# The importance and features of the distal airways in children and adults

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**Asthma remains a major problem worldwide, even with new categories of medications that have been brought into the therapeutic armamentarium. One area of disease pathology and physiology that is involved in the pathobiology of asthma is the distal (small) airways. Better understanding of this area in both the pediatric and adult asthmatic populations will lead to improved targeted therapy for all asthmatic patients. This article discusses the importance of the distal airways for both children and adults with asthma. (J Allergy Clin Immunol 2009;124:S84-7.)**

***Key words:*** *Asthma, small airways, distal airways, adult, children, clinical, therapeutic*

## UNIQUE FEATURES OF CHILDHOOD ASTHMA: INVOLVEMENT OF THE DISTAL AIRWAYS

Asthma is a disease characterized by repeated episodes of exacerbations and remissions in which airway inflammation plays a prominent role, with documented changes in both large and peripheral airways.[1-3] In the most simple terms asthma can be seen as involving 2 major phases: an initial sensitization or inception phase and a maintenance or progression phase (Fig 1).

In considering the physiologic features of the disease, childhood asthma has many distinguishing features that set it apart from adult asthma and even from childhood-onset adult asthma.[4] Asthma is more likely to be episodic in children and persistent in adults. The younger the child, the more episodic it is likely to be. Children are generally more atopic than adults, with higher serum IgE levels and evidence for atopy by means of skin testing and associated atopic diseases, such as food allergy, atopic dermatitis, or both. In both groups allergic rhinitis is common. Children are more capable of hyperinflating through an increase in residual volume leading to increases in total lung capacity and tend to have less airway resistance to airflow.[5] Because of the shorter duration of the disease in children, there is less time for disease progression with fixed decrements in flow rates. A number of studies have shown that children at all levels of asthma severity can have relatively unimpaired $FEV_1$ values when clinically stable, and even when they appear to have normal values, they can respond to bronchodilators with further increases in $FEV_1$.[4,6-9]

In children the distal airways are definitely affected, and increased peripheral airway resistance in the absence of or before significant large airway involvement likely explains the normal $FEV_1$ values typically seen in many children with asthma.[10] Furthermore, in many cases there appears to be a shift between early infancy/childhood and later childhood/adolescence/adulthood in the relative degree of involvement of small- versus large-airway involvement. Despite the inherent limitations, several studies have demonstrated abnormalities in forced expiratory flow at 25% to 75% of forced vital capacity (a possible surrogate measure of peripheral airflow obstruction) in asthmatic children with normal $FEV_1$ values.[11]

Despite new therapeutic drug developments to target a number of different mediators and pathways, clinical efficacy has been minimal in large clinical trials.[12] There are several potential reasons for the failure to gain adequate asthma control (Table I), including incorrect diagnosis, asthma heterogeneity, poor medication adherence, failure to deliver medication to the target site, and insensitivity of the pathway or target cell to corticosteroid therapy. Among these and addressed in other articles is the importance of particle size and delivery of adequate concentrations of drug to the distal airways in a consistent manner. A second concern is whether in a given patient the predominant pathophysiologic pathway leading to clinical symptoms is actually sensitive to corticosteroids.

The introduction of inhaled corticosteroids has had a major effect on asthma care in children. Despite these successes, asthma remains a challenge because the number of urgent care visits and hospitalizations for asthmatic children has had little improvement over the last decade.[13] These aspects go beyond the socioeconomic concerns that limit the benefits of any intervention. In infants and children, even in controlled clinical trials, the studied inhaled corticosteroids failed to have any disease-modifying effects and were only effective when taken regularly, without sustained benefits when discontinued.[14]

In considering some of the underlying reasons for the therapeutic limitations of corticosteroids, asthma must not be seen as a single disease entity but rather as a syndrome with many potential pathways leading to the same clinical phenotype. Thus asthma heterogeneity both between patients and in the same patient at different stages of the disease needs better understanding if we are to affect morbidity, mortality, and even prevalence. In fact, there have been pleas to abandon asthma as a disease concept.[15]

There is reason to support the concept of 2 distinct stages of asthma, the induction or sensitization phase and a maintenance or progression phase (Fig 1), in which the pathway or pathways and triggers leading to the first phase, "the origins of asthma," might differ from those contributing to the second or maintenance phase. In animal models of asthma, in which contributing factors are able to be controlled, the 2 phases can be clearly defined. In the induction phase $\alpha/\beta^+$, $CD4^+$, IL-$4^+$ T cells play a requisite role in this initial sensitization phase, whereas in the maintenance/progression phase these T lymphocytes become less obviously

