Contents lists available at ScienceDirect



Special Series

Making the GRADE in anaphylaxis management

Toward recommendations integrating values, preferences, context, and shared decision making

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Annals

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The Joint Task Force on Practice Parameters dedicates this review and the 2020 Anaphylaxis parameter update, systematic review, and GRADE analysis to Dr. Chitra Dinakar. While we grieve her loss, she continues to inspire us all as a brilliant and lasting example of compassion, kindness, and clinical excellence.

Disclosures: The Joint Task Force for Allergy Practice Parameters (JTFPP) members and work group members' conflict of interest disclosure forms can be found at www.allergyparameters.org. Jonathan Bernstein has received financial support from Sanofi Regeneron, AstraZeneca, Merck, Optinose, Takeda, CSL Behring, Biocryst, Pharming, the National Institutes of Health, and Taylor Francis; he is the editor in chief of the *Journal of Asthma*, INEOS medical immunosurveillance director, vice chair and lectureship chair of the American Academy of Allergy, Asthma, and Immunology (AAAAI) Foundation, chairman of AFI, American College of Asthma, Allergy, and Immunology (ACAAI) asthma chair, scientific chair, and Young Investigator Award chair and serves on the board of directors and Scientific

Key Messages

- The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) method of evidence appraisal and translation has emerged as a leading approach in guideline development because it facilitates a systematic transparent approach to evaluation of evidence certainty and translation of evidence to recommendations.
- Within GRADE, evidence is rated as high, moderate, low, or very low certainty within evidence profiles based on study design, risk of bias, imprecision, inconsistency, indirectness, and publication bias.
- The evidence to recommendation framework promotes consideration of patient values, balance between benefits and harms, resources required and cost-effectiveness of strategies considered, equity, acceptability, and feasibility.
- Although epinephrine is first-line pharmacotherapy for uniphasic and biphasic anaphylaxis, very low-certainty evidence suggests against the use of antihistamines or glucocorticoids as an intervention to prevent biphasic anaphylaxis.
- A conditional recommendation is a suggested course of action that must be understood within the context of patient-specific factors and for which a shared decision-making approach is appropriate.

ARTICLE INFO

Article history: Received for publication March 7, 2020. Accepted for publication March 9, 2020.

ABSTRACT

Objective: To review GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methods and discuss the clinical application of conditional recommendations in clinical guidelines, specifically in the context of anaphylaxis.

Data Sources: Articles that described GRADE, evidence synthesis, evidence to recommendation frameworks, and shared decision making were used to discuss conditional recommendations of the 2020 Anaphylaxis GRADE guideline.

Study Selections: A narrative review detailing concepts of GRADE and approaches to translate conditional recommendations to individualized and contextualized patient care.

Results: GRADE methods encourage a nuanced relationship between certainty of evidence and strength of recommendations. Strength of recommendation must incorporate key factors, including the balance between benefits and harms, patient values and preferences, and resource allocation (costs), with equity, feasibility, and acceptability also often included as considerations. GRADE guidelines provide recommendations that are characterized by directionality (for or against) and strength (strong or conditional). A conditional recommendation is tailored to context and primarily applied through a lens of patient preferences related to the likelihood of outcomes of importance and a shared decision-making approach. Although the 2020 Anaphylaxis GRADE guideline better informs the practice of anaphylaxis prevention through (1) identification and mitigation of risk factors for biphasic anaphylaxis and (2) evaluation of the use of glucocorticoid and/or antihistamine pretreatment, all GRADE recommendations, although directional, are conditional and as such should not be universally applied to every circumstance.

Conclusion: Clinical guidelines provide an important opportunity to critically appraise evidence and translate evidence to practice. Patients, practitioners, and policy makers should appreciate the strength of recommendation and certainty of evidence and understand how this affects guideline applicability and implementation.

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Intrommune and is supported by the Agency of Healthcare Research and Quality; has served on the advisory board of International FPIES Association, the Asthma and Allergy Foundation of America, and the National Peanut Board; and is associate editor of the Annals of Allergy, Asthma & Immunology. Caroline Horner has served as committee chair for the AAAAI Asthma Diagnosis and Treatment Interest Section, Interest Section Coordinating Committee, and In-Training Exam Coordinating Committee. Eddy Lang received an honorarium from the JTFPP for GRADE methods support. Jay Lieberman has received financial support from the ACAAI, Aquestive, Aimmune, DBV, Biotest Pharma, and Regeneron; is associate editor of the Annals of Allergy, Asthma & Immunology, vice chair for the ACAAI Food Allergy Committee, and medical director for Food Allergy Alliance of the MidSouth. John Oppenheimer has received financial support from DBV, TEVA, GlaxoSmithKline adjudication/data safety monitoring board, AstraZeneca, Novartis, and Sanofi; he is associate editor of the Annals of Allergy, Asthma & Immunology and AllergyWatch, an American Board of Internal Medicine (ABIM) council member, and American Board of Allergy and Immunology liaison to the ABIM (*r Oppenheimer had no role in designing CME learning objectives or CME questions), UpToDate reviewer, ACCP Cough Guideline

Introduction

Practice guidelines are an important vehicle for translating best evidence to patient care. However, in making and applying medical recommendations, guideline groups, practitioners, and patients must balance varying degrees of evidence certainty and make judgments about desirable and undesirable effects of treatments. The available evidence must also be considered in the context of individual values and preferences, within a framework of societal resource constraints. Currently, the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) method of evidence appraisal and translation has emerged as a leading approach in guideline development.¹⁻⁶ Understanding the significance of the strength of a recommendation is critical to appropriately applying guideline recommendations to patient care.

