

Interaction between the growing lung and asthma: Role of early intervention

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Asthma is a syndrome where an imbalance exists between the forces that maintain airway patency and the forces that act to narrow, or close, airways. The child with asthma is a particular problem because of the rapid growth of the lung during growth that leaves it vulnerable. There is some evidence that asthma leads to impaired lung function in children because those children with untreated asthma show a loss of lung growth velocity. For unclear reasons, asthma is more frequent in boys. What drugs to use to treat childhood asthma is uncertain. Data show that glucocorticoids prevent the structure of the lung from fully developing. In children, the rationale for early intervention seems clear, but the exact means and criteria for initiation of the intervention are uncertain. Finally, childhood asthma raises fundamental issues and questions that are unique to the child with asthma and presents unique and many unresolved treatment dilemmas. (*J Allergy Clin Immunol* 2000;105:S540-6.)

Key words: Asthma, childhood, glucocorticoid steroids, lung function, lung growth and development, gender

Asthma is an important disease of childhood with significant and sometimes fatal consequences. Because the rate of prevalence, hospitalization and death in the young continues to increase,¹⁻⁵ it becomes incumbent on the caregiver to take a wheezy child seriously. Yet, in spite of these facts, the knowledge about the natural history of asthma in childhood is sparse. Of greater concern is the relative paucity of information about how to best treat the child with asthma so as to avoid future complications.⁵

The purpose of this article is to briefly explore some of the things that are known about asthma in the child and the effects of treatment, with a particular emphasis on inhaled corticosteroids. Particular effort will be made to point out the gaps in our knowledge and understanding of childhood asthma.

Asthma is a syndrome of lung dysfunction in which an imbalance exists between the forces that maintain airway patency and those forces that operate to narrow or close the airway (Fig 1). It is within this conceptual framework that we will address, first, what is known and not known about the effect of asthma on lung function in children.

THE GROWING LUNG AND PULMONARY FUNCTION

Although the development of the morphologic structure of the lung is well described,^{6,7} the function of the lung is less well documented because of the difficulty in obtaining reliable measures of lung function in small children and infants. However, what is known is that the lung grows rapidly and that its function is dependent on both age and sex.

Lung volume and elastic recoil

Because the alveoli number becomes fixed by age 1 to 2 years,⁶ the increase in lung volume is due to an attenuation of the lung surface area. Functional residual capacity in children is determined by dynamic inspiratory action of the respiratory muscles, which set functional residual capacity above its passive relaxation position.⁸ Interestingly, this is the same factor that determines the elevation of functional residual capacity in the adult with asthma during an asthma attack. Children with severe persistent asthma often demonstrate persistent hyperinflation, which can be taken as 1 sign of the remodeled lung.⁹

Elastic recoil is low in young children and increases with age.^{8,9} It is tempting to speculate that asthma results in a failure for this increase in elastic recoil to develop and, if true, would provide a mechanical explanation for persistent hyperinflation.⁹ Because most of the elastic recoil pressure is due to surface tension, a permanent alteration in surfactant either in amount or character would probably account for the loss of recoil often observed in adults with asthma. In addition loss of surface tension causes the airways to become unstable and close. Increased airway wall compliance observed in many patients with asthma is greater in children than adults¹⁰ and is thought to be independent of the low parenchymal compliance. The presumption is that the loss of airway wall compliance is due to the inflammatory processes within the wall. The effect of current asthma treatment on hyperinflation and elastic recoil is unknown.

Flow resistive properties of the lung

Airways function as measured by the FEV₁ shows a pronounced increase during growth until about the age of 20 years (Fig 2, A). Several studies show that asthma results in a reduced acceleration in lung growth as measured by FEV₁.^{11,12} It must be remembered that FEV₁ is

