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INVITED COMMENTARY

Subarachnoid Hemorrhage Management Guidelines: Perspectives on Methodology and Clinical Guidance

Venkatakrishna Rajajee[1*] and Theresa Human[1,2]

The Neurocritical Care Society's 2023 "Guidelines for the Neurocritical Care Management of Aneurysmal Subarachnoid Hemorrhage" mark an important milestone, 12 years following the publication of the Neurocritical Care Society Multidisciplinary Consensus Conference recommendations on critical care management of patients following aneurysmal subarachnoid hemorrhage (aSAH) [1]. The landmark 2011 document was the first to provide evidence-based recommendations focused entirely on the critical care management of aSAH. The scope of the document was wide, with substantive recommendations covering every aspect of management in the intensive care unit. The authors of the 2023 guidelines should be commended for a rigorous and thorough update, as well as a willingness to critically examine key aspects of the data. The 2023 document differed in several aspects from the 2011 version. Given the society's shift toward use of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework of guideline development [2, 3], the scope was limited by design, with a focus on 12 management questions thought to be most impacted by new evidence and evolving management paradigms in the intervening decade. GRADE guidelines are developed around specific clinical questions in a population, intervention, comparison, and outcomes (PICO) format, narrowing the scope and shifting away from sweeping reviews of all aspects of disease management. A comprehensive and rigorous systematic review is then conducted to address each PICO question. Although the 2011 document was based primarily on a consensus-based approach, recommendations in the 2023 document were based on a rigorous systematic review and an evidence-to-recommendation process that placed a premium on high-quality evidence. This approach likely resulted in another notable difference from the 2011 document: the evidence base for 6 of 12 questions was judged as insufficient to support any recommendation for or against the intervention.

There are several factors within the GRADE process that contributed to the panel's inability to provide recommendations. The rigor of the GRADE methodology is achieved using the following process [3]: individual studies are evaluated for risk of bias [4], whereas the quality of the body of evidence for each question is evaluated within the major GRADE domains, which are risk of bias, inconsistency, indirectness, imprecision, publication bias, and factors that can increase the quality of evidence, such as a large magnitude of effect or a dose–response gradient [5].

GRADE recommends that panels "base the choice of outcomes on what is important, not on what outcomes are measured" [3]. Thus, the panel focused on clinical outcomes including functional outcome, mortality, the occurrence of delayed cerebral ischemia, and complications of therapy rather than surrogate physiologic outcomes. Studies with a focus purely on such surrogate outcomes were not used to inform recommendations. Additionally, although the GRADE evidence-to-recommendation process involves four major considerations—quality of evidence, balance of desirable and undesirable consequences, values and preferences, and resource use [6, 7]—the 2023 guidelines placed a premium on the

*Correspondence: venkatak@med.umich.edu
[1] Division of Neurocritical Care, Departments of Neurosurgery & Neurology, University of Michigan, Ann Arbor, MI, USA
Full list of author information is available at the end of the article

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quality of evidence. There is also little doubt that GRADE emphasizes the importance of randomized clinical trials. Five of six questions with specific recommendations in the 2023 guidelines—mostly against use of the intervention—were based on well-conducted large multicenter randomized clinical trials. It is also noteworthy that these interventions were the subject of initial optimism and enthusiasm based on observational phase 2 or smaller single-center studies until multicenter clinical trials demonstrated a lack of benefit. The negative outcome of these large multicenter trials that evaluated previously promising interventions argues in favor of the guideline panel's approach. We should note here that most of the questions addressed within the 2023 guidelines do not meet the clearly defined criteria for good (or best) practice recommendations within the GRADE framework because a significant body of evidence (albeit low quality for some PICOs) did exist and a systematic review of the body of evidence could be accomplished quite easily [8]. Finally, GRADE requires the consideration of the potential risks of therapeutic interventions, such as cardiac arrhythmias and pulmonary edema, as well as the potential benefits.

However, other perspectives on guideline development do exist that prioritize concrete and meaningful recommendations over the quality of evidence within the GRADE framework. The absence of randomized clinical trials may, in some situations, reflect a perceived lack of clinical equipoise. In the absence of high-quality clinical trials focused on measures such as functional outcome or mortality, consideration of all available clinical outcomes, including surrogate outcomes, may be important, even if the body of evidence is eventually judged to be of low or very low quality. Most importantly, GRADE methodology permits guideline panels to provide a recommendation even when the quality of evidence is low or very low, although such recommendations are typically weak or conditional [3, 6, 7]. Guideline panels must consider all four GRADE evidence-to-recommendation criteria carefully. The balance of desirable and undesirable consequences may favor use (or withholding) of the intervention despite a low quality of evidence, especially when experts are unsure about the existence of clinical equipoise. Withholding a recommendation should in fact be a rare occurrence when using the GRADE process. The most direct support for this point of view is provided by the GRADE handbook itself, which has this to say about a decision to forego a recommendation:

> *Clinicians themselves will rarely explore the evidence as thoroughly as a guideline panel, nor will they devote as much thought to the trade-offs, or the possible underlying values and preferences in the population. GRADE encourages panels to deal with their discomfort and to make recommendations even when confidence in effect estimate is low and/or desirable and undesirable consequences are closely balanced. Such recommendations will inevitably be weak, and may be accompanied by qualifications [3].*

The absence of concrete recommendations on key topics may be disappointing. *Neurocritical Care* will therefore publish a series of articles in the coming months that provide a comprehensive review of multiple aspects of aSAH management. The 2023 guidelines shine a spotlight on the paucity of major clinical trials addressing critical aspects of aSAH management. Our hope is that these guidelines will serve as an opportunity and spur multicenter collaboration on groundbreaking research.

Venkatakrishna Rajajee and Theresa Human are the co-chairs of the NCS guidelines committee.

Author details
[1] Division of Neurocritical Care, Departments of Neurosurgery & Neurology, University of Michigan, Ann Arbor, MI, USA. [2] Cumberland Pharmaceuticals, St. Louis, MO, USA.

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