The Need for Clarity in Guidelines

Over the years, a myriad of well-meaning guideline development groups have added complexity to published recommendations through the use of nonuniform codes (eg, A, B, C, and so on), numbers (eg, I, II, III, and so on), and mixed letters and numbers (eg, Ia, Ib, IIa, and so on) to describe certainty of evidence and strength of recommendations. For example, when reviewing recommendations for oral anticoagulation in 2003, Schunemann et al⁷ noted that oral anticoagulation for patients with atrial fibrillation and rheumatic mitral valve disease received a confusing array of descriptions from various groups: class I based on level B evidence by the American Heart Association, grade C recommendation based on level IV evidence by SIGN², and 1C+ by the American College of Chest Physicians. To introduce clarity to guideline systems, in 2000, the GRADE Working Group was established to create a rating system in which certainty (quality) of evidence could be transparently and independently described together with strength of recommendations.²

Evaluating Certainty of Evidence

Compared with prior approaches to evidence appraisal, GRADE creates explicit processes for evaluating the broad evidence base on a specific, structured, and answerable clinical question. GRADE allows a transparent description of evidence certainty, which is a complementary consideration to the strength (and direction) of any recommendation made. The GRADE approach has received wide endorsement because it applies a more cautious and realistic lens onto the evaluation of research, which is not uncommonly revealed for its limitations.^{2–6} Indeed, even the outcomes informed by randomized clinical trials can have significant weaknesses (eg, indirectness, imprecision, low number of events, and various types of bias).⁸

In the GRADE approach, randomized controlled trials begin the evaluation process as high certainty, whereas observational studies begin as low certainty. Evidence may be downgraded by one

Table 1	
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Certainty	Meaning
High	The true effect probably lies close to the estimated effect
Moderate	The true effect is likely to be close to the estimated effect, but there is a possibility tha it is substantially different
Low	The true effect may be substantially different from the estimated effect
Very low	The true effect is likely to be substantially different from the estimated effect

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

certainty category for risk of bias, imprecision, inconsistency, indirectness, and publication bias.^{1,8} Through this process, evidence certainty is clearly and simply described as very low, low, moderate, or high (Table 1). Each domain is critically evaluated.

Risk of Bias

Study limitations that may affect risk of bias include lack of allocation concealment, lack of blinding, large losses to follow-up, failure to adhere to an intent-to-treat analysis, or failure to report outcomes.^{1,9}

Imprecision

Certainty ratings may be downgraded when studies demonstrate wide CIs crossing the null effect or when few events or few patients lead to inadequate optimal information size.^{1,9}

Inconsistency

Inconsistency must be considered when there are widely differing estimates of treatment effect across studies, suggesting significant variability in the effect of a treatment or strategy across populations.^{1,9}

Indirectness

There are 2 major types of indirectness that GRADE evaluates: indirectness of comparator (eg, drug A vs placebo and drug B vs placebo as opposed to drug A vs drug B) and indirectness of population, intervention, or outcome (eg, length of stay or readmission as opposed to clear reporting of biphasic anaphylaxis).^{1,9}

Publication Bias

Failure to publish negative results can be more difficult to detect, but an evidence base limited to a small number of trials or only industry-funded studies can raise suspicion. Evaluation of funnel plots (eFig 1) and documentation of methods, such as searching abstracts and gray literature, can allow guideline groups to assess for bias in this regard.^{1,9}

Notably, GRADE also allows for nonrandomized controlled trial evidence to be upgraded in the setting in which (1) there is a large magnitude of effect, (2) a dose-response gradient is evident, or (3) all plausible confounding would reduce a demonstrated effect (ie, all uncertainty would only lead to an underestimation of benefit or overestimation of harm).^{1,9} In a GRADE guideline, the reader is able to easily ascertain these effects by evaluating the evidence profiles, which present the effect of these factors as they relate to a variety of outcomes.¹⁰ These outcomes are rated as being of critical, important, or limited importance.^{8,9}

A GRADE guideline differs from a systematic review in the determination of the certainty of evidence. In systematic reviews, authors rate the certainty of evidence reflecting their confidence that the estimate of effect is correct. However, guideline writing groups define the certainty of evidence level as reflecting the extent to which their confidence in an estimate of effect is adequate to support a particular recommendation. GRADE incorporates judgment and some degree of subjectivity in arriving at both the certainty of evidence and the strength of the recommendation. GRADE is not guaranteed to ensure reproducible judgments by a different guideline panel reviewing the same evidence, but the explicit judgments made by the guideline panel are made transparent to the end user.¹¹

