

# Inflammatory events in asthma: An expanding equation

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Asthma is a chronic inflammatory disorder that can lead to progressive, potentially irreversible declines in lung function in some patients. Asthmatic inflammation develops when the sequential interaction of inflammatory cells with resident cells generates a cascade of events that contribute to the chronic inflammation and clinical manifestations associated with the disease, including further inflammation, airway smooth muscle spasm (bronchospasm), airway mucus secretion, airway edema and narrowing, and bronchial epithelial damage. Because of the chronic, progressive nature of asthmatic inflammation and the early age of onset, the ability to evaluate inflammation in children would be useful. Several procedures that quantify inflammatory mediators (in peripheral blood, induced sputum, bronchoalveolar lavage fluid, and bronchial biopsies) have shown potential usefulness in the evaluation of and the monitoring of disease severity in children (and, by extension, adults) with asthma. Further research needs to be devoted to the elucidation of when the inflammatory process starts and how it changes over time, to the determination of whether the inflammatory process is the same in all patients with wheezing, regardless of the stimulus, to the definition of the relationship between atopy and asthma, and to the establishment of the usefulness of testing for inflammatory markers to help identify individual asthmatic phenotypes, to evaluate disease severity, to measure therapeutic response, and/or to predict potential outcomes. (*J Allergy Clin Immunol* 2000;105:S633-6.)

**Key words:** Adhesion molecule, cytokine, eosinophil, inflammation, leukotriene, macrophage

Until the past decade, asthma was regarded narrowly as a disorder of airway smooth muscle in which abnormal contractility causes the variable airflow obstruction and symptoms characteristic of the disease.<sup>1,2</sup> More recent investigations have led to our current understanding of asthma as a disorder in which acute inflammatory episodes superimposed on a chronic inflammatory state result in the periodic onset of clinical symptoms known as asthma exacerbations.<sup>2</sup> In addition to underlying these acute events, chronic inflammation in asthma is now known to be capable of stimulating mechanisms of airway healing and repair that can lead to progressive, potentially irreversible tissue destruction and airway remodeling and to consequent declines in lung function.<sup>3</sup> Although the recognition of the inflammatory component of asthma has led to improvements in the ability to

## Abbreviations used

BAL: Bronchoalveolar lavage  
BPD: Bronchopulmonary dysplasia  
ECP: Eosinophil cationic protein  
EDN: Eosinophil-derived neurotoxin

manage the disease, many questions remain with respect to the inflammatory process. At this juncture therefore it is useful to review our current understanding of the mechanisms, markers, and potential long-term consequences of asthmatic inflammation to provide a context and perspective for the issues that remain to be resolved.

## MECHANISMS OF ASTHMATIC INFLAMMATION

Evident across the spectrum of patients with asthma,<sup>4</sup> asthmatic inflammation develops as a result of complex interactions among a wide variety of inflammatory cells and mediators.

Infiltration of inflammatory cells into the airway walls (predominantly eosinophils and lymphocytes) is a cardinal feature of asthma.<sup>2</sup> The sequential interaction of these cells with resident cells (eg, mast cells, macrophages, epithelial cells, endothelial cells) generates a cascade of events that contributes to the chronic inflammation and clinical manifestations associated with asthma (Fig 1).<sup>5</sup> Mediators, generated by this interaction include histamine, platelet-activating factor, derivatives of the arachidonic acid cascade, such as prostaglandins and the cysteinyl leukotrienes (LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>), and toxic oxygen radicals.<sup>2,5</sup> In turn, these mediators attract other inflammatory cells, thereby contributing to further inflammation, airway smooth muscle spasm (bronchospasm), airway mucus secretion, and airway microvascular leakage that lead to airway edema and narrowing.<sup>2,5-7</sup> The granular constituents of eosinophil major basic protein (eosinophil cationic protein [ECP], eosinophil-derived neurotoxin [EDN], and eosinophil peroxidase) induce the epithelial damage seen in the bronchial mucosa of subjects with asthma.<sup>5</sup>

Macrophages, resident cells that are activated in patients with asthma, are capable of producing a large variety of cytokines and other mediators involved in the inflammatory response (Fig 2).<sup>1,2</sup> These include TNF, IL-1 $\beta$ , IL-2, IL-6, GM-CSF,<sup>8</sup> and endothelin.<sup>9</sup> These cytokines and mediators, in turn, have multiple effects on several resident and inflammatory cells. For example, the release of IL-3, IL-5, and GM-CSF that are generated by lymphocyte activation may prolong eosinophil survival

