CORRESPONDENCE

Oral Corticosteroids in Children with Wheezing

TO THE EDITOR: Panickar et al. (Jan. 22 issue)[1] conclude that oral prednisolone is not effective for virus-induced wheezing, and the accompanying editorial states that "it is clear that on the basis of [this study], current practice must change."[2] I disagree. The prednisolone group fared better clinically than the placebo group with respect to both the primary outcome (Table 2 of the article) and the secondary outcomes (Table 3 of the article). As compared with the prednisolone group, almost 50% more patients in the placebo group were still in the hospital after 24 hours, and the number of albuterol actuations was considerably higher. In addition, since the data were positively skewed, the authors compared the duration of hospitalization (the primary outcome measure) between the two groups as geometric means after the data underwent logarithmic transformation. This method does not reveal the presence of outliers and can overcompensate to the left, potentially masking differences between the groups. Thus, I do not understand the unequivocal support for the study expressed in the editorial.

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1. Panickar J, Lakhanpaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. N Engl J Med 2009;360:329-38.
2. Bush A. Practice imperfect — treatment for wheezing in preschoolers. N Engl J Med 2009;360:409-10.

TO THE EDITOR: Panickar et al. report no difference from placebo when low doses of prednisolone were given once daily to preschool-age children with asthma induced by viral respiratory infection. However, their study population had such rapid improvement with placebo that any treatment effect would have been obscured, even if the doses had been consistent with those that had been effective previously in controlled trials.[1]

On the basis of the study by Panickar et al., Bush states in his editorial, "Prednisolone should be administered to preschoolers only when they are severely ill in the hospital." A previously published consensus conference on the treatment of virus-induced asthma in young children concluded, "Oral corticosteroids reliably shorten hospitalization from asthma, prevent hospitalization of patients seen for urgent care, and prevent the need for urgent care if started early at home."[2]

Preventing the need for hospitalization through earlier administration of a sufficient dose of an oral corticosteroid appears to be a more logical approach.[3] In fact, my clinical experience and the outcomes I have observed support this approach.[4]

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1. Weinberger M, Abu-Hasan MN. Asthma in the pre-school child. In: Chernick V, Boat TF, Wilmott RW, Bush A, eds. Kendig's disorders of the respiratory tract in children. 7th ed. Philadelphia: Saunders, 2006:795-809.
2. Weinberger M. Consensus statement from a conference on treatment of viral respiratory infection-induced asthma in young children. J Pediatr 2003;142:Suppl:S45-S46.
3. *Idem.* Pediatric asthma and related allergic and nonallergic

THIS WEEK'S LETTERS

diseases: patient-oriented evidence-based essentials that matter. Pediatr Health 2008;2:631-50.
4. Najada A, Abu-Hasan M, Weinberger M. Outcome of asthma in children and adolescents at a specialty based care program. Ann Allergy Asthma Immunol 2001;87:335-43.

TO THE EDITOR: It appears that, in their study, Panickar and colleagues included children with a first-time attack of wheezing. Since the benefit of bronchodilators in the treatment of this disease is probably minimal and the response to corticosteroids is controversial, the inclusion of these children may have confounded the results. Conversely, oral corticosteroids reduce the risk of hospital admission among preschool- and school-age children with asthma by 25%; this reduction is similar to that observed in adults.[1] It would therefore be important to examine the effects of a first episode of wheezing, as compared with multiple episodes, and reversibility after the use of bronchodilators[2] on the treatment effect. Although oral corticosteroids administered in the emergency department are effective in reducing the length of stay among children with moderate-to-severe asthma,[3] they may not be indicated in the treatment of children with the mildest cases of asthma; thus, corticosteroids may not have been indicated in many of the children enrolled in this trial. For example, the mean Preschool Respiratory Assessment Measure (PRAM) score at 4, 12, and 24 hours in both study groups was less than 3; this value is indicative of mild airway obstruction. This finding raises the question of the reason for their prolonged stay.

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1. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database Syst Rev 2001;1:CD002178.
2. Chalut DS, Ducharme FM, Davis GM. The Preschool Respiratory Assessment Measure (PRAM): a responsive index of acute asthma severity. J Pediatr 2000;137:762-8.
3. Smith M, Iqbal S, Elliott TM, Everard M, Rowe BH. Corticosteroids for hospitalised children with acute asthma. Cochrane Database Syst Rev 2003;1:CD002886.

