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Efficacy of Inhaled Corticosteroids in Infants and Preschoolers With Recurrent Wheezing and Asthma: A Systematic Review With Meta-analysis

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ABSTRACT

OBJECTIVE. To compare the efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing or asthma.

METHODS. Randomized, prospective, controlled trials published January 1996 to March 2008 with a minimum of 4 weeks of inhaled corticosteroids versus placebo were retrieved through Medline, Embase, and Central databases. The primary outcome was wheezing/asthma exacerbations; secondary outcomes were withdrawal caused by wheezing/asthma exacerbations, changes in symptoms score, pulmonary function (peak expiratory flow and forced expiratory volume in 1 second), or albuterol use.

RESULTS. Of eighty-nine studies identified, 29 (N = 3592 subjects) met the criteria for inclusion. Patients who received inhaled corticosteroids had significantly less wheezing/asthma exacerbations than those on placebo (18.0% vs 32.1%); posthoc subgroup analysis suggests that this effect was higher in those with a diagnosis of asthma than wheeze but was independent of age (infants versus preschoolers), atopic condition, type of inhaled corticosteroid (budesonide metered-dose inhaler versus fluticasone metered-dose inhaler), mode of delivery (metered-dose inhaler versus nebulizer), and study quality (Jadad score: <4 vs ≥4) and duration (<12 vs ≥12 weeks). In addition, children treated with inhaled corticosteroids had significantly fewer withdrawals caused by wheezing/asthma exacerbations, less albuterol use, and more clinical and functional improvement than those on placebo.

CONCLUSIONS. Infants and preschoolers with recurrent wheezing or asthma had less wheezing/asthma exacerbations and improve their symptoms and lung function during treatment with inhaled corticosteroids. *Pediatrics* 2009;123:e519–e525

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Key Words

asthma and wheezing management, children

Abbreviations

ICS—inhaled corticosteroid
MDI—metered-dose inhaler
WAE—wheezing/asthma exacerbation
PEF—peak expiratory flow
FEV₁—forced expiratory volume in 1 second
RR—relative risk
CI—confidence interval
NNT—number(s) needed to treat

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EPIDEMIOLOGIC STUDIES HAVE shown that nearly 30% of children will have at least 1 episode of wheezing before their third birthday, with a cumulative prevalence of wheeze of 50% at the age of 6 years.¹ Also, studies of the natural history of asthma have established that in almost 80% of cases it begins during the first 6 years of life.² However, the diagnosis of asthma in children <5 years old presents a particularly difficult problem with important implications; although on one hand asthma at these ages is frequently underdiagnosed³ and undertreated,⁴ not all episodes of wheezing and cough are caused by asthma, particularly in those under the age of 3. Therefore, trying to find the best treatment for a preschooler with wheeze is a common and troublesome clinical challenge.⁵

The most recent international guidelines recommend the use of low-dose inhaled corticosteroids (ICSs) as the preferred controller therapy, with leukotriene modifiers as an alternative, for the management of persistent asthma in children under the age of 5. The treatment of those children with intermittent, viral-induced wheezing or low/intermediate probability of asthma remains controversial.^{6–8}

Older studies produced contradictory results regarding the efficacy of ICSs in children under the age of 5, perhaps because of small sample size. However, 2 large long-term clinical trials in preschoolers with a high risk of asthma showed that although the regular ICS therapy controls persistent/severe wheezing episodes and improves lung function, ICSs do not alter the progression/underlying severity of the disease and are associated with deleterious effects on growth.^{9,10} Even so, guidelines,^{6–8} popular practice,¹¹ and a recent task force report¹² have all recommended a 3-month trial of ICSs with close follow-up with regard to response to treatment. It therefore seems reasonable to have a more critical approach of the use of ICSs in preschool-aged children with recurrent wheezing.

Thus, the objective of this systematic review was to evaluate the efficacy of ICS use (compared with placebo) in infants or preschool-aged children (<5 years of age) with recurrent wheezing or asthma.

METHODS

Data Sources and Search

We identified studies from Medline (January 1966 to March 2008), Embase (January 1980 to March 2008), and the Cochrane Controlled Trials Register (central) (second quarter 2008) databases by using the following Medical Subject Headings (MeSH), full-text, and keyword terms: (wheezing or wheeze or asthma) and (inhaled corticosteroids or beclomethasone or budesonide or fluticasone or ciclesonide or mometasone or triamcinolone).