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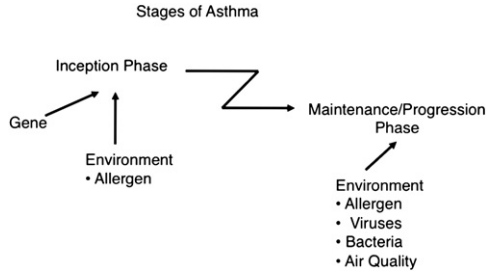


**FIG 1.** Stages of asthma from inception to maintenance/progression.

**TABLE I.** Reasons for failure to achieve asthma control

| |
|---|
| Compliance |
| Asthma heterogeneity |
| Wrong diagnosis |
| Wrong target |
| Failure to deliver drug to the target site |
| Insensitivity of the pathway or target cell to corticosteroids |

required, and the cytokine IL-13 and perhaps IgE take on increasing importance.[16]

The Tucson Birth Cohort initially characterized different wheezing phenotypes in children, with only one third of the children progressing to classic asthma and persistent wheezing.[17] Most children with virus-induced wheeze stopped wheezing by around 6 years of age. Others began later, whereas those who were sensitized at an early age persisted in wheezing. The important role of allergen exposure and allergic sensitization early in life on the course of asthma has been addressed in a large Multicenter Allergy Study Group.[18] Ninety percent of children with wheeze by 3 years of life but no atopy (negative skin test results) lost their symptoms by school age and retained normal lung function at puberty. In contrast, sensitization to perennial allergens (house dust mites and cat or dog hair) developing in the first 3 years of life was associated with a loss of lung function at school age, and concomitant exposure to high levels of perennial allergens early in life aggravated this process. Thus a predisposition to a chronic course of asthma characterized by bronchial hyperresponsiveness and loss of lung function at school age appeared to be determined by allergen sensitization and continuing allergic inflammation in the first 3 years of life. In the first years of life, IgE antibody responses are initially directed toward food allergens and later to indoor or outdoor aeroallergens. As a result, early perennial sensitization identifies atopy early in life. The association of persistent asthma with early aeroallergen sensitization is further supported by the absence of an association with early sensitization to food allergens; that is, sensitization in the lung itself is the critical determinant.[19]

Is there effective prophylactic therapy in infants and toddlers, especially those who have a strong likelihood and are at risk of asthma from early on? In all guidelines inhaled corticosteroids are proposed as first-line therapy, including in children younger than 4 years. However, as discussed, in at least 4 independent studies, inhaled corticosteroids have failed to alter the progressive loss of lung function (the risk domain) despite their advantage in controlling symptoms, need for urgent care visits, and need for rescue medication (the impairment domain).[6,14,19-21] Of interest, in a group of "decliners" identified in the Childhood Asthma Management Program study, the number of decliners was similar in all 3 groups: placebo, nedocromil, and budesonide.[22] Furthermore, in a study to determine whether early intervention with

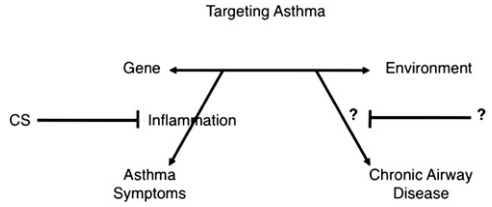


**FIG 2.** Corticosteroids *(CS)* block inflammation but might not alter the development of chronic airway dysfunction, which might be mediated by as-yet-unknown pathways that are not sensitive to CS.

corticosteroids could alter the natural history of the disease, once the drugs were discontinued, symptoms recurred.[14]

It is unclear at present what this says about the role of corticosteroids during the early sensitization phase or whether their lack of effect on pulmonary function results from delayed onset of treatment, insufficient dosing, or failure to deliver the inhaled medication to targets in the distal airways. Furthermore, although corticosteroids are highly effective in reducing asthma symptoms resulting from airway inflammation, they do little to control chronic or persistent airway dysfunction where the pathogenic pathways remain to be described (Fig 2). Does the genetic predisposition or atopic state convey a degree of steroid insensitivity to the immune response that is not present in nonpredisposed nonatopic infants. Such studies are clearly necessary if we are to affect the formative years of allergic asthma.