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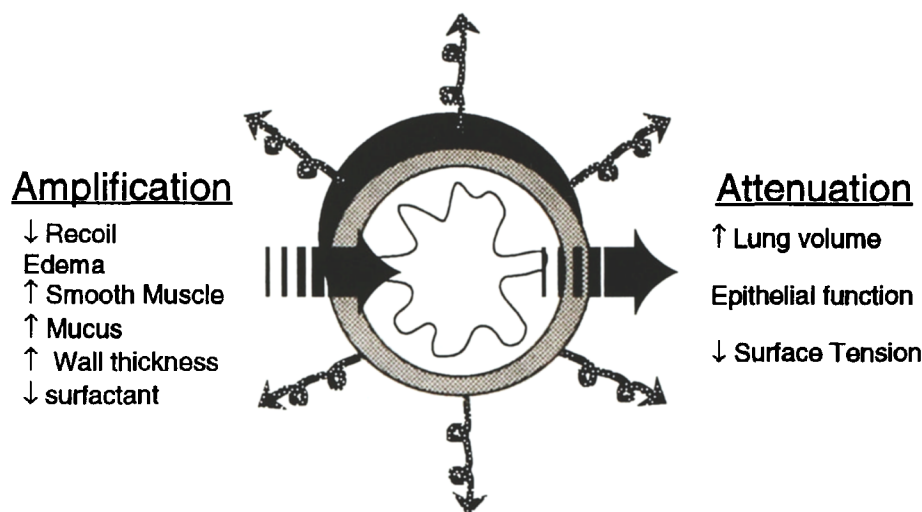


FIG 1. Conceptually, asthma is an imbalance between the forces that amplify the action of airways smooth muscle to narrow the airway (*Amplification*) and balanced against the factors that act to resist to hold the airway open (*Attenuation*). The *springs* represent the outward force vector of the lung parenchyma.

the expression of a multitude of mechanical factors, including the size of the lung and performance of an adequate maximal inspiration (total lung capacity). As a consequence, the failure of FEV₁ to develop may represent any number of factors (Fig 1) that may or may not include airway narrowing. These other factors have never been adequately explored in children with asthma.

Airway resistance falls from approximately 25 cm H₂O/L/sec in the term newborn to less than 2 cm H₂O/L/sec in the adult (Fig 2, B). When corrected for lung volume, the fall in conductance suggests an important influence of the increase in lung volume, which ceases at age 5 years.⁸ Functionally then, the lung is thought to be most vulnerable to inflammation in this early time period and might result in persistent airflow limitation. Studies attempting to determine the axial partitioning of conductance suggests that peripheral conductance is relatively low in the peripheral part of the lung of children.⁸ Given the abnormal increase in peripheral resistance¹³ and the enhanced response of the parenchyma to cold air,^{13,14} a significant site of dysfunction appears to reside in the parenchyma of the lung. Whether this is true of the young lung with asthma is unknown. It is tempting to speculate that the disproportionate growth of the parenchyma relative to the airways might make the parenchyma particularly sensitive to the ravages of inflammation.

ASTHMA AND CHILDHOOD

Asthma in infants is difficult to distinguish from other causes of wheezing, such as wheezy bronchitis.¹ As a consequence, the confirmation of the diagnosis of asthma most often cannot be obtained. However, by all reports, the prevalence of asthma in the age groups below 18 years is increasing. For example, the National Health and

Nutrition Examination Survey II study showed a 4.8% increase between 1971 and 1974, but in the period of 1971 to 1980 the increase was 7.6%. Recent studies^{1,3,15,16} show that, in the United States, there remains an increase in asthma in these age groups. Severity is also increasing, based on the increase of nearly 5% per year in asthma hospitalizations in this younger age group.

For many, asthma begins early in life. Current estimations suggest that asthma begins in the first few years.^{1,3,15,16} Fortunately, most children with asthma (approximately 75%) experience remission before or with onset of puberty, but for the rest there is further progression and a longer period of troublesome symptoms.

Factors thought to be involved are intrinsic influences (such as, genetic predisposition) because children with siblings with asthma, parents with asthma, or first-degree relatives are at increased risk.¹⁷ Atopy in general is considered a risk factor.¹⁸ Next extrinsic environmental factors (such as material smoking and other antigen exposures) are considered risk factors but less than the genetic influences. In addition many other factors have been suggested, but the relative risk is either unknown or thought to be small.¹⁷

