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The Irreversible Component of Persistent Asthma

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Abstract

Irreversible airflow obstruction or limitation occurs in some patients with asthma, may develop early in life and becomes more common as asthma becomes more severe. Efforts to understand irreversible airflow obstruction or limitation have been hampered by the lack of a standardized definition of the phenotype and by the lack of appropriate research models. Unfortunately, it appears that currently available asthma treatments do not prevent this important asthma complication. Herein, the evidence of an irreversible component of asthma, its underlying pathology and the limitations of current asthma treatments are reviewed.

Keywords

asthma; airway remodeling; irreversible airway obstruction; irreversible airflow limitation

Introduction

Asthma is a disease characterized by episodic airflow obstruction or limitation which is at least partially reversible, lung inflammation particularly in the airways, and bronchial (airway) hyperresponsiveness (BHR). However, asthma is a heterogeneous process in terms of its clinical presentation, natural history, and pathophysiology, so it is more accurately termed a syndrome. The onset or beginning of asthma apparently has different causes, and asthma may progress or evolve differently in different patients. In terms of the natural history of asthma, astute physicians long-ago observed that many of the features of asthma overlapped with bronchitis and emphysema (COPD),⁽¹⁾ a condition characterized by a component of irreversible airflow obstruction. Clearly, some asthma patients develop severe and irreversible airflow obstruction, some suffer from exacerbations with recovery to normal lung function, while others seem to have a fairly stable clinical course over many years.

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The natural history of asthma⁽²⁾, mechanisms driving remodeling⁽³⁾, and the clinical assessment of asthma progression⁽⁴⁾ were discussed in a recent issue of the Journal. Airway remodeling⁽⁵⁻⁸⁾, airway inflammation⁽⁹⁾, epithelial-mesenchymal interactions^(10;11), severe asthma⁽¹²⁾, and longitudinal changes of lung function⁽¹³⁾, have also been reviewed elsewhere. In this review, evidence that an irreversible component develops as asthma evolves or progresses, potential mechanisms underlying disease progression, and limitations to existing models will be discussed. The reader is encouraged to refer to the several recent review articles mentioned above. Despite a wealth of information about airway remodeling that has been developed using various models, including longitudinal studies with repeated lung function measurements, cross-sectional studies of severe asthmatics (a group expected to have undergone airway remodeling), investigational bronchoscopy, interventional studies using anti-inflammatory treatment, and various animal studies, many unanswered questions remain as shown in Table 1.

Defining an Irreversible Component in Asthma

The concept of “irreversibility” of airflow obstruction implies that a change in the structure-function relationship of the airway has occurred that reduces expiratory airflow, that this change would not normally revert back to the prior state, and that no endogenous mechanism or treatment would be capable of causing reversion back to the prior state. Hence, no cross-sectional study can demonstrate irreversibility, and even longitudinal studies that do not utilize a process to try to reverse what appears to be a change in airflow obstruction cannot prove irreversibility. What does exist is much indirect evidence that progressive airflow obstruction develops (longitudinal studies), that severe or progressive airflow obstruction seemingly occurs in some patients despite ongoing anti-inflammatory (glucocorticoid) or bronchodilator treatment, and that when severe airflow obstruction does develop in a patient, the obstruction typically cannot be completely reversed with conventional treatments (severe asthma studies).

Measuring an Irreversible Component

One important issue is that asthma itself is clinically defined by the presence of reversible airflow obstruction. Hence some patients (or study participants) whose lungs and airways exhibit the inflammatory features of asthma, who are not cigarette smokers, who have reduced lung function, but who are not responsive to beta agonists on a given day, may not be diagnosed with asthma, but rather with COPD. Interestingly, on a different day such potential subjects could exhibit bronchodilator reversibility; however, while that subject would usually exhibit BHR, airway challenge testing is underutilized and may be avoided if severe non-reversible obstruction is present.

