Systematic Review Snapshot

TAKE-HOME MESSAGE

The use of systemic or inhaled glucocorticoids in children aged 2 years or younger with acute bronchiolitis does not decrease admission rate or length of hospitalization.

METHODS

DATA SOURCES

A literature search with Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Latin American & Caribbean Health Sciences Literature, Scopus, and IRAN MedEx was performed in 2009 and 2013. The references of relevant articles were searched for additional studies. A search of the gray literature included clinicaltrials.gov and ICTRP Search Portal–World Health Organization, and reviews of conference proceedings from the Pediatric Academic Societies, the European Respiratory Society, and the American Thoracic Society were conducted.

STUDY SELECTION

Randomized controlled trials comparing short-term systemic or inhaled glucocorticoids versus placebo or another intervention in children aged 24 months or younger with acute bronchiolitis (defined as first episode of wheezing) were included. Primary outcomes were admissions by days 1 and 7 for outpatient studies and length of stay for inpatient studies. Studies were excluded from this review if they included patients with asthma, a history of recurrent wheezing and respiratory distress, or previous

Do Glucocorticoids Provide Benefit to Children With Bronchiolitis?

EBEM Commentators
Carrie Ng, MD
Mark Foran, MD
Department of Emergency Medicine
New York University School of Medicine
Bellevue Hospital Center
New York, NY
Alex Koyfman, MD
Department of Emergency Medicine
UT Southwestern Medical School
Parkland Memorial Hospital
Dallas, TX

Results

Pooled estimates of effect for glucocorticoids versus control.

Outcome	Quality of Evidence (GRADE*)	Relative Effect (95% CI)	Control (Assumed Risk*)	Steroid (Corresponding Risk†)	Number of Participants (Studies)
Admissions, outpatients Follow-up: day 1	High	RR 0.92 (0.78–1.08)	162/1,000	149/1,000	1,762 (8)
Admissions, outpatients Follow-up: day 7	Moderate	RR 0.86 (0.7–1.06)	250/1,000	215/1,000	1,530 (5)
Length of stay, inpatients, days	High	Unable to meta-analyze	0.8–6.6	0.41–6.64	633 (8)

CI, Confidence interval; *RR*, relative risk.
*Assumed risk for admissions was based on the median control group risks across the studies included in the meta-analysis (medium risk).
†Corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Of the 2,533 studies screened, 17 studies were included in the final analysis, totaling 2,596 patients. Different trial arms of each study were considered as separate comparisons.

Primary outcomes were the number of hospital admissions within 1 day and 7 days of the initial visit in the outpatient setting and length of stay for inpatients. Eight of the studies (N=1,824 patients) included outpatients, mostly from pediatric emergency departments (EDs), whereas 9 studies (N=772 patients) included inpatients only. The secondary outcomes were the following: (1) clinical severity scores such as the

intubations, or if they were admitted to an intensive care setting.

DATA EXTRACTION AND SYNTHESIS

Studies were evaluated for strength of evidence with the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[1] approach and appraised for bias with the Cochrane Risk of Bias assessment tool.[2] Seven investigators extracted data, 3 review authors independently assessed the risk of bias of the included studies, and 2 review authors independently graded the body of evidence. The overall strength of evidence was based on 3 key outcomes: length of stay or admission rate, clinical severity scores, and adverse events. A meta-analysis was separately performed for inpatient and outpatient results using a random-effects model. Heterogeneity reported for all primary outcomes pooled for this review was low to moderate. Prespecified subgroup analyses of participant- and study-level characteristics were conducted. In addition, sensitivity analyses were also performed with a fixed-effects model for primary outcomes of trials with overall low risk of bias.

Respiratory Distress Assessment Index and the Respiratory Assessment Change Score; (2) improvement in vital signs (oxygen saturation, respiratory rate, and pulse rate); (3) health services outcomes (hospital readmissions, return health care visits, and length of stay for outpatient studies); (4) pulmonary function tests; (5) symptoms and quality of life; and (6) short-term adverse events associated with the use of glucocorticoids (no studies addressed long-term harms).

The evidence demonstrates no clinically or statistically significant difference in admission rates or inpatient lengths of stay with systemic or inhaled glucocorticoid use compared with control (Table). Results of the clinical severity scores for the inpatients in one study suggest some short-term benefit of glucocorticoids at the 3- to 6- and 6- to 12-hour times, but there were no differences found in other secondary outcomes.[3] The sensitivity analysis using a fixed-effects model for primary outcomes of trials with overall low risk of bias found no change in the direction or magnitude of results.

