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AASLD Practice Guidelines: The Past, the Present, and the Future

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The Past

Akin to the practice of medicine itself, judgments about evidence and recommendations are often complex and controversial. Since 1995, the American Association for the Study of Liver Diseases (AASLD) has commissioned numerous practice guidelines under the auspices of the Practice Guidelines Committee. These guidelines have provided a distillation of available knowledge regarding the diagnosis and treatment of a variety of liver-related medical conditions and procedures. Ideally, at defined intervals, these guidelines have been updated and refined in keeping with advances and new data in the medical literature. By endeavoring to be current, evidence-based, and independent, the guidelines have achieved wide credibility, relevance, and practical use in the care of patients with liver disease.

The Present

Guideline Development Evolution. Recently, refinements in the policies and procedures for practice guideline development have been instituted by the AASLD in response to advances in the science of guideline development which have been reshaping the guideline enterprise in general. Changes have especially focused on making the process more transparent and on providing direction in the management of potential conflicts of interest. In 2011, the Institute of Medicine report on trustworthy guidelines emphasized that guidelines be based on a systematic review of the existing evidence, developed by a multidisciplinary panel of experts considering important patient subgroups and patient preferences for therapies and alternative interventions in an approach that minimizes distortions and biases.[1] Guidelines should have the capacity to incorporate aspects of health care economics. Previously, multiple and different systems have been employed to rate the quality (level) of the evidence and the strength of recommendations that at times have appeared arbitrary and confusing, sometimes impeding clear communication and adoption. However, consensus has recently emerged regarding a more systematic approach to making judgments. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach for guideline development represents one such methodology that has been adopted by over 90 organizations since its formal inception in 2002.[2]

Adoption of GRADE. In response to these changes, the AASLD has adopted the GRADE approach for guideline development. This will be used selectively at first for key aspects of hepatology in which guidelines for patient care were judged to be most needed at the present time. Beginning in this issue of HEPATOLOGY, the first AASLD GRADE-based practice guidelines are published for the treatment of chronic hepatitis B, accompanied by three *de novo* systematic reviews specifically commissioned to provide supporting evidence.[3-6]

In broad terms, the GRADE approach provides a framework for defining clinically important questions and identifying the outcomes of greatest interest. This is followed by a systematic, rigorous, explicit, transparent, and unbiased approach to acquiring the body of evidence. Subsequently, the quality of the evidence (i.e., certainty in the evidence) is graded. This permits explicit determination of the strength of recommendations. Given the complexity and rigor of the approach, a methodologist-led group of epidemiologists, information scientists, and professional librarians from the Mayo Clinic Evidence-Based Practice Center trained in the GRADE framework was engaged to provide direction and extensive support to content experts.

GRADE—Defining the Questions. The approach of guideline development using GRADE starts with the identification of a newly expanded multidisciplinary group of content experts. All content experts satisfy the conflict of interest policies of the AASLD. Guidelines developed using the GRADE approach endeavor to

Abbreviations: AASLD, American Association for the Study of Liver Diseases; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; PICO, population, intervention, comparator, and outcome.

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Table 1. The GRADE Approach

1. Rating the Quality of Evidence

Study Design	Initial Rating of Quality of Evidence	Rate Down When	Rate Up When
Randomized controlled trial	High	Risk of bias	Large effect (e.g., RR = 0.5) or very large effect (e.g., RR = 0.2)
	Moderate	Inconsistency	Dose–response gradient
Observational	Low	Imprecision	All plausible confounding would increase the association
	Very low	Indirectness	
		Publication bias	

2. Determinants of the Strength of a Recommendation

- Quality of evidence
- Balance of benefits and harms
- Patient values and preferences
- Resources and costs

3. Implications of the Strength of Recommendation

Strong	• Population: Most people in this situation would want the recommended course of action, and only a small proportion would not. • Health care workers: Most people should receive the recommended course of action. • Policy makers: The recommendation can be adopted as a policy in most situations.
Conditional	• Population: The majority of people in this situation would want the recommended course of action, but many would not. • Health care workers: Be prepared to help patients make a decision that is consistent with their values using decision aids and shared decision making. • Policy makers: There is a need for substantial debate and involvement of stakeholders.

Abbreviation: RR, relative risk.

answer key clinical questions that challenge clinicians and their patients in daily practice. The questions are structured in terms of answerable and actionable recommendations, with the focus on clinically relevant outcomes. Ideally, questions and outcomes are driven by their importance in clinical practice, rather than the knowledge of the evidence in the medical literature. Questions are framed in a format describing the population, intervention, comparator, and outcome (PICO). By design and necessity, a limited number of PICO questions are developed in a focused clinical area that are considered critical for decision making. Questions are refined and agreed upon by the entire content writing group. The Practice Guidelines Committee approves the scope of the guideline and provides further peer review of the questions selected.

GRADE—Evidence Acquisition. After the PICO questions have been decided upon, a predefined systematic search of the medical literature is performed by the methodologist group. Existing systematic reviews that summarize the data can be used, if considered of acceptable quality based upon predefined criteria. In the absence of preexisting or adequate quality systematic reviews, *de novo* systematic reviews are commissioned to generate the evidence. A subset of the content experts (systematic review group) works in collaboration with the methodologists to critique and distill the available evidence.