EFFECTS OF GENDER: THE MALE BURDEN

It is currently well recognized that gender has a profound influence on lung growth and development.^{6,19} Male sex is associated with larger lung volumes but proportionately smaller airways.^{6,8} The latter is generally thought to confer the often-observed predilection of asthma in boys.^{1,5} Of interest, later in life the predilection for asthma shares a slight preference for women who have both smaller and more reactive airways.⁹ Lung development is a continuous process, but lungs of boys lag

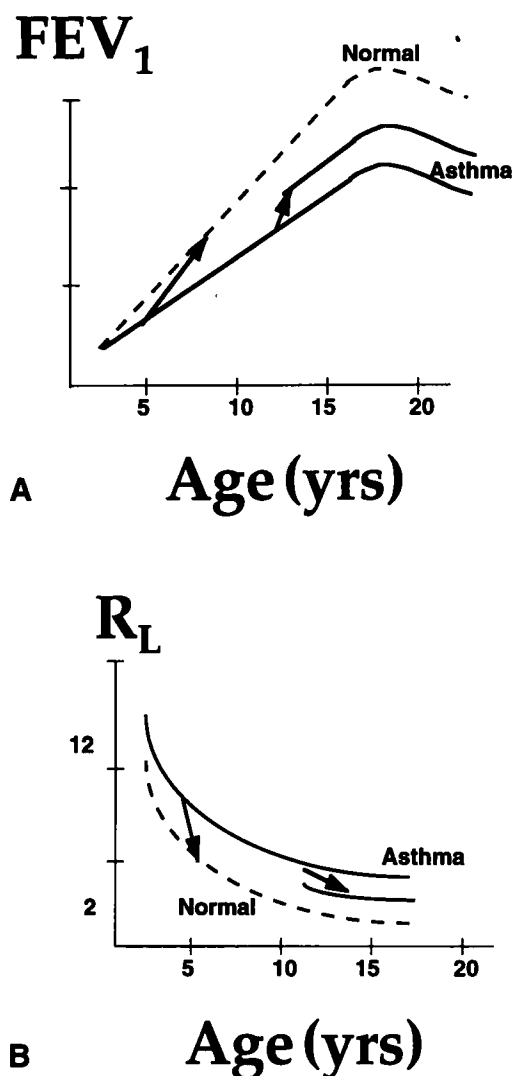


FIG 2. The effect of age and asthma on the development of lung function. **A**, Hypothetic lung growth curves for a patient who has no asthma (normal; dashed lines) and a patient with asthma (solid lines). The first arrow reflects the normalization of FEV₁ growth if early intervention of treatment occurs. The second arrow shows the failure to normalize if intervention is delayed. **B**, Pulmonary resistance with age shows a fall. Failure to intervene should hypothetically result in persistent airway narrowing and airflow limitation.

behind that of girls in terms of structured development at certain stages of development. Androgen sex hormones have been shown to stimulate the release of an epithelial-inhibiting factor by fibroblasts.^{19,20} One reason boys are at increased risk of lung immaturity is thought to be due to sex hormone effects on surfactant production.^{21,23} But in general, there is surprisingly little known about factors that change lung growth.¹

Asthma prevalence is increased in male children; indeed most studies show that the rate is approximately double that of female children.¹ Speculations have generally centered on 2 putative causes. The first is the smaller airways of boys, but this by itself seems unlikely

because the airway's size is not that much different when compared with girls in absolute terms. The theoretical rationale for small airways being a risk factor is based on overly simplistic geometric arguments whose validity is unknown. The second, which is a more likely reason, is a known increase rate of lung infections in boys. Last, because male sex renders the airways epithelium less well developed,^{19,20} it seems that a reasonable hypothesis would be that inflammation processes in the immature male lung may lead to more injury and altered lung structure (remodeling) as the lung attempts to heal itself. This hypothesis deserves some attention.

Severe or untreated asthma increases the risk of the airways progressing into a state of persistent and unresponsive narrowing (Fig 3). The factors discussed about male sex, time, viral infections, antigen exposure or atopy, and genetic predisposition favor this progression. On the other hand, antigen avoidance, female sex, and treatment, especially if initiated early, works to prevent this progression. In children, the rationale for early intervention seems clear, but the exact means and criteria for initiation of the intervention are uncertain.