Study Selection

Inclusion criteria for trials included (1) infants (1–23 months old) or preschoolers (2–5 years old) with a clinical diagnosis of wheezing or asthma for at least 6 months before study entry, (2) randomized (parallel group or crossover) controlled trials without language restriction, (3) a minimum of 4 weeks of treatment with ICSs (delivered via metered-dose inhaler [MDI] or nebulizer) compared with placebo, (4) the primary outcome measure of wheezing/asthma exacerbations (WAEs), defined as worsening symptoms that required systemic corticosteroid use, and (5) the secondary outcome measures of withdrawal because of WAEs, mean change from baseline in symptoms score, mean change from baseline in pulmonary function (peak expiratory flow [PEF] and forced expiratory volume in 1 second [FEV₁]), and mean change from baseline in albuterol use. Trials published solely in abstract form were excluded, because the methods and results could not be fully analyzed.

Data Abstraction and Quality Assessment

Titles, abstracts, and citations were reviewed independently by 2 reviewers (Drs Castro-Rodriguez and Rodrigo) to assess potential relevance for full review. From the full text, both reviewers independently assessed candidate studies for inclusion on the basis of the criteria for population, intervention, study design, and outcomes. Data extraction included (1) age, gender, number of patients studied, patient demographics, withdrawals, (2) agent, dose, route of delivery, and duration of therapy, (3) concurrent control treatments, (4) outcomes, and (5) method of randomization and allocation concealment. Methodologic quality of each candidate trial was evaluated by using the 5-point scale (0 = worst, 5 = best) described by Jadad et al.¹³ This instrument assesses the adequacy of randomization and blinding and the handling of withdrawals and dropouts.

Statistical Analysis

Binary outcomes were pooled by using common relative risks (RRs) and 95% confidence intervals (CIs). If pooled effect estimates for dichotomous outcomes were significantly different between groups, we calculated the num-

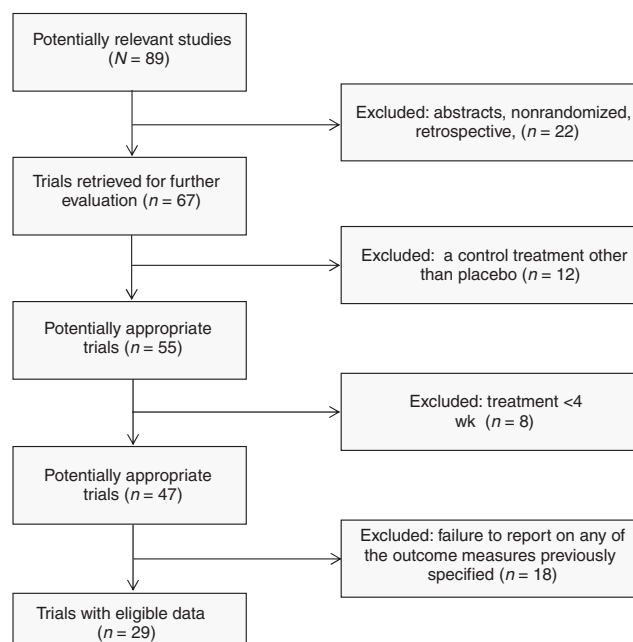


FIGURE 1
Flowchart for identification of usable studies.

ber needed to treat (NNT). For continuous outcomes, the standardized mean difference (for variables using different units of measure) and weighted mean difference (for variables using the same unit) and 95% CIs were calculated. Heterogeneity was further measured by using the I^2 test.¹⁴ Without heterogeneity ($I^2 < 40\%$), data were combined by mean of a fixed-effects model¹⁵; otherwise, a random-effects model was used.¹⁶ Sensitivity analysis of the primary outcome was conducted to explore the influence of the following factors on the results: disease (wheeze versus asthma), age (<24 months versus 2–5 years), atopic status (>50% of children with personal and/or parental atopy characteristics versus nonatopic), quality assessment (Jadad score: <4 vs ≥ 4), method of ICS delivery (MDI versus nebulizer), ICS choice (budesonide MDI versus fluticasone MDI, at equivalent doses 2:1; we did not include beclomethasone MDI, because there have been few studies), and study duration (<12 vs ≥ 12 weeks). The results of the subgroups were compared by using the interaction test.¹⁷ A P value of <.05 using a 2-tailed test was taken as being of significance. The meta-analyses was performed with Review Manager 5.0.15 software (Cochrane Review Manager, Cochrane Collaboration, Oxford, United Kingdom, 2008), and intention-to-treat analyses were used when possible.

