REVIEW

Exhaled nitric oxide to predict corticosteroid responsiveness and reduce asthma exacerbation rates

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Summary

Until recently, no point-of-care tool was available for assessing the underlying airway inflammation associated with asthma. Fractional exhaled nitric oxide (FeNO) emerged in the last decade as an important biomarker for asthma assessment and management. Evidence also indicates that FeNO is most accurately classified as a marker of T-helper cell type 2 (Th2)-mediated airway inflammation with a high positive and negative predictive value for identifying corticosteroid-responsive airway inflammation.

This manuscript evaluates the evidence for FeNO as a predictor of Th2-mediated corticosteroid-responsive airway inflammation and presents the results of a meta-analysis of three adult studies comparing asthma exacerbation rates with FeNO-based versus clinically-based asthma management algorithms, one of which was not included in a 2012 Cochrane meta-analysis. The primary purpose of the updated meta-analysis was to evaluate asthma exacerbation rates. The results demonstrate that the rate of exacerbations was significantly reduced in favor of FeNO-based asthma management (mean treatment difference = −0.27; 95% CI [−0.42, −0.12] as was the relative rate of asthma exacerbations (relative rate = 0.57; 95% CI [0.41, 0.80]).

In summary, FeNO has value for identifying patients with airway inflammation who will and will not respond to corticosteroids. Importantly, the use of FeNO in conjunction with clinical parameters is associated with significantly lower asthma exacerbation rates compared with asthma

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managed using clinical parameters alone. Together these data indicate that FeNO testing has an important role in the assessment and management of adult asthma. Further studies will continue to define the exact role of FeNO testing in adult asthma.

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Introduction

The prevalence of asthma in the United States (US) now exceeds 8%, and the proportion of asthmatics grew by 15% in the last decade.[1] Not surprisingly, the economic burden of asthma is also substantial, estimated for 2007 at $56 billion in direct medical costs and loss of productivity.[2] These facts underscore the need for more effective ways to both assess and manage asthma.

It is noteworthy that there have been important changes in both asthma treatments and asthma guidelines in the past decade. While the annual death rate for asthma in the US has declined over the past 15 years,[3] the hoped-for impact of these asthma treatment and asthma guideline changes on asthma morbidity have not been realized. For example, the Asthma in America Survey, which was conducted in 1998, demonstrated that the need for acute care (hospitalization, emergency department visits or other acute care visits) was common and occurred in approximately 36% of survey respondents.[4] When a similar survey, the Asthma Insight and Management Survey, was conducted in 2009, it was found that the need for acute care remained unchanged, occurring in approximately 34% of adult survey respondents.[4]

The reasons for the persistently high levels of asthma morbidity are multi-factorial and may include, among others, failure to implement published asthma guidelines, poor adherence to prescribed medications, differences between specialist versus primary care management, and regional differences in access to health care.[4] However, it is also important to note that while routinely available tests for the evaluation of asthma such as the Asthma Control Test and spirometry provide some information about asthma control, they provide no information about underlying airway inflammation, the central pathophysiologic feature of asthma. This has a number of practical consequences including both over and under diagnosis of asthma.[5,6] In addition, without an objective way to assess airway inflammation, decisions on which medications to prescribe to individual patients are often subjective.

Recently, point-of-care measurement of allergic airway inflammation via assessment of fractional exhaled nitric oxide (FeNO) has become available. While the measurement of FeNO bridges important gaps in asthma assessment and management, questions remain about its meaning as a marker of airway inflammation and its exact role in the assessment and management of asthma. The purpose of this paper, therefore, is 3-fold: (1) to evaluate the scientific and clinical evidence for FeNO as a marker of T-helper cells type 2 (Th2) inflammation; (2) to evaluate the positive and negative predictive value of FeNO for identifying corticosteroid-responsive airway inflammation; and (3) to present the results of an updated meta-analysis evaluating asthma exacerbation rates with FeNO-based versus clinically-based asthma management algorithms.

FeNO as a marker of Th2-mediated airway inflammation

Asthma is a heterogeneous, chronic disease characterized by two fundamental and interrelated abnormalities: airway inflammation and airway hyper-responsiveness. The airway inflammation and hyper-responsiveness associated with asthma can be triggered by exercise and numerous exogenous factors such as aeroallergens, infections, cigarette smoke and other irritants. In allergic asthma, which is the