Editorial

Facing the challenges of childhood asthma: What changes are necessary?

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Over the last 15 years, we have witnessed several paradigm shifts in the management of asthma. First, the identification of asthma as a chronic inflammatory disease of the airways shifted treatment on the basis of the use of a long-acting bronchodilator, theophylline, to anti-inflammatory therapy, inhaled corticosteroids. Second, the recognition that asthma can be associated with irrecoverable loss of pulmonary function directed management to early recognition and early intervention. Third, there has been a remarkable shift from a course of medicine based largely on trial and error to one that is evidence-based and summarized in a guidelines approach to therapy, especially for asthma.[1,2]

This theme issue of the Journal focuses on pediatric asthma. In some ways, the management of asthma in children is a new frontier. A major question is whether early-onset asthma in children is the same disease as that in adults with long-standing asthma. The answer will raise issues regarding the approach to treatment. Can we continue to go on with a 1-size-fits-all approach to treatment, or should treatment be individualized on the basis of the patient's specific disease features?

In evaluating patients with low pulmonary function that is refractory to current therapy, one ponders the question of how the patient evolved to this level of severity. Did the loss in pulmonary function occur suddenly, or did it evolve over time? As depicted in Fig 1, low pulmonary function could be caused primarily by small lung size at birth, a sudden loss in pulmonary function combined with ongoing loss over time, or a gradual ongoing loss over time. If low pulmonary function is related solely to small airway size at birth, then obviously, pushing therapy will only result in adverse effects of medications with no conceivable improvement in measured pulmonary function. If the loss in pulmonary function evolves suddenly and results in structural damage, then the window of opportunity for preventing irrecoverable loss is limited. If it is an ongoing process, then the mechanisms for loss must be understood and the effect of treatment carefully evaluated. For example, it could be related to loss associated with frequent acute exacerbations, or it may be caused by persistent inflammation leading to slow deterioration over time. Therefore, each pathway could prompt a unique approach to treatment depending on the goal of intervention.

The case report by Covar et al[3] nicely illustrates several important lessons regarding the evolution of asthma. This specific case provides an example of asthma progression as indicated by loss in percent predicted pulmonary function in a child followed over a long time in a specialty care setting. Fortunately, spirometry was followed regularly, and the summary clearly demonstrates decline in pulmonary function over time despite an appropriate course of anti-inflammatory and bronchodilator therapy. The case highlights some of the gaps in information we currently must face in treating our patients. More than this, it emphasizes the importance of long-term follow-up. This case along with similar reports based on population data[4,5] should prompt further research into pathways of asthma progression and, ideally, new approaches to treatment.

RECENT ADVANCES

The March issue of the Journal includes a review by Szefler and Apter[6] that summarizes key advances in pediatric and adult asthma published in 2004. This presentation addresses 2 major phases of the disease: origins and persistence. It is important that we begin to think of these 2 broad categories for the purposes of organizing clinical research and also for organizing patient care. Important contributions were recently made in areas related to the natural history of asthma, viral infection and asthma, the effect of allergic inflammation, and the genetics of asthma.

In this issue of the Journal, the review by Bisgaard and Szefler[7] on mild asthma proposes that this is not at all a benign disease in children. The presentation of asthma

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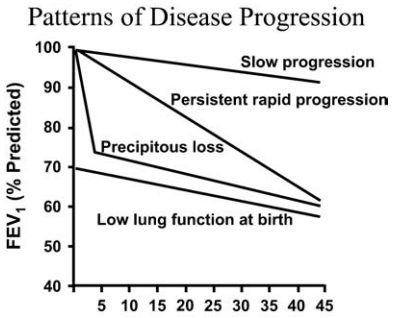

FIG 1. Model for progression of asthma in children shows patterns such as slow progression over time, rapid progression, a precipitous fall in pulmonary function followed by continuing slow progression, and low lung function at birth followed by slow progression. These different patterns could result in different approaches to management.

in young children through acute exacerbations may be the harbinger of persistent asthma. In addition, there is significant morbidity and a potential risk for mortality that should not be underestimated. However, the cost-effectiveness of instituting regular long-term therapy must be balanced by a consideration of risk for adverse effects as well as the cost and inconvenience of therapy. Further research will be important in guiding physicians to appropriate medical management of asthma in young children. It was not long ago that medications such as cromolyn were considered first-line therapy in children on the basis of an excellent safety profile along with a well documented effect on blocking the early and late-phase components and subsequent increased airway responsiveness after an allergen challenge in a sensitized patient. This impressive development of an asthma medication with a unique profile is summarized in articles by Howell[8] and Edwards.[9]

