



An update on the efficacy of oral corticosteroids in the treatment of wheezing episodes in preschool children

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Abstract: Traditionally, oral corticosteroids (OCSs) have been the mainstay of treatment for acute wheezing episodes among preschool children with a history of recurrent wheezing. Although there is substantial evidence for the efficacy of OCSs as a treatment for asthma exacerbations in school-aged children and adolescents, recent clinical studies questioned the benefits of OCSs as a treatment for acute wheezing in preschool children. This review summarizes the current evidence on the efficacy of OCSs as a treatment for acute wheezing episodes among preschool age children with episodic wheezing, focusing on studies performed in three different settings: OCS treatment initiated by parents in the outpatient setting, OCS treatment initiated in the emergency department (ED), and OCS treatment among hospitalized preschool children. The results of most studies reviewed in this paper do not support the efficacy of OCS treatment among preschool children with recurrent wheezing. The heterogeneity of early childhood wheezing and asthma might be part of the explanation for lack of efficacy of this intervention noted in multiple studies.

Keywords: asthma, oral corticosteroids, preschool children, wheezing

Introduction

International and national asthma guidelines recommend oral corticosteroids (OCSs) as a treatment for acute exacerbations that are not responsive to bronchodilators [National Asthma Education and Prevention Program, 2007; GINA, 2011]. There is substantial evidence for the efficacy of OCSs as a treatment for asthma exacerbations in school-aged children and adolescents, especially in the acute care setting where OCS treatment is associated with lower risk of relapse, fewer hospitalizations, and less need for β_2 -agonist treatments [Rowe *et al.* 2007]. Traditionally, wheezing episodes among preschool children have been treated with OCSs based on the established efficacy of OCSs among school-aged children and adolescents with asthma. However, many of the preschool children have a disease phenotype that is different than that seen among older children with established asthma, as many of these young children experience significant morbidity during acute episodes of wheezing, but have minimal respiratory symptoms consistent with persistent asthma between these episodes (i.e. the ‘severe

intermittent wheezing’ phenotype) [Bacharier *et al.* 2007]. Recently, the results of clinical studies questioned the benefits of OCSs for acute wheezing in preschool children; and numerous editorials that have followed these studies have suggested that the role of OCS treatment among preschool children should be reevaluated due to concerns of lack of efficacy and its potential side effects [Bush, 2009; Grigg, 2010; Gergen, 2013]. The purpose of this review is to present the current evidence for the efficacy of OCSs in preschool age children with recurrent wheezing.

Selection of studies in this review

This review focuses on the efficacy of OCSs in preschool age children with recurrent wheezing. Therefore, we have not reviewed the evidence from studies in which most/all patients presented in their first wheezing episode [Jartti *et al.* 2006; Lehtinen *et al.* 2007; Lukkarinen *et al.* 2013]. A summary of the management of this distinct clinical scenario has been reviewed elsewhere [Beigelman and Bacharier, 2014].

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This review focuses on the evidence originating from randomized double-blinded and placebo-controlled trials (RDBPCTs), and from observational trials that took specific measures to minimize selection and measurement biases. Thus, this review does not include the result of a small ($n = 32$) nonrandomized and nonblinded trial by Brunette and colleagues [Brunette *et al.* 1988], as well as a prospective observational trial by Najada and colleagues [Najada *et al.* 2001] that investigated the efficacy of OCSs to prevent urgent visits while using a historical cohort as the control group. Since the recurrent wheezing phenotype in preschool children is the focus of this review, it does not include studies that reported outcomes for wide age ranges of children without specific subgroup analysis for preschool age children [Harris *et al.* 1987; Storr *et al.* 1987; Gleeson *et al.* 1990; Scarfone *et al.* 1993; Jartti *et al.* 2007a].

