



Use of Oral Corticosteroids in the Wheezy Toddler

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The treatment of acute wheeze in the toddler is a common clinical dilemma, as more than 50% of children in the preschool years have at least 1 wheezing episode.¹ In addition, the toddler age bracket is associated with poorer asthma symptom control and increased rates of emergency department (ED) visits for wheeze compared with school-aged, or adolescent, children.²⁻⁴ However, despite the high morbidity of early childhood wheeze, most toddlers who wheeze repeatedly in toddlerhood do not progress to persistent asthma.¹

Previous studies have noted that it is largely the atopic characteristics of the child and their immediate family that assist in predicting the persistence of asthma into later childhood.¹ For example, the Asthma Predictive Index (API) is a validated tool that uses largely atopic criteria (such as parental asthma and allergic eczema [atopic dermatitis] as major criteria and eosinophilia, wheeze apart from colds, and allergic rhinitis as minor criteria) to predict persistence of asthma into school age.⁵ Toddlers with a positive API (frequent wheeze during the first 3 years of life and either 1 major or 2 minor risk factors) are 4.3-9.8 times more likely to develop persistent asthma into school age than toddlers with a negative index.⁵ As a result, the use of a toddler's atopic history as a means of stratification may help differentiate transient, viral infection-associated wheezing from emerging persistent asthma.

Oral corticosteroids (OCS) often are used to treat acute wheeze in the toddler age group, largely extrapolating from the strong evidence base for their use in older children. Studies in school-aged children have found the use of OCS to decrease reliever medication burden, reduce risk of hospitalization, and prevent asthma relapse.⁶ In addition, delayed administration of OCS therapy in older children has been shown to be a risk factor for prolonged time for wheeze resolution.⁷ However, this effect has been demonstrated less clearly in the child who is of preschool age. Although the National Heart, Lung, and Blood Institute's Expert Panel Report 3 guideline recommends the use of OCS for toddlers with severe asthma exacerbations,⁸ the Global Initiative for Asthma notes that the "evidence is weak" for this approach.⁹ In addition, significant side effects have been demonstrated, even with short-term use of OCS therapy in young children.¹⁰

We review the role of OCS therapy in the treatment of early childhood wheeze and examine whether its role may be different based on the setting of the child, such as whether they are in a home/outpatient environment, vs ED or hospital, setting. Our methodology for this review was a search of PubMed for articles published from January 1, 1990, to March

8, 2018, with the terms "asthma," "wheeze," "oral corticosteroids," and "preschool." We filtered the search with the terms "human," "preschool," and "English." Articles resulting from this search (as well as relevant references from these articles) were reviewed and cited based on relevance.

The Role of OCS in the Management of Acute Wheeze in the Toddler

There is significant heterogeneity in the studies examining the role of OCS therapy in the management of acute wheeze in the toddler age group, and efficacy appears to vary based on the setting of the toddler (ie, outpatient vs ED/in-hospital use). A recent meta-analysis of OCS use for acute wheezing episodes in preschool-aged children by Castro-Rodriguez et al analyzed 11 studies (n = 1733) of toddlers with predominantly moderate acute asthma or recurrent wheeze exacerbations.¹¹ There was a decrease in hospitalization rates when OCS was used for young children in the ED and a decreased need for additional OCS courses in the inpatient hospital studies but among outpatient studies, OCS use was associated with a significantly increased hospitalization rate among toddlers who received them compared with placebo. In addition, although pooled analysis was not possible, the majority of studies did not report differences in hospital length of stay between OCS and placebo. However, there are limitations in generalizing the results of meta-analyses to the care of the general pediatric population, as early childhood wheeze may represent a variety of underlying etiologies, which may respond differently to therapy.

There have been 2 randomized controlled trials examining the role of home-initiated OCS in the preschool aged child, and both have come to the same conclusion that OCS use lacks efficacy in the treatment of acute wheeze in this setting (Table).^{12,13} Grant et al conducted a randomized, double-blind, placebo-controlled crossover study of 86 children aged 2-14 years with a history of 2 or more outpatient visits for

API	Asthma Predictive Index
ED	Emergency department
OCS	Oral corticosteroids

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Table. Randomized controlled trials examining use of OCS therapy in toddlers with wheeze

