

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)

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Do inhaled corticosteroids have a role for bronchiolitis?

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Abstract

INTRODUCTION

Bronchiolitis consists of an acute small airways inflammation secondary to a viral infection and is a frequent pathology among children under 2 years. The use of inhaled corticosteroids during bronchiolitis has been proposed to reduce recurrent wheeze or asthma, however there is controversy about it.

METHODS

To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

RESULTS AND CONCLUSIONS

We identified three systematic reviews including 11 randomized trials. We concluded that inhaled corticosteroids do not reduce recurrent wheeze or asthma in patients with bronchiolitis.

Problem

Bronchiolitis consists of an acute small airways inflammation commonly caused by a viral infection, predominantly respiratory syncytial virus. It is frequent in children under 2 years and is associated with high hospitalization rates and even mortality. Considering the inflammatory component and the reduction of recurrent wheeze or asthma in other respiratory pathologies with the use of inhaled corticosteroids, they have been proposed to be useful in bronchiolitis.

This article aims to review if inhaled corticosteroids are an alternative to reduce recurrent wheeze or asthma in patients with bronchiolitis.

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and

reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an

evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- Inhaled corticosteroids do not reduce recurrent wheeze or asthma in patients with bronchiolitis.
- Inhaled corticosteroids probably do not reduce hospital readmission.
- Despite the low cost of this intervention, the use of corticosteroids is not cost-effective for bronchiolitis.

About the body of evidence for this question

<p>What is the evidence. See evidence matrix in Epistemonikos later</p>	<p>Three systematic reviews were identified [1],[2],[3], including 11 primary studies [4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14]. All primary studies were randomized trials.</p>
<p>What types of patients were included*</p>	<p>All trials consider only patients with bronchiolitis. Regarding age, all trials included patients under 24 months. Specifically, one trial included patients aged 9 months or less [8], one trial 42 weeks or less [7] and five trials included patients under 12 months [4],[5],[6],[11],[12],[13]. Mean age was five months, with a range from two to 11 months. Five trials included only patients with confirmed respiratory syncytial virus [4],[6],[8],[13],[14]. In remaining trials, respiratory syncytial virus confirmation varied from 26 to 83% [5],[7],[10],[11],[12]. One trial did not report viral etiology [9]. The main exclusion criteria were: previous wheeze in six trials [6],[10],[11],[12],[13],[14], prematurity in four trials [4],[8],[10],[12], immunodeficiency in five trials [4],[5],[8],[11],[12], previous use of systemic corticosteroids in five trials [4],[5],[6],[12],[14], and assisted ventilation in five trials [5],[7],[8],[11],[12]. All of the trials excluded patients with chronic respiratory or cardiac illness. Seven trials included inpatients [4],[6],[8],[9],[10],[11],[14]. Four trials included outpatients [5],[7],[12],[13]. Three trials were multicenter studies [4],[5],[6].</p>
<p>What types of interventions were included*</p>	<p>Seven trials compared inhaled corticosteroids versus placebo [4],[6],[7],[10],[11],[12],[14]. Remaining four trials compared them versus no treatment [5],[8],[9],[13]. Particularly, seven trials used budesonide [4],[7],[8],[9],[10],[11],[13], two used beclomethasone [5],[6], one used fluticasone [12] and one used dexamethasone [14]. In six trials corticosteroids were administered via metered dose inhaler [5],[6],[7],[8],[12],[13]. In remaining five trials, they were nebulized [4],[9],[10],[11],[14]. Regarding intervention length, in two trials it lasted less than 21 days [4],[8], in two it lasted up to 8 weeks [7],[11], in four it lasted three months [5],[6],[12],[13] and in two trials it lasted 4 months [9],[10]. One trial did not report exact intervention length [14].</p>
<p>What types of outcomes were measured</p>	<p>Systematic reviews reported the following outcomes: recurrent wheeze, asthma, hospital readmission, need of bronchodilator, length of oxygen supplementation, oxygen supplementation at night, symptoms frequency and adverse effects. Follow-up was three months in one trial [14], six months in one trial [11], a year in six trials [4],[5],[6],[7],[9],[12], two years in two trials [8],[13] and three years in one trial [10].</p>

