduced incidence of shunt-dependent hydrocephalus.<sup>401</sup> The overall incidence of shunt-dependent hydrocephalus in the fenestrated cohort was 10% compared with 14% in the nonfenestrated cohort ( $P=0.089$ ). The RR of shunt-dependent hydrocephalus in the fenestrated cohort was 0.88 (95% CI, 0.62–1.24).<sup>401</sup>

**Knowledge Gaps and Future Research**

- *ICP monitoring:* Limited data exist on the benefit of ICP monitoring in patients with high-grade aSAH without hydrocephalus.
- *Rebleeding:* There are limited data on whether treatment of acute hydrocephalus before treatment of the ruptured aneurysm increases the risk of rebleeding. In addition, there are limited data on the management of hydrocephalus, comparison of

EVD and lumbar drainage, and risk of rebleeding before aneurysm treatment.

- *EVD bundles:* There are no clear best-practice EVD bundles identified to date in current studies. Variability within the literature includes, but is not limited to, type of antibiotic-coated catheter, frequency of CSF sampling, type and frequency of dressing changes, and weaning protocols. Future RCTs comparing bundled EVD protocols may help guide best practice for the management and care of EVDs.
- *Drainage management:* Weak or inconclusive data exist on how to manage continuous versus non-continuous CSF drainage and daily drainage volume through an EVD or lumbar drain for acute hydrocephalus.

**8.5. Management of Seizures Associated With aSAH**

**Recommendations for Management of Seizures Associated With aSAH**  
 Referenced studies that support recommendations are summarized in online Data Supplement 12.

COR	LOE	Recommendations
Patients who present without seizures		
2a	B-NR	1. In patients with aSAH and either fluctuating neurological examination, depressed mental state, ruptured MCA aneurysm, high-grade SAH, ICH, hydrocephalus, or cortical infarction, cEEG monitoring is reasonable to detect seizures. <sup>291,405,406</sup>
2b	B-NR	2. In patients with aSAH and high-seizure-risk features (ie, ruptured MCA aneurysm, high-grade SAH, ICH, hydrocephalus, and cortical infarction), use of prophylactic antiseizure medication(s) may be reasonable to prevent seizures. <sup>407–413</sup>
3: No benefit	B-R	3. In patients with aSAH without high-seizure-risk features (ie, ruptured MCA aneurysm, high-grade SAH, ICH, hydrocephalus, and cortical infarction), prophylactic treatment with antiseizure medication is not beneficial. <sup>392</sup>

Recommendations for Management of Seizures Associated With aSAH (Continued)		
COR	LOE	Recommendations
3: Harm	B-NR	4. In patients with aSAH, phenytoin for seizure prevention and/or antiseizure prophylaxis is associated with excess morbidity and mortality. <sup>407-411,413-415</sup>
Patients who present with seizures		
2a	B-NR	5. In patients with aSAH who present with seizures, treatment with antiseizure medications for $\leq 7$ days is reasonable to reduce seizure-related complications in the perioperative period. <sup>411,416,417</sup>
3: No benefit	B-NR	6. In patients with aSAH without prior epilepsy who present with seizures, treatment with antiseizure medications beyond 7 days is not effective for reducing future SAH-associated seizure risk. <sup>408,410,411</sup>

### Synopsis

Although the incidence of aSAH-associated seizures is relatively common, an understanding of the management of seizures is poorly supported by randomized, controlled studies. Since the 2012 aSAH guideline,<sup>12</sup> meta-analyses, single-center studies, and evaluations of next-generation antiseizure medications are the best sources from which to obtain management recommendations. Although seizure-like episodes have been reported in up to 26% patients with aSAH, a better understanding of the incidence of seizures has been attained with improved EEG monitoring capability. More recent studies suggest a lower seizure incidence of 7.8% to 15.2%.<sup>410,411,417</sup> Early and late postoperative seizures have an incidence of 2.3% and 5.5%, respectively.<sup>411</sup> In patients with aSAH who present with seizures, the use of antiseizure medications for  $< 7$  days is reasonable to reduce delayed seizure or hemorrhage risk.<sup>411,416,417</sup> Endovascular coil embolization compared with neurosurgical clipping seems to be associated with a lower incidence of late seizures.<sup>113,411</sup> In addition to the surgical management of aneurysms, clinical grade (HH grade  $\geq 3$ ), MCA aneurysm location, and hydrocephalus appear to be associated with an increased incidence of seizures.<sup>12,407,410,418</sup> It may be reasonable to use EEG monitoring in these cases or in those with a depressed neurological examination.<sup>405,406,412,417,418</sup> With these characteristics, prophylaxis may be reasonable. However, although prophylactic use of antiseizure medications may be reasonable when high-risk characteristics are present, the use of phenytoin appears potentially harmful and thus is not recommended for this purpose.<sup>406,407,410,419</sup>