GLUCOCORTICOIDS AND THE GROWING LUNG

The waterfront of nonpharmacologic and pharmacologic choices for intervention are covered in recent, excellent chapters on the topic.^{5,22,23} Because the topic is early intervention with the goal of preventing long-term adverse effects of disease, only the role of anti-inflammatory (or controllers) will be discussed.

In this regard the pediatrician in the United States has only 3 choices (theophylline, sodium cromoglycate and inhaled corticosteroids) in treating children under 12 years of age.^{5,22,23} Theophylline and similar agents are enjoying a renaissance largely because of their rediscovered anti-inflammatory properties. In children, the ease of administration, dosing schemes, and ability to individualize doses of theophylline are advantages. The disadvantages are several and include a low margin of safety, uncertain absorption or elimination, and unfounded concerns about effects on learning and behavior.²⁴ Recently, the potential of efficacious low-dose therapy makes revisiting this issue, especially in children, attractive.²⁵

The cromone, sodium cromoglycate, is an especially attractive choice in the treatment of children with asthma. Accordingly, it is currently recommended as a first line of intervention in children in the International Treatment Guidelines.²⁶ The major reason for this recommendation in children is that sodium cromoglycate has the low incidence of side effects, is available in a formulation for nebulization, and has blocking effects on antigen responses. Unfortunately, the efficaciousness of these agents declines in the increasing asthma severity. The reason is uncertain, but the author would suggest that, because this drug stabilizes epithelial membranes, this effect would decrease because the epithelium is lost as a consequence of increased inflammation.