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of Findings

Information regarding the effects of inhaled corticosteroids is based on ten randomized trials including 927 patients [4],[5],[6],[7],[8],[10],[11],[12],[13],[14]. One included trial had no extractable data from systematic reviews, therefore it was not added to a meta-analysis [9]. Seven trials reported recurrent wheeze [4],[5],[6],[7],[11],[12],[14], and three reported asthma [8],[10],[13]. Five trials reported hospital readmission [4],[7],[11],[12],[14]. Three trials mentioned adverse effects [7],[11],[12], but only oral candidiasis could be analyzed from one trial [12]. The summary of findings is the following:

- The use of inhaled corticosteroids does not reduce recurrent wheeze or asthma in patients with bronchiolitis. The certainty of the evidence is high.
- The use of inhaled corticosteroids probably does not reduce the rate of hospital readmissions. The certainty of the evidence is moderate.
- The use of inhaled corticosteroids probably increases importantly the risk of oral candidiasis.
- No additional studies were found reporting information about other adverse effects.

Inhaled corticosteroids versus placebo or no treatment for bronchiolitis				
Patients	Children under 24 months presenting with bronchiolitis			
Intervention	Inhaled corticosteroids			
Comparison	Placebo or no treatment			
Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT inhaled corticosteroids	WITH Inhaled corticosteroids		
	Difference: patients per 1000			
Recurrent wheeze or asthma	546 per 1000	541 per 1000	RR 0.99 (0.91 to 1.08)	⊕⊕⊕⊕ High
	Difference: 5 patients less per 1000 (Margin of error: 44 less to 49 more)			
Hospital readmission	275 per 1000	289 per 1000	RR 1.05 (0.63 a 1.75)	⊕⊕⊕○ ¹ Moderate
	Difference: 14 patients more per 1000 (Margin of error: 102 less to 207 more)			
Adverse effects	4.8% of patients receiving intervention presented oral candidiasis, compared to none in control group. Trials did not report data regarding additional adverse effects.		RR 5.58 (0.28 a 113.04)	⊕⊕⊕○ ² Moderate

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITHOUT inhaled corticosteroids** is based on the risk in the control group of the trials. The risk **WITH inhaled corticosteroids** (and its margin of error) is calculated from relative effect (and its margin of error).

¹ The certainty of the evidence was downgraded in one level for imprecision, because the confidence interval implies effect could possibly be in either direction.
² The certainty of the evidence was downgraded in one level for imprecision, because of the wide confidence interval which includes the possibilities of no effect or even larger risk.

Follow the link to access the interactive version of this table ([Interactive Summary of Findings – iSoF](#))

About the certainty of the evidence (GRADE)*
<p>⊕⊕⊕⊕</p> <p>High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.</p>
<p>⊕⊕⊕○</p> <p>Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate</p>
<p>⊕⊕○○</p> <p>Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.</p>
<p>⊕○○○</p> <p>Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.</p>
<p>*This concept is also called ‘quality of the evidence’ or ‘confidence in effect estimates’.</p> <p>† Substantially different = a large enough difference that it might affect a decision.</p>

Other considerations for decision-making

To whom this evidence does and does not apply

- The evidence presented in this summary applies to inpatients and outpatients under 24 months with bronchiolitis.
 - Even though respiratory syncytial virus predominates, it is reasonable to extrapolate results to different viral etiologies.
 - Results do not apply to patients with chronic cardiac or respiratory pathologies, because of direct exclusion of these patients in all including trials.
-

About the outcomes included in this summary

- As outcomes, we selected recurrent wheeze or asthma, hospital readmission and adverse effects, because they are critical outcomes for decision making. This selection was based on the authors opinion.
 - We initially considered including mortality as an outcome, however it was not reported. Considering the absent effect on other outcomes, we believe an effect on mortality is not to be expected.
-