### Recommendation-Specific Supportive Text

1. In prior guidelines for the management of aSAH,<sup>12,16</sup> clinical (HH grade  $\geq 3$ ) or radiographic (MCA aneurysm or ICH) findings correlated with elevated seizure incidence in the first 24 hours of the hemorrhage. With or without these characteristics,

depressed consciousness or a fluctuating neurological examination should raise clinical suspicion for nonconvulsive seizures, and monitoring for a period of 24 to 48 hours is reasonable. Patients in a coma may require a longer period of monitoring.<sup>291,405,417</sup> Recent technical advances (eg, remote monitoring) have made it possible to bring cEEG monitoring to more patients with aSAH. In addition, cEEG is now being used with quantitative techniques for the evaluation of DCI. The neurocritical care team should determine what EEG parameters (quantitative or otherwise) will be used to define seizures. Similar to the 2022 AHA/ASA guideline on the management of spontaneous intracranial hemorrhage,<sup>13</sup> we suggest the definition outlined by the American Clinical Neurophysiology Society: "epileptiform discharges averaging  $> 2.5$  Hz for  $\geq 10$  seconds ( $> 25$  discharges in 10 seconds) or any pattern with definite evolution and lasting  $\geq 10$  seconds."<sup>421</sup> Standardized criteria like this are especially important with the rising number of care extenders who are less experienced with EEG interpretation.

2. Although the concept of seizure prophylaxis in aSAH is significantly contested, the effect of an uncontrolled seizure on the rupture risk of an unsecured aneurysm is not. Prior guidelines have suggested that seizure prophylaxis may be considered in the immediate posthemorrhagic period ( $< 7$  days).<sup>12</sup> Subsequent meta-analyses have not produced sufficient evidence to support the routine use of antiseizure medications for the primary or secondary prevention of seizures after aSAH.<sup>408</sup> Framing this discussion is the benefit of reducing seizures, along with the adverse effects related to the historical use of phenytoin. A recent guideline addressing the management of patients with ICH suggested that there was no benefit in prophylactic antiseizure medications in the isolated setting of ICH.<sup>13</sup> However, the presence of MCA aneurysm, high clinical/radiological grade (HH grade  $> 3$  or Fisher grade III/IV), cortical infarction, or hydrocephalus has been associated with an elevated seizure risk.<sup>12,409,412,413</sup> Seizure prophylaxis may be reasonable when associated with aSAH and any of these findings.
3. Please refer to supporting text for Recommendation 2.
4. The data supporting the prophylactic use of antiseizure medications clearly lack the support of RCTs.<sup>408</sup> This is especially clear in patients who do not meet the clinical or radiographic characteristics that correlated with a higher risk for seizures (see prior supporting text). Nonrandomized data do highlight that although control of identified seizures can be achieved with phenytoin, the side-effect profile of this drug produces risks that outweigh the benefits of seizure prophylaxis in



many instances.<sup>422</sup> Studies that discuss the effect of antiseizure medications on global functional outcomes are inconclusive.<sup>407,423</sup> Poorer cognitive outcomes have been related to phenytoin administration. Whether this increased morbidity is related to an effect on DCI through metabolic competition with nimodipine or undiagnosed transaminase elevations is unclear. Use of newer-generation antiseizure medications that may be more effective or less toxic than phenytoin remains a topic of discussion.<sup>424</sup> A single-blinded randomized study of levetiracetam versus phenytoin demonstrated the same outcomes with respect to mortality or seizure control as evaluated by cEEG. Therapy with levetiracetam resulted in a lower incidence of adverse effects as evaluated by the Glasgow Outcome Scale–Extended and Disability Rating Scale. The excess morbidity associated with the use of phenytoin should prompt the use of alternative antiseizure medications.<sup>415</sup>

