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The Effects of Inhaled Steroids on Recurrent Wheeze After Acute Bronchiolitis: A Systematic Review and Meta-Analysis of 748 Patients

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Abstract

Background. Acute bronchiolitis infection during infancy is associated with an increased risk of asthma later in life. The objective of this study was to determine if inhaled steroids are effective in preventing the development of recurrent wheeze or asthma following acute bronchiolitis. *Methods*. Multiple databases and bibliographies of selected references were searched. Inclusion required (*a*) a randomized controlled trial of inhaled steroids and control group, (*b*) at least 2 weeks duration of therapy started during the acute phase of disease, and (*c*) identification of the rate of recurrent wheeze or asthma at least 6 months after therapy. *Results*. Of 1410 studies reviewed, 8 reports were included in this meta-analysis (748 patients). The overall odds ratio for developing recurrent wheeze or asthma with treatment versus without treatment was 1.02 (95% confidence interval = 0.58-1.81). *Conclusions*. A course of inhaled steroids after acute bronchiolitis is not effective in preventing recurrent wheeze or asthma.

Keywords

bronchiolitis, corticosteroid, budesonide, asthma, wheeze

Introduction

Acute bronchiolitis, a viral respiratory infection of infancy, is the most common cause of hospitalization for infants <23 months of age.[1] A longitudinal birth cohort study in the United Kingdom found that 38% of children with respiratory syncytial virus (RSV) bronchiolitis developed asthma.[2] While the association between bronchiolitis and recurrent wheeze or asthma is well documented, the pathophysiology of this relationship remains unclear. It has been suggested that early infection with RSV or other respiratory viruses produces chronic inflammatory changes and increased airway hyperresponsiveness.[3]

The role for inhaled corticosteroid therapy in acute bronchiolitis is controversial. Inhaled corticosteroid therapy has not been shown to be effective in the treatment of acute bronchiolitis and is not currently recommended for this indication.[4] The efficacy of inhaled corticosteroids to prevent recurrent wheeze or asthma after acute bronchiolitis is unclear.[1] The results of multiple studies have not been consistent. A Cochrane review from 2007 failed to make a definitive recommendation regarding inhaled corticosteroids and recurrent wheeze due to small study sizes and inability to pool all data.[5] This review included 5 studies with follow-up data for 358 infants; however, only pooled data from 3 studies (119 infants) were used to examine the impact on recurrent wheeze.[5] Several randomized, controlled trials were excluded from the 2007 Cochrane review because control patients did not receive a placebo and were largely unblinded.[5]

Since that review, a large, randomized, placebo-controlled trial examining the efficacy of inhaled corticosteroids on subsequent recurrent wheeze after bronchiolitis has been published.[6] The present systematic review and meta-analysis includes data published since the 2007

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Cochrane review as well as the randomized, controlled trials without placebo control previously identified.[5-9]

Objective

The purpose of this systematic review and meta-analysis is to determine if inhaled corticosteroid therapy administered to infants after acute bronchiolitis reduces the rate of subsequent recurrent wheeze or asthma.

Methods

Protocol

This study followed the guidelines described in the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA).[10]

Eligibility

To be included in this review, studies needed to meet the following criteria: (*a*) subjects less than 24 months of age with clinically diagnosed, acute bronchiolitis and without existing cardiopulmonary disease; (*b*) a randomized, controlled design where the experimental group received inhaled corticosteroid therapy and a contemporary control group was identified; placebo administration was not required; (*c*) therapy started during the acute phase of the infection and was administered for at least 2 weeks; and (*d*) final outcome assessment was a minimum of 6 months after the completion of treatment.

Sources

The following databases were searched: PubMed (1966 to January 2015), Cochrane Central Register of Clinical Trials, Cochrane Database of Systematic Reviews, EMBASE, and ProQuest COS Conference Papers Index. Bibliographies of selected studies were also reviewed. Contact with the author of one study was attempted for additional clarification.[11]

Search

The search terms used were "bronchiolitis," "inhaled budesonide," "inhaled steroid," and "inhaled corticosteroid." No language filters were used, but an English abstract was required to be included for review.

Study Selection

Reports were assessed by 2 authors using the eligibility criteria detailed previously. When articles appeared to report the same patient sample, the report with the follow-up period most similar to the other included studies was selected. Disagreements about study eligibility were determined by a third author.

