

Table 3

Advantages of the GRADE System for Classification of Level of Evidence and Strength of Recommendations

Separation between quality of evidence and strength of recommendation
Ability to downgrade or upgrade evidence based on methodologic criteria
Consideration of the relative importance of various outcomes to patients
Assessment of values and preferences in association with making recommendations
Clear understanding of the implications of “strong” and “weak” recommendations

Abbreviation: GRADE, Grades of Recommendation, Assessment, Development, and Evaluation.

- ☐ Was assignment of subjects randomized?
- ☐ Was there concealment of randomization?
- ☐ Except for the experimental intervention, were the groups of subjects treated equally?
- ☐ Were subjects, study personnel, and outcome adjudicators “blinded” to treatment?
- ☐ Were subjects analyzed in the groups to which they were randomized?
- ☐ Was follow-up complete?

When major methodologic shortcomings are identified, the quality of evidence can be lowered. Alternatively, observational studies begin at a low level of quality but can be upgraded based on consideration of factors such as effect size or whether there is a remarkable dose-response gradient. The GRADE approach entails a transparent process, in which there is a clear separation of evidence from recommendations. For instance, using the GRADE system we can make a strong recommendation when an intervention offers benefit that outweighs considerations of harm, burden, or cost—such as epinephrine administration for acute anaphylaxis—despite the absence of an RCT demonstrating efficacy. We can stipulate in the context of moving from evidence to recommendations, as we did in our current allergic rhinitis guideline,¹ that based on the balance of the potential for benefit compared with the potential for harm or burden and consideration of cost, use of combination intranasal corticosteroid and intranasal antihistamine, compared with intranasal corticosteroid monotherapy, is associated with a weak recommendation. With a strong recommendation, the decision-making process is more straightforward: most patients should receive (or not receive) the recommended management. A weak recommendation is a navigational signal for clinicians indicating that treatment decisions can vary based on patient circumstances and implies further research is very likely to have an important impact on our confidence in the estimate of effect and can change the estimate. This evidence-based management recommendation means that for our college student seen at spring break, it is important to carefully consider the potential for benefit, compared with the potential for harm and burden, cost, and patient

circumstances, and invite our patient to express her values and preferences and participate in the medical decision-making process. Our patient will consider what the advantages are for combination therapy compared with intranasal corticosteroid monotherapy. The allergy-immunology clinician can serve a vital role in guiding this patient to a decision that is in her best health care interest.

The allergic rhinitis guideline appearing in this issue of the *Annals*¹ will be accompanied by a companion synopsis of our management recommendations for pharmacotherapy of allergic rhinitis that will appear in the *Annals of Internal Medicine*. In addition to these documents, we plan to publish a more traditional “practice parameter” on allergic rhinitis that you can expect to see in the *Annals of Allergy, Asthma, and Immunology* in the next several months.

We welcome feedback regarding our first GRADE-based guideline. Our transition to use the GRADE framework for our guidelines is consistent with recommendations from the IOM⁹ and reflects our desire to engage in a process of continuous performance improvement in developing future iterations of our “guidelines” and “parameters.” We hope that you will find them useful.

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Could calcium channel blockers treat 2 illnesses with 1 pill?



Ever since Middleton’s¹ suggestion that excessive permeability of airway cells to calcium ions might play a role in the underlying mechanism of bronchial hyperresponsiveness (BHR)

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and asthma, researchers have questioned whether calcium channel blockers (CCBs) might be efficacious in the treatment of this illness. Their potential utility makes a great deal of sense, because cytoplasmic calcium is involved in bronchoconstriction, mast cell mediator release, vagal reflex stimulation, airway mucous gland secretion, chemotaxis of eosinophils, and possibly even smooth muscle remodeling.^{2,3} Despite this theoretical possibility, multiple studies of the efficacy of CCBs in asthma

have consistently suggested that they are of limited value but hoped that future development of more potent CCBs would demonstrate efficacy.^{4–6}

In this month's *Annals*, Chiu et al⁷ examine the efficacy of CCBs on lung function in asthma by performing a meta-analysis of the data, specifically assessing their potential effects on exercise-induced asthma, BHR, and resting lung function. For exercise-induced asthma, CCB use resulted in a statistically significant decrease in mean maximal percentage of decrease in postexercise forced expiratory volume in 1 second, lessening the decrease by approximately one third ($P < .001$). For resting lung function, postdose forced expiratory volume in 1 second significantly improved ($P = .01$), but only by 0.08 L, with no significant change in forced vital capacity or peak flows. This modest bronchodilation was further confirmed with studies of BHR with direct-acting bronchoconstrictors (histamine and methacholine) that failed to demonstrate significant improvement with the addition of CCBs.

There are several limitations to this analysis as noted by Chiu et al. There were several different classes of CCBs analyzed, including dihydropyridines (nifedipine, felodipine, and darodipine), phenylalkylamines (gallopamil and verapamil), and benzothiazepines (diltiazem). Although all these CCBs block the L-type calcium channel, which is responsible for airway smooth muscle contraction,⁸ consideration of the specific CCB could be of importance. This is exemplified in the case of resting lung function, in which nifedipine and darodipine demonstrated significant improvement in baseline forced expiratory volume in 1 second ($P < .01$ for each), whereas diltiazem and felodipine demonstrated no such efficacy ($P = .24$ and $P = .5$, respectively). In addition, the studies included only patients with mild asthma, and heterogeneity, unknown selection bias, small samples, and lack of control of baseline medicines were problematic.

Overall, this meta-analysis confirms prior reviews on the topic, that there is minimal bronchodilator effect and no antagonism against direct-acting bronchoconstrictive agents that measure BHR. Hoping for more potent CCBs is unlikely to be fruitful because they could produce greater systemic adverse effects. Of interest is the modest protection in exercise-induced asthma that could

indicate a significant mast cell stabilizing effect. Although not as great as that produced by β_2 -agonists or leukotriene receptor antagonists,⁹ further research might be warranted on this topic. Future studies should include larger numbers of subjects and consider stratification of the CCB used. In the meantime, CCBs are certainly reasonable agents to consider in patients with cardiac disease and asthma, but alas do not result in the treatment of 2 illnesses with 1 pill.

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Baseline asthma burden, comorbidities, and biomarkers in omalizumab-treated patients in PROSPERO



The Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO) study was designed to better understand the types of patients who are begun on omalizumab in the real-world setting, including asthma burden, comorbidities, and biomarker profiles, and to evaluate what clinical parameters might be associated with better outcomes with the use of this biologic agent. In this month's issue of the *Annals*, Griffin et al¹ report on the first of these 2 outcomes.

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To make this trial as real world as possible, minimal inclusion and exclusion criteria were required for enrollment, thus allowing the physician to use solely clinical judgment when identifying appropriate candidates for omalizumab treatment in subjects at least 12 years old with persistent allergic asthma. To better understand the characteristics of patients begun on omalizumab, extensive baseline assessment was undertaken, including spirometry, fractional exhaled nitric oxide, complete blood cell count and differential, periostin levels, Asthma Control Test, Asthma Quality of Life Questionnaire for 12 Years and Older, Work Productivity and Activity Impairment: Asthma, Mini Rhinoconjunctivitis Quality of Life Questionnaire, and evaluation of total and specific immunoglobulin E levels to perennial and seasonal allergens.

Griffin et al found, not surprisingly, that most adolescents were male, whereas most adults were female in this study's makeup. Prior to the use of short acting beta agonist, baseline forced expiration volume in 1 second was 87.9% in the adolescent group and 74.2% in the adult group, with a bronchodilator response of 7.9% and