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**FIG 1.** Inflammatory cells and mediators involved in asthmatic inflammation. *EOS*, Eosinophil; *PAF*, platelet-activating factor; *MBP*, major basic protein; *EPO*, eosinophil peroxidase; *ICAM*, intercellular adhesion molecule; *VCAM*, vascular cell adhesion molecule. (Adapted from Björnsdóttir US, Quau SF, Busse WW. Eosinophils and asthma. In: Busse WW, Holgate ST, editors. Asthma and rhinitis. Cambridge (MA): Blackwell Science; 1995. p. 328-46. Reprinted by permission of Blackwell Science, Inc.)

and augment eosinophil function.<sup>5</sup> Moreover, the ability of cytokines to induce the expression of adhesion molecules, such as intercellular adhesion molecule and vascular cell adhesion molecule, mediates the movement of inflammatory cells from the circulation to the airway epithelium or lumen.<sup>2,10</sup>

#### MARKERS OF AIRWAY INFLAMMATION IN CHILDREN

Epidemiologic studies have demonstrated that 80% of children with asthma experience the development of symptoms before 5 years of age.<sup>11</sup> In light of the early age of onset and the fact that airway inflammation that leads to physiologic effects on the airway is present in even the mildest forms of asthma, it is interesting to examine current knowledge about the characteristics of

airway inflammation in children with asthma. Research in this area has involved the use of a variety of procedures to analyze and quantify inflammatory mediators in peripheral blood, induced sputum, bronchoalveolar lavage (BAL) fluid, and bronchial biopsies.

#### Peripheral blood studies

A recent controlled study of premature infants with and without bronchopulmonary dysplasia (BPD), a lung condition that in many cases leads to chronic asthma, showed significant increases in eosinophil counts and concentrations of ECP in peripheral blood of the infants with BPD compared with those infants with no BPD ( $P < .05$ ).<sup>12</sup> The same abnormalities were observed in an older group of children with asthma (4 to 14 years of age) in addition to significantly increased urine concentrations of EDN ( $P < .01$  vs control subjects). Moreover, the

investigators were able to correlate increases in both eosinophil counts in peripheral blood and EDN in urine with decreases in FEV<sub>1</sub>.<sup>13</sup> A study in children with asthma (6-17 years of age) also demonstrated that concentrations of ECP and EDN correlated with disease severity.<sup>14</sup>

In contrast, a study in children (6-9 years of age) showed that eosinophil counts and ECP concentrations in 12 children with asthma were similar to those in 24 nonatopic children who were born prematurely and 12 healthy children with no asthma. However, generation of LTC<sub>4</sub> by eosinophils from prematurely born children with bronchial hyperresponsiveness was comparable to that of patients with asthma and was significantly greater than that of prematurely born children with no bronchial hyperresponsiveness ( $P < .05$ ) and control subjects ( $P < .01$ ).<sup>15</sup>

In a study of premature infants with respiratory distress syndrome, plasma intercellular adhesion molecule concentrations were significantly increased at 14 days of age in infants whose lung problems did not eventually resolve ( $P = .02$ ), indicating a relationship between this adhesion molecule and the persistence of airway inflammation.<sup>16</sup>

A study in children with asthma (8-15 years of age) showed that pulmonary function was significantly correlated both with the number of CD4<sup>+</sup> lymphocytes that expressed the CD25 activation marker and with eosinophil counts ( $P < .05$ ).<sup>17</sup>

These studies provide evidence of the potential value of peripheral blood testing for inflammatory mediators in gauging asthma disease severity and the effects of therapy.

### Induced sputum studies

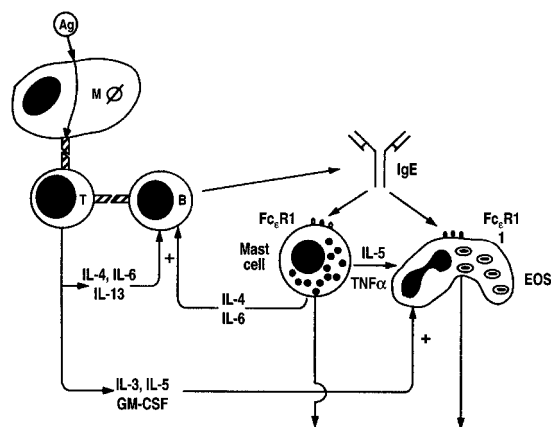
Sputum induction is gaining more widespread use because it is less invasive than BAL or biopsies. In children with asthma (<1-4 years of age), Nagayama et al<sup>18</sup> performed a pharyngeal aspiration after coughing and found that the proportion of children with 11 or more eosinophils per 5 high-powered fields increased with age: 33% in children up to 1 year of age, 55% in children at 1 year of age, and 79% to 80% in children 2 to 3 years of age. Moreover, eosinophilic infiltration was noted before the appearance of IgE antibodies to mite protein. These intriguing data support the theory that the onset of asthmatic inflammation occurs early in life, even before the formation of IgE antibodies.