Studies investigating the efficacy of OCSs in preschool age children with episodic wheezing are very heterogeneous in their study designs, wheezing phenotypes, settings (e.g. parents initiated treatment at home *versus* inpatient study), and dosing regimens. Therefore, we grouped the studies based on their primary outcome, which is related to the setting of the intervention. The main goals of studies performed in the outpatient setting are to prevent urgent visits and to relieve respiratory symptoms by OCSs provided by the parents. Studies performed in emergency departments (ED) predominantly aim to prevent hospitalization, while studies in the inpatient setting aim toward shortening the duration of hospitalization.

Studies performed in the outpatient setting

Outpatient RDBPCTs

Three clinical trials have investigated the efficacy of OCSs for recurrent wheezing among preschool children in the outpatient setting. A RDBPCT by Oommen and colleagues [Oommen *et al.* 2003] enrolled children 1–5 years old with a history of hospital admissions for viral-induced wheeze. Children were randomized to parent-initiated prednisolone 20 mg/day for 5 days, or placebo at the next episode of viral wheeze, defined as wheeze occurring within 2 days of the onset of coryzal upper respiratory tract symptoms. The primary outcome was the parent-reported 7-day respiratory symptom scores that assessed daytime

and nighttime cough, wheeze, and respiratory difficulties as well as daytime play limitations. Additional stratification was performed based on the child's level of eosinophilic priming defined by serum levels of eosinophilic cationic protein and eosinophilic protein X. The purpose of this stratification was to evaluate OCS response among those children at greater risk for developing persistent atopic asthma. Outcome data was available for 120 children. Grant and colleagues [Grant *et al.* 1995] conducted a crossover RDBPCT (6 months in each block) of children 2–14 years old ($n = 86$) with at least two previous urgent asthma visits in the preceding 12 months. Children were randomized to a single 2 mg/kg (up to 60 mg) dose of parent-initiated prednisone, or placebo, given if children did not respond to treatment with 3 hours of their regular asthma rescue medications. The primary outcome was the number of outpatient clinic or ED visits for acute asthma. Secondary outcomes included the number of episodes resulting in hospital admissions. This review will present the results of the subgroup analysis that included only the subpopulation of 2–5-year-old children.

Webb and colleagues [Webb *et al.* 1986] conducted a small double-blinded, partial crossover trial of children ($n = 38$) less than 18 months of age with at least two previous wheezing episodes. Children were randomized to either receive parent-initiated prednisolone 1 mg/kg BID for 5 days, or placebo, for an acute wheezing episode. Crossover analysis was done if patients did not improve within 8 days of initiating treatment or if they had a second attack. Outcomes were reported for the entire study population and for age-stratified groups: 0–6 months, 6–2 months, and 12–18 months of age. The primary outcome was the difference in parent-recorded symptom scores over eight days.

Results of the RDBPCT outpatient studies

Effect on prevention of clinic visits, ED visits, and hospitalization. The results from the studies by Oommen and colleagues [Oommen *et al.* 2003] and Grant and coworkers [Grant *et al.* 1995] found that OCS treatment initiated at home by the parents did not prevent unscheduled clinic visits, ED visits, or hospital admissions. Grant and colleagues reported outcomes for those attacks in which the study medication was given (more than 60% of the episodes) and surprisingly revealed that in the subgroup of 2–5 year olds

prednisone administration compared to placebo was associated with a greater proportion of episodes that resulted in unscheduled clinic or ED visits: 35% *versus* 14%, $p = 0.04$). Oommen and colleagues [Oommen *et al.* 2003] revealed a similar trend toward less favorable outcomes associated with parent initiated OCSs at home by reporting a numerically, but not statistically significant, higher proportion of episodes that resulted in hospitalization in the prednisolone group (12% *versus* 3% $p = 0.06$).

Effect on symptoms and reduction rescue albuterol use. Oommen and colleagues [Oommen *et al.* 2003] and Webb and coworkers [Webb *et al.* 1986] found no significant improvement in symptom scores between treatment and placebo groups. Moreover, Oommen and colleagues found no difference in symptom scores in children with either high or low eosinophilic priming suggesting that OCSs are not beneficial during an acute wheezing episode even in those at greater risk of developing persistent atopic asthma. Finally, early parent OCS treatment at home compared with placebo was not associated with a reduced number of rescue albuterol treatments [Oommen *et al.* 2003].