Earlier this year, a publication from the National Heart, Lung, and Blood Institute Childhood Asthma Research and Education Network addressed the question of choosing first-line therapy in childhood asthma. By using pulmonary function as an indicator of response, Szefler et al[10] concluded that low pulmonary function or elevated markers of allergic inflammation, such as exhaled nitric oxide, IgE, or total eosinophil count, should prompt the physician to choose inhaled corticosteroid therapy over a leukotriene receptor antagonist, whereas the absence of these indicators could allow the choice of either medication as a therapeutic trial. This information, combined with the past experience in a study conducted in adult patients,[11] suggests that the choice of medications for first-line intervention could be assisted with a careful evaluation of the individual patient's asthma phenotype. An illustration of the application of these measures is summarized in Fig 2. Similar studies must now be conducted to determine whether these principles can be applied to first-line intervention in young children. Also, the interpretation of these markers in the presence of ongoing treatment must be evaluated. Although exhaled nitric oxide correlates well with other markers of allergic airway inflammation, it is reduced during treatment with inhaled corticosteroids and leukotriene receptor antagonists.[12-14] Other markers, such as total eosinophil count and serum IgE, tend to change slowly or not at all over time after introduction of inhaled corticosteroid therapy.

Also in this issue, Dr James Gern provides an excellent overview of the effects of viral respiratory infections on lung development and childhood asthma.[15] If his proposed hypothesis is true that certain patients, on the basis of genetic susceptibility, are predisposed to asthma and alterations in lung function when exposed to certain viruses at certain times, we will need new tools to identify patients at risk and to monitor changes in pulmonary function over time.

An important component of asthma control is normalizing pulmonary function. This is important not only in assessing response to treatment but also for long-term follow-up of patients, as an indicator of progression. In this issue of the Journal, Larsen et al[16] provide a state-of-the-art review on the methods of measuring pulmonary function in young children. Continuing development in this area along with clinical application of these tests will provide additional tools for evaluating and managing asthma in children.

Another important contribution is the aspect of genetic analysis and the potential applications of this clinical tool to the management plan. The National Heart, Lung, and Blood Institute Asthma Clinical Research Network has published a series of reports on the relationship of β-adrenergic receptor polymorphisms with the clinical response after regular versus intermittent short-acting β-adrenergic agonists.[17,18] The results of these studies suggest that patients who bear the Arg-Arg genotype at position 16 on chromosome 5q31-32 are predisposed to loss in pulmonary function and increased symptoms during regular use of a short-acting β2-adrenergic agonist, albuterol. An alternative treatment approach could apply anticholinergic therapy on the basis of preliminary observations derived from these studies.[18] Further studies are needed and in progress to determine whether the same phenomenon recognized during treatment with albuterol is true for long-acting β-adrenergic agonists. Therefore, in addition to biomarkers, knowing the genotype of the patient could prompt alternative treatment decisions. This approach differs significantly from the current guidelines approach, which is based on attaining response for the general asthma population and does not take into consideration the individual variability in response to medications.

MOVING FORWARD

Therefore, to meet the challenges of childhood asthma, several changes will have to take place in the coming years. First, we must begin to follow pulmonary function over time to assess the component of progression with asthma. Second, we must continue to explore the application of biomarkers and genetics for their association

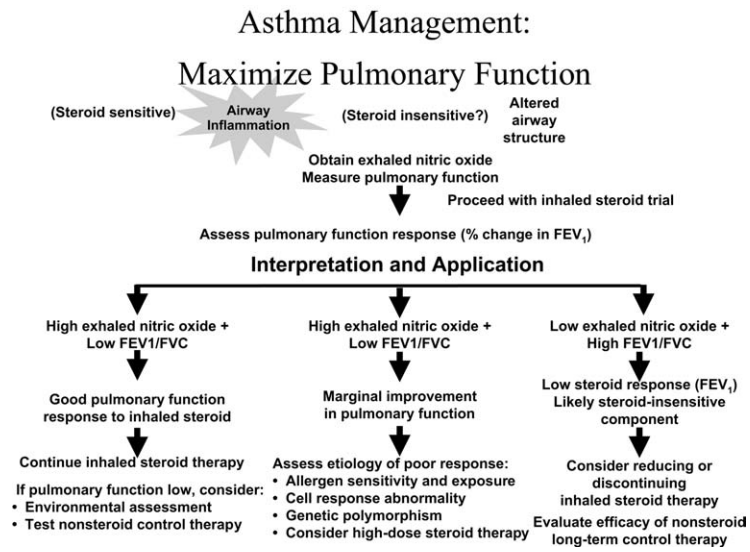

FIG 2. Algorithm-based approach for selecting medications to improve pulmonary function on the basis of information derived from a measurement of pulmonary function and exhaled nitric oxide.

with response to treatment. The potential benefits would be an efficient selection of medications that would provide an optimal effect in the shortest time, as well as the avoidance of adverse effects to medications.