5. An important distinction in the management of patients with aSAH-associated seizure is whether seizure is a component of the patient presentation. This has resulted in literature and subsequent recommendations that are based on onset, early, and late seizures. Onset seizures occur at the time of the hemorrhage; early seizures occur during the first week; and late seizures are either postoperative or occur after 1 week. Onset seizures have been found to predict poor outcome after aSAH.<sup>417</sup> The possibility of preventing nonconvulsive status or rerupture of an unsecured aneurysm in the onset seizure group has led to a practice of administering antiseizure medications on presentation. Despite the absence of randomized data, providing antiseizure medications to patients with aSAH and onset seizures for a period of ≤7 days serves to minimize early complications related to the onset seizure in the perioperative period and decrease long-term medication side effects. Early and late seizures are distinct from onset seizures in that they are not the immediate result of the initial hemorrhage and potentially are related to the treatment modality or posthemorrhage infarct. Accordingly, both categories warrant longer-term antiseizure medication that should be managed in the postoperative period by a clinician who specializes in seizure management.
6. It is useful to conceptualize the management of aSAH-associated seizures into the management of perioperative risk and the management of delayed seizure risk. Although onset seizures may be best stabilized by early administration of antiseizure medication, there are no randomized data and little other literature to suggest that treatment for >7 days positively or negatively influences the

development of late seizures. Recent meta-analyses suggest that compared with short-term use (<3 days), the long-term use (>3 days) of prophylactic antiseizure medications in patients with aSAH has a similar effect on in-hospital seizure prevention but is associated with poor clinical outcomes.<sup>410</sup> These data cannot be applied to the patient group that has a preexisting seizure disorder.

### Knowledge Gaps and Future Research

#### Antiseizure medications:

- The impact of antiseizure medications, especially when given in a targeted and time-limited manner, on outcome in patients with aSAH associated seizures is not well defined.
- Although the improved side-effect profiles of newer-generation antiseizure medications may reduce the risk of primary or secondary prevention of seizures after aSAH, the benefit of routine administration of antiseizure medications is not supported by randomized evidence.
- *Medication-related morbidity:* The morbidity attributed to the routine use of phenytoin for seizure prophylaxis is well documented. The effect of this medication-related morbidity on the outcome of patients with aSAH and seizures is a significant confounding factor in the understanding of the true impact of seizures on the outcome of these patients. Randomized evidence evaluating the treatment of patients with aSAH with modern antiseizure medications is needed to guide optimal management.
- *Treatment modality:* Although the literature suggests that endovascular treatments are associated with a lower incidence of late seizures, a matched comparison between surgery and endovascular therapies over similar patient groups, aneurysm locations, and time periods does not exist to suggest a persistent beneficial effect on the incidence of late-onset seizures.

## 9. aSAH RECOVERY

### 9.1. aSAH Acute Recovery

Recommendations for aSAH Acute Recovery		
Referenced studies that support recommendations are summarized in online Data Supplement 13.		
COR	LOE	Recommendations
1	B-NR	1. In patients with aSAH, use of validated grading scores or patient-reported outcome measures prior to hospital discharge is recommended to screen for physical, cognitive, behavioral, and QOL deficits. <sup>39,425–431</sup>
1	B-NR	2. In patients with aSAH, use of validated screening tools in the postacute period is recommended to identify post-aSAH depression and anxiety. <sup>429,432</sup>

Recommendations for aSAH Acute Recovery (Continued)		
COR	LOE	Recommendations
1	B-NR	3. In patients with aSAH and depression, psychotherapy and pharmacotherapy are recommended to reduce symptoms of depression. <sup>429,432–435</sup>
1	B-NR	4. In patients with aSAH, use of a validated screening tool in the postacute period is useful to identify cognitive dysfunction. <sup>430,436–439</sup>
1	B-NR	5. In patients with aSAH, an early multidisciplinary team–based approach to treatment and rehabilitation is recommended to reduce LOS and identify discharge needs. <sup>231,440</sup>
2a	B-NR	6. In patients with aSAH and no other medical or neurological contraindications, early rehabilitation after the ruptured aneurysm is secured is reasonable to improve functional outcome and reduce LOS. <sup>267,441–445</sup>
2b	C-LD	7. In patients with aSAH in a coma, early use of neurostimulants may be reasonable to promote consciousness recovery. <sup>446–448</sup>
3: No benefit	A	8. In patients with aSAH without depression, fluoxetine therapy is not effective to enhance poststroke functional status. <sup>449–452</sup>