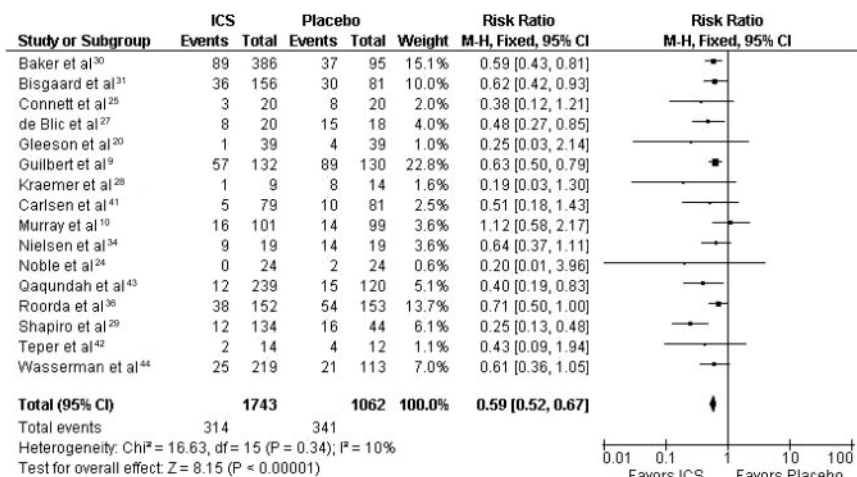
RESULTS

Eighty-nine abstracts were identified in the initial search. Of them, 29 randomized, controlled trials (3592 children) met the inclusion criteria and were selected for analysis.^{9,10,18–44} Details of the selection process are shown in Fig 1. Twelve trials included fluticasone MDI^{9,10,31,35,36,38–44}, 7 nebulized budesonide suspension,^{23,26,27,29,30,32,33} 7 budesonide MDI,^{19–22,24,25,34} 2 beclomethasone MDI,^{28,37} and 1 nebulized beclometha-

TABLE 1 Characteristics of Selected Studies

Reference	Study Design	n	Age, Mean (Range), mo	Treatment	Jadad Score	Duration of Therapy, wk
Webb et al ¹⁸	R, DB, CO	16	41 (23–60)	BDP 150 µg Neb	2	8
Carlsen et al ¹⁹	R, DB, PG	44	16 (6–24)	BUD 400 µg MDI	4	8
Gleeson and Price ²⁰	R, DB, CO	39	51 (26–71)	BUD 400 µg MDI	3	6
Greenough et al ²¹	R, DB, CO	19	51 (24–60)	BUD 400 µg MDI	2	6
Bisgaard et al ²²	R, PG	77	24 (11–36)	BUD 800 µg MDI	2	12
van Bever et al ²³	R, DB, CO	23	10 (3–17)	BUD 1 mg Neb	4	4
Noble et al ²⁴	R, DB, CO	24	11 (4–17)	BUD 300 µg MDI	3	6
Connett et al ²⁵	R, DB, PG	40	22 (12–36)	BUD 400 µg MDI	3	24
Ilangoan et al ²⁶	R, DB, PG, M	3	27 (10–60)	BUD 2 mg Neb	3	8
de Blic et al ²⁷	R, DB, PG	38	17 (6–30)	BUD 2 mg Neb	3	12
Kraemer et al ²⁸	R, DB, PG	23	12 (2–25)	BDP 300 µg MDI	3	6
Shapiro et al ²⁹	R, DB, PG, M	178	80 (48–108)	BUD 0.5–2 mg Neb	3	12
Baker et al ³⁰	R, DB, PG, M	481	55 (7–108)	BUD 0.25–3 mg Neb	3	12
Bisgaard et al ³¹	R, DB, PG	237	28 (12–47)	FLUT 100–200 µg MDI	3	12
Kemp et al ³²	R, DB, PG, M	359	56 (5–107)	BUD 0.25–1 mg Neb	4	12
White et al ³³	R, DB, PG, M	481	55 (7–108)	BUD 0.25–1 mg Neb	4	12
Nielsen and Bisgaard ³⁴	R, DB, PG	38	53 (35–71)	BUD 800 µg MDI	3	8
Chavasse et al ³⁵	R, DB, PG	37	9 (3–12)	FLUT 300 µg MDI	5	12
Roorda et al ³⁶	R, DB, PG	305	28 (12–47)	FLUT 400 µg MDI	3	12
Barrieto et al ³⁷	R, DB, PG	36	16	BDP 400 µg MDI	3	8
Pao and McKenzie ³⁸	R, DB, CO	61	16	FLUT 200 µg MDI	4	6
Teper et al ³⁹	R, DB, PG	30	13 (6–24)	FLUT 250 µg MDI	4	24
Hofhuis et al ⁴⁰	R, DB, PG	62	11 (4–24)	FLUT 200 µg MDI	5	12
Carlsen et al ⁴¹	R, DB, PG, M	160	28 (12–47)	FLUT 200 µg MDI	4	12
Teper et al ⁴²	R, DB, PG	28	13 (7–20)	FLUT 250 µg MDI	4	24
Guilbert et al ⁹	R, DB, PG	262	36	FLUT 176 µg MDI	5	24
Murray et al ¹⁰	R, DB, PG	200	30 (12–47)	FLUT 200 µg MDI	4	36
Qaqundah et al ⁴³	R, DB, PG	359	30 (12–47)	FLUT 176 µg MDI	4	12
Wasserman et al ⁴⁴	R, DB, PG	332	36 (24–48)	FLUT 88–176 µg MDI	4	12