Understanding the Evidence to Recommendation Framework

Simply understanding the certainty of evidence is not sufficient to make guideline recommendations on a population level. In addition to evidence certainty, strength of recommendation must



Strength (and directional) of Recommendation

Figure 1. The balance of strong and conditional recommendations. In addition to evidence certainty, strength of recommendation must incorporate a balance between benefits and harms, patient values and preferences, resource allocation (costs), equity, feasibility, and acceptability. These considerations are explicitly evaluated and the balance of desirable and undesirable effects considered to reach a strong or conditional recommendation for or against a course of action. Reprinted with permission from Brozek et al.¹³

incorporate a balance between benefits and harms or burdens, patient values and preferences, resource allocation (costs), equity, feasibility, and acceptability (Fig 1).^{1,12,13} Cost-effectiveness can be an important aspect of the evidence to recommendation framework, but depending on the balance of other factors, a therapy or strategy may still be considered contextually even if it is not cost-effective (often in the setting of shared decision making).^{14,15} Equity is considered in the evidence to recommendation framework with specific judgments made with regard to how recommendations may affect underserved, socioeconomically disadvantaged, and other populations.¹⁶ In a GRADE document, the reader can find these assessments described in an evidence to recommendation

Table 2

Strong	vs	Conditional	Recommend	lations
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Strength of recommendation	Meaning
Strong	 For patients—most people in your situation would want the recommended course of action and only a small proportion would not; request discussion if the intervention is not offered For practitioners—most patients should receive the recommended course of action For policy makers—the recommendation can be adopted as a policy in most situations
Conditional (suggest)	 For patients—most people in your situation would want the recommended course of action, but many would not For practitioners—you should recognize that different choices will be appropriate for different patients and that you must help each patient to arrive at a management decision consistent with her or his values and preferences For policy makers—policy making will require substantial debate and involvement of many stakeholders

framework in which research evidence and additional considerations are summarized to reach recommendations stated as *for* or *against*. A qualifier is added in the GRADE system to describe whether the recommendation is strong (most patients, practitioners, and policy makers would adopt the course of action) or conditional (a navigational signal that preference-sensitive care is needed and variation in following the recommendation is appropriate, depending on situational context) (Table 2).^{8,12} In the ideal world, patient values, feasibility, and acceptability have been objectively studied. However, in the real world of allergy and immunology (and many other areas of medicine), that is usually not the case and the expert panel or guideline group must use subjectivity: their collective expert opinion (and expert evidence based on patient interaction and documentation) to reach the best conclusions.

A strong recommendation is typically associated with high or at least moderate-certainty evidence; however, in situations of high confidence of some critical outcomes (ie, benefits) but low confidence in others (ie, harms), a conditional recommendation is appropriate.⁸ Conversely, some situations exist in which a strong recommendation may be justified in the face of low or very low-certainty evidence, such as when low-certainty evidence suggests benefit in a life-threatening situation (eTable 1).⁸

After critical appraisal of the evidence base on a topic, guideline groups often realize that the certainty of evidence and situational context do not support a strong recommendation. However, guidelines are most useful if they are able to make recommendations for (or against) a treatment or strategy (even if conditional) as opposed to making no recommendation at all or simply calling for further research.¹⁷ In the face of very-low- or low-certainty evidence, provided an explicit framework is used, a conditional recommendation based on sparse evidence neither precludes nor preempts further research.^{12,17} Such conditional recommendations are made with the acknowledgment that with the evolution of medical science, best practice recommendations may change and

that in the context of a conditional recommendation, individual care will vary based on unique patient circumstances.¹⁷

Limitations of GRADE

The benefit of GRADE, and a reason it has been widely adopted, is because it is easily understood and transparent^{3-6,18}; however, GRADE has some limitations. Some might argue that GRADE's critical eye makes it somewhat nihilistic because high-ranking evidence and strong recommendations tend to crumble when GRADE is used. However, GRADE is useful when the evidence is critically appraised and found to be of low or very low certainty because this cautions us to keep in mind that if the ideal studies were to be performed, the conclusions may or may not fall within the range of the conclusions of the prior literature.⁹ Invariably, guidelines that move to GRADE almost always ascertain their evidence base to be less certain than previously believed; thus, there is a move to conditional recommendations (still recommendations with a given direction) but away from strong recommendations.¹² Indeed, many would see this as representing progress because enthusiasm is reigned in, and realism prevents the recommendation cart from being placed ahead of the evidence horse.