**Synopsis**

Although mortality from aSAH has improved over the past decades, the number of survivors who have deficits in multiple domains is increasing. These domains include function, cognition,<sup>430,436</sup> behavior,<sup>432</sup> difficulty in returning to work, and QOL, among others. Depression can occur in about one-third of aSAH survivors; anxiety and posttraumatic stress disorder can be seen in ≈15% to 20%,<sup>429,432,453</sup> and cognitive impairment can occur in 40% to 70%.<sup>430</sup> These impairments may persist in the long term, even in aSAH survivors who make a good functional recovery. Mortality and functional outcomes such as Glasgow Outcome Scale and mRS scores are commonly used as primary outcome measures in SAH RCTs, but there is variability in the timing of measuring functional outcomes.<sup>454</sup> Outcome assessments for other domains are rarely used as end points for SAH clinical trials. There is heterogeneity in the scales and timing of administration of scales for such outcomes in cohort studies. The postacute recovery phase, defined as the first 6 months of survivorship, should capture the cumulative burden of early brain injury, DCI, and hospital-acquired complications. Although global scales have been used, aSAH-specific outcome scales are needed to understand the true impact of illness. The SAH Outcome Tool, which includes 56 items, is the only disease-specific patient-reported outcome measure<sup>455</sup> but has not been implemented clinically because of a complex Rasch-based interval analysis.

**Recommendation-Specific Supportive Text**

1. Routine clinical examinations may not be sufficient to identify issues in function, cognition, behavior,

and QOL for aSAH survivors. Supporting data for validated scores come from all stroke survivors, but there are not enough data to recommend one score over another for aSAH. A systematic review (n=65 studies) found that functional assessments may not be sensitive enough to capture cognitive impairments for aSAH survivors.<sup>430</sup> In a narrative review, 1 in 3 stroke survivors was found to have poststroke depression, anxiety, and posttraumatic stress disorder.<sup>429</sup> Validated scores can help risk-stratify patients and detect such impairments, providing an opportunity for early intervention.<sup>426</sup> In a pooled analysis (n=10936), the SAHIT score was derived and validated with data available at the time of admission for predicting mortality and 3-month functional outcomes.<sup>39,427</sup> The Functional Recovery Expected After Subarachnoid Hemorrhage score, derived from a cohort of 1519 patients, included variables available within the first 48 hours to predict cognition and QOL at 1 year.<sup>425</sup> The Full Outline of Unresponsiveness score at admission and 7 days has been associated with mortality and functional outcomes at 1 and 6 months.<sup>428</sup> A review (n=20 studies) found that functional status, fatigue, cognitive complaints, depression, and coping mechanisms correlate with health-related QOL in aSAH.<sup>431</sup>

2. Although observational cohort studies have used several scales and variable timing of administering these scales, we recommended screening patients for depression and anxiety before discharge and in the postacute period to capture the cumulative impairments from both the initial aneurysm rupture and DCI. A review that summarized the best available evidence for poststroke depression, anxiety, and posttraumatic stress disorder found that the Hospital Anxiety Depression Scale and General Anxiety Disorder-7 have been used to screen for anxiety, and the Hospital Anxiety Depression Scale, Patient Health Questionnaire-2, Patient Health Questionnaire-9, and Beck’s Depression Inventory have been used to screen for depression. There is currently a lack of data on specific screening tools and timing of screening for poststroke depression and anxiety after aSAH.
3. Patients with aSAH and depression should be treated with appropriate psychotherapy and pharmacotherapy.<sup>429</sup> Prestroke depression, prestroke anxiety, age <50 years, living alone, socioeconomic hardship, and cognitive symptoms have been associated with higher risks of developing poststroke depression and anxiety.<sup>429,432</sup> Depression and anxiety may coexist in aSAH survivors. In a Cochrane review evaluating the safety and efficacy of selective serotonin reuptake inhibitors for poststroke depression, 75 studies were included

with differences in the dose, duration, and type of selective serotonin reuptake inhibitors used. Among patients with stroke who were on selective serotonin reuptake inhibitors, there was a reduction in the proportion of patients with post-stroke depression (RR, 0.75; 3 studies with high-quality evidence including 5907 participants).<sup>434</sup> In another review (n=8 trials), pharmacological interventions (n=1025 participants) decreased depressive symptoms at the end of treatment.<sup>433</sup> The use of selective serotonin reuptake inhibitors is appropriate for patients with preexisting symptoms of depression. Various psychosocial interventions that have been studied for stroke survivors include music therapy, mindfulness, and motivational interviewing. Although data supporting the efficacy of these interventions are limited, they are safe and may reduce the risk of poststroke depression.<sup>429</sup> In a meta-analysis of 23 studies including 1972 patients, cognitive behavioral therapy with or without pharmacological interventions was found to reduce depression, but the overall quality of the studies included in the review was low.<sup>435</sup>