Another group of investigators performed sputum induction in children with acute asthma (8-15 years of age) 1 hour after arrival to the emergency room and again at least 14 days later. These investigators found intense infiltration of eosinophils, neutrophils, and mast cells in the acute episode but a significant decrease in these polymorphonuclear leukocytes during the resolution process ( $P < .06$ ).<sup>19</sup>

These results support the use of the technique of induced sputum induction in the assessment of asthma severity in children and, perhaps adults, over time.

### BAL studies

Azevedo et al<sup>20</sup> compared levels of inflammatory cells and mediators obtained by BAL in 2 groups of infants (6-



**Cytokines and mediators of allergy**

**FIG 2.** Cytokine pathways involved in the regulation of asthmatic inflammation. Ag, Antigen. (Adapted from Holgate ST, Bradding P, Sampson AP. Leukotriene antagonists and synthesis inhibitors: new directions in asthma therapy. *J Allergy Clin Immunol* 1996;98:1-13. With permission.)

36 months of age) who underwent flexible bronchoscopy; 13 infants with wheezing and 6 infants with no wheezing. The 13 infants with wheezing had experienced moderate to severe episodes of wheezing and/or persistent wheezing between episodes; BAL was performed at an asymptomatic time. Of the 6 infants with no wheezing, 4 infants had tuberculosis and 2 infants had persistent pulmonary infiltrates. None of the study infants had cystic fibrosis, congenital or acquired immune deficiencies, or congenital malformations. These investigators found that alveolar macrophages from the infants with wheezing contained significantly greater concentrations of thromboxane A<sub>2</sub> and LTB<sub>4</sub> under resting conditions and significantly greater concentrations of thromboxane A<sub>2</sub> after stimulation with ionophore-A23187 ( $P < .05$  vs control subjects). The administration of dexamethasone significantly decreased the release of these eicosanoids ( $P < .05$ ). These patterns were similar to those observed in adults with asthma.

A comparison of BAL findings in 52 atopic children with asthma (1-15 years of age), 23 nonasthmatic atopic subjects (1-14 years), and 20 patients with virus-associated wheeze (1-8 years of age) showed significantly higher numbers of eosinophils ( $P \leq .005$ ) and mast cells ( $P \leq .05$ ) in the atopic children with asthma compared with children in the other 2 groups. Surprisingly, within the groups of children with asthma, these counts did not differ between children receiving antiinflammatory therapy (inhaled corticosteroids or cromolyn) and those receiving only bronchodilator medication.<sup>21</sup>

### Bronchial biopsy study

A comparison of the bronchial mucosa in children with bronchial asthma in remission with that of children who died in status asthmaticus showed similar histopathologic changes (ie, goblet cell hyperplasia,

mucus plugging, increased collagen deposition beneath the epithelial basement membrane, smooth muscle hypertrophy, and local eosinophilia). Notably, the only features observed in patients who died in status asthmaticus that did not occur in the asymptomatic patients were greater peribronchial eosinophilic infiltration and more extensive denudation of the airway mucosa, which probably reflected a more acute and active disease process.<sup>4</sup>

### POTENTIAL LONG-TERM CONSEQUENCES OF ASTHMATIC INFLAMMATION

The chronic inflammation characteristic of asthma stimulates a continuous process of healing and repair in the airways that can lead to progressive, permanent tissue destruction. Whereas the bronchial epithelium (which constitutes the outermost layer lining the bronchi) appears to regenerate without any trace of the previous injury, the underlying submucosa regenerates abnormally, resulting in smooth muscle hypertrophy. This defect, in turn, leads to increased airway contractility and is accompanied by collagen deposition and extracellular matrix reorganization abnormalities that cause a gradual decline in pulmonary function.<sup>3</sup> The potential for development of these long-term structural changes in patients with chronic asthma implies the need for early intervention to modify the inflammatory process.<sup>2</sup>

### AIRWAY INFLAMMATION IN ASTHMA: UNANSWERED QUESTIONS

Although the recognition of the presence of inflammation even in mild-to-moderate asthma has improved therapeutic approaches to asthma management, many questions remain. Specifically, we need to know when the inflammatory process starts and how it changes over time, both in response to therapeutic interventions and as a result of the natural history of asthma. Further studies also are needed to determine whether the inflammatory process is the same in all patients who wheeze, regardless of the stimulus (eg, allergen, exercise, virus). The relationship between atopy and asthma needs to be clarified; as yet, it is not known why some atopic individuals become asthmatic and others do not and why some asthmatic individuals are atopic and others are not. Finally, the usefulness of testing for inflammatory markers remains to be established, in terms of its ability to help identify individual asthmatic phenotypes, evaluate disease severity, measure therapeutic response, and/or predict potential outcomes. Clarification of these issues will improve and advance our efforts to evaluate and effectively treat patients with asthma.

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