Completing a GRADE document entails a high degree of dedicated effort and methodologic expertise across a wide range of domains, often including the ability to perform and complete systematic reviews, meta-analyses, evidence synthesis and critical review, cost-effectiveness analyses, stakeholder engagement, and directed, iterative, guideline group discussion, consensus, and rational decision making.^{1,12} Although GRADE allows focused effort to address specific questions, traditional practice parameters can complement GRADE guidelines by providing a broader perspective on a topic and offering advice on best practice.¹⁸

Communicating Best Practice

The Joint Task Force on Practice Parameters (JTFPP) has been producing GRADE documents since 2017, with GRADE documents produced or in development for rhinitis, anaphylaxis, eosinophilic esophagitis, diagnostic testing for peanut allergy, chronic sinusitis, and atopic dermatitis.¹⁸ Guidelines are publicly available on the JTFPP website (https://www.allergyparameters.org), which also provides helpful material on resources to understand GRADE.¹⁸ Although GRADE guidelines are an important aspect of JTFPP work, the task force continues to also develop traditional practice parameters familiar to practicing allergists.¹⁸

From a more multidisciplinary perspective, the National Guideline Clearinghouse (NGC) was a home for the many guidelines developed by more than 100 different medical guideline groups, but its funding from the Agency for Healthcare Research and Quality expired on July 16, 2018, and has not been renewed.¹⁹ To be included as an NGC clinical guideline required strict inclusion criteria, and NGC guidelines had to be based on a systematic review of the literature with a clear synthesis of evidence to reach systematically developed statements, including recommendations.¹⁹ With the closure of the NGC, the Alliance for the Implementation of Clinical Practice Guidelines was formed as a nonprofit clinical guideline dissemination resource and contains an archive of NGC guidelines.²⁰ The Appraisal of Guidelines for Research and Evaluation tool is a useful publicly available checklist that allows the reader to evaluate the scope and purpose of a guideline, stakeholder involvement, methodologic rigor, clarity of presentation, applicability, and editorial independence of workgroup and task force guidelines.²¹ In determining whether a GRADE approach has been used in a guideline, it is important to evaluate that guideline groups have performed key steps because many guidelines may indicate GRADE methods but not fulfill minimum GRADE criteria (eTable 2).⁸

Anaphylaxis: A Case Study in Making Conditional Recommendations

The 2020 Anaphylaxis GRADE guideline from the JTFPP focused on questions to better inform the practice of anaphylaxis prevention through (1) identification and mitigation of risk factors for biphasic anaphylaxis and (2) evaluation of the use of supplemental glucocorticoid and/or antihistamine premedication.²² The workgroup developed a list of 5 key clinical questions using the PICO (Patient, Intervention, Comparator, and Outcome) method.²³ In the guideline, every GRADE recommendation was conditional. Notably, this did not indicate an absence of evidence to inform practice. Although overall evidence was very low certainty, the meta-analysis of question 1 involved 2308 individuals, question 2 involved 21,130 individuals, question 3 involved 4009 individuals, question 4 involved 20,128 individuals, and question 5 involved 25,395 individuals.²²

A systematic review was performed with the assistance of medical librarians using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials, and each article identified was reviewed by at least 2 task force or workgroup members for inclusion or exclusion.²² GRADE recommends that systematic reviews and meta-analyses form the basis of making health care recommendations, using forest plots to summarize effect size, uncertainty, and heterogeneity²⁴ (Table 3).⁸ Subsequently, evidence certainty was evaluated, evidence profiles were constructed (Fig 2), and an evidence to recommendation framework explored, discussed, and presented as a summary of judgments (Table 4).

Key Findings of the 2020 Anaphylaxis GRADE Guideline

Question 1: What risk factors should practitioners take into consideration in determining the likelihood of biphasic anaphylaxis?

Recommendation 1: The guideline suggests that a practitioner incorporate severity of anaphylaxis presentation and/or the administration of more than 1 dose of epinephrine for the treatment of initial anaphylaxis as a guide to determining a patient's risk for developing biphasic anaphylaxis. Conditional recommendation; certainty rating of evidence: very low²²

Recommendation 2: The guideline suggests in favor of extended clinical observation in a setting capable of managing anaphylaxis (to detect a biphasic reaction) for patients with resolved severe anaphylaxis and/or those who need more than 1 dose of epinephrine. Conditional recommendation; certainty rating of evidence: very low²²

Question 2: Should antihistamines and/or glucocorticoids be used to prevent biphasic anaphylaxis?

Recommendation: The guideline suggests against glucocorticoids or antihistamines as an intervention to prevent biphasic anaphylaxis. Conditional recommendation; certainty rating of evidence: very low²²

Question 3: Should antihistamine and/or glucocorticoid premedication be used to prevent index hypersensitivity/infusion reactions to chemotherapy?

Recommendation: The guideline suggests in favor of administering glucocorticoids and/or antihistamines to prevent anaphylaxis or infusion-related reactions when indicated for specific agents in chemotherapy protocols. Conditional recommendation; certainty rating of evidence: very low²²

Question 4: Should antihistamine and/or glucocorticoid premedication be used to prevent recurrent hypersensitivity reactions to radiocontrast media?

Table 3

Glossary of Terms Used in GRADE

Glossary

GRADE: The Grading of Recommendations Assessment, Development, and Evaluation framework provides an explicit, transparent, and systematic approach to assess certainty of evidence and translate evidence to recommendations to make clinical practice recommendations.