Data Extraction

Data extracted from each report included number of patients, inclusion and exclusion criteria for patients, patient ages, corticosteroid used and dosage, treatment length, follow-up period, and country of origin. The primary outcome was asthma diagnosis and/or recurrent episodes of wheeze subsequent to the acute episode of bronchiolitis as diagnosed by a physician or as recorded in a symptom diary evaluated by a study investigator. Data were extracted independently by one author and verified by a second author.

Risk of Bias in Individual Studies

To decrease the risk of bias in individual studies, only studies that were randomized and controlled were included in this meta-analysis.

Summary Measures

The primary outcome measure was the odds ratio of developing recurrent wheeze or asthma after bronchiolitis with or without treatment using inhaled corticosteroids.

Synthesis of Results

The number of subjects experiencing asthma or remote wheeze and the total number of subjects reported in each group for each study were recorded. The odds ratio for each study was calculated and the overall odds ratio was determined using the DerSimonian-Laird estimator for random effects.[12] Residual heterogeneity among studies was estimated by τ^2 and tested by Cochrane's Q test.[13] P values $<.05$ were considered significant. Interstudy heterogeneity was estimated by I^2.[14] To determine the impact of individual studies on the overall outcome, composite odds ratios were reiteratively calculated following the stepwise exclusion of each study. Publication bias was estimated by the method of Galbraith.[15] All analyses were performed in R using the "metaphor" package.[16]

Risk of Bias Across Studies

There was variability in the reporting of outcomes in each study, which may be a source of bias when outcomes are combined. The outcomes ranged from physician-diagnosed asthma to respiratory symptoms as noted in parental diary.

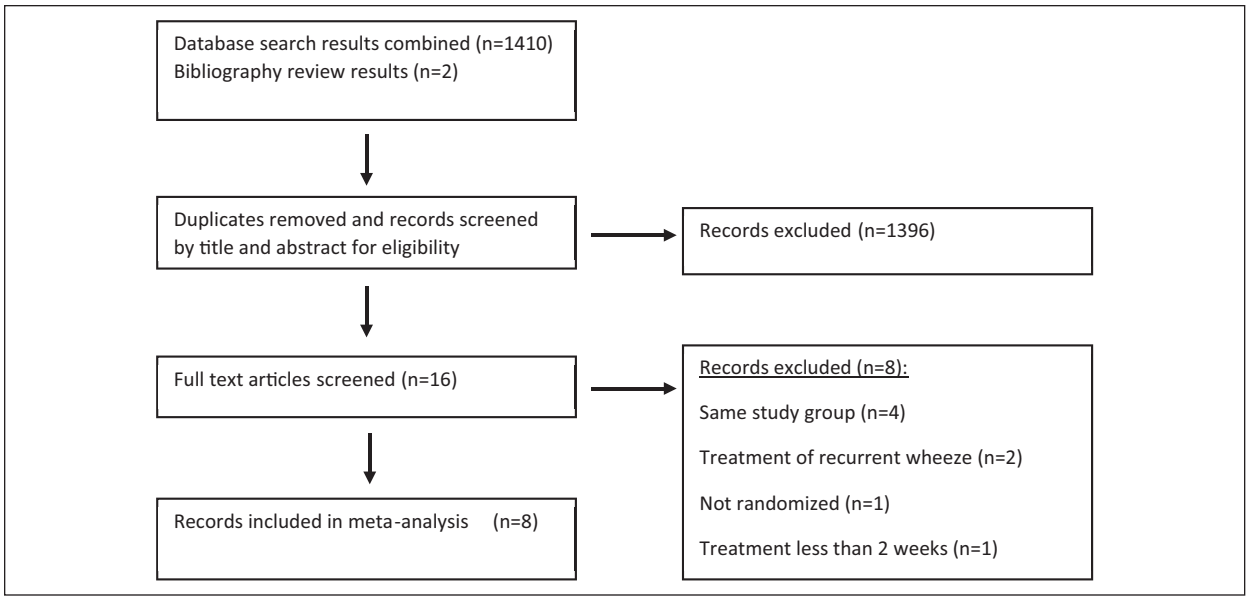

Figure 1. Literature search.

