

Should systemic corticosteroids be used for bronchiolitis?

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Abstract

Introduction

Bronchiolitis is an acute small airways inflammation mainly caused by a viral infection. It is frequent in children under two years of age, particularly under 12 months. The use of systemic corticosteroids has been proposed for bronchiolitis, especially for severely ill patients. However, its efficacy is still controversial.

Methods

To answer this question we gathered information using 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 from primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified four systematic reviews, including 20 randomized trials overall. We concluded the use of systemic corticosteroids has no benefit for the treatment of bronchiolitis, even for patients with mechanical ventilation.

Problem

Bronchiolitis is an acute small airways inflammation mainly caused by a viral infection, being respiratory syncytial virus one of the most important etiologies. It is highly frequent in children under two years of age, particularly under 12 months, being an important cause of hospital admission in this age group. Given its antiinflammatory effects and its efficacy in other respiratory conditions like asthma, the use of systemic corticosteroids has been proposed for patients presenting with bronchiolitis, especially for those severely ill.

The present summary aims to review if systemic corticosteroids are useful as an alternative treatment for patients presenting with an episode of bronchiolitis.

Key messages

- Systemic corticosteroids do not substantially reduce the clinical score in patients with bronchiolitis.
- Systemic corticosteroids probably do not reduce length of stay for inpatients without mechanical ventilation, and might not reduce it for patients with mechanical ventilation.
- Systemic corticosteroids might not reduce the duration of mechanical ventilation.
- Systemic corticosteroids might not reduce mortality in patients with mechanical ventilation.

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.

About the body of evidence for this question

<p>What is the evidence. See evidence matrix in Epistemonikos later</p>	<p>Four systematic reviews were identified¹⁻⁴. They included 20 randomized trials overall⁵⁻²⁴.</p>
<p>What types of patients were included*</p>	<p>All trials included patients presenting with bronchiolitis.</p> <p>Regarding age, 18 trials included patients less than 24 months⁵⁻²⁴. Among them, four trials included patients less than 12 months^{11,13,19,23}, one trial included patients less than 15 months¹⁰, and two trials included patients less than 18 months [5,21]. On the other hand, two trials included patients less than 36 months^{20,22}. Mean age was 7.4 months, with a range from four to 17 months.</p> <p>Six trials included only patients with confirmed respiratory syncytial virus^{6,8,14,15,16,17}. In the remaining trials, respiratory syncytial virus was confirmed in 28 to 71% of patients^{5,9,10,11,12,18,19,21,22}. Five trials did not report viral etiology^{7,13,20,23,24}.</p> <p>Patients were excluded if they presented with: previous wheezing in nine trials^{8,9,10,11,12,13,20, 21,22}, chronic respiratory disease in 11 trials^{5,8,9,10,11,12,19,20,21,22,24}, cardiac disease like congenital cardiopathies in ten trials^{5,8,9,10,11,12,19,21, 22,23}, neurological disease in four trials^{9,10,12,22}, prematurity in six trials^{8,9,12,17,19,24}, immunodeficiency in seven trials^{6,8,9,10,12,19,22}, previous use of systemic corticosteroids in 13 trials^{5,6,10,12,14-17,19-22,24}, and assisted ventilation in eight trials^{5,9,11,12,19,21,22,24}.</p> <p>Four trials included patients with mechanical ventilation^{6,14-16}. Six trials did not report if they included patients with mechanical ventilation^{7,8,10,13,18,20}. Fifteen trials were conducted in inpatient setting^{6,7,8,10,11,13-18,21-24}. The remaining five trials were</p>

	<p>conducted in an outpatient setting (emergency department)^{5,9,12,19,20}.</p> <p>Six trials were multicenter studies^{6,16,17,19,21,24}.</p>
What types of interventions were included*	<p>All trials compared systemic corticosteroids versus placebo.</p> <p>Nine trials used dexamethasone^{6,8,10,11,12,16,19,23,24}, one used prednisone⁵, one used methylprednisolone⁷, seven used prednisolone^{9,14,15,18,20-22}, one used either prednisolone or methylprednisolone¹⁷, and one used an initial course of hydrocortisone followed by prednisone¹³.</p> <p>In eleven trials the corticosteroid was administered orally^{5,9,10,12,14,15,18-22}, in three it was intravenous^{6,8,16}, in four it was intramuscular^{7,11,23,24}, in one it was either oral or intravenous¹⁷, and in one it was initially intravenous and then oral¹³.</p> <p>In 11 trials, intervention lasted on average four days, with a range from two to ten days^{5-12,14-24}. In one trial, intervention was administered until 3 days after hospital discharge¹³.</p>
What types of outcomes were measured	<p>Systematic reviews reported the following outcomes: length of stay in hospital, length of stay in intensive care unit, duration of invasive mechanical ventilation, death of patients with mechanical ventilation, clinical score and duration of symptoms.</p> <p>Follow up was seven days or less in six trials^{8-10,14,21,23}, two to four weeks in eight trials^{6,7,11-13,16,20,24}, two months in one trial²², a year in one trial¹⁷, two years in one trial⁵, and five years in one trial¹⁴.</p>