Overall, these RDBPCTs revealed no benefit of parent-initiated OCSs at home with regard to prevention of urgent visits or improvement of clinical symptoms. The suboptimal study adherence in Oommen and colleagues' study reduces its external validity and precludes drawing a firm conclusion about lack of efficacy of OCS treatment for outpatient wheezing, as approximately 70% of parents were not fully adherent to study protocol. However, Grant and colleagues' study had a higher study adherence and showed an unexpected result: OCS treatment was associated with an increased number and proportion of episodes that resulted in ED visits. The exact cause of this unexpected finding could not be determined.

Outpatient post-hoc analysis

Challenges such as low adherence to study procedures and intervention make it difficult to investigate the efficacy of OCSs in the outpatient setting by a prospective randomized trial. Therefore, we recently took a different approach to investigate the efficacy of OCSs in the outpatient setting [Beigelman *et al.* 2013]. The study included *post-hoc* and replication analyses in two outpatient

cohorts of children aged 1–5 years with recurrent wheezing participating in two clinical trials of the Childhood Asthma Research and Education (CARE) Network: the Acute Management Intervention Strategies (AIMS) [Bacharier *et al.* 2008], and the Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST) clinical trials [Zeiger *et al.* 2011]. In both studies, prednisolone (once daily dose at 2 mg/kg/day for 2 days, followed by 1 mg/kg/day for an additional 2 days) was a rescue treatment prescribed for significant lower respiratory tract illnesses (LRTIs), based on specific predefined protocol criteria. Symptom scores during LRTIs (more than 700 episodes in each cohort) were compared between episodes that were and were not treated with OCSs after adjusting for differences in disease and episode severity covariates that could result in a selection bias (i.e. the more severe episodes are more likely to be treated with OCSs), while using a propensity score adjustment [Beigelman *et al.* 2013]. The results in the initial cohort (AIMS [Bacharier *et al.* 2008]) showed that the addition of OCS treatment during significant LRTI did not reduce symptoms severity, measured by symptoms scores, and it did not hasten clinical recovery measured by the time to resolution of symptoms. The results were confirmed in the validation cohort (MIST [Zeiger *et al.* 2011]), which includes only preschool children who have higher risk for future asthma based on a positive modified asthma predictability index (mAPI) status, suggesting that in this study OCS treatment did not reduce symptoms severity even among these preschool children with recurrent wheezing who have personal history of atopy and/or family history of asthma. Although the methodological approach of this study was very sound, an unknown residual bias could not be excluded based on the *post-hoc* nature of this study. Therefore, this study should be viewed as hypothesis generating, and should be followed by outpatient prospective trials.

Studies performed in ED setting

RDBPCTs in the ED

Two RDBPCTs investigated the efficacy of OCSs in the ED setting. Tal and colleagues [Tal *et al.* 1990] conducted an age-matched RDBPCT of children ($n = 76$) 7–54 months old with a history of at least three previous wheezing episodes seen in the ED with acute asthma symptoms. Children were randomized to a single dose of 4 mg/kg of

IM methylprednisolone, or placebo, given within 30 minutes of ED arrival, as well as inhaled open-label salbutamol. Patients were admitted or discharged after 3 hours based on clinical criteria. The primary outcome was the rate of hospital admission. Subgroups analysis for children 7–24 months old and for children 25–54 months old was reported.

A RDBPCT by Csonka and colleagues [Csonka *et al.* 2003] studied the effect of oral prednisolone (2 mg/kg once then 2 mg/kg/day BID for 3 days) given in the ED on hospital admission rates among 123 children 6–35 months old with not more than one previous physician diagnosed wheezing episodes. A total of 44% of the placebo group and 37% of the prednisolone group had never been treated for wheezing before.

