

Prednisone for acute virus-associated wheeze in children: Panacea or one more brick in the wall?

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For decades, it has been a standard practice among community pediatricians, allergists, and pulmonary specialists to treat young children who present with acute episodes of wheeze with prednisolone. This practice is based on the general belief that episodes of wheeze likely are manifestations of asthma caused by inflammation and narrowing of the airways. Although most practitioners are aware of the strong association between colds and wheeze in children, the presence or absence of viral symptoms typically does not affect the decision of whether to treat with prednisolone. The practice is furthermore supported by recommendations from the National Institutes of Health/National Heart, Lung, and Blood Institute position statements on the management of asthma, recommendations from the Global Initiative for Asthma guidelines, and, somewhat ironically, marketing strategies of pharmaceutical companies. Indeed, it is well established that the common cold is often followed long term by loss of asthma control.¹ Therefore most clinicians use systemic prednisolone to treat acute episodes of wheeze, even in young children.

In 1987, Harris et al² published a small trial in the *Journal of Pediatrics* that supported oral prednisone as an effective therapy for acute episodes of asthma in children. This was followed the next year by a larger study wherein a short burst of prednisone given to children with asthma and acute respiratory tract infections in the ambulatory setting reduced relapses of subsequent wheeze and unscheduled health care use.³ However, this benefit was not confirmed by a later interventional study in a relatively higher-risk sample,⁴ and thus the efficacy and safety of treating children with acute virus-associated symptoms with prednisone came into question.^{5,6} A much discussed trial by Panickar et al⁷ in hospitalized children with symptoms of a viral respiratory tract infection and wheeze showed no benefit of prednisone over placebo in decreasing length of hospital stay. In the same issue of the *New England Journal of Medicine*, Ducharme et al⁸ published

a study that endorsed a class effect of corticosteroid therapy in acute virus-associated wheeze. Inhaled fluticasone given to preschool children immediately at the onset of viral respiratory symptoms was deemed safe and reduced the subsequent number of prednisone rescue bursts for refractory symptoms. Professor Andrew Bush, in writing the accompanying editorial in that issue of the *Journal*, strongly challenged both the efficacy and safety of routine use of oral prednisone in acute exacerbations of wheeze in children with viral respiratory tract infections but was careful to point out they might be indicated in critically ill children and those with markers of atopy.⁹ Although Dr Bush's position was based on a thoughtful evaluation of the evidence, it created a significant dilemma for practicing physicians. In 2007, the Joint Commission created a national standard on the inpatient care of children admitted to the hospital for asthma that included a course of systemic corticosteroids as a quality indicator.¹⁰

This issue of the *Journal of Allergy and Clinical Immunology* includes the first placebo-controlled randomized clinical trial conducted by Jartti et al¹¹ to address the effectiveness of prednisolone treatment for the first acute wheeze episode in young children infected with human rhinovirus. This is an important study with advantages over earlier trials insofar as the presence and burden of human rhinovirus infection was confirmed with molecular techniques, assignment to treatment was randomized, treatment groups were well characterized, and participants were followed both short and long term. Limitations of the trial were that it was done at a single site and the study sample was relatively small, underpowered, and confined to infants and toddlers during the first 3 years of life with an acute enough presentation to seek urgent care. In this age group the efficacy of systemic corticosteroids for acute wheeze is more difficult to determine and controversial compared with their effects in older children. Furthermore, the study results do not affect prednisolone treatment for other viruses, including respiratory syncytial virus, human metapneumovirus, and influenza, which can cause acute wheeze in this age range. Another limitation of the study is the relatively long period of time (45 hours) between the time of presentation for acute care and administration of the study drug. Nonetheless, Jartti et al¹¹ found that prednisolone treatment had subacute benefits of reducing respiratory symptoms but did not prevent long-term wheezing episodes. The results of subgroup analyses, which are problematic in a small clinical trial, showed no selective treatment effect in the 28% of infants with atopy but suggested that infants with high viral loads (>7000 copies/mL) did receive long-term benefit. This result is probably confounded by time to presentation for acute care insofar as viral loads might peak early in infection well before the infant is brought to the acute care department.

Where do we go from here? The study is less helpful in informing clinical practice insofar as assessment of viral cause and load at presentation is not feasible in preschool children who

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present with wheeze. However, Jartti et al¹¹ found benefit of prednisolone treatment in acute symptoms of the first human rhinovirus infection independent of viral load. Whereas human rhinovirus infection is the most important cause of wheezing episodes in young children, its use by general and specialty clinicians in the ambulatory setting is reasonable given that repeated bursts are monitored and adverse effects are considered. A large, pragmatic, and community-based study will be required to answer this question, especially to identify children at risk for long-term morbidity who are the most likely to benefit from prednisone treatment of acute viral infections. The answer is likely to be a complex one, and benefits will not only depend on risk factors present in the children *per se* but also the category of virus, specific strain features, and load at presentation. Nonetheless, the mandate to do such a study is clear based on the high prevalence and morbidity of virus-associated wheeze in young children the world over.

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