This phenomenon has also been observed for COPD wherein various degrees of bronchodilator reversibility may be exhibited within a given subject over time. Some practitioners falsely believe that the airflow obstruction is completely reversible in the asthmatic and conversely, not at all reversible in COPD. However, even a cursory examination of the typical pre- and post-bronchodilator forced expiratory volume in 1 second (FEV₁) measurements in most asthma studies show that the average post-

bronchodilator FEV₁ measurements are often less than 100% predicted, which is what would be expected if the airways were restored to a normal state. In a group of subjects that does not reach 100% predicted FEV₁ in the face of aggressive bronchodilator treatment, one would postulate that airflow obstruction is not reversible. However, this does not necessarily mean that it is permanently irreversible, just not completely responsive to that single treatment episode. Unfortunately, most of the data from severe asthma studies, though showing substantial reductions in average FEV₁ and typically reversal that is far short of complete, are cross-sectional, and do not definitively show “irreversibility” as we have defined it.

Similarly, several important longitudinal studies which will be discussed show that airflow obstruction worsens at an accelerated rate in asthma patients when compared to control patients, but there is often no specific attempt to reverse this loss and hence “irreversibility” cannot really be confirmed in this case either. Longitudinal study data are suggestive of the concept that as obstruction worsens for most asthma patients, there will not be spontaneous reversion back to normal. If one assumes that severe asthma usually evolves from mild asthma, and hence results in progressive airflow obstruction, and also assumes that bronchodilator reversibility is often not complete, one can infer that irreversible changes in structure-function relationships have occurred. This is most easily demonstrated with more severe airflow obstruction, although more mild changes may also be irreversible. So, practically speaking data, that show an incomplete reversibility of obstruction upon bronchodilator challenge or progressive loss of lung function in subjects despite their being treated, can be considered to suggest an irreversible component in persistent asthma. In summary, the argument that irreversible airflow obstruction occurs in severe asthma cannot be proven using existing models but there are several lines of evidence strongly suggestive of its occurrence.

From a practical standpoint, irreversibility of airflow obstruction is usually defined by persistently low FEV₁ measurements over time, or failure of low FEV₁ or FEV₁/FVC to improve to within normal limits or above a defined threshold with treatment. Across studies there is significant variability in the stated criteria used to define the irreversibility of airflow obstruction; hence it is difficult to compare results from one study to another.

Longitudinal Studies

As shown in Table 2, a number of longitudinal studies have been performed in an attempt to elucidate the natural history of asthma. Other studies were designed to determine risk factors for the onset of asthma, especially in children. Important observations from these studies include the fact that lung function defined by FEV₁ or FEV₁/FVC ratio tends to decline more rapidly over time in subjects with asthma. Cigarette smoking further accelerates loss of lung function or the worsening of airflow obstruction. Perhaps not surprisingly since BHR also tracks with more severe disease, a greater degree of bronchial hyperresponsiveness in childhood has been associated with the development of irreversible or persistent airflow obstruction in adulthood.^(14–16) However, this is not a consistent finding in all populations.⁽¹⁷⁾ Importantly, seminal studies show that on average, loss of lung function can occur at a very early age.^(14;18) Some data suggest that a subset of patients lose significant

lung function early in life as the lung is maturing and growing, with little further loss in % predicted FEV₁ over the ensuing years.⁽¹⁹⁾

Other childhood studies show that wheezing is very common with lower respiratory tract infections but that asthma tends to develop in those “wheezers” that also developed early allergic sensitization.^(14;20–22) Interestingly, reductions in FEV₁/FVC may occur as asthma develops whereas the FEV₁ itself may change less, suggesting that lung elastic recoil may be lost while the growth of lung volume may be more preserved. Importantly, although inhaled corticosteroids improve quality of life, and reduce exacerbations, they do not seem to be effective in preserving lung function in asthmatics in many instances. This suggests that glucocorticoids may have less effect on remodeling mechanisms than they do on inflammatory mechanisms.

