

Asthma in the preschool child: Still a rose by any other name?

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Key words: Asthma, preschool

"What's in a name? That which we call a rose
By any other name would smell as sweet..."

William Shakespeare, *Romeo and Juliet*, 1594

In this issue of the Journal, Bacharier et al¹ from the Childhood Asthma Research and Education (CARE) network of the National Heart Lung and Blood Institute address an important common question in their Acute Intervention Management Strategies trial: "How can we best treat intermittent wheezing episodes in young children?" Wheezing illnesses are common and may affect as many as 50% of preschool children, resulting in substantial impact on the children, their families, and the health care system. In this study, episodic use of an inhaled wet nebulized corticosteroid (budesonide) or an oral leukotriene receptor antagonist (montelukast) did not affect the primary outcome parameter, proportion of episode-free days, but did significantly decrease morbidity in the children during the wheezing episodes. In the year before study entry, the children had an average of 3.4 episodes of "wheezing illness," missed an average of 4.8 days from school or daycare, and received 1 course of oral corticosteroids (median, 1.0; range, 0.02-2.0).² The current study was powered for the primary outcome on the basis of data from a previous study of preschool children with recurrent acute asthma episodes.³ In that study, children had frequent, severe wheezing episodes with an average of more than 12 episodes per year, requiring 8 to 9 courses of oral corticosteroids per year. Given the relatively few episodes per child in the current study, it would have been surprising to fulfill the requirement for a significant change in the defined primary outcome of episode-free days or in a secondary outcome such as number of courses of oral corticosteroids.

Although considered a negative study on the basis of the predefined primary outcome parameter, treatment for 1 week with both wet nebulized budesonide and oral montelukast had a statistically significant and clinically meaningful impact on the severity of these wheezing episodes, particularly in children with

a positive Asthma Predictive Index (API). Those children who fulfilled the criteria for a positive API and those who had required a course of oral corticosteroids in the previous year had a substantive reduction in episode severity when treated for 1 week with the inhaled corticosteroid or oral leukotriene receptor antagonist. Inhaled wet nebulized budesonide and oral montelukast treatments were both associated with significant improvement in the symptom scores for trouble breathing and interference with activity, whereas those children receiving montelukast also had significantly decreased wheezing. For children with a negative API, neither treatment led to significant improvement compared with use of β -agonist alone.

There is increasing recognition, especially for the preschool child, that asthma represents a heterogeneous group of illnesses which present as a "wheezing syndrome." Investigators from the Tucson Children's Respiratory Study longitudinally assessed children from a general population-derived birth cohort from birth into the teenage years. They identified a group of children who had wheezing during the first 3 years of life but had no further episodes by the time they were school age ("transient wheeze"), a group of children who had wheezing illnesses beginning in the first 3 years of life and continued to have wheezing episodes into their school-age years ("persistent wheeze"), and children whose wheezing episodes began after 3 years of age ("late onset wheeze").⁴ The investigators created a clinical index which defined the risk of asthma for children with recurrent wheezing.⁵ Children who wheezed during the first 3 years of life and met at least 1 of the major criteria (parental asthma diagnosed by a physician or physician-diagnosed atopic dermatitis) or 2 of 3 minor criteria (physician-diagnosed allergic rhinitis, wheezing apart from colds, or eosinophilia) were defined as having a positive API. The most impressive aspect of the API was actually its ability to rule out the likelihood of asthma by school age in the young child with wheezing. For a child who was "an early wheezer during the first three years of life" a negative predictive value for the API for asthma ranged from 93.9% at 6 years of age to 86.5% at 13 years of age. For the current study, the CARE Network investigators have used a previously modified API⁶ in which allergy skin testing results for inhalant aeroallergens were added to the major criteria and skin testing to food was added to the minor criteria. The impressive aspect of using the modified API in the current study is its ability to predict a positive response to short-term treatment with the 2 most common asthma preventive medications: inhaled corticosteroid or oral leukotriene receptor antagonist.

