

Asthma progression: Can we and should we measure it?

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Over the last year, we have covered several important asthma themes in the Journal, including the National Institutes of Health asthma guidelines (November 2007) and the National Institutes of Health asthma networks (January 2007).^{1,2} Other theme issues have focused on other features of asthma, including specific cell types, as summarized in my “Advances in pediatrics” review³ for this issue focused on asthma progression. Progression is an important feature of asthma that we need to understand better to advance asthma care. It is the silent architect that determines whether asthma will persist, whether it will be severe, and whether it will be associated with significant morbidity. It can begin in childhood or adulthood, although we do not know whether the causes are the same in children and adults. Furthermore, we have no reliable management plan to prevent progression other than our own body immunomodulator response. Where do we go from here in understanding asthma progression? How will the new developments in science, namely the application of genetics and biomarkers, help us? Will new treatment strategies evolve out of translational studies that attempt to tie together measures of disease progression and these new scientific tools?

In the Expert Panel Report 3, released in full form in August 2007 and as an executive summary in November 2007, new terminology was introduced into the asthma guidelines to help focus our management.^{4,5} The new terms include *asthma severity*, *control*, *impairment*, and *risk*, as well as *responsiveness to management*. Within the term *risk*, a recommendation was made to follow loss of pulmonary function over time. A systematic follow-up of pulmonary function over time, along with the careful monitoring of measures of asthma control and treatment requirements, provides a method to identify asthma progression over time in individual patients. If these steps are implemented, we will have a better way to identify patients who are rapidly progressing over time and to monitor those patients at risk for asthma progression. However, additional features need to be added to this picture. This

editorial will highlight how 4 articles in this theme issue provide information that help guide us along this path of discovery.

WHAT DO WE NOT KNOW ABOUT ASTHMA?

After the release of the asthma guidelines, we now have a compilation of knowledge assembled by a group of authorities, as well as a plan to move forward.^{4,5} This is a good time to reflect on what we do not know about the disease and its management. Dr Charles Reed, a longstanding leader in asthma research and clinical care, points to several gaps in our knowledge.⁶ He raises a series of questions, most related to asthma progression, that include the following: Why do a few individuals have asthma but most do not? Why does it develop when it does? Is there more we could do to prevent it? Why do many patients recover from asthma spontaneously? Why do they recover when they do? Could we develop strategies to increase recovery? Why do mature individuals more often have asthma that is intrinsic rather than allergic? What are the environmental/genetic relationships? He also goes on to identify some important areas that could be explored to answer these questions, such as the role of innate immunity, endotoxin, and proteases in the pathogenesis of asthma and the role of environmental control in altering the course of the disease.

WHAT DO WE KNOW ABOUT ASTHMA PROGRESSION?

To approach an understanding of asthma progression, we must first reflect on where we have been. Drs Joseph Spahn and Ronina Covar assemble the available literature on asthma progression that will help us appreciate the key messages in various studies that attempt to study the natural history of asthma, as well as the interventions applied to prevent the evolution of asthma.⁷

They conclude that wheezing occurs frequently in infancy and early childhood and is usually transient, with less than 50% likely to have persistent asthma in childhood. Loss of lung function is the best-studied measure of asthma progression, with more studies in adults than children. Available data suggest that approximately 25% of children with mild-to-moderate asthma will have a progressive loss of lung function with risk factors that include male sex and also high baseline FEV₁ early in the course of the disease. Although airway inflammation and airway remodeling are thought to contribute to disease progression over time, few longitudinal studies are available to support this hypothesis. On a sobering note, it is not clear that any currently available controller medication consistently prevents asthma progression.

WHAT ARE THE MOLECULAR MECHANISMS THAT CONTRIBUTE TO ASTHMA PROGRESSION?

The cover picture in this theme issue depicts the 3 witches in Shakespeare's *Macbeth* (Fig 1). The witches have been adapted to

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FIG 1. This picture depicts the 3 witches in Shakespeare's *Macbeth* conjuring up a brew of allergens, viruses, environmental pollutants, and genetics that might play a role in developing bad outcomes of asthma. The scene of Macbeth meeting with the witches is not unlike that of the clinician trying to listen to the many signals that might predict the future outcome in managing their asthmatic patients.

show the myriad of suspected factors that go into the “brew” we call asthma, including viruses, allergens, environmental pollutants (oxidants), and genetics. We look at some of the ingredients and listen to the witches’ message about the potential outcomes. However, like Macbeth, we can be easily misled by the apparent messages. We have to be prepared to make our own interpretation of study data because some of the messages might not be clear or might even upset our current hypotheses. We then have to be ready to venture “out of the box” and test other theories. There are some great examples in the areas of molecular mechanisms and genetics on which to reflect.