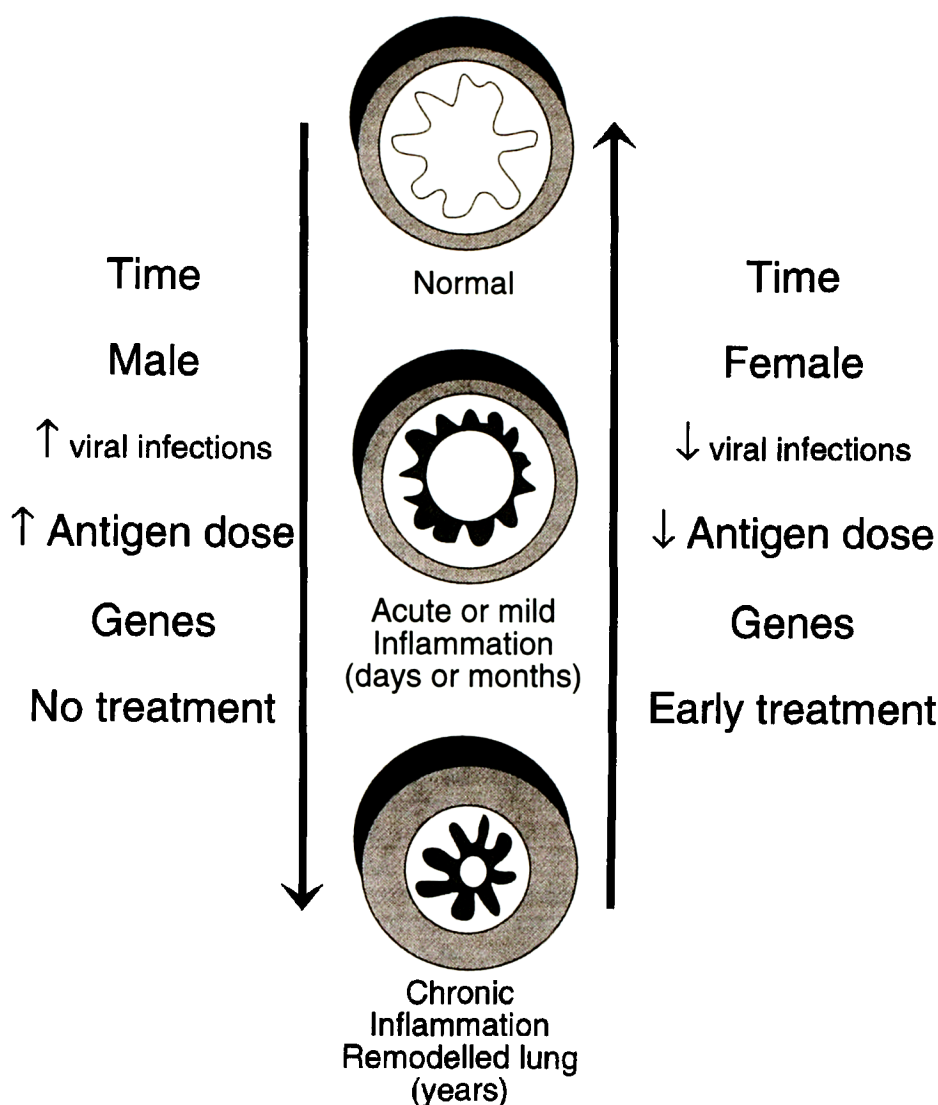


FIG 3. The factors that influence the progression of the normal airway to, first, a mild or acute state of airway narrowing and then on to a more severe, persistent narrowed state. The factors on the left are those that favor this progression, and the factors on the right are factors that prevent or reverse this progress.

Inhaled glucocorticoids are currently considered to be the most effective approach to the treatment of asthma.^{5,22,23,26,27} Unfortunately, no available form of steroid in solution for nebulization is available in the United States, although a nebulized form of budesonide exists outside the United States. In adults high doses of inhaled steroids effect bone density and studies show similar effects in children, it is known that asthma per se is associated with decreased growth velocity.²⁷ The only study investigating these issues of somatic and lung growth with early intervention with an inhaled corticosteroid is that of Agertoft and Pedersen.¹² The effect of budesonide in children was investigated, and the results show that the weight, prepubertal growth velocity, or height velocity were unaffected by treatment. However, when the data were segregated by dose, the subgroup receiving more

than 800 $\mu\text{g}/\text{day}$ was associated with reduced growth velocity. Children with untreated asthma showed loss of lung growth velocity. Steroid treatment improved lung growth but only if begun early (that is, within 3 years of asthma presentation). However, this study was not well controlled nor were the subjects randomized; the study suffers from a number of other design problems. Nevertheless, because similar findings have been obtained in several studies in adults, the results of this study are probably correct.

The National Institutes of Health—National Heart Lung and Blood Institute initiated a randomized, controlled trial of treatment intervention in childhood asthma or childhood asthma management program. The trial was multicentered and involved 1041 children between 5 and 12 years old. The central hypothesis was that regular

TABLE I. Question facing the caregiver with a child with suspected asthma

1. Does the child have asthma?
2. Does the child have a disease other than asthma?
3. What is the level of asthma severity?
4. When to intervene?
5. What modality of therapy needs to be used?
6. What are the side effects of asthma treatment in children?
7. What determines success or failure of the treatment of childhood asthma?

treatment with budesonide or nedocromil sodium when compared with standard therapy will improve lung growth velocity (Δ FEV₁/year) in children with asthma over a 5-year treatment interval. When the trial is finished in three more years, some of the questions concerning early intervention and treatment in this age group will be answered.

A word of caution needs to be raised concerning steroid usage, particularly because there are several studies in animals that demonstrate significant effects on growth and development.^{19,20,28-30} Clearly, what is needed to treat the child with asthma is a therapy that preserves the efficaciousness of steroids but without the effects on growth and development.

QUESTIONS AND ISSUES: CHILDHOOD ASTHMA

The child or infant with recurrent wheeze presents an important and largely unresolved set of questions and issues that need to be addressed (Table I). Let us consider in turn each of these questions because they have a major impact on whether to intervene and which treatment to use in the child with wheeze, cough, and shortness of breath.

Does the child have asthma?

The first question facing the physician is whether or not the patient, in fact, has asthma. The most common situation is that there is no objective pulmonary function data available, such as FEV₁, bronchodilator response, or bronchial challenge procedure. As a result, the diagnosis becomes very subjective, especially in view of the fact that chest auscultation is not very definitive.³¹ One is left wondering whether the child has a process that will pass with time and not require any further attention (eg, viral) or whether the disease process will escalate.³²

Does the child have a disease other than asthma?