4. In a systematic review that included 65 studies, acute hydrocephalus requiring CSF diversion, seizures, fever, prolonged ICU stay, and development of DCI were associated with cognitive impairments. Even in patients with good functional outcomes, 25% were found to have cognitive impairments, including memory issues, executive dysfunction, and inattention.<sup>436</sup> Screening for these impairments with validated screening tools may help refer patients to appropriate cognitive rehabilitation.<sup>430</sup> In a small comparative study (n=32), SAH survivors with good functional outcomes at 3 months were administered the Montreal Cognitive Assessment (MoCA), Mini-Mental Status Examination (MMSE), and neuropsychological tests. The MoCA was found to be more sensitive than the MMSE in diagnosing cognitive impairments. High performance on specific MoCA domains such as animal naming and abstraction was more closely associated with returning to work.<sup>438</sup> However, in a single-center study that included 180 patients, MoCA administered at 2 to 4 weeks did not predict functional outcomes at 1 year.<sup>457</sup> In a case-control study that included 288 patients with aSAH and 80 control subjects whose cognitive outcomes were assessed with MoCA at discharge, severe cognitive impairment was seen in 48.7% of aSAH survivors with good functional outcomes. The authors concluded that cognitive screening should be performed in all aSAH survivors, regardless of functional outcomes.<sup>439</sup>
5. A multidisciplinary team-based approach including neurocritical care, neurosurgery, rehabilitation specialists, physiatrists, physical therapists,

occupational therapists, and speech therapists can reduce LOS and improve patient outcomes. Such a team-based approach can guide timely decision-making and identify barriers to safe transition of care. In a single-center retrospective study, 174 patients with aSAH were enrolled in a physician-led multidisciplinary huddle to identify patient discharge needs and decrease ICU and hospital LOS.<sup>231</sup> Huddle team participants discussed anticipated discharge needs and possible discharge locations. Mean LOS times decreased to less than those cited in earlier studies, with mean hospital LOS dropping from 21.6 to 14.1 days. Transitions of care during acute hospitalization and to inpatient rehabilitation facilities require anticipatory guidance and a coordinated team approach between the acute care and rehabilitation teams. In a single-center study, 1190 patients with stroke were enrolled in an intervention with multidisciplinary team huddle rounds led by physiatrists and a virtual rounding tool leveraging electronic health record data.<sup>440</sup> Discharges for patients with acute stroke to inpatient rehabilitation facilities increased from 24.2% in 2018 to 30.1% in 2020. For hemorrhagic stroke, the average onset days to inpatient rehabilitation facilities decreased from 12 days in 2018 to 9.9 days in 2020.

6. Retrospective studies have shown that early rehabilitation after the ruptured aneurysm is secured is feasible without an increase in adverse events.<sup>267,441,442,444,445</sup> To decrease the potential risk of rerupture of a patient's aneurysm, bed rest would be safest before the aneurysm being secured.<sup>442,443</sup> Patients with DCI are usually not considered for participation in rehabilitation or ambulation while they are receiving BP augmentation and other therapies for DCI. No RCT has addressed the question of early mobilization in aSAH. The AVERT trial (A Very Early Rehabilitation Trial), which included 11 000 patients, did not include patients with aSAH and showed harm in patients with stroke undergoing ultraearly rehabilitation, defined as verticalization and ambulation within 24 hours of stroke onset.<sup>443</sup> In a meta-analysis<sup>442</sup> to evaluate the effect of early mobilization on functional outcomes in patients with stroke, 6 studies were included and showed no difference in functional outcomes between the early mobilization group and control group. Most of the studies in this review comprised patients with acute ischemic stroke and the few studies that included patients with hemorrhagic stroke did not provide subgroup analysis of patients with aSAH versus patients with ICH.
7. After other reversible causes of coma (eg, hydrocephalus, DCI, nonconvulsive seizures/status