Results

Study Selection

The literature search is summarized in Figure 1. A total 1410 references were found by searching PubMed, Cochrane Central Register of Clinical Trials, Cochrane Database of Systematic Reviews, EMBASE, and ProQuest COS Conference Papers Index. Two additional studies were found by searching the bibliographies of selected studies. After studies were screened by title and abstract, 16 reports remained for full text screening. Eight of these reports were excluded. Four reports duplicated the subject sample and reported follow-up periods outside of inclusion criteria.[17-20] Two studies included subjects with recurrent wheeze who were treated after the acute phase of an episode of bronchiolitis.[21,22] The treatment period failed to meet inclusion criteria in 1 study.[23] One study was excluded after communications with the author clarified that the study was not randomized.[11] The remaining 8 reports form the basis for this review.[6-9,24-27]

Study Characteristics and Outcomes

The characteristics of each study are shown in Table 1. The total sample included 748 children, ranging in age from 0 to 24 months. For therapy, 5 studies used budesonide,[7,9,25-27] 2 used beclomethasone,[6,8] and 1 used fluticasone propionate.[24] The duration of therapy ranged from 2 weeks to 3 months, and follow-up periods ranged from 6 months to 3 years.

Study outcomes are summarized in Table 2. In 3 studies symptom diaries kept by parents were used to determine subsequent episodes of wheezing or asthma.[6,25,27] In 3 studies subsequent wheeze or asthma was identified when the patient sought[24] or received[8,26] medical intervention. In 2 studies the outcome was determined by physician diagnosis[9] of asthma or current asthma medication.[7]

Data Synthesis

The individual and overall odds ratios are summarized in Figure 2 and Table 3; odds ratios greater than 1 support the use of inhaled steroids. Heterogeneity was not statistically significant ($Q = 13.6$, $P = .06$) and less than half of the variability seen among the 8 studies was attributable to interstudy variability ($\tau^2 = .29 \pm .35$; $I^2 = 48.4\%$). When all of the studies were considered, the overall odds ratio was 1.02 (95% confidence interval = 0.58-1.81). By sensitivity analysis, the overall odds ratio ranged from 0.86 to 1.19; in all cases, the 95% confidence intervals included 1. The radial plot for publication bias is shown in Figure 3. The effect size to study size is within the expected range, suggesting that publication bias is unlikely.

Discussion

Summary of Evidence

The present systematic review and meta-analysis demonstrates that a course of inhaled steroids after acute bronchiolitis is not effective in preventing recurrent wheeze or asthma. Although a Cochrane review in 2007

Table 1. Characteristics of Included Studies.

Study Citation	Number of Patients	Age Range	Inhaled Steroid	Length of Treatment	Follow-up	Country of Origin
Ermers et al (2009)[6]	243	<13 months	Beclomethasone	3 months	1 year	Netherlands
Callén Blecua et al (2000)[8]	89	<13 months	Beclomethasone	3 months	1 year	Spain
Kajosaari et al (2000)[7]	70	0-9 months	Budesonide	2 months	2 years	Finland
Wong et al (2000)[24]	43	0-12 months	Fluticasone propionate	3 months	1 year	United Kingdom
Cade et al (2000)[25]	155	<12 months	Budesonide	2-3 weeks[a]	1 year	United Kingdom
Reijonen et al (2000)[9]	60	<24 months	Budesonide	16 weeks	3 years	Finland
Fox et al (1999)[26]	49	<12 months	Budesonide	8 weeks	1 year	United Kingdom
Richter et al (1998)[27]	39	<12 months	Budesonide	7 weeks	6 months	United Kingdom

[a]Treatment was started at admission and ended 2 weeks postdischarge up to maximum of 21 days.

Table 2. Outcome of Recurrent Wheeze or Asthma by Study.

Study Citation	Outcome	Outcome in Steroid Group/N (%)	Outcome in Control Group/N (%)
Ermers et al[6]	Patients with any wheeze episode recorded in daily log during follow-up	73/119 (61)	77/124 (62)
Callén Blecua et al[8]	Patients with episodes of wheezing who sought medical advice during follow-up	21/42 (50)	27/47 (57)
Kajosaari et al[7]	Patients on current asthma therapy at end of follow-up	4/32 (12)	14/38 (37)
Wong et al[24]	Patients who experienced respiratory events where they sought medical advice during follow-up	19/21 (90)	19/22 (86)
Cade et al[25]	Patients with any wheeze or cough episode recorded in daily diary	78/79 (99)	75/76 (99)
Reijonen et al[9]	Patients with current asthma diagnosis at follow-up	15/31 (48)	16/29 (55)
Fox et al[26]	Patients with cough or wheeze that required treatment by general practitioner during follow-up	21/25 (84)	12/24 (50)
Richter et al[27]	Patients with any episode wheeze recorded on diary card during follow-up	15/20 (75)	15/19 (79)

came to a similar conclusion, it was unable to make a strong clinical recommendation due to the small number of subjects included in the review.[5]