R indicates randomized; DB, double-blind; CO, crossover; PG, parallel group; M, multicenter; BDP, beclomethasone; BUD, budesonide; FLUT, fluticasone; Neb, nebulizer.

**FIGURE 2**
Pooled RRs for WAEs (with 95% CIs) of eligible studies comparing ICSs with placebo.

sone suspension¹⁸ like ICS treatment. The main characteristics of these studies are described in Table 1.

Wheezing/Asthma Exacerbations

Data from 16 studies* with 2805 patients showed a significant reduction in the incidence of WAEs between

the ICS and placebo groups (18.0% and 32.1%, respectively), with a RR of 0.59 (95% CI: 0.52–0.67; $P = .0001$; $I^2 = 10\%$) (Fig 2). Treatment of 7 subjects with ICS therapy prevented 1 person from experiencing a WAE compared with placebo (NNT: 7 [95% CI: 6–9]). Although patients with wheeze who received ICSs showed a significant reduction of WAEs compared with

*Refs 9, 10, 20, 24, 25, 27–31, 34, 36, and 41–44.

TABLE 2 Sensitivity Analysis of WAEs

Subgroup Comparison	RR (95% CI)	Interactive Test, ¹⁰ RR (95% CI)	P
Wheeze vs asthma	0.65 (0.55–0.80) vs 0.50 (0.41–0.61)	0.76 (0.58–0.99)	.04
Infants vs preschoolers	0.59 (0.40–0.86) vs 0.59 (0.51–0.67)	1.00 (0.66–1.50)	.99
Atopic vs nonatopic	0.64 (0.54–0.76) vs 0.59 (0.42–0.73)	0.92 (0.66–1.27)	.62
Study quality (Jadad score: <4 vs ≥4)	0.55 (0.47–0.66) vs 0.63 (0.52–0.76)	1.12 (0.86–1.45)	.37
MDI vs nebulizer	0.62 (0.53–0.72) vs 0.49 (0.38–0.63)	0.79 (0.58–1.06)	.12
Budesonide MDI vs fluticasone MDI	0.47 (0.28–0.79) vs 0.65 (0.55–0.73)	1.38 (0.80–2.36)	.24
Duration of study (<12 vs ≥12 wk)	0.47 (0.27–0.80) vs 0.61 (0.53–0.70)	1.29 (0.74–2.27)	.36

TABLE 3 Analysis of Secondary Outcomes

Outcome	n	Measure (95% CI)	P	I ² , %
Withdrawals caused by WAEs	2976	RR: 0.52 (0.43–0.63)	.0001	0
Mean change from baseline in symptom score	2288	SMD: 0.93 (0.49–1.37)	.0001	94
Mean change from baseline in albuterol use	1309	SMD: 0.63 (0.30–0.63)	.0001	80
Mean change from baseline in FEV ₁ , L	1242	WMD: 0.07 (0.05–0.09)	.0001	0
Mean change from baseline in PEF, L/min	766	WMD: 13.8 (5.34–22.4)	.0001	0