Results of the RDBPCT ED studies

Prevention of hospital admissions and reduction in length of stay. The ED trials yielded conflicting results. Tal and colleagues [Tal *et al.* 1990] reported that systemic corticosteroid treatment was associated with a significantly smaller proportion of participants requiring admission (20% *versus* 43%, $p < 0.05$). The treatment effect was significant among children 7–24 months old but not among children 25–54 months old. However, Csonka and colleagues [Csonka *et al.* 2003] found no significant difference in the percentage of those admitted from the prednisolone compared with the placebo group (54% *versus* 53%; $p = 0.88$); OCS treatment, among the children who were eventually hospitalized, was associated with numerically shorter, but not statistically significant, duration of hospital stay (2 *versus* 3 days, $p = 0.06$).

Improvement in respiratory symptoms. Tal and colleagues reported a significant improvement in symptom scores ($p < 0.01$) and Csonka and colleagues reported a reduced median duration of symptoms in hospitalized children from 2.0 days in the placebo group to 1.0 day in the prednisolone group ($p < 0.001$). Csonka and colleagues found no significant difference in asthma revisits within 14 days after ED discharge in the prednisolone *versus* placebo group (25% *versus* 28.8%; $p = 0.67$).

Overall, these two studies, which investigated the efficacy of systemic steroids in the ED setting, yielded conflicting results regarding the effect of

systemic corticosteroids on hospitalization prevention; however, the intervention was beneficial for improvement in respiratory symptoms. There were important differences between study populations as approximately 40% of the children in Csonka and colleagues' trial never wheezed before, compared with Tal and colleagues' study population that included only children with at least three previous wheezing episodes

Studies performed in the inpatient setting

Until recently, only one relatively small study has investigated the efficacy of OCSs in a cohort of hospitalized preschool children: Fox and colleagues [Fox *et al.* 1996] conducted a RDBPCT enrolling children ($n = 62$) 3–15 months of age with at least one previous episode of wheeze hospitalized due to acute wheezing. Children were randomized to one of three groups: group A received oral salbutamol and prednisolone 2 mg/kg/day for 5 days, group B received oral salbutamol and placebo, and group C received placebo and placebo. The investigators reported on a reduction in number of treatment failure, defined as readmission to the hospital and/or the presence of wheeze on day 14, with oral salbutamol compared to placebo. However, adding oral prednisolone did not reduce the risk of treatment failure, and did not improve symptom scores.

The main evidence on the efficacy of OCS treatment for hospitalized children with viral wheeze has originated from a multicenter RDBPCT by Panickar and colleagues [Panickar *et al.* 2009]. The study population included children between 10 and 60 months of age ($n = 687$) with acute wheezing preceded by viral upper respiratory tract infection (URI) symptoms. A total of 68% of the placebo group and 63.6% of the prednisolone group had at least one previous wheezing episode, and 124 (18%) children had a positive API. Children were randomized to receive prednisolone: 10 mg/day for 5 days for children 24 months old and younger, or 20 mg/day for 5 days for children older than 24 months; or placebo. There was no significant difference in the primary outcome: the median time until actual discharge between the prednisolone and placebo groups (13.9 *versus* 11.0 hours, $p = 0.18$), or in the median time until ready for discharge (12.0 *versus* 10.1, $p = 0.16$). There was no significant difference between the groups in all secondary outcomes including: clinical symptoms measured by the study team using the Preschool Respiratory Assessment Measure

(PRAM) scale scores over the first day of admission, the mean 7-day symptom score assessed by the parents, the mean number of albuterol treatments given at home over a 7-day period, the time required for the child to be 'back to normal', and the number of hospital readmissions for wheezing within a month after discharge. No positive treatment effect was noted among patients with higher risk for future asthma as there was no difference in the duration of hospital stay among patients with a positive API. Stratification by baseline PRAM score did not reveal any significant differences in the time to actual discharge, suggesting that OCSs response was not dependent on the initial severity of the episode.