Wheeze and shortness of breath are not symptoms specific to asthma. Even if one could measure airway responsiveness, it too is not specific even in adult patients, unless the hyperresponsiveness is marked. Many disease processes mimic the clinical picture of asthma in the child. In particular, several processes deserve some consideration. Unlike adults, gastroe-

TABLE II. Diseases with presentation that mimic asthma

Chronic or serial viral infections
Gastroesophageal reflux or aspiration
Vocal cord dysfunction
Tracheal web
Cystic fibrosis
Cardiac disease
Interstitial lung disease (hypersensitive pneumonitis)

sophageal reflex and aspiration are common occurrences in the child and are thought to be linked to wheeze. Clearly, recurrent and chronic viral infections would mimic an asthma-like syndrome. Other processes (Table II) have also been associated with asthma-like symptoms, and it is important that they be assessed and eliminated from the differential diagnosis because the treatments for these conditions are different than the treatment required for asthma.²³

What is the level of asthma severity?

The decision to intervene is often linked to the perception of asthma severity; however, this decision is often a personal one based on little more than subjective impressions. In one sense, if treatment were efficacious with minimal attendant side effects, then determination of the level of severity would not be needed. Then too, one is faced with establishing some threshold criteria for treatment initiation for which there are no guidelines. Most agree that exercise intolerance, nocturnal symptoms or awakenings, type or amount of treatment required to control symptoms, and symptom frequency are reasonable endpoints; but no firm and validated treatment guidelines exist.

When to intervene?

This too is a difficult question. Does one intervene after the second episode of wheeze, after the third or fourth episode, or after a length of time? As the one study suggests,¹² lack of aggressive treatment (especially for years) results in an irreversible effect on growth, both somatic growth and lung development. The current trend is certainly to intervene sooner¹² than later,²³ but well-designed trials on which to rationally base this bias are lacking.

What modality of therapy needs to be used?

Here little agreement exists. Some of the issues facing the physician are whether to use mono versus combination therapy. The role of allergen avoidance seems to be indicated,³³ but what and how seems to be unresolved. Because parents and children lead active often chaotic lives, the hassle factor of allergen reduction seems unfeasible, resulting in poor compliance. Given the uncertainties of aerosol or powder penetration into the lung of an infant or small child,^{5,12,22,23} the dosage of drugs is at best a guess. Delivery system, especially for very young or uncooperative patients, presents a challenge. One can appreciate that patient compliance is a complex interaction that involves a new player: the parent. One then is

faced with the combined factor of the parent and child dynamic; at least 1 study shows that children have poor compliance, which was directly related to poor asthma control.³⁴ Clearly, there are many questions about the treatment of childhood asthma but with no or few answers.

What are the side effects of asthma treatment in children?

The simple most pressing question in the treatment of childhood asthma is potential adverse effects of the treatment. There is no question that the threshold of tolerance of treatment side effects is lower in children. Although many of the perceived side effects or adverse responses are similar to those in adults, many issues are unique. The simple most important concern about adverse side effects is the impact of inhaled corticosteroids on growth, both somatic and lung growth. It is for these reasons that trials of asthma therapy in children need to be conducted over the long term (>2 years) to adequately assess the effects of a proposed treatment on growth and development.

What determines the success or failure of the treatment of childhood asthma?

Here the endpoints are perhaps the most similar to adults. Most would agree that outcomes of significance are the use of rescue treatments, some as yet unproven marker of inflammation, and activities of daily life. It would be particularly useful to have available objective measures of lung function. Use of healthcare is, of course, important, but one needs to account for the confounding variables of the parent. In like fashion, subjective symptom reports are of concern because one needs to ascertain the accuracy of the report, be it parent or child.

CONCLUSION

Because asthma is the most common chronic disease of childhood, it seems remarkable that so little is known about the treatments and role of early intervention. It is known that asthma in many people begins very early in life. There are several well-established risk factors for the development of asthma in a child that include the genetic predisposition and atopy. The burden of the male sex is known, but the factors determining this burden are largely unproved. Antigen avoidance and early intervention with inhaled corticosteroid are currently thought to be efficacious, but this is based on little data. Finally, childhood asthma presents unique and many unresolved treatment issues. It therefore is concluded that there is a need for carefully designed trials of long enough duration to resolve and clarify the concerns about treating the growing child who has asthma.

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