Asthma Is Underdiagnosed in Children Under 4

BY BRUCE JANCIN

KEYSTONE, COLO. — Failure to appreciate the key differences between childhood asthma and the adult version of the disease has led to widespread underdiagnosis of young asthmatics.

"Many of us grew up with a whole list of synonyms—reactive airway disease, wheezing bronchitis—that we used without saying a child has asthma . . .which leads to underdiagnosis and undertreatment. We still see a large body of physicians not using controller medications when there is persistent wheezing and instead giving a 3- to 5-day burst of oral steroids to the kids. That's something we have to change," Dr. Erwin W. Gelfand declared at a meeting on allergy and respiratory disease sponsored by National Jewish Health, Denver.

The Centers for Disease Control and Prevention statistics are revealing. During 2003-2005, the prevalence of asthma among children up to 4 years of age was 6.2%, well below the 9.3% figure for 5- to 10-year-olds and the 10.0% rate in 11- to 17-year-olds. Yet the rate of emergency department visits for asthma in 2003-2004 was 164/10,000 people among the under-5 set, markedly greater than the 83/10,000 for children aged 5-10 years and the 69/10,000 for those aged 11-17 years.

Moreover, the hospital admission rate for asthma was 61/10,000 in children through age 4 years, compared to just 24/10,000 in 5- to 10-years olds and 12/10,000 in 11- to 17-year-olds.

The rate of ambulatory visits for asthma was more than 50% higher in children younger than age 5 years than in older pediatric cohorts, added Dr. Gelfand, chairman of the department of pediatrics at National Jewish Health and professor of pediatrics and immunology at the University of Colorado.

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DR. GELFAND

Childhood asthma is more likely to be episodic, especially in younger children. Also, children tend to have greater involvement of the peripheral, airways, so larger particle size inhaled medications may never reach the hyperresponsive portion of their airways.

Also, many children with asthma have normal-range forced expiratory volume in 1 second (FEV_1) values when stable because they can hyperinflate and increase their total lung capacity with less airway resistance to airflow; that feature has led to many missed pediatric asthma diagnoses. In children, the forced expiratory flow over the middle half of forced vital capacity, or FEF25%-75%, is a more sensitive indicator of airflow obstruction than is FEV_1, he said.

The Childhood Asthma Management Program Research Group (CAMP) study (N. Engl. J. Med. 2000;343:1054-63) provided the first signal of the limitations—or as Dr. Gelfand put it, the failures—of long-term corticosteroid therapy in children with asthma. While aggressive therapy with oral and high-dose inhaled corticosteroids often improve symptoms as long as the child is using them, they are not disease modifying and don't prevent severe airway remodeling.

"The Achilles heel of corticosteroid therapy is that it doesn't inhibit increased reticular basement membrane thickness. Basically, all we have for childhood asthma are bronchodilators and anti-inflammatory therapies. We don't have a cure, and we certainly don't have good drugs to target airway remodeling," Dr. Gelfand noted.

New and better drugs, and perhaps combination therapies, are clearly needed in childhood asthma. More comprehensive targeting of the leukotriene pathway may be beneficial. Montelukast and the other current-generation leukotriene receptor antagonists target leukotriene C4 and D4, but not E4, which recent studies from Children's Hospital of Boston suggest is another important pathway in asthma. And then there is leukotriene B4, which increasingly looks to be a major player in asthma pathogenesis but also is not addressed by the leukotriene modifiers now on the market.

Another priority is developing alternatives to spirometry for monitoring lung function and inflammation in young children. The Asthma Predictive Index hinges on the finding of one major criterion—either a parent with asthma, early sensitization to an aeroallergen, or concurrent atopic dermatitis—or two minor criteria in the form of wheezing apart from colds, food sensitization, or eosinophilia.

An ongoing initiative, especially in Europe, is to try to prevent the induction phase of asthma and the so-called "atopic march" through interventions during the narrow window of opportunity thought to exist antenatally and in the first few years of life. Ongoing clinical trials toward this end variously involve immunotherapy in infancy, early pharmacotherapy, allergen avoidance, and paradoxically, allergen exposure. "The idea is that, while one cat is bad for an infant, having seven cats could be good."