Panickar and colleagues concluded that the most likely explanation for lack of OCSs efficacy in their trial, in contrast to the beneficial effects reported by Tal and colleagues [Tal *et al.* 1990] in the ED setting, is related to disease phenotype, as the majority of children in their trial did not have 'the classic atopic asthma phenotype'. However, even stratification by API status did not detect any beneficial effects of OCS therapy suggesting a lack of OCS effect even in patients with atopic characterizations. We suggest that the negative results of this study could also be related to the relatively mild disease severity of these exacerbations, as the mean duration of hospitalization in the placebo group was 13.9 hours, making it hard to detect additional reduction in duration of hospitalization. It should not be excluded that potential OCSs benefits might be detected among a cohort with more severe episodes and/or longer duration of hospitalization. Although we highlighted this potential limitation of this study, we still believe that the negative results of this large and well-designed trial are likely an accurate reflection of the lack of efficacy of OCSs for viral-induced wheeze.

Although most current evidence suggests that OCSs are not an effective treatment for viral-induced wheeze, it may be that OCS response is virus related. This was recently suggested by Jartti and colleagues [Jartti *et al.* 2007] who conducted a *post-hoc* analysis of a RDBPCT that investigated the effect of 3 days of prednisolone *versus* placebo on the duration of hospitalization among children 3 months to 7 years old (mean age of 2.1 *versus* 2.9 years in the prednisolone *versus* placebo groups) who had at least two previous wheezing episodes. Among the entire study population

there was no difference in time until ready for discharge between the prednisone and placebo groups. However, there was a significant reduction in the time until ready for discharge in children treated with prednisone among the subgroup of children with positive viral polymerase chain reaction (PCR) studies for rhinovirus or enterovirus. This is the first study to demonstrate a potential virus-specific effect of OCS treatment. As these findings originated from a *post-hoc* analysis, confirmation by a future prospective trial is warranted.

Summary of evidence and discussion

The available data suggest that there is little high-quality evidence to support the efficacy of OCSs in preschool children with recurrent wheeze (i.e. the severe intermittent wheezing phenotype), as only one RDBPCT clearly showed benefit for this intervention when provided in the ED [Tal *et al.* 1990] (Table 1). The largest RDBPCT investigating the efficacy of OCSs for episodic wheeze among preschoolers was performed in the inpatient setting and did not detect any benefit for the intervention [Panickar *et al.* 2009]. RDBPCTs in the outpatient setting also failed to demonstrate clinical efficacy of OCSs given by the parents at home. However, the exact role of OCSs in the treatment of outpatient wheezing episodes could not be definitely determined, as the largest outpatient RDBPCT was complicated with low parents' adherence to study procedures, which affects the external validity of its results. A *post-hoc* analysis conducted to overcome this obstacle of low adherence in outpatient trials revealed no benefit of OCS treatment [Beigelman *et al.* 2013].

The negative results of the outpatient studies may be related to the relatively mild severity of these episodes leaving little room for clinical improvement. However, the study by Panickar and colleagues [Panickar *et al.* 2009] that was performed in the inpatient setting, and theoretically should have included the most severe patients, failed to show benefits for OCS treatment. Nevertheless, mild severity of exacerbation as a reason for negative results could not be completely ruled out as even this inpatient study [Panickar *et al.* 2009] included not very severe patients, as evident by a relatively short duration of hospitalization. It was recently suggested that lack of OCS efficacy in previous trials might be related to relatively low OCS dosing, and that

Table 1. Summary of studies investigating the efficacy of oral corticosteroids in the treatment of wheezing episodes in preschool children.