Authors	Year	Study design	Patient characteristics	Outcome
Grant et al ^{*12}	1995	RDBPCT; crossover study for 12 months—6 months each of oral prednisone (2 mg/kg) and placebo—given for asthma attack not improving after a dose of child's regular asthma medication.	In total, 86 children aged 2-14 years with >2 outpatient asthma visits in past year. Interval symptoms were present in 80% of sample (nocturnal or exertional wheeze). No comment on atopic characteristics.	↑ Outpatient visits in prednisone group; N/S difference in hospital admissions or number of hospital days
Oommen et al ¹³	2003	RDBPCT comparing oral prednisolone (20 mg OD for 5 days) with placebo given to children admitted to hospital with viral infection—associated wheeze to be used with next wheeze episode	In total, 217 children aged 1-5 years admitted to hospital with viral infection—associated wheeze; most (75% prednisolone, 69% placebo) had no wheeze triggers other than viral infection. History of eczema in 38% prednisolone group and 33% placebo group. Family history of asthma in 77% prednisolone group, 74% placebo group.	N/S difference in mean daytime and nighttime respiratory symptom scores or need for hospital admission (trend for more frequent hospital admissions in prednisolone group). No difference in stratification for serum eosinophil cationic protein and eosinophil protein X.
Panickar et al ¹⁴	2009	RDBPCT comparing oral prednisolone (10-20 mg OD for 5 days) with placebo given to children presenting to hospital with viral infection—associated wheeze	In total, 700 children aged 10-60 mo; majority (63.3% placebo; 61.4% prednisolone) had wheeze attacks in past year; most (81.4% placebo; 78.8% prednisolone) first hospital presentation. Eczema present in 39.4% of placebo group and 41.2% of prednisone group.	N/S difference in duration of hospitalization, interval between admission and discharge between groups, PRAM score, albuterol use, 7-d symptom score
Foster et al ¹⁵	2018	RDBPCT comparing oral prednisolone (1 mg/kg/d for 3 d) with placebo given to children presenting to the ED with viral infection—associated wheeze	In total, 605 children aged 24-72 mo; the majority (63% placebo; 62% prednisolone) had a family history of asthma; most (70% placebo; 69% prednisolone) had previous wheeze.	↓ Length of stay with prednisolone. No serious adverse events reported.

N/S, nonsignificant; OD, once daily; PRAM, Preschool Respiratory Assessment Measure; RDBPCT, randomized, double-blind, placebo-controlled trial.

↑: increased; ↓: decreased.

*Results reported for the preschool aged-group.

asthma in the preceding year, the majority of whom (80%) had interval symptoms such as nocturnal or exertional cough.¹² These children were enrolled for a year and given either oral prednisone (1 dose of 2 mg/kg, up to a maximum of 60 mg) or placebo with onset of acute wheeze that did not respond to the child's regular acute asthma medication.

Although this study included both preschool-aged and school-aged children, a subgroup analysis limited to 2- to 5-year-old children found no difference between the prednisone and placebo arms of the study in either number of asthma attacks resulting in hospital admission, or number of days of hospitalization, between the groups. In fact, there were significantly more attacks resulting in ED visits (0.87 ± 1.50 vs 0.41 ± 0.81 ; $P = .05$) in the prednisone compared with the placebo group. Grant et al concluded that “this intervention cannot be recommended for children with asthma,” although noting that further studies were required to confirm these results in other pediatric populations. However, this study did not comment specifically on atopic characteristics of the pediatric population and as a result possibly recruited less of the atopic toddlers who are more likely to develop persistent asthma. In addition, the study's use of a one-time dose of prednisone is less typical in the treatment of acute asthma than a 5-day prednisone course.

Oommen et al randomized 217 toddlers aged 1-5 years admitted to hospital with viral infection—associated wheeze to either a 5-day course of parent-initiated prednisolone (20 mg orally daily for 5 days) or placebo with the next episode of viral infection—associated wheeze.¹³ The majority had no wheeze triggers other than viral infection; only 25% in the prednisolone group and 31% in the placebo group had previous wheeze or cough without colds before hospitalization. In addition, only

32% of the patients had doctor-diagnosed asthma. However, the population was highly atopic, with atopic dermatitis present in more than 30% of the children (38% of the prednisolone group and 33% of the placebo group), and family history of asthma in more than 70% of the children (77% of the prednisolone group, 74% of placebo group). Of those who had subsequent viral infection—associated wheeze, there was no difference in mean daytime (difference in means -0.01 [-0.22 to 0.20]) or nighttime (difference in means 0.10 [-0.12 to 0.32]) respiratory symptom scores or need for hospitalization between the prednisolone and placebo groups (although there was a trend for more hospitalizations in the OCS group that failed to reach significance).

The study also allocated children based on serum eosinophil cationic protein and eosinophil protein X, both predicting a more atopic population (who theoretically are at increased risk of persistent asthma), and noted no difference in primary outcomes between treatment groups. The conclusion of this study was that there was “no clear benefit to parent-initiated oral prednisolone for viral infection-associated wheeze” in preschool-aged children. However, the young age group (with inclusion of children as young as 1 year of age) likely included some toddlers with viral bronchiolitis (ie, first episode of viral infection-associated wheeze) instead of emerging asthma, in whom OCS therapy has been shown to be less effective.¹⁶ In addition, compliance with study protocol and procedures was low, with 68% of children who had a further episode of viral infection—associated wheeze not receiving the trial medication or not filling out the symptom diary. In conclusion, the studies to date have not demonstrated efficacy for OCS therapy in the treatment of wheeze in the preschool-aged child, in the outpatient setting.