Dr. Gelfand disclosed serving on advisory boards for Merck & Co., Sanofi-Aventis, and Schering-Plough Corp. ■

New Meta-Analysis Shows Safety of LABA Combinations

BY BRUCE JANCIN

KEYSTONE, COLO. — A new meta-analysis of more than 23,000 asthma patients randomized either to formoterol-containing combination regimens or to treatment without a long-acting beta-adrenergic agent showed no asthma-related deaths.

The analysis looked at all 42 AstraZeneca-sponsored randomized, blinded, prospective clinical trials and found no evidence of increased risks of all-cause mortality, asthma-related deaths, or intubations in patients receiving combination therapy with the long-acting beta-agonist (LABA) formoterol.

The findings support those of an earlier meta-analysis (Ann. Intern. Med. 2008;149:33-42) involving all of the more than 28,000 participants in the 66 GlaxoSmithKline-sponsored randomized trials comparing outcomes with the LABA salmeterol plus an inhaled corticosteroid (ICS) versus an ICS alone, Dr. Harold S. Nelson said at a meeting on allergy and respiratory diseases.

Together, these two meta-analyses totaling more than 50,000 asthma patients paint a consistent and reassuring picture of the safety of LABAs when used in conjunction with an ICS. It's a picture at odds with the "rather frightening" conclusions about LABA safety drawn by the Food and Drug Administration's Office of Surveillance and Epidemiology in a Dec. 2008 meeting, said Dr. Nelson, professor of medicine at the University of Colorado/National Jewish Health, Denver.

It's noteworthy that the FDA analysis incorporated 1,270 of the 23,510 subjects included in the new meta-analysis. The regulators excluded data involving non–U.S.-approved drug dosages and age groups and thereby constructed for themselves a rather limited database, he said at the meeting, sponsored by the National Jewish Medical and Research Center.

FDA concerns regarding LABA safety arose in large part from the findings of the Salmeterol Multicenter Asthma Research Trial (SMART). The key findings of SMART, however, have not stood the test of time, he said.

One by one, the major SMART conclusions—that salmeterol is associated with increased risk of asthma-related mortality, that African Americans and children are subgroups uniquely vulnerable to asthma exacerbations while on LABAs, as are patients homozygous for arginine at codon position 16 on the beta-2-adrenergic receptor—have subsequently been knocked down, said Dr. Nelson, who was the lead author of SMART (Chest 2006;129:15-26) and has been among those who've subsequently criticized the study.

One of the major problems with SMART, he said, was that compliance with ICS therapy wasn't monitored, and many patients assigned to salmeterol weren't taking the topical anti-inflammatory agent.

"There's no question that the outcomes with combination therapy in SMART were bad. The only question is was it because they weren't taking an inhaled corticosteroid," he said.

Dr. Nelson stressed that the results of the two meta-analyses underscore the folly of recent much-publicized editorials calling for a new prospective trial of the safety of LABAs (Eur. Respir. J. 2009;33:3-5; N. Engl. J. Med. 2009;360:1671-2).

"We've got more than 50,000 patients in clinical trials without an asthma death. When you look at the data and see the lack of difference between patients who are treated with an inhaled corticosteroid and those who are treated with an inhaled corticosteroid and LABA, you can calculate that the number of patients required for this new study would be somewhere between 1 million and infinity," he said.

"There's no need to wipe out the black box warnings on salmeterol and formoterol as monotherapy; that's very appropriate. What's needed is to say that when you put them in a container with an inhaled corticosteroid those dangers have never been shown to exist," he said.

The new AstraZeneca-supported meta-analysis included 13,542 patients on formoterol-containing combination therapies and 9,968 on non-LABA regimens. All subjects were at least 4 years old.

Dr. Nelson disclosed having served as a consultant to AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, Genentech Inc., Novartis, Schering-Plough Corp., Sepracor Inc., Abbott Laboratories, and Array BioPharma Inc. ■

Outcomes, Formoterol vs. Non-LABA Therapies

	Formoterol combinations	Non-LABA therapies
Patient-years of exposure	6,500	5,000
All-cause mortality (per 1,000 patient-years of exposure)	0.53	0.82
Asthma-related deaths	0	0
Asthma-related hospitalizations (per 1,000 patient-years of exposure)	12.05	16.4
Study discontinuation rate	12.7%	15.4%

Source: Dr. Nelson