Balance between benefits and risks, and certainty of the evidence

- This summary shows there is no benefit in the use of inhaled corticosteroids.
 - Regarding adverse effects, we were only able to analyze the outcome of oral candidiasis from one trial [12].
 - We identified one systematic review regarding the use of inhaled corticosteroids in asthma which could not identify significant differences in bone density, growth or cortisol levels [15]. This findings are not completely applicable to our analysis, because the review included patients older than 2 years with asthma and intervention length was 2 years or more.
-

Resource considerations

- Despite corticosteroids being of low cost, if we consider the absence of benefits, it does not correspond to a cost-effective intervention.
-

What would patients and their doctors think about this intervention

- Considering we did not find an effect on recurrent wheeze or asthma or hospital readmission with the use of inhaled corticosteroids, most of patients and physicians should be against the intervention.
 - The latter is even more probable considering possible adverse effects, intervention length and estimated cost, and difficulties associated to administration via aerochamber or nebulization.
-

Differences between this summary and other sources

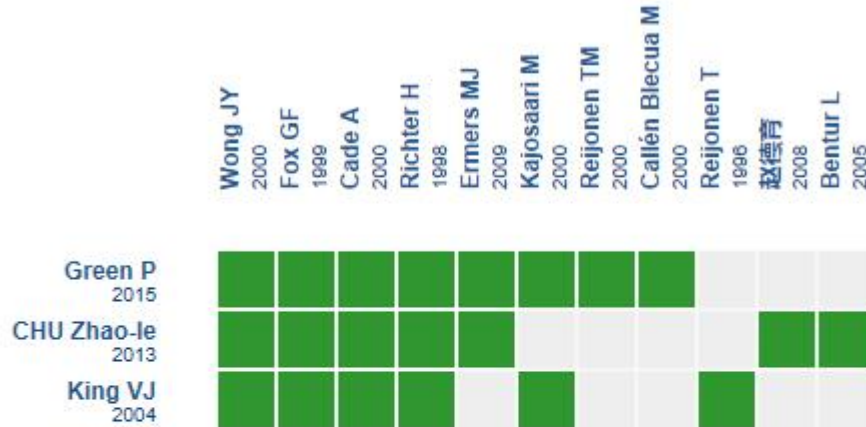
- The present summary reaches coincident conclusions to the included systematic reviews.
 - The American Academy of Pediatrics guideline about diagnosis, management and prevention of bronchiolitis does not review the use of inhaled corticosteroids in particular [16].
 - The United Kingdom National Institute for Health and Care Excellence (NICE) guideline presents a specific recommendation against the use of inhaled corticosteroids for bronchiolitis [17].
-

Could this evidence change in the future?

- Given the certainty of the evidence, the probability of future research changing conclusions of this summary is low.
 - During the redaction of this summary, we identified two additional systematic reviews on the use of inhaled corticosteroids [18],[19]. These were not included, because they did not differentiate the inhaled route of administration from systemic routes (oral, intravenous or intramuscular). Through this reviews, we found only two additional randomized trials not included in the present summary [20],[21]. The analyzed systematic reviews in this summary did not included those trials, because the intervention length was shorter than required according to their inclusion criteria.
 - We did not identified ongoing studies in the International Clinical Trials Registry Platform (World Health Organization) regarding the use of inhaled corticosteroids in bronchiolitis.
 - In PROSPERO International prospective register of systematic reviews we identified one ongoing systematic review including the use of inhaled corticosteroids in bronchiolitis [22].
-

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.

Rows represent systematic reviews, and columns show primary studies.

The boxes in green correspond to studies included in the respective revisions.

The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version**: [Inhaled corticosteroids for bronchiolitis](#)

Notes

The upper portion of the matrix of evidence will display a warning of “new evidence” if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and

analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here

(<http://dx.doi.org/10.5867/medwave.2014.06.5997>)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

Potential conflicts of interest

The authors do not have relevant interests to declare.

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