PICO: The Patient, Intervention, Comparator, and Outcome method allows clear framing of research questions to specify patient (or population), intervention, comparator, and outcome.

GRADE handbook: The GRADE Working Group began in 2000 to develop a systematic method for guideline development. The GRADE handbook describes the detailed process of rating and summarizing best evidence and applying GRADE.

Evidence profile: The GRADE evidence profile provides detailed information, including outcomes, number of studies, study design, risk of bias, inconsistency, indirectness, impression, publication bias, relative risk, absolute risk, overall certainty of evidence, and importance of each outcome.

Certainty of evidence: Also described as quality of evidence, certainty of evidence can be graded as high, moderate, low, and very low. In general, randomized controlled trials begin as high-certainty evidence, whereas observational studies begin as low-certainty evidence. Factors that reduce evidence certainty include limitations in study design, inconsistency of results, indirectness of evidence, imprecision, and publication bias.

Risk of bias: Study limitations that may affect risk of bias include lack of allocation concealment, lack of blinding, large losses to follow-up, failure to adhere to an intent-to-treat analysis, or failure to report outcomes.

Imprecision: Certainty ratings may be downgraded when studies demonstrate wide CIs crossing the null effect or when few events or few patients lead to inadequate optimal information size.

Inconsistency: Inconsistency must be considered when there are widely differing estimates of the treatment effect across studies, suggesting significant variability in the effect of a treatment or strategy across populations.

Indirectness: There are 2 major types of indirectness that GRADE evaluates—indirectness of comparator (eg, drug A vs placebo and drug B vs placebo as opposed to drug A vs drug B) and indirectness of population, intervention, or outcome.

Publication bias: Failure to publish negative results can be more difficult to detect, but methods such as searching abstracts and gray literature, an evidence base limited to a small number of trials or only industry-funded studies, and use of funnel plots can allow guideline groups to assess for bias in this regard.

Meta-analysis: A quantitative systematic analysis that combines and synthesizes scientific studies related to a specific topic and develops a summary estimate. Analyses may be performed under assumptions of homogeneous groups (fixed-effect model) or heterogeneous groups (random-effects model). Compared with a fixed-effect model, a random-effects model is more influenced by smaller studies with wider Cls. However, the assumptions underlying a fixed-effect analysis are often unrealistic.

Estimate of effect: The observed relationship between an intervention and an outcome that may be expressed in relative or absolute terms.

Heterogeneity and variance: Heterogeneity, a measure of whether findings are due to chance variation or population variation, can be quantified using the l^2 statistic. l^2 values greater than 50% can signify large variance between studies. The τ^2 is another measure of heterogeneity that relates to the SD of true effects and must be interpreted in the context of the overall estimate. The DerSimonian-Laird method is the most widely used method for random effects. The Mantel-Haenszel method is commonly used for fixed-effects models and may be preferred with low event rates.

Certainty of estimate (95% CI): A measure of the likelihood that the observed estimate is reflective of a true finding that reflects the range over which a true finding would be included in the interval 95% of the time if a study was repeated indefinitely.

Evidence to recommendation framework: A tool used by guideline groups to facilitate judgments about priority of a problem, benefits and harms, resource use, equity, acceptability, feasibility, and preference-sensitive care.

Cost-effectiveness: An assessment of resources and costs of a therapy or strategy compared with benefits provided, often evaluated as an incremental cost-effectiveness ratio comparing 2 competing strategies where cost-effective care would be considered less than \$50,000 to \$100,000 per quality-adjusted life-year.

Equity: Equity relates to equal access of subpopulations to best practices and is considered in the evidence to recommendation framework with specific judgments made with regard to how recommendations may affect underserved, socioeconomically disadvantaged, and other populations.

Strength of recommendation: The extent to which a guideline group has confidence that desirable effects of a treatment or intervention outweigh undesirable effects.

Recommendation: The guideline suggests against routinely administering glucocorticoids and/or antihistamines to prevent anaphylaxis in patients with prior radiocontrast hypersensitivity reactions when readministration of a low- or iso-osmolar, nonionic radiocontrast media (RCM) agent is required. Conditional recommendation; certainty rating of evidence: very low²²

Question 5: Should antihistamine and/or glucocorticoid premedication be used to prevent anaphylactic reactions to allergen immunotherapy or other agents?

Recommendation: The guideline suggests in favor of the administration of glucocorticoids and/or antihistamines as an intervention to prevent anaphylaxis in patient undergoing aeroallergen rush immunotherapy. Conditional recommendation; certainty rating of evidence: very low²²

2020 Anaphylaxis GRADE Guideline Good Practice Statements

A good practice statement may be used by guideline groups when there is high certainty that a recommendation will do more good than harm but little direct evidence is available.^{25,26} A common example often cited where a good practice statement is appropriate is with regard to use of parachutes by skydivers²⁷—a situation in which a good practice statement can be confidently endorsed in the absence of randomized trials or observational studies demonstrating benefit. Good practice statements are valuable; however, they are intentionally not GRADED. The anaphylaxis parameter endorsed the following good practice statements with regard to anaphylaxis management²²: Good Practice Statement 1: Administer epinephrine as the firstline pharmacotherapy for uniphasic and/or biphasic anaphylaxis.

