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# Monitoring Disease Activity in Asthma

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## Citation

G Pesola, S Abdul-Waheed, H Daniel. *Monitoring Disease Activity in Asthma*. The Internet Journal of Asthma, Allergy and Immunology. 2004 Volume 4 Number 2.

## Abstract

Asthma is characterized by waxing and waning episodic wheezing, reversible airway obstruction, bronchial hyperresponsiveness, and chronic inflammation of the airways. It is often considered a gene-environment interaction. This means that, even with a genetic predisposition toward asthma, development of disease may not occur without proper environmental priming or exposure (1,2). In all likelihood, asthma consists of many genetic diseases that interact with many environments, with only some of the gene-environment interactions resulting in the constellation of findings consistent with the asthma syndrome. Without thinking, we label this syndrome a disease because it has many characteristics consistent with a disease.

## INTRODUCTION

At this point in time, we monitor disease activity and characterize asthma severity using symptoms and pulmonary function criteria. The theoretical problem with treating disease using this framework is the current paradigm we believe is the sequence of events that result in a reduction in lung function and asthma symptoms (3). First, the right genetic background is needed that results in immune hyperresponsiveness to some specific antigen or antigens. Possibly, this genetic background needs to be primed at a specific age. It is felt that airway inflammation then occurs secondary to some environmental antigenic exposure that is undoubtedly chronic and recurrent in nature. The inflammation may result in bronchial hyperresponsiveness, then airway narrowing with a reduction in pulmonary function, and finally wheezing and symptoms including dyspnea and cough. This implies that by the time symptoms occur with a reduction in pulmonary function, ongoing airway inflammation and resulting bronchial hyperresponsiveness have been silently preceding these indicators for some time. Logically, monitoring airway hyperresponsiveness and/or airway inflammation and treating these aspects as a proxy for disease activity (airway hyperresponsiveness) or as actual disease activity (airway inflammation), respectively, might be a better way of following asthma. Reducing airway inflammation through sequential longitudinal sampling of inflammatory biomarkers with pre-emptive treatment if indicated should prevent the progression to gradual or acute lung function

reduction, symptoms and asthma exacerbations.

The commonly used biomarkers that may reflect airway inflammation in asthma are airway hyperresponsiveness, inflammatory cells (particularly eosinophils) in the airway obtained by sputum induction, and exhaled nitric oxide. These three markers as a guide to asthma therapy will be reviewed.

## AIRWAY HYPERRESPONSIVENESS

A study compared standard treatment using pulmonary function and patient symptoms versus the same with the addition of bronchial hyperresponsiveness (BHR) as a surrogate for airway inflammation to guide treatment (4). The two year study results suggested that the asthma exacerbation rate was reduced 1.8-fold in the BHR group relative to standard therapy, improvement in BHR was inversely correlated with eosinophil counts on bronchial biopsy, and there was significant reduction in the subepithelial reticular layer of the airways in the BHR group relative to the traditional therapy group. This long-term study is also consistent with subsequent data that suggest that improvement in bronchial wall inflammatory cell infiltrates occur with inhaled steroids within three months but improvement in the thickening of the reticular subepithelial layer of the airways takes up to a year (5). Improvement in both factors, airway inflammation and reduction in thickening of the subepithelial reticular layer of the airways, has been implicated in less BHR (5). In addition, there may be an inverse relationship between subepithelial

fibrosis in asthma and the concentration of methacholine causing airway hyperresponsiveness (6). This may explain the continued improvement in BHR even to the normal range that can occur in some asthmatics who are treated for a year or more with inhaled steroids (5, 7, 8). If one believes that some airway remodeling can be reversed (thickened subepithelial layer of the airway) with inhaled steroids, long-term monitoring of BHR might be the answer. The inability to reverse BHR to the normal range with prolonged inhaled steroid therapy suggest that airway inflammation may be controlled without the ability to improve some aspects of airway remodeling that have become irreversible. In other subjects who improve with inhaled steroids to a state of normal BHR, this might suggest that either thickening of the subepithelial layer had not yet occurred or was totally reversible ie had not developed characteristics that prevented reversal of the process.

BHR is an objective way that patients can be followed to determine the effectiveness of treatment for their asthma. It appears to be a relatively safe test even with reduced lung function (6). Drawbacks to using this method are the time it takes to do the test ie at least 30 minutes including reversal, expense, patient tolerance, and technician expertise and time. Interpretation of the test would also require the expertise of a sub specialist. Therefore, BHR is an excellent research tool to determine the efficacy of different anti-inflammatory therapies in controlled studies for asthma but may not catch on as a routine clinical test. In addition, other complicating factors that make it more difficult to interpret are other causes that promote BHR separate from asthma including allergic rhinitis in the nonasthmatic or asthmatic, smoking in the asthmatic or nonasthmatic, and patients with no history lung disease who have isolated BHR (10).