Limitations

There are a number of limitations to the conclusions drawn by this study. First, the type of inhaled steroid and the length of treatment were not uniform across all studies and whether one regimen was more effective than another was not analyzed. Second, the inclusion and exclusion criteria for patients across studies were not the same. For example, some studies included patients on mechanical ventilation[6] or who previously wheezed.[9] Other studies did not explicitly exclude preterm infants,[6,8,26,27] a recognized risk factor for respiratory disease, particularly asthma.[28] Third, the measurement of the primary outcome varied from study to study. In some studies asthma or recurrent wheeze was based on a physician diagnosis while in other studies it was based on symptom diaries kept by parents. Fourth, the follow-up period varied from study to study. Six of the 8 trials had a follow-up period of 1 year or less producing a study population less than 4 years of age and possibly underestimating the endpoint incidence.[6,8,24-27] Conversely, 2 population-based studies demonstrated that persistence of asthma into adulthood was associated with onset of wheezing at a young age.[29] Last, as opposed to the Cochrane review, several studies were included that did not use placebo for the control group.[5,7-9] Due to the lack of placebo control, there is a risk for induction of bias in these studies. Two of these studies showed no differences between the treatment and nontreatment groups.[8,9] One of the 3 studies did show treatment was effective.[7] However, based on the sensitivity analysis the inclusion of these studies did not significantly affect the overall outcome.

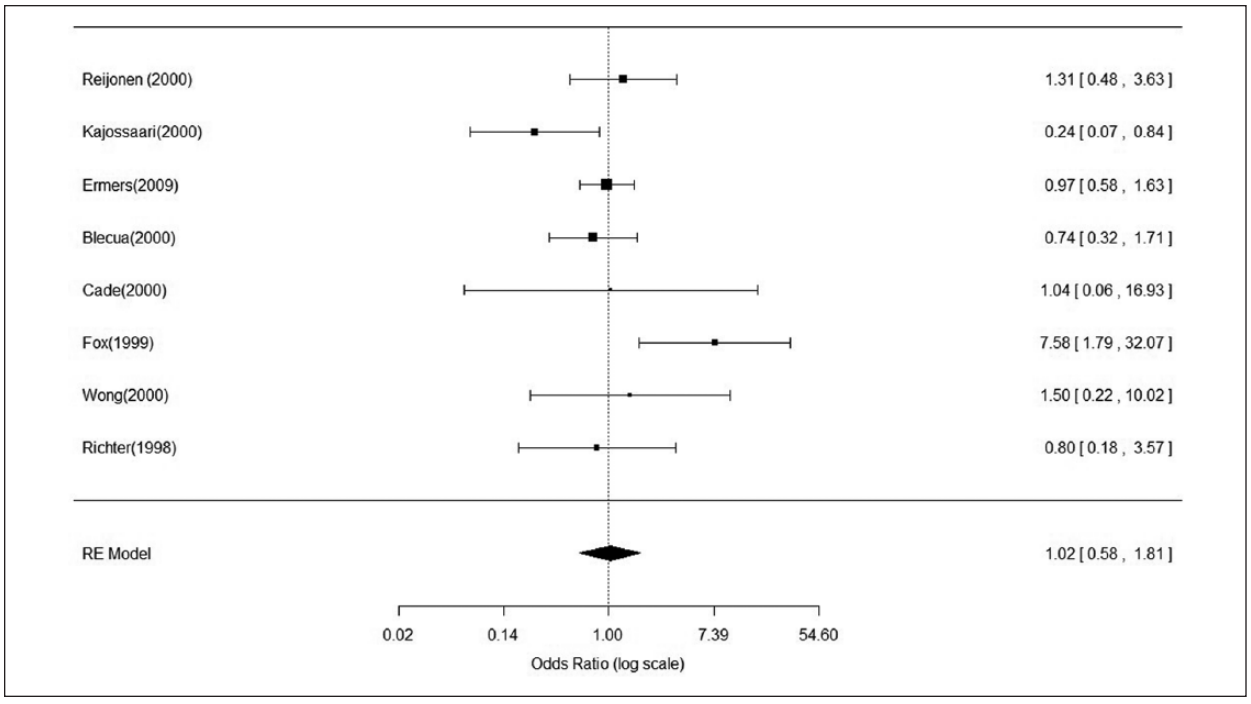

Figure 2. Forest plot.