epilepticus) have been treated, few interventions have been studied to promote consciousness recovery in the acute setting. Cognitive motor dissociation may be seen in 15% of patients with severe acute brain injuries, including aSAH,<sup>459</sup> as determined by machine learning with cEEG monitoring. This has prognostic implications because patients with cognitive motor dissociation have a higher likelihood of not only recovering consciousness but also having a better functional outcome at 1 year.<sup>459,460</sup> Although no RCTs have been conducted in patients with aSAH, the safety and possible efficacy of neurostimulants in aSAH can be extrapolated from literature on traumatic brain injury.<sup>448</sup> In a systematic review that included 20 retrospective studies, with only 11% of patients with aSAH—10 studies that included amantadine and 10 studies with modafinil—the authors found that it was reasonable to use neurostimulants to promote consciousness recovery. No pooled analysis was done because of the heterogeneity of the included studies.<sup>446</sup> The median time from aSAH to initiation of neurostimulants was ≈19 days. Although these studies show that the neurostimulants could be initiated safely in patients with stroke in the subacute period,<sup>446,447</sup> they did not address whether patients should undergo cEEG monitoring to evaluate for breakthrough seizures. Similarly, limited data exist to guide different combinations and doses of neurostimulants.

8. Fluoxetine has been studied extensively in patients with stroke to promote neuronal plasticity. This recommendation is based on multiple RCTs on fluoxetine<sup>449–452</sup> that included patients with ischemic and hemorrhagic stroke. All of these trials had similar designs, randomizing patients to receive fluoxetine 20 mg versus placebo. Patients in the intervention arm experienced an increased incidence of osteoporosis, fractures, and seizures with no improvement in motor recovery. Hence, fluoxetine is not recommended to enhance poststroke functional status. (In patients with preexisting depression on fluoxetine, this medication should be continued to treat depression.)

### Knowledge Gaps and Future Research

#### Multimodal prognosis and multidisciplinary follow-up:

- Multimodal prognostication needs to be studied to improve prediction of patient-centered outcomes. Studies should include clinical assessments, structural and functional imaging, biomarkers, electrophysiology, premorbid patient characteristics (eg, frailty, resilience, cognitive reserve, comorbidities), and complications during index hospitalization.
- In patients with high-grade aSAH, coma science, machine learning, and strategies to promote consciousness recovery need to be studied further.

- The frequency, timing, and types of screening tools and neuropsychological evaluations need to be studied. In addition, the role of early ICU rehabilitation, early supported discharge, telerehabilitation, peer-to-peer support groups, and post-ICU recovery clinics should be investigated in prospective studies.

#### Patient-family dyad support:

- Surrogate decision makers for patients with severe acute brain injury have several concerns, including prognostic uncertainty. Understanding the communication needs for the aSAH patient-family dyads, their role in shared decision-making, and use of decision aids remains an understudied area.
- Targeted interventions with the potential to reduce the survivorship burden for the patient-family dyad should be studied in RCTs.
- *Patient-reported and patient-centered outcomes:* Patient-reported outcome measures that include impairments in the functional, cognitive, and behavioral domains; return to work; positive psychological outcomes such as happiness; and the neurochemical, neuroendocrine basis of different impairments should be studied prospectively for meeting the needs of aSAH survivors. Incorporating patient-centered outcomes into standard outcome measures is important for aSAH survivors and their families.
- *Delirium and post-intensive care syndrome:* Delirium and post-intensive care syndrome can impact outcomes in patients with aSAH. Studies to better understand how ICU-related factors versus aSAH-related factors affect multidomain outcomes are needed.
- *Headache management:* Multimodal management of headaches, including pharmacological and nonpharmacological strategies, to minimize opioid use in the acute and postacute settings should be studied.

## 9.2. aSAH Long-Term Recovery

Recommendations for aSAH Long-Term Recovery		
Referenced studies that support recommendations are summarized in online Data Supplement 14.		
COR	LOE	Recommendations
1	B-NR	1. In adult patients with aSAH, screening and intervention for depression, anxiety, and sexual dysfunction are recommended to improve long-term outcomes. <sup>461–465</sup>
2a	B-NR	2. In patients with aSAH, it is reasonable to choose the MoCA over the MMSE to identify cognitive impairment. <sup>438,466,467</sup>
2b	B-NR	3. In patients with aSAH, counseling patients and caregivers on the high long-term risk of cognitive dysfunction can be beneficial to identify long-term needs. <sup>468</sup>

**Synopsis**

Long-term recovery extends beyond the first 3 months in individuals with aSAH. Neurological deficits can result in an increased incidence of depression, anxiety, and cognitive impairments, resulting in changes in familial roles and a negative impact on overall QOL for months to years after the initial injury. These recommendations focus on evaluations done for the purpose of identifying treatable cognitive and behavioral sequelae after aSAH. The variable yield of testing, including the potential influence of caregiver input, means that clinicians should exercise discernment when initiating treatment plans.

