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Clinical Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients: Applying the GRADE System to Development of A.S.P.E.N. Clinical Guidelines

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(A.S.P.E.N.) Board of Directors

Introduction

As an interdisciplinary organization dedicated to advancing the science and practice of nutrition support therapy, the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) works vigorously to support quality patient care, education, and research in the fields of nutrition and metabolic support in all healthcare settings. To promote safe and effective patient care by nutrition support practitioners, the A.S.P.E.N. Board of Directors published "Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients" in 1993[1] and 2002.[2]

The format and methodology of the Clinical Guidelines (CG)s have changed over time, as a result of A.S.P.E.N.'s on-going efforts to improve the clarity and usefulness of the guidelines. The Institute of Medicine (IOM) has recently redefined Clinical Practice Guidelines as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."[3] To be trustworthy, IOM states that CGs should be based on a systematic review of existing evidence, be developed by a knowledgeable, multidisciplinary panel of experts with representatives from key affected groups, consider important patient preferences as appropriate, be based on a transparent process to minimize biases and conflicts of interest, provide an explanation between logical alternative care options and health outcomes, rate both quality of evidence and strength of recommendations, and be revised when important new evidence warrants.[3] In 2009,[4] rather than publishing a single, all-encompassing compilation of guideline recommendations, A.S.P.E.N. began to issue a series of focused CG documents addressing specific nutrition support practices in age and diagnostic groups. More recently, A.S.P.E.N moved to endorse the recommendations of a working group for the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE),[4-6] with modifications needed for nutrition support research while continuing A.S.P.E.N.'s rigorous review and approval processes. This paper provides the reader with an introduction to the GRADE methodology as applied to A.S.P.E.N Clinical Guidelines.

Background

The implementation of the GRADE methodology represents a further advance in the process of guideline development at A.S.P.E.N. The GRADE system was developed to standardize clinical guideline language and grade levels across documents from many professional organizations.

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Box 1. Organizations that have Endorsed or are using GRADE Methodology

- Agency for Healthcare Research and Quality (AHRQ)
- American Association for the Study of Liver Diseases
- American College of Chest Physicians
- American Gastroenterological Association (AGA)
- American Society for Gastrointestinal Endoscopy (ASGE)
- American Thoracic Society
- British Medical Journal
- CDC's Healthcare Infection Control Practices Advisory Committee (HICPAC)
- Cochrane Collaboration
- Endocrine Society
- Infectious Diseases Society of America
- Society of Critical Care Medicine (SCCM)
- Society for Vascular Surgery
- Surviving Sepsis
- Up-to Date
- World Health Organization (WHO)

Source: GRADE Working Group[7]

Box 2. Advantages of GRADE Methodology in Developing Clinical Guidelines

- Developed by a widely representative group of international guideline developers
- Clear separation between quality of evidence and strength of recommendations
- Explicit evaluation of the importance of outcomes of alternative management strategies
- Explicit, comprehensive criteria for downgrading and upgrading quality of evidence ratings
- Transparent process of moving from evidence to recommendations
- Explicit acknowledgment of values and preferences
- Clear, pragmatic interpretation of strong versus weak recommendations for clinicians, patients, and policy makers
- Useful for systematic reviews and health technology assessments, as well as guidelines

Adapted from: Guyatt GH, Oxman AD, Vist G, et al for the GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-926.[5]

Table 1. Evidence Table Question 1

Author (ref #) Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments

The number of professional organizations (Box 1) that have endorsed or are using GRADE since its introduction in 2004 attests to an emerging consensus regarding the applicability of this system across a broad spectrum of clinical circumstances.

In addition, GRADE separates into two distinct processes the evaluation of the body of evidence from the statement of a recommendation. Situations may exist, for example, in which consideration of clinical risk results in a strong recommendation despite relatively weak published evidence. The GRADE process is rigorous, provides the basis for clinically relevant recommendations, and includes tables of evidence with complete references that serve as a resource to readers seeking more in depth information. Box 2 provides further information regarding the advantages of the GRADE system over other approaches to development of CGs.

The A.S.P.E.N. Clinical Guidelines are based on a series of pertinent clinical questions that have been articulated by the authors, Clinical Guidelines Editorial Board, reviewers, and A.S.P.E.N. members. A careful search of the published literature is used to find the best available evidence to answer the question. Each identified article is then evaluated with its data entered into an Evidence Table for each question (Table 1). The GRADE system recognizes that the quality of the available evidence underlies our confidence in any recommendation that is made (Table 2).

Table 2. The Quality of Evidence and Definitions

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

Adapted from: Guyatt GH, Oxman AD, Vist G, et al for the GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-926.[5]

Clinical studies that are randomized controlled trials (RCT) are recognized as the strongest published clinical

Table 3. GRADE Criteria for Grading Evidence for Each Question

Type of Evidence	Initial Grade	Criteria to Decrease Grade	Criteria to Increase Grade	Final Quality Grade
RCT	High	Study Limitations Serious (−1) or very serious (−2) limitation to study quality Consistency Important inconsistency (−1) Directness Some (−1) or major (−2) uncertainty about directness Precision Imprecise or sparse data (−1) Publication bias High probability of reporting bias (−1)	Strong Association Strong evidence of association—significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1) Very strong evidence of association—significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2) Dose-response gradient Evidence of a dose response gradient (+1) Unmeasured Confounders All plausible confounders would have reduced the effect (+1)	High Moderate Low Very Low
OBS	Low			
Expert Opinion	Very Low			Very Low

Adapted from: Grade Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004, 328 (7454): 1490-1494.[8]

OBS, observational study; RCT, randomized controlled trial

Table 4. GRADE Table Question 1

Comparison	Result	Quantity, Type Evidence	Findings	GRADE of Evidence for Outcome	Overall Recommendation GRADE

evidence, however weaknesses in the design or implementation of the RCT will decrease the quality of that evidence. Many research reports with nutrition support outcomes are observational, either prospective or retrospective reports of clinical outcomes associated with a given therapy (but not randomized, controlled protocol-driven care). The evidence provided by these observational studies is strengthened, however, when the effects shown are strong, when the sample size is large, or when there is a dose-response relationship. The criteria in Table 3 are used to adjust the evidence grade based on assessment of the quality of study design and execution. When the only available evidence is expert opinion, most commonly from expert panels, then the quality of the evidence is very low.

After all references have been evaluated, the authors meet to decide by consensus the recommendation that should be made. Table 4 is the GRADE Table that summarizes the body of evidence to support a given recommendation and states the grade or strength of that recommendation. Table 5 describes the standard language and rationale for the grade assigned to a recommendation.

The A.S.P.E.N Clinical Guidelines process retains the many layers of internal, external, and legal review that have taken place in earlier guidelines documents. These combined efforts should result in transparent, evidence-based, safe and effective clinical guidelines for use in nutrition support decision-making, using the best available evidence at the time of the review.[3] An ongoing literature search has been implemented in order to monitor when new publications suggest a need to reevaluate a given topic and its clinical guideline.

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Table 5. Developing and Grading the Clinical Guideline Recommendation

Quality of Evidence	Weighing Risks vs. Benefits	GRADE Recommendation	Clinical Guideline Statement
High to very low	Net benefits outweigh harms	Strong	We recommend
High to very low	Tradeoffs for patient are important	Weak	We suggest
High to very low	Uncertain tradeoffs	Further research needed	We cannot make a recommendation at this time

Adapted from: Grade Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004, 328 (7454): 1490-1494.[8]

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