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 irreversible 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 al3 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 data4,5 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 Apter6 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 Szefler7 on mild asthma proposes that this is not at all a benign disease in children. The presentation of asthma

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There is a unique profile, summarized in articles by Howell and Edwards. 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 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. 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. Further studies are needed and in progress to determine whether the same phenomenon recognized during treatment with albuterol is true for long-acting β2-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...
Asthma Management:
Maximize Pulmonary Function

![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.](image)

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


