

The Recommendation To Not Use Bronchodilators Is Not Supported by the Evidence

We read with interest the current guidelines on the management of bronchiolitis.¹ Here we raise our concern with the recommendation that bronchodilators not be used.

The guideline authors imply that our randomized controlled trial in 703 children with bronchiolitis supports their assertion that “clinical scores may vary from between observers”.^{1,2} This is a selective reading of our Limitations section. The cited article in fact showed an 18% (adjusted relative risk: 1.18; 95% confidence interval [CI]: 1.02–1.36) relative increase in successful hospital discharges from the emergency department (ED) when albuterol rather than epinephrine was administered. This study also addressed the limitations of consecutive enrollment with random allocation, previous episodes, and study site effect.² The severity of illness tool we used has been validated³ and has adequate interrater agreement (92%; $\kappa = 0.676$).

The guideline authors rely in part on older meta-analyses predating this work and on a meta-analysis from 2011 that systematically excluded studies showing a benefit to using albuterol over epinephrine.⁴ Therefore, these meta-analyses could provide only a limited view of what is known about bronchodilators in bronchiolitis.

The guideline’s assertion that bronchodilators should not be used must then rest on the meta-analysis in the Cochrane review library published by Gadomski⁵ in 2014. This meta-analysis included only placebo-controlled studies and consequently excluded some studies that showed a benefit between bronchodilators.

However, even this 2014 Cochrane review found a significant benefit to

using bronchodilators (odds ratio [OR]: 0.18; 95% CI: 0.06–0.50) as measured by improved clinical scores.⁵ In the version cited, there were only 187 patients included in the analysis to address the most important question to emergency physicians and pediatric hospitalists: Does albuterol decrease admissions to the ED? This meta-analysis showed a nonsignificant trend toward decreased admissions (OR: 0.76; 95% CI: 0.38–1.53), as also shown in a subsequent analysis in 404 patients (OR: 0.77; 95% CI: 0.44–1.33).⁵ This 23% reduction in odds of admission is not dissimilar to the 18% decrease in the relative risk of admission that we found with albuterol.² Neither nonsignificant underpowered studies nor meta-analyses should form the basis for treatment recommendations any more than null results should form the basis for concluding “no effect.”

Given that data from some studies finding a benefit to bronchodilators in the ED have been ignored, and given the actual findings of the 2014 Cochrane review, the recommendation that a bronchodilator not be used is charitably described as weak, particularly for the ED. This recommendation risks doing a disservice to our patients. It is not acceptable for the authors to seek refuge in the statement that this is a guideline and should not be used as the sole guidance for clinical management; experience tells us that that is exactly what will happen.

Available evidence clearly suggests that nebulized albuterol decreases hospital admissions to the ED. The guideline should be amended to reflect this.

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Conflict of Interest:

None declared

REFERENCES

1. Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014;134(5). Available at: www.pediatrics.org/cgi/content/full/134/5/e1474
2. Walsh P, Caldwell J, McQuillan KK, Friese S, Robbins D, Rothenberg SJ. Comparison of nebulized epinephrine to albuterol in bronchiolitis. *Acad Emerg Med*. 2008;15(4):305–313
3. Walsh P, Rothenberg SJ, O’Doherty S, Hoey H, Healy R. A validated clinical model to predict the need for admission and length of stay in children with acute bronchiolitis. *Eur J Emerg Med*. 2004;11(5):265–272
4. Hartling L, Fernandes RM, Bialy L, et al. Steroids and bronchodilators for acute bronchiolitis in the first two years of life: systematic review and meta-analysis. *BMJ*. 2011;342:d1714
5. Gadomski AM. Bronchodilators for bronchiolitis. In: Scribani M, ed. *Cochrane Acute Respiratory Infections Group*. John Wiley & Sons; 2014

doi:10.1542/peds.2014-3676A

Author’s Response

In response to the concerns raised by Walsh and Rothenberg that the guideline ignores the potential clinical benefit of bronchodilators in bronchiolitis, the committee respectfully disagrees and reiterates our logic. To recommend the use of a medication in any disease, the preponderance of benefit should outweigh the likelihood of harm across the entire population for whom the medication is prescribed. Although we clearly acknowledged in the guideline that a small proportion of children may appear to get a clinical benefit from bronchodilators (and there is significant disagreement as to whether the magnitude of said benefit is clinically meaningful), the majority of children with bronchiolitis do not stand to benefit. The pathology of early viral wheezing is hypothesized to result from the concomitant effects of virus-induced edema and debris in airways that are already small in

diameter. A minority of patients with early viral wheezing will also exhibit airway obstruction due to smooth muscle contraction, which may be at least partially reversible with bronchodilators. Unfortunately, there is no way to reliably distinguish which patients who suffer early wheezing will have reversible airway obstruction. Therefore, a recommendation to use albuterol in all patients with first-time viral wheezing would mean that the majority of patients given the medication would have no chance of benefiting from it. Such a recommendation would still be acceptable if the consequences of failing to administer the medication to the cohort who is expected to benefit were grave. In the case of bronchiolitis, there is no evidence to suggest that such a situation exists, that is, there is no convincing evidence that albuterol alters meaningful outcomes in

bronchiolitis. Although a small change in respiratory scores has been interpreted by some to justify the use of the medication in the entire cohort of patients with bronchiolitis, the bronchiolitis committee saw no evidence to suggest that the change in scores was clinically meaningful or that the absence of providing such treatment would substantially harm anyone. Furthermore, the committee felt the harm suffered, including significant side effects and costs, for the majority of patients who would not benefit from the medication outweighed the potential benefit to the much smaller cohort who might respond.

In response to the other concerns raised in their letter, we also disagree with the authors' interpretation of the existing literature. We would like to point out that evaluation of a therapy

against a placebo is considered the highest quality study design and not a weakness; therefore, we fail to see the significance of that particular critique, or of comparing albuterol to epinephrine when placebo-controlled trials are available. Finally, we offer no response to Walsh and Rothenberg's nonstandard use of the term "trend" to describe clearly negative results in hypothesis testing on the impact of albuterol on hospitalization rates except to note that such usage is expressly forbidden in the instructions to authors for this and most other high-quality medical journals.

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Conflict of Interest:

None declared

doi:10.1542/peds.2014-3676B

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Pediatrics 2015;135:e556
DOI: 10.1542/peds.2014-3676B

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Pediatrics 2015;135:e556

DOI: 10.1542/peds.2014-3676B

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