TO THE EDITOR: In the article by Panickar et al., it would have been useful to include the PRAM score at presentation, before the administration of the initial bronchodilator therapy, in order to determine the change in the score in response to this therapy. A previous study in this clinical setting has shown that the greater the decrease in the PRAM score, the greater the decrease in the need for hospitalization.[1] The differential response to bronchodilator therapy could be a predictor of the need for additional therapy with corticosteroids.

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1. Ducharme FM, Chalut D, Plotnick L, et al. The Pediatric Respiratory Assessment Measure: a valid clinical score for assessing acute asthma severity from toddlers to teenagers. J Pediatr 2008;152:476-80.

TO THE EDITOR: As a pediatric hematologist–oncologist, I was happy to see the article by Panickar et al. regarding the use of corticosteroids in children presenting with virus-associated wheezing. The use of oral corticosteroids can be an important part of the management of selected diseases in children. However, it is distressing to occasionally see oral corticosteroids used for nonurgent indications in an outpatient population.

Acute lymphoblastic leukemia is the most common malignant condition of childhood, with a peak incidence at 2 to 4 years of age. Exposure to corticosteroids before definitive therapy for childhood acute lymphoblastic leukemia increases the risk of resistant disease.[1] In fact, the current Children's Oncology Group study (ClinicalTrials.gov number, NCT00103285) of standard-risk acute lymphoblastic leukemia mandates more intensive therapy for some children who were treated with oral corticosteroids (but not inhaled corticosteroids) before the initiation of chemotherapy. The overlapping ages of children with acute lymphoblastic leukemia and children presenting with virus-associated wheezing mean that each year, a number of children in whom acute lymphoblastic leukemia is diagnosed have already received oral corticosteroids. I urge caution in prescribing oral corticosteroids for virus-associated wheezing in children in order to minimize the risk of these events.

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1. Révész T, Kardos G, Kajtár P, Schuler D. The adverse effect

of prolonged prednisolone pretreatment in children with acute lymphoblastic leukemia. Cancer 1985;55:1637-40.

THE AUTHORS REPLY: Koumbourlis expresses concern that the differential skewness between the study groups with regard to the primary outcome affected the results. We view this possibility as being extremely unlikely and have analyzed the data using alternative methods (i.e., with the Wilcoxon rank-sum test and Cox model), with similar nonsignificant results. The difference in the total number of albuterol actuations (mean, 66.7 in the placebo group and 52.8 in the prednisolone group), albeit nonsignificant, is interesting. However, a beneficial effect of prednisolone was consistently absent on the basis of the objective markers of the severity of wheezing. The difference in actuations therefore probably does not reflect a clinically significant difference in the severity of wheezing.

Weinberger suggests that earlier administration of prednisolone by parents at the first sign of wheezing may be effective. In a previous randomized, placebo-controlled trial, we found that initiation of treatment with prednisolone by parents at the first sign of wheezing in preschool children did not reduce symptom scores or the need for hospitalization. Taken together, our trial[1] and that of Panickar et al. do not provide support for previous consensus statements that oral corticosteroids are effective in treating wheezing in preschool children.

Ducharme et al. suggest that responsiveness to prednisolone may be a function of the previous number of attacks. To limit the number of post hoc secondary analyses,[2] we have not performed a subgroup analysis according to the number of previous attacks, but we will be delighted to share our raw data for additional analysis. The issue of the severity of wheezing at enrollment is important for assessing generalizability. We agree with Mroueh that obtaining a PRAM score before the administration of the first dose of inhaled albuterol would have been useful. Since the PRAM was not part of our routine management protocol, obtaining the PRAM score before the administration of albuterol carried the ethically unacceptable risk of delaying therapy until informed consent could be obtained. The typical pattern of wheezing in children who remained in the hospital was a transient improvement after treatment with inhaled albuterol, followed by increasing wheezing. We can therefore reassure Ducharme et al. that all children who remained in the hospital had clinically significant wheezing at some stage after they received the first dose of albuterol.

Prescribing an ineffective medication for all preschool children with wheezing in order to not overlook a minority who may have a response is appropriate if the medication is inexpensive and without side effects. Walter highlights a potential adverse effect of oral corticosteroids in young children that we have not previously considered. The lack of a clinical benefit of oral corticosteroids in preschool children with wheezing, and the potential for expected and unexpected side effects, suggest that their routine use should be reconsidered.