**Recommendation-Specific Supportive Text**

1. Identification and treatment of psychological and sexual sequelae can have a positive impact on QOL after aSAH. Screening tools to evaluate patterns of depression, anxiety, mobility, and activities of daily living detailed in the literature include the State Trait Anxiety Inventory, Hospital Anxiety and Depression Scale, Telephone Interview for Cognitive Status, and Barthel Index at 6 months, 1 year, and 2 years.<sup>462</sup> Use of the International Index of Erectile Function and the Female Sexual Function Index within the first 4 years<sup>465</sup> is recommended to evaluate sexual dysfunction in men and women, respectively. For long-term follow-up after aSAH, the Hospital Anxiety and Depression Scale can be used within the first 8.9 years<sup>463</sup> to examine anxiety and depression incidence, and the EuroQol-5D can be used within the first 10 years to evaluate health-related QOL.<sup>461</sup> Furthermore, the 36-item Short Form can be used within 4.7 years to evaluate outcomes in 8 domains: physical and social functioning, role limitations because of physical or emotional problems, bodily pain, mental and general health perception, and vitality.<sup>464</sup> Although the time frame for use of these screening tools is described here in accordance with the studies, their use can be considered beyond the suggested time frames for individual patients.
2. After aSAH, cognitive dysfunction is an important cause of disability. The most common cognitive complaints include mental slowness, memory, and attention difficulties. Although most deficits improve, ≈50% of patients with aSAH continue to experience cognitive difficulties for a year.<sup>469,470</sup> Both the MMSE and the MoCA are useful tools in the identification of cognitive impairment after aSAH. In comparative studies, the MoCA seems to have a higher sensitivity than the MMSE<sup>438,466,467</sup>; however, a lack of a baseline assessment in the aSAH population may contribute to test-result variability. Although the MMSE and MoCA have

the strongest evidence demonstrating efficacy in patients with aSAH, other assessment tools can be used, including formal comprehensive cognitive evaluation when indicated.

3. Dementia is one of the leading causes of both medical and social disability, which increases in patients with a history of stroke. In a large prospective 30-year study, which included 9872 SAH survivors and a 49360-person comparison cohort, the hazard ratio for dementia was 2.72 (95% CI, 2.45–3.06).<sup>468</sup> The median age at dementia diagnosis was 74 years for aSAH compared with 79 years for ICH and 81 years for ischemic stroke.

**Knowledge Gaps and Future Research**

- *Interventions to improve long-term outcomes:* Although we can improve recognition of the treatable causes of cognitive and behavioral sequelae after aSAH, more studies are needed to determine the best screening tools, timing, and effectiveness of interventions for these conditions.
- *Return to driving:* Return to driving may be a better predictor of long-term outcomes after aSAH than return to work. Data on visuospatial impairments affecting the ability to drive are limited, particularly in patients with aSAH, who may have multiple mechanisms of visual impairment.
- *Effect of post-SAH sequelae on the ability to return to work:* Determining the effect of headache, hydrocephalus, ventriculoperitoneal shunt malfunction, or epilepsy on subjective health impairment and the ability to return to work is a critical component of long-term recovery. The inability to work has implications at the patient, community, and societal levels.

**10. RISK FACTORS, PREVENTION, AND SUBSEQUENT MONITORING FOR RECURRENT aSAH**

**Recommendations for Risk Factors, Prevention, and Subsequent Monitoring for Recurrent aSAH**  
 Referenced studies that support recommendations are summarized in online Data Supplement 15.

COR	LOE	Recommendations
1	B-NR	1. In patients with aSAH who have undergone aneurysm repair, perioperative cerebrovascular imaging is recommended to identify remnants or recurrence of the aneurysm that may require further treatment. <sup>113,116,131</sup>
1	B-NR	2. In patients with aSAH who have undergone aneurysm repair, follow-up cerebrovascular imaging is recommended to identify recurrence or regrowth of the treated aneurysm, changes in another known aneurysm, or development of de novo aneurysm(s) that may require further treatment to reduce the risk of aSAH. <sup>116,131</sup>