There have been 2 randomized controlled trials examining OCS use with viral infection–associated wheeze in toddlers admitted to hospital, and the studies have conflicting findings with respect to OCS use in the hospital setting. Panickar et al randomized 700 children aged 10–60 months who presented to the hospital with an acute attack of viral induced wheeze to either a 5-day course of oral prednisolone (10 mg once a day for age 10–24 months, 20 mg once a day if older) or placebo.¹⁴ The majority of these children had no cough or wheeze without a cold in the previous year, and for approximately 80% of children in both groups, this was their first hospital presentation. The study found no significant difference in duration of hospitalization (13.9 hours vs 11.0 hours [95% CI 0.77–1.05]) or interval between hospital admission and discharge (12.0 vs 10.1 hours [95% CI 0.76–1.05]) between the groups. A subgroup analysis limited to 124 toddlers at increased risk of atopic asthma (based on positive API) also found no significant difference in outcomes compared with children who were API negative ($P = .31$). The conclusion of this study was that oral prednisolone was “not superior to placebo” in the treatment of toddlers presenting to the hospital with viral-induced wheeze. However, the young age of this population, and low rates of atopy, suggests that some of these children may have had predominantly transient, viral infection–induced wheeze (and outgrow asthma by school age), instead of emerging persistent asthma.

In contrast, a newly released randomized controlled trial by Foster et al of 605 toddlers (aged 24–72 months) presenting to the ED with viral infection–associated wheeze randomized toddlers to prednisolone (1 mg/kg/d for 3 days) vs placebo.¹⁵ The majority of these children (69% placebo, 70% prednisolone group) had previous wheeze history, although the majority (73% placebo, 79% prednisolone) had no previous diagnosis of asthma. There was a strong family history of asthma (63% placebo, 62% prednisolone). The study found that prednisolone significantly reduced the length of stay in hospital compared with placebo (median 370 minutes vs 540 minutes; $P = .02$) with no serious adverse events reported during either the study or the follow-up period. The conclusion of this study was that oral prednisolone “had a clear benefit over placebo” in reducing hospital length of stay.

Beigelman et al conducted a post hoc and replication analyses of 2 randomized controlled trials of toddlers aged 1–5 years of age with a previous history of episodic wheeze to examine symptom scores during 1500 outpatient episodes of lower respiratory tract infections that were, or were not, treated with OCS.¹⁷ Post hoc analysis demonstrated no reduction in symptom severity and no accelerated clinical recovery with OCS use ($P = .46$) in either trial. The conclusion of this large study was that in 2 separate cohorts of preschool children with acute wheezing episodes, use of OCS in the home setting did not reduce symptom severity during acute viral infection. However, methodologic limitations exist with a post hoc analysis, which limits the studies’ broad applicability.

As demonstrated previously, several studies suggest a lack of efficacy to OCS therapy, although the studies on ED/in-hospital use are more heterogeneous, with some studies, such

as a recent randomized controlled trial, suggesting a benefit. In addition, there are significant limitations to the literature that exist to date. Some of these studies grouped all the toddlers together despite emerging evidence that there are various presentations of early childhood wheeze, which carry different prognoses. Some of the aforementioned studies enrolled infants younger than a year of age, in whom first episode of wheeze is more likely bronchiolitis than asthma. Steroid therapy has been noted in several studies to lack efficacy in bronchiolitis,¹⁶ which may complicate the results. In addition, there is also significant heterogeneity in the studies done to date, with respect to study design, populations recruited, as well as length and dose of OCS therapy, which makes results difficult to generalize.

Despite these limitations, there is no consistent benefit of OCS therapy in the toddler population, in particular when used in the home/outpatient setting. A recent randomized controlled trial, however, does demonstrate some benefit in the hospital setting.

What Are the Harms of OCS Therapy in the Toddler Population?

Significant side effects are possible with even short-term OCS use. In 2015, Aljebab et al conducted a systematic review of the toxicity of short-course OCS in children, examining 38 studies of 3200 children, of whom 850 had an adverse event reported.¹⁰ Common adverse events from short course (<14 days) OCS included vomiting (5.4%), behavioral changes (4.7%), and sleep disturbance (4.3%). Studies also noted adrenal suppression, increased blood pressure, weight gain, and hyperglycemia. The most concerning side effect was increased susceptibility to infection. Five randomized controlled trials noted infection due to immunosuppression (incidence of 0.9%), including 3 cases of varicella zoster requiring intensive care admission, and 1 mortality due to varicella zoster.