Studies of Severe Asthma

As shown in Table 3, a number of studies examining patients with severe asthma have been carried out in an attempt to determine risk factors and characteristics that differentiate severe asthma from non-severe asthma. As discussed before, the cross-sectional nature of most studies does now allow for conclusions about reversibility. However, several important observations have been made including the fact that more severe air-trapping has been shown to be associated with severe asthma.^(23–25) This demonstrates that important physiologic mechanisms that do not necessarily relate to FEV₁ may also relate to an irreversible component of airflow obstruction. Whether or not onset of asthma during childhood or adulthood results in more severe asthma is not clear because of conflicting data^(26;27) Importantly, although enrollment in studies of severe asthma tends to be defined more by medication use, and morbidity,^(23;28) low lung function (FEV₁) and less bronchodilator reversibility are strongly associated with severity.

Airway Remodeling Mechanisms and Pathophysiology

A detailed discussion of mechanisms driving airway remodeling is beyond the scope of this review. These mechanisms have been discussed recently in the Journal,^(3;6;8;11) and elsewhere,⁽²⁹⁾ so they will be discussed only briefly here. Most studies that have examined tissue in asthmatic patients have been performed in patients with mild disease, without clinical evidence of remodeling, although some studies have been done in severe asthma, and several are currently ongoing. Reticular basement membrane (RBM) or subepithelial basement membrane thickening,^(30–32) has been a consistently reported finding that can occur early in life^(33–35) probably sometime after infancy (after one year old).⁽³⁶⁾ Although RBM thickness or subepithelial basement membrane thickening is a characteristic of the airway and asthma, the degree of thickening does not seem to be associated with the severity of asthma.⁽³⁷⁾ Interestingly the types of proteins expressed in the RBM may vary over time, as asthma evolves. For example, in one study using airway challenge, RBM tenascin expression was upregulated early in bronchial biopsy specimens but resolved after one week as increased pro-collagen III expression was seen. In the same biopsies at the same time, inflammation was seen at 24 hours after antigen challenge but resolved after one week, although BHR persisted.⁽³⁸⁾ This example illustrates the principle that while inflammation

may drive remodeling, different mechanisms may regulate the persistence of remodeling or BHR.

Another common finding in remodeled airways is the presence of increased airway smooth muscle mass.^(33;39) This finding can also be found in children, but in contrast to RBM, smooth muscle mass tends to increase with increasing asthma severity. Findings of increased RBM thickness and airway smooth muscle area in biopsies performed in subjects with severe asthma (remodeled airways) have led to interest in the use of non-invasive imaging techniques, such as computed tomography, to assess for changes in the bronchial wall thickness and structure. Studies correlating histopathology with imaging findings are ongoing. One recent retrospective study of “difficult” asthma subjects showed that bronchial wall thickening, bronchiectasis, and emphysema were common findings in severe asthma patients, and reduced post-bronchodilator FEV₁/FVC predicted the presence of bronchial wall thickening or bronchiectasis.⁽⁴⁰⁾ Additionally, the infiltration of the airway wall or lumen (sputum)⁽⁴¹⁾ by granulocytes (eosinophils or neutrophils) or mast cells⁽⁴²⁾ has been a consistent finding in asthma, with some studies showing that the severity of eosinophilic inflammation in the epithelium is a determinant of BHR or persistent airflow limitation.⁽²⁷⁾

The current dogma is that changes in the structure that lead to changes in the function of the airway wall are primarily responsible for irreversible airflow obstruction. However, some physiologists in non-human model systems have shown that changes in the function of the airway, including increased airway smooth muscle contractility, can be induced without apparent changes in airway wall structure by chronically changing lung volume.⁽⁴³⁾ Indeed, it was shown many years ago that an impaired bronchodilation response to airway wall stretch by deep breathing was characteristic of asthma in humans.⁽⁴⁴⁾ The relationships of lung volume to smooth muscle function have recently been reviewed.⁽⁴⁵⁾ These data have obvious implications in that obesity is a disease associated with both lower lung volumes and more severe asthma.

Can Available Medications Reverse Airway Remodeling?