In many countries, intermittent treatment of wheezing episodes has become a community standard. Families frequently are advised (or decide themselves) to treat an acute wheezing episode in a young child for some predefined period of days or weeks and then discontinue regular preventive therapy. This practice has evolved in the absence of substantive data to support such an approach. The Acute Intervention Management Strategies trial in

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Disclosure of potential conflict of interest: A. B. Becker has received research support from the Canadian Institutes of Health Research, AllerGen, and the Children's Hospital Foundation/Manitoba Institute of Child Health and has served as an Advisory Board member for AstraZeneca Canada, Merck Frosst Canada, GlaxoSmithKline Canada, and Novartis Canada.

Received for publication October 22, 2008; accepted for publication October 23, 2008.

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J Allergy Clin Immunol 2008;122:1136-7.

0091-6749/\$34.00

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doi:10.1016/j.jaci.2008.10.038

this issue of the Journal provides the best data to date that children with a wheezing syndrome who have a positive API will benefit from short-term treatment with wet nebulized budesonide or oral montelukast. However, it is important to note that alternative approaches to delivery of inhaled corticosteroid may not be equally effective. Although use of a metered-dose inhaler with a spacer device has shown equivalent efficacy and replaced wet nebulized β -agonist for the treatment of children in some emergency departments,⁷ there are no similar data in children for the equivalency of a metered-dose inhaler corticosteroid with wet nebulized corticosteroid. For children who truly have no or very few symptoms between these episodes, one would anticipate that use of a once-daily oral medication during the episode would be the approach of choice for most families. It is also important for physicians and families to recognize that some of these children have more persistent disease that may warrant regular preventative therapy. In the current study, children had an average of about 25% of days with asthma symptoms. Concern should be raised particularly for children who experience symptoms with activity. In those children, conscious or subconscious choices to avoid exercise may result in a variety of biologic and sociologic adverse effects.

It is frequently said that "all that wheezes is not asthma." In fact, not everything called "wheezing" is truly the wheeze we as physicians classically define. For the current study, the investigators recognized "the variability in symptoms which parents may report as indicators of early respiratory tract infections . . . [and] were able to identify a common set of signs and symptoms that precedes and signals the development of severe wheezing during respiratory tract infections in young children."¹ Parents noted that cough, breathing problem, or noisy chest was the first or second important symptom that led them to suspect an impending severe episode and begin use of inhaled β -agonist for their children. Bisgaard et al,⁸ in their study of infants with wheezing episodes, noted that "[w]heezing was explained to the parents as any symptom severely affecting the child's breathing and manifested, as for example, noisy breathing (wheezing or whistling sounds), breathlessness, shortness of breath, or persistent troublesome coughing." Although we (and families) often describe these as wheezing episodes, the interpretation of wheeze is extremely varied. For large-scale, multicenter, epidemiologic studies, questionnaires describing wheezing as a primary symptom representing asthma are commonly used. The International Study of Allergy and Asthma in Childhood primarily defined asthma in children 6 to 7 years old as a positive response to the written question, "Has your child had wheezing or whistling in the chest during the past 12 months?"⁹ In that study, a video questionnaire had substantially fewer positive responses from parents for the question of wheeze. For the individual child, it is clear that what we define as wheezing is not always the primary symptom

recognized by the family but a constellation of symptoms presenting as a "wheezing syndrome" in the young child. Clearly, not all that wheezes in preschool children represents asthma.

As Silverman and Wilson¹⁰ note, "the term 'asthma,' without any qualification or definition, has begun to hinder rather than facilitate progress . . . [in] the management of wheezy children." Physicians and families use (or avoid use of) the term *asthma*, and this leads to confusion and potentially inappropriate management. This is particularly important during the preschool years when wheezing syndromes are especially common and where no objective, biologic gold standard exists to assist physicians in making the diagnosis of asthma that may assist in directing therapy. Physicians should assess the likelihood of asthma in preschool children with intermittent wheezing in light of the API. For those children with a negative API, treatment other than symptom relief is unlikely to be of help. For those children with a positive API, intermittent (or regular) use of oral montelukast or wet nebulized budesonide may be of value. The current study by Bacharier et al¹ from the CARE network provides important information that should help to guide the practicing physician in the treatment of young patients with intermittent wheezing.

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