In summary, children with asthma are different than adults with asthma. They are not "little adults" and appear to have greater involvement of peripheral airways than central airways. Corticosteroids do not alter the natural history of the disease and likely do not prevent progressive loss of lung function in the subset of "decliners." The pathobiology involved in the decrease of lung function remains to be elucidated. Inhaled medications might not reach the distal airways, where many of the disease manifestations can be initiated. New and noninvasive techniques for monitoring lung function and inflammation are required in children to track and monitor effects in the distal airways, as is the development of drugs and delivery devices that ensure peripheral airway delivery in this vulnerable population.

## THE IMPORTANCE OF DISTAL LUNG IN ADULT ASTHMA

Data from the last 4 decades have suggested that the distal lung, which includes airways smaller than 2 mm and the lung parenchyma, contributes to asthma pathogenesis. Because of the challenges raised in evaluating this part of the lung, this region has not been studied at the same level of detail as the larger airways. However, a significant amount of pathologic data from autopsy specimens and recently from patients with chronic stable asthma evaluating the small airways and lung parenchyma are available. These data, combined with physiologic data, support a significant role for the distal lung as a contributor to airway inflammation, hyperresponsiveness, and asthma control. The following discussion will present this evidence and explore the clinically important issue of the distal lung as a therapeutic target in adult asthma.

### The role of the distal lung in asthma

Because inhaled corticosteroid therapy is inadequate in some patients with asthma, it has been suggested that distal regions in the asthmatic lung might be beyond the reach of these agents.

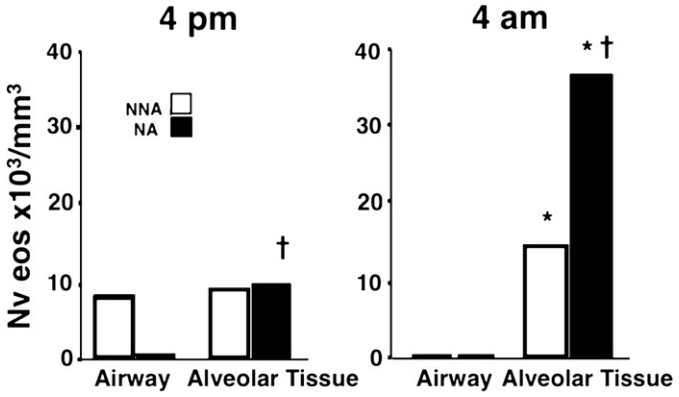


**FIG 3.** Number per volume *(Nv)* eosinophils *(eos)* per cubic millimeter of lung tissue obtained by means of endobronchial (airway) and transbronchial (alveolar) biopsy in subjects with nocturnal asthma *(NA)* and nonnocturnal asthma *(NNA)*. Adapted from Kraft et al.[1] *†$P < .05$.

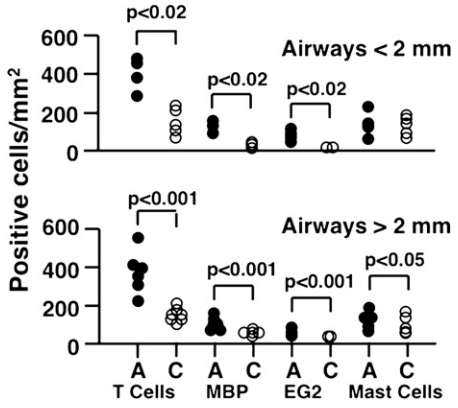


**FIG 4.** Number of inflammatory cells per square millimeter of T lymphocytes *(T cells)*, eosinophils staining positive for major basic protein *(MBP)* and eosinophil cationic protein *(EG2)*, and mast cells in lung tissue obtained from asthmatic subjects *(A)* and control subjects *(C)* through surgical resection. Adapted from Hamid et al.[30]

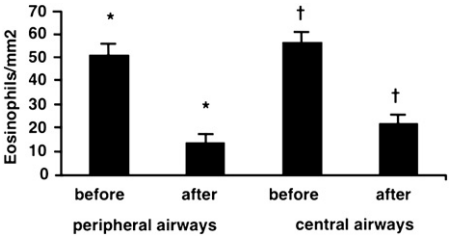


**FIG 5.** Eosinophils before and after hydrofluoroalkane-flunisolide in peripheral and central airways. Values are presented as means ± SEMs. *†$P <$ .001 versus pretreatment. Adapted from Hauber et al.[40]

Until relatively recently, the role of the distal airways in patients with asthma and the effect of inhaled corticosteroids on distal inflammation have not been thoroughly studied because of the difficulty of evaluating the effect of asthma on the peripheral airways. The development of more sophisticated imaging and immunohistochemical techniques has fostered the recognition that distal airways are significant sites of inflammation and might be an important target for therapy in patients with asthma.