**Table 5. Risk Factors for Rerupture and De Novo Aneurysms**

Characteristics	Risk factors
Rerupture	
Residual aneurysms	Incomplete aneurysm occlusion results in a higher risk of rerupture. <sup>106,107</sup> However, even completely obliterated aneurysms carry a risk of rerupture in the long term. <sup>476</sup>
Coiled aneurysms	Coiled aneurysms have a higher rate of incomplete occlusion <sup>130,477</sup> and recurrence <sup>478</sup> and therefore have a higher risk of rerupture. <sup>107</sup>
De novo	
Formation	Risk factors for de novo aneurysms in patients with ruptured aneurysms include younger age, family history, and multiple aneurysms. <sup>479–481</sup>
Growth and rupture	Risk factors for growth and rupture of de novo aneurysms include female sex, shorter interval to formation of the de novo aneurysm, multiple aneurysms, and larger size. <sup>481</sup>

### Synopsis

Patients with aSAH who have undergone aneurysm repair should undergo perioperative imaging after treatment to identify residual or recurrent aneurysms because they may result in rebleeding. Although large randomized clinical trials such as ISAT evaluated rebleeding,<sup>113,116,131</sup> intraoperative/postoperative imaging was a requirement only for endovascular treatment. Intraoperative and postoperative imaging in surgically clipped aneurysms has been studied but not specifically for the purpose of determining rebleeding risk in ruptured aneurysms.<sup>471–473</sup> The recommendations here are based on the occurrence of rebleeding and the assumption that rebleeding in treated aneurysms may be prevented by preemptively treating residual or recurrent aneurysms that are concerning.

### Recommendation-Specific Supportive Text

1. In ISAT, the risk of recurrent aSAH from the target aneurysms in the endovascularly treated and surgically treated groups in the first 30 days after treatment was 1.9% and 0.6%, respectively.<sup>113,116,131</sup> Of the 20 patients in the endovascular group who rebled within 30 days, 5 had no coils placed, 7 had incomplete occlusion, 3 were felt to be completely occluded, and 5 had thrombolytic therapy to treat a thromboembolic complication.<sup>116</sup> Thus, incompletely occluded aneurysms had a higher risk of rebleeding in the short term, and perioperative imaging is recommended to evaluate for remnants or recurrence that may require treatment.
2. In ISAT, the risk of recurrent SAH from the target aneurysms in the endovascularly treated and surgically treated groups at 30 days to 1 year was 0.6% and 0.4%, at 1 to 5 years was 0% and 0%, and at >5 years was 0.5% and 0.3%, respectively.<sup>131</sup> Long-term recurrence of endovascularly treated

aneurysms is increased with incomplete occlusion and with larger aneurysms.<sup>474</sup> In a meta-analysis, regrowth risk of clipped aneurysms was 2.1%/y in those with residuals and 0.26%/y in those without residuals.<sup>475</sup> Thus, aneurysms, especially those that are incompletely occluded, can recur over the long term and have the potential to rerupture. In addition to rerupture of the target aneurysm, the risk of recurrent SAH from another known, unknown, or de novo aneurysm after aSAH is 0% in the first 12 months, 0.3% at 1 to 5 years, and 0.3% at >5 years.<sup>116,131</sup> Delayed imaging is therefore recommended to identify residual or regrowth of the treated ruptured aneurysm and other known, unknown, or de novo aneurysm(s) (Table 5) that may require further treatment to reduce the risk of recurrent aSAH.

### Knowledge Gaps

- *Follow-up imaging and outcome:* Large trials such as ISAT showed that there is a risk of rebleeding after treatment of aneurysms and that there are incompletely treated aneurysms that may be predisposed to rerupture. However, data on how postoperative imaging affects retreatment or the risk of rebleeding are limited.
- *Timing and duration of follow-up:* Although the risk of recurrent SAH from a treated ruptured aneurysm remains nonzero even at >5 years, the optimal timing and duration of follow-up imaging remain unknown.

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## Disclosures

### Appendix 1. Writing Group Relationships With Industry and Other Entities (Relevant)–2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage

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(Continued)

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Dr. Chethan Rao also served as peer reviewer.

**Appendix 1. Continued**

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity or owns \$5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest (<\$5000).

†Significant (≥\$5000).

‡Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply.



**Appendix 2. Peer Reviewer Relationships With Industry and Other Entities (Comprehensive)—2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage**

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Appendix 2. Continued

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Stacey Q. Wolfe	Wake Forest Baptist Health School of Medicine	None	None	None	None	None	None	None
Richard Zorowitz	MedStar Health Research Institute	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

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