It is clear that our current medications provide very impressive benefits for the general population, but a proportion of patients may not see benefits for certain features of the disease—for example, improvement in pulmonary function or reduction in severe exacerbations—and a certain proportion of the patient population may be at risk for adverse effects. Perhaps the assessment of patient characteristics, biomarkers, and genetics will help streamline the approach to medication selection.

If these projections are true, this will require another shift in the paradigm of treatment, specifically moving from an evidence-based approach directed to the general population to an individualized approach based on knowledge of the patient's individual disease presentation and genetic make-up. This will present a challenge to people who develop guidelines for asthma care as well as clinicians who seek to embrace this new approach to asthma management. This will represent a transition from a simple table of disease severity matched with preferred and alternative medication selection to an algorithmic approach for individualized care. This approach could be illustrated as a road map guided by road markers consisting of the individual patient's phenotype and genotype. Understanding treatment failures within this system should lead to the discovery of new treatment strategies and possibly new medications. This issue of the Journal provides insight into new directions for asthma management in children. These advances will bring forth a period of rapid transition for techniques developed at the bench to help minimize the need for bedside asthma care that is associated with the management of acute asthma exacerbations. We can then lead the effort to change the popular term *bench to bedside* to *bench to clinic* for our children with asthma.

REFERENCES

1. National Asthma Education and Prevention Program report: guidelines for the diagnosis and management of asthma update on selected topics—2002. J Allergy Clin Immunol 2002;110:S141-219.
2. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Bethesda (MD): National Heart, Lung, and Blood Institute, National Institutes of Health; 2002. NIH publication 02-3659. Available at: http://www.ginasthma.com. Accessed February 27, 2005.
3. Covar RA, Cool C, Szefler SJ. Progression of asthma in childhood. J Allergy Clin Immunol 2005;115:700-7.
4. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based cohort study of childhood asthma followed to adulthood. N Engl J Med 2003;349:1414-22.
5. Covar RA, Spahn JD, Murphy JR, Szefler SJ, for the Childhood Asthma Management Program Research Group. Progression of asthma measured by lung function in the Childhood Asthma Management Program. Am J Respir Crit Care Med 2004;170:235-41.
6. Szefler SJ, Apter A. Advances in pediatric and adult asthma. J Allergy Clin Immunol 2005;115:470-7.
7. Bisgaard H, Szefler S. Understanding mild persistent asthma in children: the next frontier. J Allergy Clin Immunol 2005;115:708-13.
8. Howell JBL. Roger Altounyan and the discovery of cromolyn (sodium cromoglycate). J Allergy Clin Immunol 2005;115:882-5.
9. Edwards AM. The discovery of cromolyn sodium and its effect on research and practice in allergy and immunology. J Allergy Clin Immunol 2005;115:885-8.
10. Szefler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, et al. for the Childhood Asthma Research and Education Network of the National Heart, Lung and Blood Institute. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Clin Allergy Immunol 2005;115:233-42.
11. Szefler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, et al. for the Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute. Significant variability in response to inhaled corticosteroids for persistent asthma. J Allergy Clin Immunol 2002;109:410-8.
12. Strunk RC, Szefler SJ, Phillips BR, Zeiger RS, Chinchilli VM, Larsen G, et al. for the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. Relationship of exhaled nitric

oxide to clinical and inflammatory markers of persistent asthma in children. J Allergy Clin Immunol 2003;112:883-92.
13. Covar RA, Szefler SJ, Martin RJ, Sundstrom DA, Silkoff PE, Murphy J, et al. Relationships between exhaled nitric oxide and measures of disease activity among children with mild to moderate asthma. J Pediatr 2003; 142:469-75.
14. Silkoff PE, Carlson M, Bourke T, Katial R, Ogren E, Szefler SJ. The Aerocrine exhaled nitric oxide monitoring system, NIOX®, is cleared by the FDA for monitoring therapy in asthma. J Allergy Clin Immunol 2004;114:1241-56.
15. Gern JE. Effects of viral respiratory infections on lung development and childhood asthma. J Allergy Clin Immunol 2005;115:668-74.
16. Larsen GL, Kang JKB, Guilbert T, Morgan W. Assessing respiratory function in young children: developmental considerations. J Allergy Clin Immunol 2005;115:657-66.
17. Israel E, Drazen JM, Liggett SB, Boushey HA, Cherniack RM, Chinchilli VM, et al. The effect of polymorphisms of the β2-adrenergic receptor on the response to regular use of albuterol in asthma. Am J Respir Crit Care Med 2000;162:75-80.
18. Israel E, Chinchilli VM, Ford JG, Boushey HA, Cherniak R, Craig TJ, et al. for the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomized, placebo-controlled cross-over trial. Lancet 2004;364:1505-12.