### **EOSINOPHILIC AIRWAY INFLAMMATION DETERMINED BY SPUTUM INDUCTION**

The best way to monitor disease activity would be direct monitoring of inflammation in the airways. Bronchoscopy with biopsy is much too invasive for routine clinical practice whereas sputum induction is much less invasive and more amendable to clinic care. Sputum induction has been used to monitor inflammatory cells including eosinophils in particular (11). It appears that eosinophilic inflammation in the airways is characteristic of the majority of poorly controlled or more severe asthmatics (12, 13). In patients with sputum eosinophilia and asthma, normalization of sputum eosinophil counts to below 3% using increasing doses of inhaled steroids was effective in reducing both

hospitalizations for asthma and overall asthma exacerbations relative to standard asthma guideline therapy in one study (14). In two other studies, evaluating baseline sputum eosinophil counts after reducing (15) or completely eliminating inhaled steroids for several weeks (16) or longer (15) was done. In addition, changes from baseline airway eosinophil count were evaluated after steroid reduction (15,16). Results reveal that patients with higher baseline airway eosinophil counts or those that increase with the reduction in steroid dose identify a large group of asthmatics who are more likely to have an exacerbation of asthma. The general conclusions from these two studies suggest that asthmatics with an increase in airway eosinophil counts after reduction or elimination of inhaled steroids need to have their anti-inflammatory therapy increased. They were the ones most likely to have an asthma exacerbation relative to those without an increase in sputum eosinophils (15,16).

Problems with sputum induction for eosinophilic and inflammatory cell airway monitoring include cost, processing of samples that require a certain skill, and patient ability to produce samples. Results take a day to come back if not longer and are probably not yet ready for prime time, albeit this is the most direct and reliable method so far to monitor asthma airway inflammation. Another theoretic problem relates to the probability that the primary abnormality of airway inflammation is related more to mast cell myositis that results in the secondary influx of eosinophils (17). This is consistent with data in which interleukin-5 blocking monoclonal antibody reduces airway and blood eosinophils in asthma without affecting BHR or the late asthmatic response (18). In this situation, monitoring eosinophils may actually be a surrogate marker for the recurrent activation of mast cells in the smooth muscles of the airway. Inhaled steroid suppression of eosinophilic inflammation may reduce mast cell presence in the airways and over long periods of time possibly eliminate airway hyperresponsiveness since there is an inverse relation between mast cell presence in smooth muscle cells of the airways and BHR (19).

### **EXHALED NITRIC OXIDE**

Inflammometry, or monitoring inflammation in the airways using exhaled nitric oxide, is another option that is attractive since it is very easy to do and can give immediate results in an office setting. The major drawbacks are that steroids inhibit the actual production of nitric oxide (20), inflammation of any type such as allergic rhinitis in the upper airway can increase nitric oxide production, viral and

other lower respiratory tract infections can elevate nitric oxide levels, and it has never been demonstrated that using exhaled nitric oxide would be clearly better at directing asthma therapy than more traditional research biomarkers such as BHR or eosinophilic airway inflammation. However, given the ease of use and good correlations with BHR and sputum eosinophils (21), it is likely that routine measurements of exhaled nitric oxide will be used to monitor asthma therapy in the near future. In fact, one study has just come out and compared nitric oxide guided asthma therapy versus traditional symptom/lung function (GINA) guidelines with the primary endpoint being asthma exacerbations (22). The null hypothesis of no difference was not rejected. In addition, there was a significant reduction in steroid dose in the group guided by expired nitric oxide, suggesting less is truly more (23). A second preliminary study has suggested that lung function and nitric oxide levels may predict which stable asthmatics will develop an asthma exacerbation in the near future (24). These early studies suggest that the addition of exhaled nitric oxide as a guide to treatment, despite a number of limitations, is better than current (symptom and lung function based) guidelines. Most likely exhaled nitric oxide analysis will be incorporated into new asthma management guidelines including home monitoring until a better system comes along. The better system will be one that gets even closer to airway inflammation such as BHR or airway inflammatory cell monitoring that can be done in a more rapid and economical way.

In the future, clinical research studies will still use sputum analysis, BHR and even bronchial biopsies to help determine the degree of inflammation in asthma using different therapies since this brings the researcher much closer to actual airway inflammation and pathology. These markers and measures of inflammation have proven more accurate than exhaled nitric oxide, at least as currently measured. For the clinician seeing the patient in the office, however, an elevated nitric oxide level during an office visit for asthma will make the clinician ponder a number of possibilities. Is the inhaler technique of borderline quality such that the inhaled steroid is not getting to the site of action? Is the patient noncompliant with controller therapy? Should anti-inflammatory therapy be increased due to poorly controlled asthma? Does the patient have an underlying viral infection (or bacterial) since the peak flow variability is not increased despite an increased exhaled nitric oxide level? Is this a peripheral or bronchial elevation of nitric oxide? What is the patient's lowest and highest nitric oxide level and how does

today's level fit in? Etc. Office visits for asthma should definitely be more interesting.

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