Commentary

Bronchiolitis in the United States accounts for an average of more than 280,000 ED visits per year[4] and 31.2 pediatric admissions per 1,000.[5] Patients with bronchiolitis have a mean inpatient length of stay of 3.3 days[5-7] and cost more than $500 million per year.[7] As such, treatment that alters the clinical course of bronchiolitis in the ED would be beneficial to both patients and payers. However, determining the effectiveness of interventions for bronchiolitis has been challenging for several reasons.

First, the definition of bronchiolitis is imprecise and heterogeneous. In some studies, it is the presence of crackles with viral respiratory illness, whereas in others, it is wheezing with viral respiratory illness.[8] In this Cochrane Review, the latter definition was used.

Second, the patient characteristics that may determine responsiveness to glucocorticoids are diverse. For example, some authors have suggested that glucocorticoids are effective in subgroups of patients with atopy, older age, or specific viral infections (ie, respiratory syncytial virus or rhinovirus).[9,10] The prespecified subgroup analyses of both respiratory syncytial virus and age in this review found that each of these factors had limited predictive value in glucocorticoid responsiveness. However, the heterogeneity among trials did not allow adequate analysis of patients with atopy, and this review did not investigate the subgroup of patients with rhinovirus.

Third, the benefits of glucocorticoids may be specific to the intervention characteristics. For example, the benefits of glucocorticoids may depend on the dose, the type of steroid, and the method of medication administration (eg, inhalation, oral, intramuscular injection). The subgroup analysis of drug type and dose that was performed in this review found no difference, and a subgroup analysis of method of medication administration was not performed.

Fourth, the absence of standardized patient-important outcome measures has been a serious limitation in establishing the consistency and validity of bronchiolitis trials. This review used admission rates and hospital lengths of stay as the primary outcome measures. A major limitation of this review was the lack of consistent reporting of admission and discharge criteria in studies that were included. Also, the majority of trials had unclear risk of bias because of inadequate or incomplete reporting.

Nevertheless, the findings from this review do not support the routine use of glucocorticoids in young children with acute bronchiolitis, which is consistent with the recommendations from the 2006 American Academy of Pediatrics clinical practice guideline on the diagnosis and management of bronchiolitis.[11] There was one large trial from this review that suggested a synergistic effect when glucocorticoids were used with nebulized epinephrine; however, further studies are needed to support this conclusion.[3]

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals*' Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: Fernandes RM, Bialy LM, Vandermeer B, et al. Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane Database Syst Rev*. 2013;(6):CD004878. http://dx.doi.org/10.1002/14651858.CD004878.pub4.

1. Schünemann H, Brozek J, Oxman A, eds. *GRADE Handbook for Grading Quality of Evidence and Strength of Recommendation Version 3.2* [updated March 2009]. Grading of Recommendations Assessment, Development & Evaluation (GRADE) Working Group; Cochrane Handbook: England. 2009. Available at: http://www.gradeworkinggroup.org. Accessed February 4, 2014.
2. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. Cochrane Collaboration; 2011. Available at: http://handbook.cochrane.org/. Accessed February 4, 2014.
3. Plint AC, Johnson DW, Patel H, et al. Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med*. 2009;360:2079-2089.
4. Teeratakulpisarn J, Limwattananon C, Tanupattarachai S, et al. Efficacy of dexamethasone injection for acute bronchiolitis in hospitalized children: a randomized, double-blind, placebo-controlled trial. *Pediatr Pulmonol*. 2007;42:433-439.
5. Hasegawa K, Tsugawa Y, Brown DF, et al. Temporal trends in emergency department visits for bronchiolitis in the United States, 2006-2010; 2014.
6. Shay DK, Holman RC, Newman RD, et al. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA*. 1999;282:1440-1446.
7. Pelletier AJ, Mansbach JM, Camargo CA. Direct medical costs of bronchiolitis hospitalizations in the United States. *Pediatrics*. 2005;118:2418-2423.
8. Everard ML. Acute bronchiolitis and croup. *Pediatr Clin North Am*. 2009;56:119-133.
9. Jartti T, Lehtinen P, Vanto T, et al. Evaluation of the efficacy of prednisolone in early wheezing induced by rhinovirus or respiratory syncytial virus. *Pediatr Infect Dis J*. 2006;25:482-488.
10. Lehtinen P, Ruohola A, Vanto T, et al. Prednisolone reduces recurrent wheezing after a first wheezing episode associated with rhinovirus infection or eczema. *J Allergy Clin Immunol*. 2007;119:570-575.
11. Lieberthal AS, Bauchner H, Hall CB, et al. Subcommittee on diagnosis and management of bronchiolitis. Clinical practice guideline: diagnosis and management of bronchiolitis. *Pediatrics*. 2006;118:1774-1793.

Michael Brown, MD, MSc, Alan Jones, MD, and David Newman, MD, serve as editors of the SRS series.