Study	Population	Intervention	Outcomes	Results
Outpatient studies				
Oommen <i>et al.</i> [2003] RDBPCT	1–5 year olds ($n = 120$) with history of hospitalization for wheeze, stratified by eosinophilic priming status	Early parent-initiated prednisolone 20 mg/day x 5 days, or placebo	1. Parent reported symptom scores 2. Admission rates, frequency of rescue medication use, and ED visits	No significant difference in symptom scores (independent of eosinophilic priming status) No significant difference in hospitalization or ED visits rate
Grant <i>et al.</i> [1995] RDBPCT, crossover design	2–14 year olds ($n = 86$) with history of 2 acute visits for asthma in past 12 months. Specific subgroup analysis of the 2–5 year olds	Parent-initiated prednisone 2 mg/kg x 1 (max 60 mg), or placebo, if no response to rescue asthma medication within 3 h from the initiation of exacerbation	1. Unscheduled outpatient and ED visits 2. Admission rates	Results for the 2–5 years old group: Higher number and a greater proportion of episodes that resulted in unscheduled outpatient visits or ED visits once the children were treated with prednisone
Webb <i>et al.</i> [1986] Double-blinded partial-crossover trial	<18 months old ($n = 38$) with ≥ 2 previous wheezing episodes	Parent-initiated prednisolone 1 mg/kg BID x 5 days, or placebo	1. Difference in symptom scores over 8 days	No significant improvement in symptom scores on days 1, 3, 5, or 8 between the treatment groups
Beigelman <i>et al.</i> [2013] <i>Post-hoc</i> analyses of 2 RDBPCTs	1–5 year olds with episodic wheeze (at least 2 previous episodes) participating in 2 clinical trials (more than 700 episodes in each cohort)	Prednisolone 2 mg/kg/day x 2 days, then 1 mg/kg/day x 2 days, prescribed as a rescue treatment based on predefined protocol criteria	1. Difference in symptom scores 2. Time until resolution of symptoms	Prednisolone treatment was not associated with a reduction in symptoms severity or in a shorter time until symptom resolution
Emergency department studies				
Tal <i>et al.</i> [1990] Age-matched RDBPCT	7–54 months old ($n=76$) with ≥ 3 previous wheezing episodes, 7–24 months old and 25–54 months old subgroup analysis	Single dose of IM methylprednisolone 4 mg/kg, or placebo within 30 minutes of ED arrival	1. Admission rate 2. Symptoms score	Significant reduction in admission rate (significant in 7–24 month olds, but not in the 25–54 month olds) Significant improvement in symptoms score
Csonka <i>et al.</i> [2003] RDBPCT	6–35 month olds ($n = 123$) with ≤ 1 previous wheezing episodes (35–45% in each group with no history of previous wheezing episodes)	Prednisolone 2 mg/kg once then 2 mg/kg/day x 3 days, or placebo	1. Admission rate 2. Length of hospital stay, duration of symptoms, revisits within 14 days of ED discharge, revisits after hospitalization	No significant difference in admission rate Significant reduction in symptom duration No significant difference in length of hospital stay, revisits after initial ED visit, or after the hospitalization
Inpatient studies				
Fox <i>et al.</i> [1996] RDBPCT	3–15 months old ($n = 62$) with ≥ 1 previous wheezing episode	Group A: oral salbutamol + prednisolone (2 mg/kg/day x 5 days) Group B: oral salbutamol + placebo Group C: placebo + placebo	1. Clinical symptom scores on days 3, 5, 7, 10, and 14 2. Duration of hospitalization, salbutamol use, treatment failures	Reduction of treatment failures with the addition of salbutamol, but not with the addition of prednisolone No significant decrease in symptom scores

(Continued)

Table 1. (Continued)

Study	Population	Intervention	Outcomes	Results
Outpatient studies				
Panickar <i>et al.</i> [2009] RDBPCT	10–60 months old ($n = 687$) with acute wheeze preceded by URI symptoms. Two third of participants with history of previous wheeze. Subgroup analysis based on API positivity status and additional stratification based on initial symptoms score	Prednisolone 10 mg/day x 5 days (≤ 24 months old), Prednisolone 20 mg/day x 5 days (≥ 24 months old); or placebo	1. Duration of hospitalization 2. Symptoms score over the first 24 hours, mean 7-day symptom score, albuterol use	No significant difference in duration of hospitalization, 24 h symptom score, mean 7-day symptom score, or albuterol use (independent of API status, or initial symptom score)
Jartti <i>et al.</i> [2007] Post hoc analysis of RDBPCT	3 months to 7 years old (median age 2.1–2.9 years) with ≥ 2 previous wheezing episodes	Prednisolone 2 mg/kg once then 2 mg/kg/day divided TID x 3 days, or placebo	Time until ready for discharge	No significant difference in the primary outcome for the entire study population Significant reduction in the time until ready for discharge among patients with evidence for rhinovirus or enterovirus respiratory infection
API, asthma predictability index; ED, emergency department; LRTI, lower respiratory tract illnesses; URI, upper respiratory tract infection; RDBPCT, randomized double-blinded and placebo-controlled trial.				

