advance understanding and treatment of other lung diseases as well.

Finally, efforts to translate research advances into the practice of pulmonary medicine and to ensure the training and development of future investigators will be central to capitalizing on these and other opportunities in pulmonary medicine. This will require enhanced efforts by the full respiratory community.

This Editorial has highlighted only a few of the many promising frontiers in respiratory medicine. As biomedical research shifts more and more to the characterization of complex systems, the lung might become a preferred organ system for studies of integrated genomics and physiology at the whole human level. As such, the current funding climate should not signal a time to step back, but rather, an opportune time to step up to the challenge to accelerate the biomedical research needed to cure and prevent lung disease.

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Controversies in the Treatment of the Acutely Wheezing Infant

Frequently, the first wheezing episodes in young children are associated with viral infections. Preschool children with wheezing experience disproportionately high morbidity and health care utilization, including a 50% greater rate of ambulatory visits, nearly double the rate of emergency department (ED) visits, and nearly triple the rate of hospitalization relative to school-age children (1). Furthermore, particular viruses have been proposed to lead to the establishment of the asthmatic phenotype (2, 3). Children who experience severe viral respiratory infections in early life have a higher chance of developing asthma later in childhood (2, 4, 5). It has also been postulated that the immune system of susceptible infants may have delayed maturation leading to allergic sensitization and may not be able to mount an adequate antiviral defense, increasing the likelihood of virus spreading to the lower airways resulting in a severe low respiratory tract infection (6). Furthermore, the presence of both early-onset allergic sensitization and wheezing respiratory illnesses confer the highest risk of developing persistent asthma (7), suggesting that both of these processes may injure the airway, leading to inflammation, hyperresponsiveness, and recurrent wheezing.

The management of these wheezing episodes remains a distinct clinical challenge in 2011. While research over the last two decades has shed substantial light on this problem, clinicians remain uncertain as to the optimal management strategies in this heterogeneous population.

TREATMENT OF THE INITIAL EPISODE OF VIRUS-INDUCED WHEEZING IN INFANCY

Virus-induced wheezing in infants who have not experienced previous wheezing, termed bronchiolitis, leads to significant morbidity, and can be particularly difficult to treat. Despite a multitude of trials, no consistent benefits in clinical outcomes have been observed when inhaled bronchodilators, corticosteroids (systemic or inhaled), or montelukast have been studied during bronchiolitis episodes (8). However, a *post hoc* analysis reported that while infants who wheezed with rhinovirus did not derive benefit from oral corticosteroid (OCS) therapy during the acute severe rhinovirus-induced episode, they appeared less likely to develop recurrent wheezing over the following year (9). This finding, if confirmed, suggests a distinct pathogenesis and therapeutic approach for infants diagnosed with rhinovirus-induced wheezing illnesses.

To date, the treatment of acute bronchiolitis remains largely supportive. However, two therapies have recently been studied for their utility in children with bronchiolitis: a combination of nebulized epinephrine with oral dexamethasone and inhaled hypertonic saline. A large randomized controlled trial examined the combinination of nebulized epinephrine with oral dexamethasone administered in the ED in preventing hospital admission (10). While the authors found a small synergistic effect with the combination of nebulized epinephrine and oral dexamethasone (11 infants would require treatment to prevent one hospital admission), there was no effect of either medication alone. A recent systematic review that included four randomized trials concluded that inhaled 3% hypertonic saline reduced length of hospital stay and improved clinical severity score in infants with bronchiolitis (11), and another recent study supports its lack of adverse effects when used without adjunctive bronchodilators (12). Both of these therapeutic strategies will need further study before widespread adoption of their use.

ORAL CORTICOSTEROID TREATMENT OF RECURRENT VIRAL-TRIGGERED WHEEZING EPISODES

Recently, there has emerged an apparent contradiction between the effects of a time-honored and evidence-supported gold standard treatment of acute wheezing episodes in older children with asthma and in preschool-aged children with recurrent wheezing. Three relatively recent trials have examined the role of OCS during episodes of (presumably) viral-triggered wheezing in preschool children with inconsistent findings. Csonka and colleagues demonstrated that a 3-day course of oral corticosteroids initiated in the ED modestly reduced illness severity and shortened the duration of episode and hospitalization by approximately 1 day each relative to placebo, although hospitalization rates were not affected (13). Oommen and colleagues found that parent-administered of OCS at the "start of an

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episode of viral wheeze" in children 1–5 years of age recently hospitalized for viral wheeze did not alter symptom scores or need for hospitalization compared with placebo (14). Most recently, Panickar and colleagues randomized 700 children 10 to 50 months of age hospitalized with viral-induced wheeze to treatment with either OCS or placebo for 5 days (15). There were no significant differences in the durations of hospitalization between the treatment groups (13.9 h versus 11.0 h) or in rates of symptom resolution following discharge. In total, these three trials begin to cast doubt upon the efficacy of OCS therapy in episodic viral wheeze in preschool children.

Why do the findings in the trials involving children with preschool wheezing differ so much from those demonstrated in older children with acute asthma exacerbations? A major explanation most likely lies in the heterogeneity of subjects in early childhood wheezing trials. Two potentially important sources of heterogeneity of subjects within and between trials include the presence or absence of previous wheezing (i.e., bronchiolitis versus recurrent viral-triggered wheezing) and the inclusion of children with and without underlying atopic diatheses. For example, the study by Panickar and coworkers clearly included several distinct subpopulations—approximately 1/3 of the children had not wheezed previously, while 2/3 had wheezed before. In addition, 1/4 had a parental history of asthma, and 16 to 18% of participants had a physician diagnosis of asthma. While subgroup analyses did not identify a significant interaction between asthma risk factors and duration of hospitalization, less than 20% of the entire study population had such risk factors. Given the established associations between atopic features and the likelihood of early childhood wheezing persisting to become school-age asthma (16), it is possible that children with these atopic features might respond better to OCS than those without atopic tendencies. Unfortunately, the effectiveness of OCS in recurrently wheezing preschool children with an atopic phenotype has not yet been prospectively addressed in an adequately powered trial. Other potential explanations for lack of efficacy include the relatively short duration of hospitalization in the placebo group (13.9 h) and a relatively low dose of OCS.

Based on these findings, recent editorials have suggested serious reconsideration of OCS use in preschool wheeze, reserving its use for only the seriously ill hospitalized child (17, 18). Until further trials confirm these findings, while at the same time addressing the challenges created by the heterogeneity of preschool wheezing, the optimal treatment strategy in this situation remains unclear.

It is encouraging that there continues to be active research to refine our approach to the clinical management of wheezing during the preschool years. In our opinions, there remain at least three areas in critical need for study in this population: (*1*) definitive trials of OCS therapy among children with recurrent wheeze, which clearly exclude those with bronchiolitis; (*2*) determination of specific subgroups where treatment benefit may most substantial, such as previous wheezing, asthma risk factors, and underlying atopy; and (*3*) trials that examine novel therapeutic strategies for managing this common problem.

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