Good Practice Statement 2: Do not delay the administration of epinephrine for anaphylaxis because doing so may be associated with higher morbidity and mortality.

Good Practice Statement 3: After diagnosis and treatment of anaphylaxis, all patients should be kept under clinical observation in a setting capable of managing anaphylaxis until symptoms have fully resolved.

Good Practice Statement 4: All patients with anaphylaxis should receive education on anaphylaxis, including avoidance of identified triggers, presenting signs and symptoms, biphasic anaphylaxis, treatment with epinephrine, the use of epinephrine autoinjectors, and referral to a board-certified allergist. Of note, there may be some circumstances where self-injectable epinephrine is deferred (ie, resolved anaphylaxis and drug trigger with high likelihood of successful avoidance), and shared decision making may play a role in some circumstances.

Conditional Recommendations in Anaphylaxis Management

Very-low-certainty evidence exists regarding supplemental therapies to inform anaphylaxis management. Although epinephrine remains the cornerstone of anaphylaxis management in any setting, the role of antihistamines and/or glucocorticoids had not been previously subjected to rigorous methodologic evaluation in a GRADE analysis. The 2020 Anaphylaxis GRADE guideline suggested that although glucocorticoids and antihistamines should not be relied on to prevent biphasic anaphylaxis, there are some circumstances in which these agents may provide significant benefit in

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			Certainty ass	essment			No. of	patients	Effe	ct	6.	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Premedication	No premedication	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
Subseq	uent RCM react	ion with	or without pren	nedication								
6	Observational studies	Serious*	Serious†	Not serious	Serious‡	None	523 of 4277 (12.2%)	1218 of 15,851 (7.7%)	RR 1.07 (0.67-1.71)	5 more per 1000 (from 25 fewer to 55 more)	⊕⊖⊖⊖ Very low	Important

Boldface indicates guideline group judgment in each domain.

RR, Risk ratio.

*Due to observations study design sources of bias could affect effect estimate.

†Significant heterogeneity among studies.

\$Several studies with wide ranging 95% CIs.

В

	Premed	lication	No Prem	edicatio	n	Risk Ratio	Ris	k Ratio	
Study or Subgroup	Events	Totals	Events	Toatal	Weight	M-H, Random, 95%	CI M-H, Rar	ndom, 95% Cl	
Abe 2016 with media change	5	172	3	38	6.2%	0.37 (0.09, 1.47)		<u> </u>	
Abe 2016 without media change	47	271	61	220	12.6%	0.63 (0.45, 0.88)	-	- ¦	
Katayama 1990 without media chang	e 140	988	903	13999	13.3%	2.20 (1.86, 2.59)		-	
Kolbe 2014 without media change	21	67	5	66	8.9%	4.14 (1.66, 10.32)			
Lee 2016 without media change	29	273	21	108	11.5%	0.91 (0.54, 1.55)	-		
Park 2017 with media change	11	77	15	117	10.2%	1.11 (0.54, 2.30)	-		
Park 2017 without media change	15	41	20	86	11.3%	1.57 (0.90, 2.74)			
Park 2018 with media change	148	1947	105	872	13.0%	0.63 (0.50, 0.80)	-	- i	
Park 2018 without media change	107	441	85	273	13.0%	0.78 (0.61, 0.99)	0	<u>-</u> -	
Total (95% CI)		4277		15851	100.0%	1.07 (0.67, 1.71)		-	
Total events Heterogeneity: Tau ² = 0.42; Chi ² = 118	523 .33, df = 8	8 (P < 0.00	1218 0001); l ² = 93 ⁰	%					
Test for overall effect: Z = 0.29 (P = 0.7	7)								
								1 1	
						0.01	0.1	1 10	100
							Favors Premedication	Favors No Premedica	ation

Figure 2. Examples of an evidence profile and forest plot. Evidence table and forest plot for 2020 Anaphylaxis GRADE guideline question 4: Should antihistamine and/or glucocorticoid premedication be used to prevent recurrent hypersensitivity reactions to radiocontrast media? The evidence profile (A) shows certainty assessment, relative risks, absolute risks, and importance of outcome. The forest plot (B) shows risk ratio of repeated hypersensitivity radiocontrast media reaction with or without premedication. Reprinted with permission from Shaker et al.²² GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

anaphylaxis prevention (specifically, in some chemotherapy protocols and in rush aeroallergen immunotherapy). The guideline did not find clear evidence to support glucocorticoids and/or antihistamines to prevent biphasic anaphylaxis.