Dr David Broide addresses the immunologic and inflammatory mechanisms that drive asthma progression to a pathway of airway remodeling.⁸ He indicates that the mechanisms to this

pathway are poorly understood. It appears to be due to persistent inflammation, aberrant tissue repair mechanisms, or both. Also, different features of airway remodeling are likely mediated by different inflammatory pathways with candidate mediators, such as TGF- β , T_H2 cytokines, vascular endothelial growth factor, a disintegrin and metalloproteinase 33, and matrix metalloproteinase 9. Although several mechanisms have been identified by mouse models and supported by observations in clinical studies, strategic clinical studies must be conducted to confirm these observations, and development of alternate studies for targeting individual cell types, cytokines, and mediators must be pursued to determine the role of candidate mediators of inflammation on the development and progression of airway remodeling.

WILL GENETICS HELP US IN IDENTIFYING PATIENTS AT RISK FOR ASTHMA PROGRESSION?

It is very clear that asthma is a heterogeneous disease with many different components and a range of phenotypes that can be described. The potential is great that a careful study of genetics could help link the phenotype with the genotype predisposing to the disease presentation. Drs John Holloway, Ian Yang, and Stephen Holgate discuss the interpatient variability in rates of asthma progression and whether genetics can provide some clues to unraveling the mystery.⁹ They indicate that interpatient genetic variability has been shown to affect multiple facets of asthma progression from susceptibility to disease, progression to severe disease, and response to treatment. However, at present, we are not in a position to use the rapidly accumulating knowledge of genetic variants that influence progression in clinical practice. In addition, some social and ethical issues will need to be addressed before genetic testing can be used in everyday clinical practice.

WHERE DO WE GO FROM HERE?

The first step is to find ways to implement the guidelines. This will help us identify signs of progression in individual patients. The second step is to define what to do with these data as they emerge. The third step is to assemble this information for studies to understand the mechanisms of progression and to define the efficacy of various treatment strategies in preventing progression.

In regard to the first step, I would venture to say that few practitioners systematically follow pulmonary function over time. This technique is the best objective measure of progression but will not occur unless clinicians embrace the concept of measuring pulmonary function and then monitoring it over time. By beginning to follow indicators of progression in asthmatic patients and also including those patients at risk for asthma, we can appreciate the magnitude of the problem among patients and the gravity of the situation in individual patients. If indeed allergens are risk factors for worsening asthma, steps can be taken to identify those risk factors, focus environmental control, and see whether this step has any effect in overall management. The same can be said regarding our current treatment strategies, including the application of immunomodulators. The systematic application of monitoring progression over time will demonstrate to insurance providers whether an expensive intervention is effective and what feature of the disease it modifies.

For example, in a patient who has evidence of ongoing loss of pulmonary function, one specific measure would be to counsel regarding smoking avoidance in those who do not smoke and institute measures of smoking cessation in those who have already taken up smoking. This would be an obvious step to take. The recent studies that have systematically evaluated the role of inhaled corticosteroids in preventing asthma progression have been disappointing to date. This should prompt us to look at other treatment strategies. Perhaps they will be immune based, such as

an immunomodulator, allergen immunotherapy, or a vaccination. Perhaps dietary strategies can also be effective in altering the relevant immune activity. Right now, the door is wide open because no therapeutic strategies are consistently effective.

In regard to biomarkers and genetics, none have reached the level of clinical application in routine disease management for asthma. Will they? The closest has been exhaled nitric oxide for a biomarker and the β -adrenergic polymorphisms for genetics. However, both are fraught with controversy based on inconsistent study findings and require special expertise in interpreting the results. Even if they were readily available, some insurers refuse to cover the costs of these special tests until they are validated.

CONCLUSIONS

It is now necessary to appreciate that progression is a key component of asthma and that it can be followed in individual patients. This simple step can be the basis for identification and validation of techniques to predict those at risk, research of mechanisms of progression, and evaluation of the best ways to manage asthma progression. Hopefully, this theme issue will prompt the study of this disease component and provide a base to move forward in the quest to advance the management of asthma. The outcome of this work should be that judicious application of biomarkers and genetics and use of a better system of monitoring asthma progression lead to an individualized approach to asthma management with better techniques for early diagnosis, strategies for early intervention, and the discovery of treatment modalities that successfully prevent progression. This should consequently lead to a reduction in asthma deaths and significant exacerbations, along with better symptom control and an improved quality of life for our patients.

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