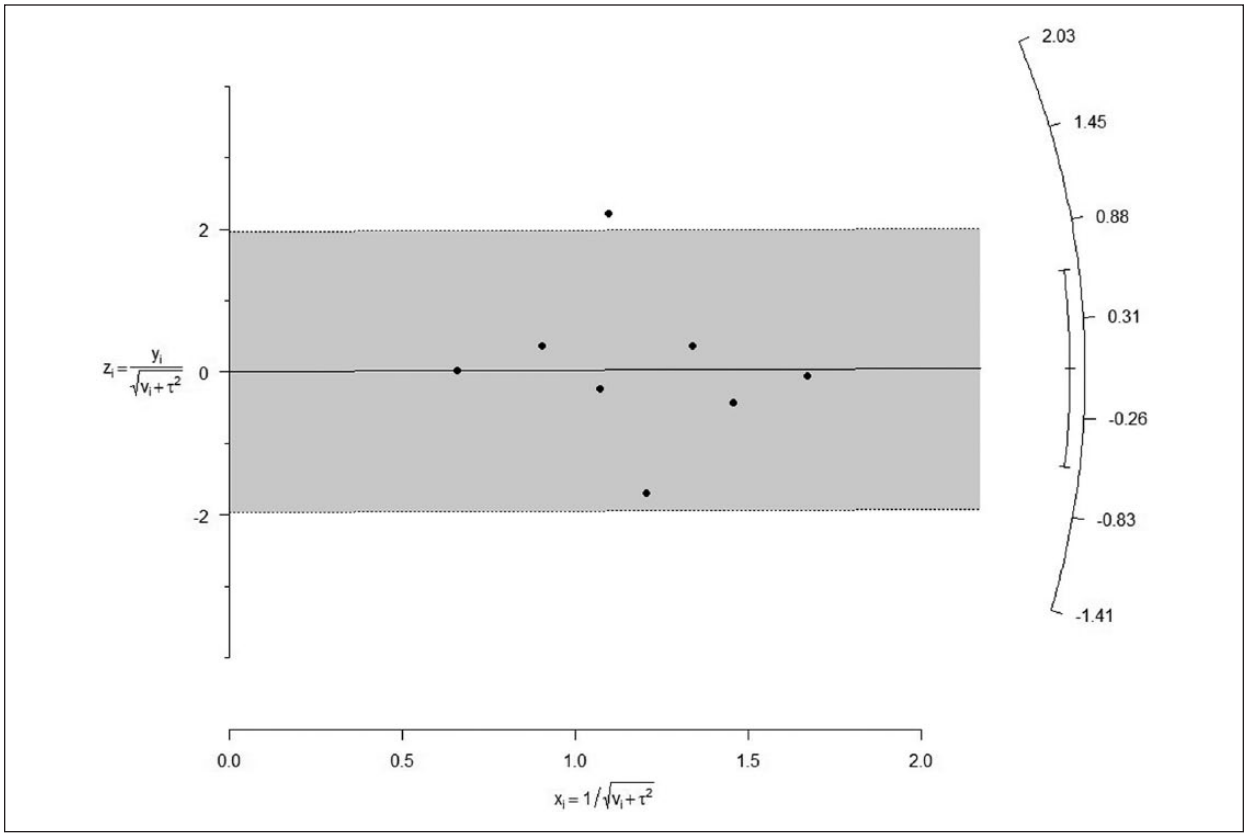

Figure 3. Galbraith plot.

Table 3. Sensitivity Analysis: Overall Odds Ratio With One Study Removed.

Study Removed	OR	95% LCL	95% UCL
None	1.02	0.58	1.81
Reijonen et al[9]	0.99	0.5	1.94
Kajosaari et al[7]	1.19	0.72	1.96
Ermers et al[6]	1.06	0.49	2.31
Callén Blecua et al[8]	1.11	0.55	2.23
Cade et al[25]	1.03	0.56	1.89
Fox et al[26]	0.87	0.6	1.23
Wong et al[24]	1	0.54	1.89
Richter et al[27]	1.06	0.56	2.01

Abbreviations: OR, odds ratio; LCL, lower confidence limit; UCL, upper confidence limit.

Conclusions

The evidence from the present meta-analysis does not support the use of inhaled corticosteroids for the prevention of recurrent wheeze or asthma after acute infantile bronchiolitis. Given the size of the analysis, a strong recommendation can be made against the use of such interventions.

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Author Contributions

PG performed the database searches, carried out the initial data extraction, drafted the initial manuscript and approved the final manuscript. SCA performed the statistical analysis, reviewed and revised the initial manuscript and approved the final manuscript as submitted. MD conceptualized and designed the study, did a secondary database search, reviewed all abstracted data, reviewed and revised initial manuscript, approved the final manuscript, and submitted the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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