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The challenge of treating preschool wheezing episodes: the need for evidence based approaches

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Young children with intermittent wheezing suffer substantial disease morbidity, particularly related to acute exacerbations. In the June 2013 issue of the *Journal*, we presented the results of post-hoc analyses of two clinical trials conducted by the Childhood Asthma Research and Education (CARE) Network on the effect of oral corticosteroids (OCSs) on episode severity in young children with intermittent wheezing. With due diligence given to the limitations of post-hoc analyses, we presented data which suggested that OCSs did not reduce symptom severity during acute outpatient lower respiratory tract illnesses (LRTI) in preschool children with recurrent wheeze¹. Furthermore, we did not recommend abandonment of this therapeutic approach, but rather suggested that our findings should serve as a note of caution and be followed by further prospective trials. These conclusions were supported by the accompanying editorial by Dr. Gergen². In this issue of the *Journal*, Dr. Weinberger presents an additional editorial expressing concerns with our findings and conclusions³, which he describes as “nihilistic” and contradictory to his personal experience.

Dr. Weinberger states that “asthma is an uncommon pediatric admission at the University of Iowa Children’s Hospital”, and attributes this to the local medical practice of early parent-initiated OCS treatment. While hospitalization rates for asthma among preschool children have declined in recent years⁴, there exists no evidence that parental administration of OCSs at home is a major determinant of this national trend. The literature does not include any high quality trials in support of this strategy, as two double-blind placebo-controlled studies^{5, 6} have not shown benefit for early parent-directed OCSs among preschool

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children. While one of these trials was complicated by parental reluctance to begin this intervention, manifest as poor adherence to the study protocol⁶, a subgroup analysis of the other trial including only preschool children actually showed a higher rate of ED visits among those receiving OCSs⁵.

A potential explanation for lack of efficacy of OCSs in our study, as identified by Dr. Weinberger, is the potentially mild severity of the exacerbations. While these episodes did not require hospital-based care, these were typical outpatient episodes with moderate level of disease severity, and with median time to complete resolution of respiratory symptoms of 7 days¹. Furthermore, we used propensity scoring to identify episodes of greatest severity, and even among the most severe episodes, a beneficial effect of OCSs was not apparent. We agree that many of these episodes are generally self-limited, and this should also prompt reconsideration of this traditional treatment. As noted in our manuscript, our findings pertain to outpatient episodes and should not be extended to more severe episodes, such as those requiring hospital-based care (including the emergency department). Even the efficacy of OCSs among hospitalized preschool children with viral-associated wheeze is uncertain, since OCSs did not shorten the duration of hospitalization compared with placebo among more than 700 hospitalized children⁷. These findings prompted an editorial suggesting against using OCSs for outpatient episodes, and reserving this treatment for the most severely ill hospitalized patients⁸.

Dr. Weinberger suggests that the dosing of prednisolone may have contributed to the findings. Our study dosed prednisolone at 2 mg/kg/day for 2 days, followed by 1 mg/kg/day for an additional 2 days as utilized in previous NHLBI-supported trials⁹, and consistent with the evidence-based NAEPP/EPR3 Guidelines¹⁰. While Dr. Weinberger cites a 30-year old study suggesting that higher OCS dosing might be more effective among adults, there is no compelling evidence that higher OCS dosing in children would provide additional benefits, as a randomized controlled study in children hospitalized for asthma exacerbation that compared the efficacy of 3 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 scores¹¹. Of greater concern is the dose-dependent association between OCS cumulative exposure and reduction in bone mineral accretion and an increased risk for osteopenia¹². Furthermore, the occurrence of behavioral side effects including anxiety and aggressive behavior were twice as common among children receiving 2 mg/kg/day of OCS compared to children receiving 1 mg/kg/d for acute asthma exacerbations¹³. While we were cautious in our description of clinical implications in our manuscript, Dr. Weinberger's dosing recommendations come without solid evidence or citation of supporting reference(s). Although we cannot fully exclude the possibility that a higher dose might have been effective, Dr. Weinberger's suggestion to change OCS dosing to 30mg/m² twice daily is not supported by any clinical trials in this disease state or age group, and extending the finding of efficacy of greater OCS dosing in nephrotic syndrome may not be appropriate for early childhood wheezing.

A proven way through which medicine advances is by demonstrating established dogma to be incorrect. This evolution in therapeutic strategies should not be viewed as a negative, but rather as an opportunity to provide effective treatments while withholding ineffective or

potentially harmful ones. OCSs have traditionally been used for treatment of intermittent wheezing in young children largely based upon their benefits in older children and adults with established asthma experiencing exacerbations requiring acute care. In that scenario, OCS treatment has been associated with lower risk of relapses, fewer hospitalizations, and with less need for β 2-agonists treatments¹⁴. However, a growing number of studies have questioned the role of OCSs as a treatment for intermittent wheezing episodes among preschool children^{5–7}. We do not suggest that “OCS response begins *de novo* at age 5–6 years”. Instead, we believe that the established heterogeneity of early childhood wheezing/asthma, potentially related to different patterns of airway inflammation, is a plausible explanation for OCSs not being an effective treatment for every preschooler wheezing phenotype.

Treatment recommendations should be primarily based upon directly applicable evidence, when available, including studies in the specific population of interest rather than extension of findings from other populations or age groups. This should be coupled with a willingness to shift thinking as evidence builds. The evidence base for the management of recurrent wheezing in preschool children remains incomplete and the exact role of OCSs remains uncertain; additional prospective trials in this population are needed to definitively assess the clinical utility of OCSs. In addition, new treatment strategies are needed to improve the management of respiratory episodes in these preschool children.

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