Biomarkers in Asthma
A Real Hope to Better Manage Asthma

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KEYWORDS

• Asthma • Biomarkers • Asthma management

KEY POINTS

- Diagnosis and treatment of asthma are currently based on assessment of patient symptoms and physiologic tests of airway reactivity.
- This article provides an overview of blood, urine and airway biomarkers that can provide information on airway inflammation and asthma severity.
- Mechanistic biomarkers that identify pathologic pathways also provide critical insight for new therapeutic approaches for asthma.

THE CLINICAL NEED FOR BIOMARKERS TO INFORM THE CARE OF PATIENTS WITH ASTHMA

Asthma is defined as reversible airflow obstruction in the setting of airway inflammation. Asthma prevalence increased dramatically between 1970 and 2000, with more than 22 million people, of whom over 4.8 million are children, now living with asthma in the United States.[1,2] The increase of asthma has been variously ascribed to improved hygiene worldwide, acetaminophen use, increased exposure to allergens and pollution, and/or increased transmission of respiratory viruses.[3] This epidemic has occurred against a backdrop of a variety of genetic, biochemical, and immunologic host characteristics that substantially affect asthma phenotype.

Currently, standard clinical practice relies on patient history of symptoms and the measure of bronchial obstruction and reactivity, which are surrogates of the inflammatory and biochemical processes that give rise to the inflammation underlying all asthma.[4] For example, the phenotype of severe asthma, which comprises up to 5% of patients with asthma, is based on a compilation of criteria, the most important of which is the documentation of the lack of clinical treatment response.[5,6] Asthma treatment is directed equally toward reversing bronchoconstriction and treating airway inflammation. Common, noninvasive measures of airflow are usually able to quantitate the efficacy of the treatment of bronchoconstriction in adults. However, commonly available methods do not precisely measure the biology of inflammation underlying the bronchoconstriction. Further, the care of children with asthma is often inadequate because of the lack of bronchial obstruction on lung function tests even when symptoms are severe, and the reluctance to prescribe corticosteroids because of actual or perceived associated morbidities in children.[7] Thus, quantifiable noninvasive biomarkers that are informative for asthma control and, optimally, for assessing

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the pathobiologic pathways leading to the chronic airway inflammation in a specific patient will be of clinical utility in designing successful personalized treatment plans.

Based on this rationale, the National Institutes of Health and the Agency for Health Care Quality Research have launched efforts to promote the use of biomarkers in clinical studies of new therapies of asthma and ultimately in the evaluation of routine clinical care. A recent National Heart, Lung, and Blood Institute (NHLBI) report identifies biomarkers, most of which assess atopic inflammation, such as the multiallergen screen, sputum and blood eosinophil numbers, serum IgE, exhaled nitric oxide, and urine leukotrienes.[8] Although asthma tends to be particularly problematic in patients with allergies, and more than 40% of some populations suffer from allergies, allergic diathesis genes do not seem to be uniquely associated with asthma.[2,6,9] Thus, whatever is driving the asthma epidemic, the asthma syndrome has affected a tremendous spectrum of individuals with diverse immunologic and biochemical responses.[9,10] This heterogeneity in the human population has resulted in a heterogeneity among asthma phenotypes.[10–12] Therefore, biomarker tests were recently developed and extended to identify and quantitate specific pathways of inflammation to identify specific asthma phenotypes, particularly those amenable to biologically based antiinflammatory therapy. The benefit of a noninvasive biomarker in assessing therapeutic strategies is clear; the alternative is inspection and biopsy of the airway using invasive bronchoscopy.[13]

The mechanism-based biomarker approach avoids the limitations that occur with unbiased genotyping and phenotyping approaches.[10] For example, unbiased genetic analyses did not reveal a unifying asthma gene. Rather, asthma susceptibility genes are manifest in populations depending on environmental exposures, such as secondhand cigarette smoke.[14] Similarly, unbiased asthma clinical phenotypes, although clearly revealing the heterogeneity of asthma,[15] require association with underlying pathobiologic mechanisms for clinically meaningful use. In a large asthma population of nonsevere and severe asthma, nonbiased hierarchical cluster analysis of clinical variables, such as age at asthma onset, duration of episodes, gender, race, lung functions, atopy, and questionnaire data, identified three phenotype clusters that contained patients with the most severe asthma.[15] Similar cluster analyses of children confirmed heterogeneity in childhood severe asthma.[16] This variety supports that asthma encompasses a range of underlying biochemical and immunologic disorders. Thus, an informed biochemical and pathophysiologic approach is most likely to lead directly to clinical applications. This article describes biomarkers and their potential use to stratify patients into medically meaningful unique asthma phenotypes (**Table 1**).

THE EOSINOPHILIC OR T-HELPER TYPE 2 HIGH INFLAMMATION PHENOTYPE: SPUTUM EOSINOPHILS, URINARY 3-BROMOTYROSINE, AND PERIOSTIN

Asthma phenotyping was first performed based on atopic status (ie, classification of asthma as extrinsic allergic or intrinsic nonallergic).[9] Allergic asthma is common, and documentation of this phenotype has been helpful in avoiding allergen triggers and considering immunologic-based therapies. Classification as atopic asthma, which is typified by interleukin (IL)-4, IL-5, and IL-13 cytokines, has traditionally used standard clinical tests, including circulating numbers of eosinophils and total and allergen-specific IgE. These biomarkers are used in planning immunotherapy and anti-IgE therapy. In extension of these biomarkers, several groups describe that the number of eosinophils in sputum is closely related to airway obstruction and hyperresponsiveness.[17–19] Exciting early data suggested that sputum eosinophils predict asthma control and loss of control, particularly in children who predominantly experience atopic asthma.[20,21] The presence of more than 2% eosinophils in sputum has been used to define the eosinophilic or atopic asthma phenotype, which is also usually corticosteroid-responsive.[22] A recent study of severe asthma validates that sputum eosinophils can identify individuals with poor asthma control, and greater health care use[23]; however, the test requires sputum induction, specialized processing of the sputum sample, and an experienced cytotechnologist for accurate counting, all of which have limited the use of sputum eosinophils in general clinical care. More recently, Woodruff and colleagues[24] further identified a T-helper type 2 (Th2)–high inflammation phenotype based on a combination of biomarkers, which include the presence of high serum IgE (>100 ng/mL), blood eosinophilia (>0.14 x 10^9 eosinophils/L), and high sputum eosinophils.[25] The use of microarrays has also identified a Th2-high blood biomarker, periostin, which is an IL-13–inducible protein produced by the airway epithelium. The use of periostin as a biomarker of the Th2-high phenotype to select patients who benefitted the most from treatment with an inhibitor of IL-1325 provided a proof of concept that biomarkers may be used to stratify patients for