Concerns have been raised about the effects of OCS use and bone mineral density in children. A cohort follow-up study for a median of 7 years in 877 children aged 5–12 years enrolled in the Childhood Asthma Management Program study noted a dose-dependent reduction in bone mineral accretion in male patients ($P = .0002$) and increased risk of osteopenia in the lumbar spine in male patients ($P = .02$) with OCS bursts in childhood, with increased risk associated with increased number of OCS bursts.¹⁸

Studies also suggest that OCS therapy may be overused, particularly in the outpatient setting. A survey of physicians involved in the care of asthma in Australia noted that among 252 physicians, 85% (95% CI 80.0%–89.1%) reported recommending parent-initiated OCS therapy to parents of children with asthma.¹⁹ A data extraction study of children enrolled in the Texas Children’s Health Plan noted that among children with a diagnosis of asthma between the years 2011 and 2015, 42.1%–44.2% of these children had 1 or more OCS courses dispensed.²⁰ Dispensing rates were greatest in the toddler aged group and repeat OCS dispensing was more common in toddlers as well.

Perhaps most concerning was that 81%-83% of children prescribed OCS therapy had no other indicators of poor asthma control (such as excessive use of asthma reliever medication, ED, or hospital visits). The conclusion of this study was that patterns of dispensing suggest "substantial overprescribing" of OCS in children which is worrisome especially for those children with more persistent symptoms.

As pointed out in a review by Vuillermin et al, parent administration of OCS therapy may result in overuse of OCS as well—parents may have a lower threshold for using OCS therapy in their children, and OCS therapy may be initiated for an exacerbation that would have otherwise spontaneously resolved.²¹

As a result, the possible benefits of OCS therapy in young children also must be weighed with the uncommon, but potentially significant, risk of adverse events that have been documented, and care should be taken to ensure that OCS are prescribed judiciously.

Future Research Needs

In designing future studies, it will be very important to stratify toddlers based on those most likely to respond to corticosteroid therapy. Studies have documented that a toddler's response to steroid therapy may be preferential, and, at least for inhaled corticosteroids, largely based on the atopic history of the toddler or blood eosinophil count. For example, in the Individualized Therapy for Asthma in Toddlers (INFANT) trial, Fitzpatrick et al found that 74% of 230 toddlers had a differential response to asthma therapies (daily inhaled corticosteroid, daily leukotriene receptor antagonist, or as-needed inhaled corticosteroid with albuterol), with markers of atopy (eosinophilia and aeroallergen sensitization) predicting the best response to daily inhaled corticosteroid therapy.²² However, whether this stratification will apply to OCS as well is unclear.

The pre-emptive use of high-dose inhaled corticosteroids for intermittent wheezing episodes requires further study. In a meta-analysis of preschoolers with recurrent wheeze, this approach was shown to reduce exacerbations compared with placebo (5 studies, $N = 422$; risk ratio 0.65; 95% CI 0.51-0.81).²³ However, a recent randomized controlled study of 254 children aged 5-11 years old with persistent asthma noted no benefit to quadrupling inhaled corticosteroid dose for 7 days at onset of an asthma exacerbation ($P = .30$).²⁴ Another option might be a study of a short course of azithromycin, which recently was shown in more than 600 toddlers to decrease risk of wheeze exacerbation.²⁵ Again, it would be useful in future studies to stratify by evidence of atopic history in the child (aeroallergen sensitization, eczema, parental asthma) and/or blood eosinophils. One additional research area is the need to develop indicators of atopy that are accessible in the ED or primary care setting with adequate specificity and sensitivity.

Conclusions

In light of a lack of demonstrated efficacy for OCS use in toddlers in an outpatient setting, its frequent use is concerning.

Although adverse events are rare, they can be significant and must be weighed into the decision about OCS use as well, in particular in the outpatient setting, where benefit has not been shown clearly in the toddler age group. In contrast, although the evidence is mixed, there may still be some benefit to OCS use in the ED or in-hospital setting in toddlers, with a recent study noting a very favorable response to OCS therapy in the in-hospital setting.

Until definitive studies are performed, there is little evidence that OCS therapy is beneficial in the home/parent initiated treatment of acute wheeze in the preschool-aged child in the outpatient setting. However, pending more definitive studies, it should still be considered for those most at risk, such as those hospitalized with a wheeze exacerbation, or for those toddlers with recurrent wheeze episodes (which is more likely to indicate emerging asthma instead of viral bronchiolitis, which is generally first episode of viral infection-associated wheeze in the toddlers).

In the home/outpatient setting, little endorsement of OCS use can be made in the absence of atopic history (based on the API and/or previously documented aeroallergen sensitization or eosinophilia), although some of these measures may not be readily available at the time of assessment. As the studies are more favorable in the ED/in-hospital setting, the authors would recommend that toddlers in these settings continue to be prescribed OCS therapy at this time for wheeze. ■

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