Although the 2020 Anaphylaxis GRADE guideline was consistent with the prior suggestion that most individuals who have had a prior hypersensitivity reaction can be effectively managed by selecting an alternative low- or iso-osmolar RCM without premedication,²⁸ some controversy exists around this recommendation and management of such patients. For example, the American College of Radiology Manual on Contrast Media, version 10.3, emphasizes that although a premedication strategy may be considered in patients with prior RCM hypersensitivity if it does not adversely delay care or treatment decisions, it is not a substitute for anaphylaxis preparedness because breakthrough reactions can occur. Use of a low- or iso-osmolar contrast RCM has been associated with a greater effect size than premedication alone.²⁹ The American College of Radiology manual suggests that regardless of patient status, a history of a severe contrast reaction be considered a relative contraindication to the future use of the same class of media and premedication be considered (if feasible) if there are no alternatives.²⁹

It is important to acknowledge, as discussed in the 2020 Anaphylaxis GRADE guideline, that a diversity of clinical circumstances may exist with regard to RCM prophylaxis. The systematic review of RCM prophylaxis expressed low confidence in the literature base and called for higher-quality evidence to better inform practice, acknowledging that future recommendations could potentially change as a result of new information. The guideline highlighted that practitioners may reasonably consider RCM premedication in clinical circumstances associated with a high level of perceived risk of anaphylaxis or comorbidities associated with greater anaphylaxis fatality risk (such as underlying cardiovascular disease, use of β -blockers, asthma, or prior severe anaphylaxis), although clear evidence is lacking to support this practice. Importantly, the analysis of RCM prophylaxis evaluated patients with both mild and severe RCM reactions but was unable to stratify prophylaxis by severity of index reaction. Furthermore, only low- and iso-osmolar nonionic radiocontrast agents were evaluated, and this recommendation did not apply to patients receiving high-osmolar contrast agents for whom prophylaxis may be appropriate in some settings.

Given the controversy surrounding RCM prophylaxis and very low certainty of evidence, it could be argued that the most appropriate course of action would be to make no recommendation with regard to radiocontrast premedication. Conversely, it is important to acknowledge that unnecessary premedication is associated with significant costs and delays in care delivery. The 2020 Anaphylaxis GRADE guideline did not identify significant *benefit* from premedication before RCM administration to prevent recurrent reactions (relative risk, 1.07; 95% CI, 0.67-1.71). Moreover, there is a potential for *harm* in terms of untoward effects

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Example of Summary of Judgments for the Use of Supplemental Glucocorticoid and/or Antihistamine Premedication to Prevent Anaphylaxis

Consideration	Judgment						
Problem is a priority	No	Probably no	Probably yes	Yes	Varies	Do not know	
Desirable effects	Trivial	Small	Moderate	Large	Varies	Do not know	
Undesirable effects	Large	Moderate	Small	Trivial	Varies	Do not know	
Certainty of evidence	Very low	Low	Moderate	High	No included studies		
Values	Important uncertainty	Possibly important	Probably no important	No important			
	or variability	uncertainty or	uncertainty or	uncertainty or			
		variability	variability	variability			
Balance of effects,	Favors the comparison	Probably favors the	Does not favor either	Probably favors the	Favors the intervention	Varies	Do not know
benefits, and burdens		comparison	the intervention or	intervention			
			the comparison				
Resources required	Large costs	Moderate costs	Negligible costs and	Moderate savings	Large savings	Varies	Do not know
			savings				
Certainty of evidence of required resources	Very low	Low	Moderate	High	No included studies		
Cost-effectiveness	Favors the comparison	Probably favors the	Does not favor either	Probably favors the	Favors the intervention	Varies	No included studie
		comparison	the intervention or	intervention			
			the comparison				
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Do not know
Acceptability	No	Probably no	Probably yes	Yes	Varies	Do not know	
Feasibility	No	Probably no	Probably yes	Yes	Varies	Do not know	
Reprinted with permission	from Shaker et al. ²²						

Box 1. Clinical Vignette

A 65-year-old man with diabetes and a prior history of truncal urticaria and throat tightness during contrast-enhanced computed tomography (CT) requires urgent contrastenhanced imaging. Using the Care Everywhere feature of the electronic medical record, you confirm that the culprit contrast agent he received 15 months ago was iohexol (Omnipaque), a low-osmolar nonionic monomer. You discuss management options with the patient, including potential benefits and harms of premedication with antihistamines and glucocorticoids in the setting of an alternative contrast agent, iodixanol (Visipaque), a low-osmolar nonionic dimer. Through a process of shared decision making and informed consent, the patient receives iodixanol and undergoes imaging without premedication and experiences no additional hypersensitivity reaction.

(eg, hyperglycemia in a patient with diabetes) and cost because length of stay may be increased in association with the need to administer the pretreatment regimen; for this reason, the risk for undesirable effects of the intervention may exceed the likelihood of desirable effects (Fig 1).^{30,31} Within GRADE, it is necessary for guideline groups to make conditional recommendations when appropriate, and such recommendations must often be made in the setting of imperfect information.^{17,30}



Figure 3. Certainty of evidence. GRADE explicitly considers certainty of evidence in the process of making strong or conditional recommendations. Reprint with permission from Guyatt et al.³⁹ GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

Indeed, although premedication before high-osmolar agents reduces immediate reactions of all severity in average-risk patients and mild immediate adverse effects in average-risk patients receiving low- osmolar agents,^{30,32} protection from premedication against moderate to severe reactions in high-risk patients receiving low-osmolar agents is unproven by high-certainty evidence. In fact, estimates suggest the number needed to treat to prevent a fatal reaction in a high-risk patient to be 50,000 (at a cost of \$131,211,400 per death prevented).^{29,30,33} As such, the 2020 Anaphylaxis GRADE guideline issued a *conditional* recommendation against *routine* prophylaxis to prevent anaphylaxis in patients with prior radiocontrast hypersensitivity reactions. Clearly, additional studies are needed to better inform the practice of RCM premedication in high-risk patients.