SMD indicates standardized mean difference; WMD, weighted mean difference.

those taking placebo, they presented a higher rate of WAEs compared with asthmatic patients (Table 2). Otherwise, there were no significant differences according to age (infants versus preschoolers), atopic status, Jadad score (<4 vs ≥4), method of ICS delivery (MDI versus nebulizer), ICS choice (budesonide MDI versus fluticasone MDI), or duration of study (<12 vs ≥12 weeks).

Secondary Outcomes

Fifteen studies† reported a significant lower rate of withdrawals because of WAEs in patients taking ICSs (11.2%) compared with placebo (15.3%) (NNT: 25 [95% CI: 15–78]) (Table 3). Ten studies‡ showed that the mean change from baseline in symptom score of patients who received ICSs decreased significantly compared with placebo. In the same way, data showed a significant decrease of albuterol use in patients treated with ICSs^{25,26,32,33,35,44} (Table 3). Finally, data from 4 trials indicated that ICSs increased the final change from baseline in mean FEV₁^{29,30,32,33} (mean increase: 0.07 L) and PEF^{30,33,43,44} (mean increase: 13.8 L/min) (Table 3).

DISCUSSION

To our knowledge, this is the first meta-analysis performed exclusively to explore the efficacy of ICSs in infants/preschoolers with wheeze or asthma. Regarding the primary outcome, we found that ICS therapy was associated with significant reduction in WAEs (in nearly 40% and with a NNT of 7). This is a very relevant finding, because WAEs account for the largest part of direct health costs for asthma. Although this WAE reduction appeared in both wheeze and asthmatic groups, posthoc subgroup analysis suggests that this effect was more relevant in children with a diagnosis of asthma. On the other hand, this beneficial effect was independent of

age, atopic condition, type of ICS, mode of delivery, and study quality and duration.

In addition, children treated with ICSs had significantly fewer withdrawals because of WAEs (in nearly 50%), less albuterol use, and more clinical (change in symptoms score) and functional (change in PEF and FEV₁ from baseline) improvement than those children on placebo treatment.

There is no doubt that chronic asthma in school-aged children responds well to ICSs, accounting for their adoption by most of the latest guidelines worldwide.^{6–8} However, the efficacy of ICSs in infant/preschooler wheezing has been controversial, with the different response at this age hypothesized to be a consequence of dissimilar underlying pathology.⁵ From epidemiologic studies, we know that before the age of 6, mainly 2 phenotypes of wheezing can coexist: “transients” (those who have symptoms in the first 3 years of life, and after that 70%–80% become asymptomatic and without risk for later development of asthma) and “persistents” (those who continue to be symptomatic into childhood). This latter group can be further divided into 2 groups: “immunoglobulin E-associated wheezers,” who almost certainly have eosinophilic airway inflammation, the counterpart of adult atopic asthma, and “nonatopic wheezers,” who also have persistent symptoms and in whom viral infection will be implicated.¹

Obviously, these divisions are an oversimplification, because some atopic children may stop wheezing by 5 years of age, whereas others (nonatopic children) could wheeze with viral infection into midchildhood. Moreover, an apparent phenotype may change with time (eg, an infant may initially not have any atopic manifestations but may wheeze with viral colds and only later in life develop skin-prick test sensitivity and interval symptoms). However, a recent study⁴⁵ revealed similar pathologic features (epithelial reticular basement membrane thickness and eosinophilic inflammation on the bron-

†Refs 18, 20, 22, 25, 27, 29, 30, 32, 33, 36, 39, and 41–44.