Several studies suggest that the distal airways are a predominant site of airflow obstruction in patients with asthma,[23-27] and distal airway inflammation contributes to a variety of clinically significant asthma phenotypes, including nocturnal asthma, spontaneous exacerbations, asthma complicated by smoking or viral respiratory tract infections, and severe steroid-dependent asthma. Because the total volume and combined surface area of the distal airways are much greater than the combined volume and surface area of the large airways,[23] inflammatory changes in the distal airways in patients with asthma can have a dramatic effect on the pathogenesis and treatment of the disease.

Preliminary evidence of the involvement of the distal airways in the pathophysiology of asthma originated from autopsy studies of patients who died from asthma.[28] Autopsy studies have reported significant mucus plugging, thickening, and the presence of inflammatory cells in the distal airways. For example, in an examination of the distribution of inflammatory cells throughout the bronchial tree of patients with fatal and nonfatal cases of asthma, Carroll et al[28] reported an increased number of lymphocytes and eosinophils uniformly distributed throughout the large and distal airways of patients with mild and severe asthma compared with that seen in control subjects. In fact, eosinophils appear to be frequently observed in distal airway tissue of patients with asthma, and the numbers of eosinophils correlated with asthma severity (Fig 3).[1,2] In addition, an analysis of resected lung specimens from asthmatic and nonasthmatic patients who underwent thoracic surgery reported increased numbers of T cells, total eosinophils, and activated eosinophils in both the large and distal airways from asthmatic patients when compared with control subjects (Fig 4).[28,30] Greater numbers of activated eosinophils were present in the distal airways than in the central airways, suggesting greater inflammatory activity in the distal airways. Another study of the same cohort of patients reported increased expression of mRNA for the cytokines IL-4 and IL-5 in the distal airways compared with that seen in the large airways.[31]

Studies in patients with chronic asthma indicate that distal inflammation might play a role in airway hyperresponsiveness, nocturnal asthma, spontaneous exacerbations of symptoms, asthma complicated by smoking or viral respiratory tract infections, and severe steroid-dependent asthma.[27] For example, several studies have demonstrated a correlation between circadian changes in inflammatory activity in the distal airways and nocturnal lung function.[29,30,32-35] In 2 studies, patients with nocturnal symptoms demonstrated a significant increase in inflammatory cells in the distal airways and alveoli in the late night compared

with that seen in patients without nocturnal symptoms.[29,30] Lung hyperinflation was also shown to correlate with symptoms of asthma, which improved as lung volume normalized with treatment.[36] Moreover, accumulating evidence demonstrates that remodeling can occur in the distal airways of patients with asthma.[28,37-39] Studies have also shown that remodeling in the distal lung might result from poorly controlled and persistent inflammation and loss of elastic recoil.[36,38] How persistent inflammation in this compartment leads to parenchymal remodeling, loss of elastic recoil, and decreased response to bronchodilators is the subject of ongoing investigation.

One study has evaluated the effect of a small-particle inhaled corticosteroid (flunisolide-hydrofluoroalkane) on proximal and distal airway inflammation. Hauber et al[40] performed bronchoscopy with endobronchial and transbronchial biopsy in subjects with asthma before and after treatment with flunisolide-hydrofluoroalkane for 6 weeks (Fig 5).[40] They demonstrated a reduction in proximal and distal airway eosinophil numbers and IL-5 and eotaxin levels. Airway tissue neutrophil numbers increased, and lymphocyte numbers remained unchanged. Further study with small-particle corticosteroids could further elucidate how reducing inflammation in the distal lung compartment, in addition to a reduction in proximal inflammation, contributes to improvement in asthma control.

## CONCLUSIONS

Increasing evidence suggests that inflammation occurs in the distal airways, as well as the central airways. Although further clarification on the clinical effect of inflammation in the distal airways is needed, it is likely that poorly controlled inflammation in the peripheral airways might exacerbate asthma, contributes to the accelerated decrease in lung function, and promotes airway remodeling. These processes support the distal lung as a therapeutic target in asthma.

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