GRADE—Rating the Quality (i.e., Certainty) of the Evidence. The quality of the evidence acquired is then rated (Table 1). The quality of evidence reflects the level of confidence that the estimates of an effect are adequate to support a particular recommendation. Studies are initially rated on the quality of evidence based on study design, e.g., high for a randomized controlled trial. Then, five domains of each study are evaluated that can lower the confidence in and quality of the evidence. These include limitations in study design (bias) and execution, inconsistency of results or heterogeneity, directness of evidence (i.e., how similar is the available evidence to the guideline question of interest), imprecision (small sample size or wide confidence intervals), and publication bias. Alternatively, three factors can raise confidence in and quality of the evidence derived from observational studies: a large magnitude of effect (relative risk of 2 or more), a dose–response relationship, and the presence of opposing, plausible confounders. For some of the key questions, sufficient comparative evidence is found and summarized in the systematic

reviews. For others, where evidence is sparse or absent, indirect and noncomparative evidence is identified.

Finally, evidence profiles (tables that summarize for each comparison and each outcome of interest, across all available studies, the absolute and relative effects of the intervention with the associated quality of evidence) are generated. The quality of evidence is rated as high (signifying a high confidence that the true effect lies close to that of the estimate of effect), moderate, low, or very low (indicating very little confidence in the effect estimate). By multiple face-to-face meetings, phone conferences, and electronic communication, the systematic review group supported by the methodologists comes to consensus on the quality of evidence for each group of studies addressing a particular PICO question. Again, the Practice Guidelines Committee provides further peer review of the systematic reviews and evidence profiles. Moreover, the systematic reviews were also subjected to an external peer-review process with final approval by the governing board of the AASLD.

GRADE—From Evidence to Recommendations. Using the systematic reviews and evidence profiles generated, the guidelines writing subset of content experts led by an appointed chair and cochair and assisted by a methodologist formulates recommendations based upon the evidence provided. It is worth noting that GRADE provides consideration of non–evidence-based factors that affect the strength of a recommendation. These may include the balance between benefits and harms, patients' values and preferences, and the use of resources. These considerations are included in the technical remarks section associated with each recommendation. Therefore, while the GRADE approach may still have subjective components, it demands to be transparent about this subjective judgment.

As a result of this approach, two strengths of recommendations emanate—either a strong recommendation or a conditional recommendation. For patients, a strong recommendation implies that most patients in this situation would want the recommended course of action and only a small proportion would not. For clinicians, this would imply that patients should receive the recommended course of action, with consistent benefits and few side effects. For policy makers, the recommendation could be adopted as a policy in most situations and potentially could be used as a quality measure. For strong recommendations, the recommendation is prefaced by "The AASLD recommends." In contrast, a conditional recommendation (also sometimes termed a "weak" recommendation) for patients would imply that the majority of patients in this situation would want the recommended course of action, but many would not. For clinicians making a conditional recommendation, the balance of benefits, harms, and burdens is uncertain; and they should be prepared to help patients make a decision that is consistent with their own values using a shared decision-making approach. For policy makers, this recommendation type could imply a need for substantial debate and involvement of all stakeholders and is likely insufficient to be used as a quality measure. For conditional recommendations, the recommendation is prefaced by "The AASLD suggests."

New Guideline Format

The new guideline format begins with the guiding principles and objectives, which include the PICO questions. A concise and general background is provided to bring context to the questions. Each question follows with an associated recommendation(s). Technical remarks accompany each recommendation, which serve to facilitate its implementation. This is followed by a brief, focused background section to each question. A summary of the evidence profile and rationale is then presented, ending with a section addressing areas of future research opportunities relevant to that question. Evidence profiles are available in the appendix of the guideline. Again, the Practice Guidelines Committee provides further detailed peer review of the guidelines with final approval by the governing board of the AASLD.

The Future

The first GRADE-based practice guidelines developed by the AASLD are published in this issue of HEPATOLOGY addressing treatment of chronic hepatitis B, accompanied by three *de novo* systematic reviews providing supporting evidence.[3-6] In marked contrast with prior guideline documents, this guideline is focused only on the treatment of chronic hepatitis B in specific patient populations. By adhering strictly to the GRADE approach, this guideline is built on a rigorous, systematic, and thorough review of the medical literature. Biases are minimized and transparency is emphasized throughout. A notable strength is the separation of the strength of recommendations from the quality of the evidence. Despite increased rigor, the guidelines development time line has been condensed to 18 months from concept to publication by an engaged all-volunteer group of content experts and Practice Guidelines Committee members.

Greater rigor in guideline development has demanded substantially greater use of time and resources, including the involvement of methodologists and information

scientists in the generation of this document. As a result, it is a more focused guideline than previous hepatitis B guidelines. Inevitably, some may lament the narrower scope of this publication. Through a practice of addressing topics in a modular format as started with the treatment of chronic hepatitis B, it is anticipated that other focused aspects of the topic will be addressed in a GRADE format in the future. In addition, by placing evidence profiles in a repository and with a systematic, transparent approach as the basis of recommendations, it is anticipated that the process of producing a future update to GRADE guidelines will be greatly simplified, facilitating more frequent guideline updates.

While developing every practice guideline following the GRADE approach is our ultimate goal, such a task will take the AASLD several years. Therefore, we have selected several areas in which guidelines are more urgently needed in the field (e.g., in the hepatitis B guideline, we chose antivral therapy to address first). Other topics not chosen for the GRADE approach at the present time (e.g., hepatitis B screening and vaccination) in which previous AASLD guidance exists will be summarized in a future companion document. The intention of such a document is to provide clinicians with a comprehensive and practical overview of the topic.

This use of the GRADE framework for practice guideline development represents a clear commitment by the AASLD to improve the overall quality of its practice guidelines and to deliver guidelines that are rigorous, transparent, and up to date. In doing so, this will further facilitate the delivery of high-quality care by clinicians to their patients with liver disease.

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