‡Refs 26, 28–30, 32, 33, 35, 37, 43, and 44.

chial biopsies) from preschoolers with wheezing with and without atopic characteristics as those seen in adults and school-aged children with asthma. Another division that can also be helpful to clinicians is the pattern of symptoms: "intermittent" (symptoms mainly associated with viral infections or virus-induced wheeze and without interval symptoms) and "persistent" (those associated with wheezing episodes both associated with viral infections and between viral infections [eg, other triggers such as allergens, cold, pollutions, etc] and with continued symptoms over time).⁵

However, our results show that the ICSs were clinically superior to placebo in children with recurrent wheezing, either among infants (the range of age in which we can speculate that more transients wheezers can exist, although no studies on children with intermittent wheeze and intermittent treatment were included) and preschoolers (in whom there is likely to be a predominance of persistent wheezing) or among children with and without atopic predisposition. However, the effect of ICSs was more efficacious in reducing WAEs in children with a diagnosis of asthma than in those with a diagnosis of wheeze. However, it is important to note that many of these children are too young to have a confirmed diagnosis of asthma and to have completely manifested atopy. Finally, the widespread guideline recommendations⁶⁻⁸ and recent task force report¹² to use ICSs in infants/preschoolers with recurrent episodes of wheeze (of appropriate severity) are supported by the present meta-analysis, with the advantage that in this one the NNT were calculated. Nevertheless, it is important to stress that, ideally, the children who are likely to outgrow symptoms (that could be those with the diagnosis of wheeze) should be treated with minimal therapy, in comparison with the child who will progress to having chronic asthma that might merit more aggressive or longer therapy.

Ten years ago, Calpin et al⁴⁶ published a meta-analysis on 24 randomized placebo-controlled trials in childhood asthma (only 10 studies were performed in infants/preschoolers [$n = 377$]) and showed that those with persistent wheezing who received ICSs (beclomethasone or budesonide) for 4 to 24 weeks had better clinical (lower symptom score and β_2 -agonist and oral steroid uses) and functional (increased PEF rate) improvement than those who used a placebo. However, there was not a significant difference in the rate of hospital admissions (only 3 of 10 trials used this outcome variable). A recent systematic review without meta-analysis⁴⁷ that included 9 additional randomized, double-blind, controlled trials of ICSs in preschool-aged children ($n = 1196$) with multiple-trigger or persistent wheeze confirmed those results, and the authors suggested that only children with troublesome symptoms and frequent use of systemic corticosteroids should receive ICSs as a maintenance treatment for reducing their symptoms.

As was stated in the recent guidelines,⁶⁻⁸ the goal of asthma therapy is to maintain the longest duration of control asthma possible with the least amount of medication and, hence, with the lowest risk for adverse effect. Therefore, it is crucial to consider the importance of

monitoring the response to ICSs, and if a clear and beneficial response is not obvious in 4 to 6 weeks with satisfactory medication technique and adherence, the treatment should be stopped and alternative therapies or an alternative diagnosis should be considered. On the other hand, if a clear and beneficial response is sustained for at least 3 months, it is appropriate to consider a step down in therapy to evaluate the need for continued, daily long-term therapy, because some children have high rates of spontaneous remission of symptoms.⁷

For selecting those preschoolers with a greater risk of asthma, several clinical scores have been developed, the most popular of which is the asthma predictive index. This score, for use in children with 3 episodes of wheezing before the age of 3 years, includes 2 major (parental history of asthma or personal history of eczema) and 3 minor (blood eosinophilia, wheezing without colds, and allergic rhinitis) criteria.⁴⁸ The presence of 1 major or 2 minor criteria is associated with an increased risk of continued wheezing at 5 years of age. However, it is one thing to identify a child who is more prone to be an asthmatic in the future and quite another to be able to modify the natural history of the disease. The latter was tested by Guilbert et al,⁹ who after studying 285 preschoolers with a positive modified asthma predictive index found that those children on fluticasone improved their clinical and functional parameters during the 2 years of treatment in comparison to those in the placebo group, but at the end of the 1-year observation study (free of ICSs) the symptoms and pulmonary function were not different from those treated with placebo for 2 years, confirming that ICSs are helpful in decreasing symptoms but do not modify the natural history of asthma.

CONCLUSIONS

This meta-analysis shows that ICSs are useful in infants and preschoolers with persistent wheeze/asthma in reducing exacerbations (nearly in 40%) and withdrawals caused by exacerbations (nearly in 50%) as compared with placebo independent of age, diagnosis, atopy, mode of delivered, and ICSs used. Also, infants/preschoolers on ICSs had less albuterol use and greater clinical (change in symptoms score) and functional (change PEF and FEV₁ from baseline) improvement than those on placebo. These results support the current recommendations of most international asthma guidelines.

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