Conditional Recommendations and Shared Decision Making

A clinical vignette related to one of the 2020 Anaphylaxis GRADE guideline recommendations is presented in Box 1. Conditional recommendations indicate that individual patient management varies based on situational factors and practitioner and patient values and preferences.^{14,34-36} For example, in the instance of the RCM recommendation, after a process of shared decision making, an inpatient with a distant history of a mild hypersensitivity reaction with an urgent need for a contrast study may be managed using a low- or iso-osmolar nonionic RCM without premedication. Conversely, a patient undergoing an elective ambulatory study who experienced severe anaphylaxis in the previous year to an unknown contrast agent may opt for an approach that includes premedication. In the setting of a conditional recommendation, both strategies are appropriate in each circumstance.^{12,17}

Given that many guidelines promote conditional (rather than strong) recommendations, there is not only a need for further research to clarify the evidence base on which recommendations are made but also a need to further understand guideline dissemination, implementation, and incorporation into practice.^{12,20} In addition, there is an ever-expanding need for investigators to engage the plethora of conditions in need of validated, maintained, and updated decision aids to assist in the process of shared decision making.^{14,34} Improved connectivity among clinical guideline repositories is also needed, not only with regard to shared decision-making tools but also for improved communication with policy makers and decision makers to enhance support and reimbursement for patient-centered practice in keeping with clinical guidelines.

Conclusion

GRADE is a useful method to consider certainty of evidence and provides a framework for translation of evidence to recommendations that has many advantages.¹ GRADE has become a standard in clinical guideline development. It is transparent and makes it easy for practitioners, patients, and policy makers to appreciate the detailed rationale underlying recommendations.^{1,3,5,6,37} However, it is important to acknowledge that although the process of GRADE is prescriptive, explicit, and transparent, it still requires judgment and consensus of guideline groups as evidence is evaluated and translated to recommendations.³⁸

GRADE frequently lays bare knowledge gaps that exist and sets a course for future investigation to better inform our routine practice, allowing the opportunity to critically evaluate assumptions that may need to be reevaluated. Importantly, a critical aspect of any GRADE guideline is to realize that the strength (strong or conditional) is just as (if not more) important as the direction (for or against) of any particular recommendation. Understanding the significance of a conditional recommendation is critical to translating evidence to guidelines to practice. GRADE teaches us that not all evidence is reliable (Fig 3), that quality beats quantity in

evidence, and that many recommendations will be contextual. Still, with careful analysis, the perfect is not the enemy of the good, and conditional recommendations provide important guidance to practitioners and patients on how to navigate the implications of the evidence and expert consensus.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2020.03.009.

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Supplementary Data



eFigure 1. Example of a funnel plot to evaluate publication bias. Symmetry of a funnel plot can help detect publication bias. Circles represent point estimates of trials with larger studies falling closer to the pooled estimate (dashed line). When the effect size of smaller studies is symmetric (A), publication bias is less likely, but when the effect size is asymmetric (B), publication bias should be suspected (https://gdt.gradepro.org/app/handbook/handbook.html).

eTable 1

Strong Recommendations in the Context of Low-Certainty Evidence

Situations Which May Justify Strong Recommendations in the Face of Uncertainty

Low-certainty evidence suggesting benefit in a life-threatening situation may justify a strong recommendation in favor of an intervention Low-certainty evidence suggesting benefit with high-certainty evidence suggesting harm or very high cost may justify a strong recommendation against a strategy Low-certainty evidence suggesting equipoise in competing strategies with high-certainty evidence indicating less harm from one intervention over another High-certainty evidence suggesting equivalence in 2 options with low-certainty evidence suggesting differential harm High-certainty evidence showing modest benefit in the face of low- or very-low-certainty evidence suggesting the possibility of catastrophic harm

eTable 2

Criteria to Determine Whether the GRADE Approach Was Used

GRADE Criteria

Indication of certainty of evidence using GWG definitions

Explicit consideration of GWG criteria for assessing certainty of evidence

Evaluation of the certainty of evidence for each outcome

Use of evidence profiles or evidence summaries to communicate evidence certainty assessments, ideally based on systematic reviews

Explicit use of the 4 GRADE criteria for determining strength of recommendation (balance of desirable and undesirable consequences, certainty of evidence, values and preferences of those effected, and resource use)

Use of GWG or equivalent terminology to describe recommendations for or against a strategy as strong or conditional (weak)

Transparent reporting of decisions about strength of recommendations

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; GWG, GRADE Working Group.