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

Summary of Findings

The information regarding the effects of systemic corticosteroids was based on ten randomized trials, including 580 patients⁵⁻¹⁵. Ten trials had no extractable data from the identified systematic reviews^{4,11,17-24}. Three trials reported clinical score^{7,10,12}, five trials reported length of stay in hospital for patients without mechanical ventilation^{6,7,9,12,13} and two reported length of stay for patients with mechanical ventilation^{13,15}. Three trials assessed the duration of mechanical ventilation^{5,13,15} and three trials reported mortality in patients with mechanical ventilation^{5,13,15}. Regarding adverse effects, four trials assessed them^{8,10,13,14}. The summary of findings is as follows:

- The use of systemic corticosteroids does not relevantly reduce clinical score for patients with bronchiolitis. The certainty of the evidence is high.
- The use of systemic corticosteroids probably does not reduce length of stay for patients without mechanical ventilation presenting with bronchiolitis. The certainty of the evidence is moderate.
- The use of systemic corticosteroids might result in little or no reduction in length of stay for patients with mechanical ventilation presenting with bronchiolitis. The certainty of the evidence is low.
- The use of systemic corticosteroids might result in little or no reduction of the duration of mechanical ventilation for patients presenting with bronchiolitis. The certainty of the evidence is low.
- The use of systemic corticosteroids might result in little or no reduction of mortality in patients with mechanical ventilation presenting with bronchiolitis. The certainty of the evidence is low.
- Probably, there are no significant adverse effects related to the use of systemic corticosteroids for bronchiolitis.

Systemic corticosteroids for bronchiolitis				
Patients	Children under 24 months of age presenting with bronchiolitis with or without mechanical ventilation			
Intervention	Systemic corticosteroids			
Comparison	Placebo			
Outcomes	Absolute effect*		Relative effect 95% CI	Certainty of evidence GRADE
	WITHOUT systemic corticosteroids	WITH systemic corticosteroids		
	Difference: patients per 1000			
Clinical score	2.2†	1.84	-	⊕⊕⊕⊕ High
	SMD: -0.36 (Margin of error: -0.65 to -0.08)			
Length of stay (for patients without mechanical ventilation)	5 days††	4.5 days	-	⊕⊕⊕○ ¹ Moderate
	MD: -0.44 (Margin of error: -1.06 to 0.18)			
Length of stay (for patients with mechanical ventilation)	16 days††	13.5 days	-	⊕⊕○○ ² Low
	MD: -2.44 (Margin of error: -9.3 to 4.42)			
Duration of mechanical ventilation	12 days††	11.5 days	-	⊕⊕○○ ² Low
	MD: -0.62 (Margin of error: -2.78 to 1.53)			
Mortality (only for patients with mechanical ventilation)	28 per 1000	21 per 1000	RR 0.73 (0.12 to 4.42)	⊕⊕○○ ² Low
	Difference: 8 less (Margin of error: 25 less to 96 more)			
Adverse effects	None of the trials assessing adverse effects reported significant differences		-	⊕⊕⊕○ ³ Moderate

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
MD: Mean difference.
SMD: Standardized mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).
*The risk WITHOUT systemic corticosteroid is based on the risk in the control group of the trials. The risk WITH systemic corticosteroid (and its margin of error) is calculated from relative effect (and its margin of error).
†Clinical score WITHOUT systemic corticosteroids extracted from trial with the highest weight.
†† Value WITHOUT systemic corticosteroids corresponding to the mean from studies with higher weight.
1 One level of certainty was downgraded because of imprecision, given the wide confidence interval which includes the possibility of either beneficial or null effect.
2 Two levels of certainty were downgraded because of imprecision, given the wide confidence interval which includes the possibilities of no effect or higher risk.
3 One level of certainty was downgraded because of publication bias, as most randomized trials did not report this outcome.