higher OCS dosing could result in clinical improvement [Weinberger, 2014]. Although this could not be excluded completely, there is no solid evidence that higher OCSs dosing in children would provide additional benefits, as a randomized controlled study in children hospitalized for asthma exacerbation that compared the efficacy of three single doses of prednisolone (0.5, 1, or 2 mg/kg) showed no differential effects on the duration of hospitalization, improvement in pulmonary function, or clinical scores [Langton Hewer *et al.* 1998]. Timing of the intervention might affect the response to treatment: Early OCSs administration given very early at the course of exacerbation potentially could prevent the development of acute airway inflammation. However, the two outpatients studies that have investigated early parents administration of OCSs at home failed to show benefit of this intervention [Grant *et al.* 1995; Oommen *et al.* 2003]. Finally, lack of OCS response noted in the studies by Csonka and colleagues [Csonka *et al.* 2003] and Panickar and coworkers [Panickar *et al.* 2009] might be related to inclusion of first-time wheezers among study participants. This might dilute a potential

effect of OCSs among populations of preschool children with viral-induced recurrent wheeze, as the lack of effect of systemic corticosteroids in first-time viral-induced wheeze (i.e. viral bronchiolitis) has been previously demonstrated [Corneli *et al.* 2007].

We do not suggest that response (or lack of response) to OCSs is solely age related, as we do not believe that there is a well-defined age cutoff after which children start to respond to OCSs. Instead, we suggest that the age-dependent differential response to OCSs may be attributed to different phenotypes of early childhood wheezing and asthma. These phenotypes might be associated with different patterns of airway inflammation, which in-turn might result in a differential OCS response. It could be that preschool children with recurrent wheezing have a greater extent of acute neutrophilic airway inflammation, which is more steroid resistant; while older school children with established asthma have more chronic eosinophilic airway inflammation, which is more corticosteroid responsive. Lack of chronic eosinophilic airway inflammation among young children with

recurrent wheezing was confirmed in one study [Le Bourgeois *et al.* 2002], but not in another study [Saglani *et al.* 2007]. The exact type of airway inflammation among these young children, and its association with disease phenotype, are yet to be determined.

Conclusions and recommendations

The vast majority of studies that evaluated the efficacy of OCSs among preschoolers with episodic wheeze failed to show benefit for this intervention (Table 1). However, the exact role of OCSs remains uncertain as the current studies have limitations including relatively mild severity of exacerbations in the inpatient study, and low compliance in the largest outpatient study. Based on the current evidence we suggest that clinicians should continue treating these preschool children with inhaled β -agonists during acute exacerbations, but may consider avoiding OCS treatment in outpatient episodes provided adequate follow up is assured. As the data regarding lack of efficacy of OCS treatment is even more compelling among hospitalized toddlers, we suggest that clinicians may consider postponing OCS treatment in many hospitalized recurrent wheezers, and reserve the treatment for patients with a current or an anticipated severe clinical course including: patients requiring intensive-care admission, patient who do not improve appropriately with β -agonist treatment, and patients who have indicators of severe disease (e.g. persistent hypoxemia) or other significant medical history (such as chronic lung disease). Overall, the evidence base for the management of recurrent wheezing in preschool children is still incomplete, and additional RDBPCTs are required, mainly in the outpatient setting.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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