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1. Oommen A, Lambert PC, Grigg J. Efficacy of a short course of parent-initiated oral prednisolone for viral wheeze in children aged 1-5 years: randomised controlled trial. Lancet 2003;362:1433-8.
2. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine — reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189-94.

THE EDITORIALIST REPLIES: From the outset, the primary end point in the study by Panickar et al. was the duration of hospitalization. I doubt that any objective person could review Figure 2 of their article and consider that the authors had shown any differences, nor could the most prolonged post hoc statistical rendition of the data show that their study was anything other than a negative one (as the authors themselves conclude). Koumbourlis believes that statistically nonsignificant changes in secondary end points are of clinical importance. However, in a study involving nearly 700 children, Panickar et al. did not establish that what Koumbourlis believes to be important was anything other than a chance finding. Moreover, preschool children may have more than 10 colds a year,[1] and if every episode led to wheezing treated with oral prednisolone, the cumulative dose would be considerable. Thus, it behooves us to be sure that there are solid data to provide support for therapeutic practices.

With regard to Weinberger's points: the children studied were sufficiently symptomatic that independent pediatricians thought they could not

safely be discharged home after immediate treatment. Certainly, many had rapid improvement with albuterol alone, and as I stated, the data do not rule out an effect of oral corticosteroids in severely ill children with episodic (viral) wheezing. Although a larger dose of prednisolone might have been more effective, the children nevertheless probably received at least 1 mg per kilogram of body weight daily, which is not a trivial dose. With all due respect to the distinguished pediatricians who reached a consensus in 2003,[2] data from the study by Panickar et al. and one other study,[3] which collectively involved more than 900 children, have shown that the initiation of treatment with oral corticosteroids by parents neither prevents the need for urgent care[3] nor is necessary treatment in a huge number of preschool children with episodic viral wheezing. High-quality data from randomized, placebo-controlled trials outrank consensus statements, no matter who is at the table.

I stand by my conclusion that practice (including my own) has to change.

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1. Bush A. Recurrent respiratory infections. Pediatr Clin North Am 2009;56:67-100.
2. Weinberger M. Consensus statement from a conference on treatment of viral respiratory infection-induced asthma in young children. J Pediatr 2003;142:Suppl:S45-S46.
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Giant Osteoclast Formation and Long-Term Oral Bisphosphonate Therapy

TO THE EDITOR: Weinstein et al. (Jan. 1 issue)[1] report on giant osteoclast formation in women receiving long-term oral bisphosphonate therapy. In accordance with the results of their study, our findings from a study of paired biopsy specimens, reported in 2006,[2] showed giant osteoclast formation after 38 months in 9 of 23 men who received bisphosphonate therapy (39%). In addition to their presence in men who received alendronate, giant osteoclasts were observed when other nitrogen-containing bisphosphonates, such as risedronate and pamidronate, were administered. All these agents appeared to be associated with cytoskeletal disruption. A prolonged effect of bisphosphonates on the morphologic features of osteoclasts, as detected in biopsy specimens obtained from the group of patients who received 20 mg of alendronate in the study by Weinstein et al., was also seen in biopsy specimens obtained after teriparatide treatment in patients who had previously received bisphosphonates.[3]

In the editorial accompanying the report by Weinstein et al., Glowacki[4] notes that the spatial resolution of intracytoplasmic details in osteoclasts is too poor with the use of conventional microscopy and staining to investigate resorptive capability (Fig. 1). Instead, the authors could have used histomorphometric resorption indexes as indirect measurements.

Considering the small groups and heterogeneity of remodeling sites at the iliac crest, the finding of a dose-dependent increase in the number of osteoclasts in the study reported by Weinstein et al. may be limited by the fact that a baseline comparison was not possible and the initial histologic bone-turnover status (high or low) in the individual patient was not investigated.[5]

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5. Eriksen EF, Melsen F, Sod E, Barton I, Chines A. Effects of long-term risedronate on bone quality and bone turnover in women with postmenopausal osteoporosis. Bone 2002;31:620-5.

TO THE EDITOR: Weinstein et al. found that alendronate treatment results in the formation of giant hypernucleated osteoclasts, and the authors suggest that these cells form by fusion of existing osteoclast cells. However, there is evidence to suggest endoploidy, or nuclear replication without cytokinesis, as an alternative explanation. First,