About the certainty of the evidence

(GRADE)*

⊕⊕⊕⊕

High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕○

Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕○○

Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕○○○

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.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

The evidence presented in this summary applies to patients under 24 months presenting with bronchiolitis at hospital and ambulatory settings. Some results only apply to patients with mechanical ventilation.

Even though respiratory syncytial virus predominates, it is reasonable to extrapolate the results to a different viral etiology of bronchiolitis.

About the outcomes included in this summary

Selected outcomes were clinical score, length of stay at hospital (for patients with and without mechanical ventilation), duration of mechanical ventilation, mortality (for patients with mechanical ventilation) and adverse effects, because they were considered critical outcomes for decision-making. This selection is based on the opinion of authors.

Balance between benefits and risks, and certainty of the evidence

The present summary shows that neither relevant decrease in clinical score exists, nor are benefits observed in terms of length of stay for patients without mechanical ventilation.

For patients with mechanical ventilation, systemic corticosteroids might not decrease length of stay, duration of mechanical ventilation or mortality.

Regarding adverse effects, in those trials that assessed them, none were observed relating systemic corticosteroids.

Supporting the conclusion above, a systematic review regarding systemic corticosteroids for asthma exacerbations indicates there is no significant increase in adverse effects with short courses, even when used several times a year²⁵. Even though these results apply to patients with asthma, it is possible to extrapolate them to the similar duration use of systemic corticosteroids for bronchiolitis.

Resource considerations

Systemic corticosteroids, especially in short courses, do not imply a high cost, but if we consider the absence of significant benefits, it would not be a cost-effective measure.

What would patients and their doctors think about this intervention

Considering there is neither relevant reduction in clinical score nor in length of stay for patients without mechanical ventilation, most caregivers and physicians should oppose their use.

Even though no adverse effects were reported, given cost and difficulty of administration orally or parenterally in children less than 24 months, it is more probable that they oppose their use.

For patients with mechanical ventilation, given the low certainty of evidence against their use and the scarcity of therapeutic alternatives, some caregivers and physicians might be in favor of systemic corticosteroids.

Differences between this summary and other sources

The present summary yields conclusions which are consistent with included systematic reviews.

The guideline about diagnosis, management and prevention of bronchiolitis from the American Academy of Pediatrics strongly recommends against the use of systemic corticosteroids for any type of patient with bronchiolitis²⁶.

Similarly, the guideline from the National Institute for Health and Care Excellence (NICE) in United Kingdom, recommends against their use²⁷.

Could this evidence change in the future?

Given the certainty of the evidence, the probability of future research changing the conclusion from this summary is low for patients without mechanical ventilation and moderate for patients with mechanical ventilation.

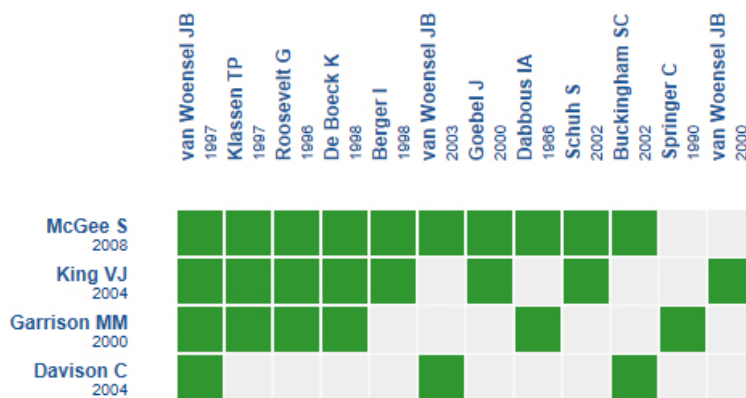
During the conduction of this summary, two additional systematic reviews on the use of corticosteroids for bronchiolitis were identified^{28,29}. These were not included, because they did not differentiate inhalatory from systemic routes (oral, intravenous or intramuscular). Related to these reviews, six additional randomized trials were found and not included in the present summary³⁰⁻³⁵. The systematic reviews analyzed in this summary did not include these trials, because of publication date was beyond the search period, or patients did not meet the inclusion criteria.

We did not identify ongoing trials in International Clinical Trials Registry of the World Health Organization regarding the use of systemic corticosteroids for bronchiolitis.

An ongoing systematic review was identified including the use of systemic corticosteroids for bronchiolitis³⁶ in PROSPERO International prospective register of systematic reviews.

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.

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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.

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