As stated above, in order to say that airway remodeling or airflow obstruction is truly “irreversible” it would have to be shown that available medications would not effectively change the measurable airway remodeling or airflow obstruction. Several studies have been done in an attempt to prevent loss of lung function in patients already diagnosed with asthma, while others have been performed to prevent asthma from developing in children at risk. Most intervention studies have been performed using inhaled corticosteroids and these drugs have been shown to universally reduce symptoms, reduce the frequency of asthma exacerbations, and reduce BHR, while at the same time improving pre-bronchodilator FEV₁. However, corticosteroids typically do not improve maximal lung function as measured by post-bronchodilator FEV₁ when compared to other agents or even placebo. Corticosteroids have variable effects on histological indicators of remodeling seen in tissue and sometimes these effects are dependent on duration of treatment. Additionally, when corticosteroids are withdrawn the FEV₁ typically reverts or declines to values similar to that obtained with placebo treatment. This suggests that corticosteroids suppressed some process that reduced lung function but did not alter the remodeling process.

In one study designed to test if inhaled corticosteroids could prevent asthma in early life, inhaled corticosteroids when compared to placebo were no more effective in preventing intermittent wheezing infants from becoming persistent wheezers.⁽⁴⁶⁾ The Childhood Asthma Management Program (CAMP) was a randomized clinical trial (intervention study) where inhaled corticosteroid was compared with placebo using treatment over several years in young children. Interestingly, inhaled corticosteroids were not effective in preventing the gradual reduction in post-bronchodilator FEV₁ over time that was seen in all treatment groups, moreover the FEV₁/FVC ratio also declined over time. However, inhaled corticosteroids had very salutary effects on BHR, frequency of exacerbations, and control of symptoms.^(18;47)

Similarly, in a subgroup of the Inhaled Steroid Treatment as Regular Therapy and Early Asthma (START) study, inhaled corticosteroids did not completely prevent the gradual decline in post-bronchodilator FEV₁ percent predicted that was seen though this decline was attenuated when compared to the placebo-treated group.⁽⁴⁸⁾ In the PEAK study long-term inhaled corticosteroids were compared to placebo in an attempt to prevent asthma in very young children (less than 3 years old) at risk for asthma. Whereas inhaled corticosteroids improved airway reactance (a measure of airway resistance) and the proportion of symptom free days, this effect was lost upon washout of medication suggesting that corticosteroids suppressed but did not prevent the remodeling process.⁽⁴⁹⁾

Clinical studies in adults have consistently demonstrated similar findings in that inhaled corticosteroids have salutary effects on exacerbations, symptoms, pre-bronchodilator FEV₁ and BHR, but tend not to improve maximal lung function (post-bronchodilator FEV₁).^(50;51) Another retrospective study showed that inhaled corticosteroids helped reduce the rate of decline in FEV₁ when compared to placebo.⁽⁵²⁾

Some studies have shown that corticosteroids can reduce subepithelial collagen III deposition,^(53;54) whereas others have not shown this effect on collagen deposition.^(55;56) Interestingly, one group using a brief oral corticosteroid trial showed that some patients exhibit corticosteroid resistance manifest as minimal changes in FEV₁ despite treatment with oral corticosteroids. Whereas corticosteroid responsive patients showed good reversal of pre-and post-bronchodilator FEV₁, corticosteroid resistant patients tend to have minimal to no improvement in lung function. However, improvements of lung function in corticosteroid sensitive patients were not complete in that lung function did not return to normal ranges.⁽⁵⁷⁾ The duration of corticosteroid treatment may be a factor as one bronchoscopy study showed that inhaled corticosteroids improved inflammatory parameters at 3 months with no further improvement at 12 months whereas changes in the RBM thickness only occurred after 12 months of treatment. In that study, FEV₁ was improved at 3 months but did not improve further whereas BHR continued to improve at 12 months.⁽³²⁾

Since corticosteroids may not be particularly efficacious in modifying remodeling other treatment strategies may be desirable. One study in which anti-IL5 antibody (mepolizumab) was compared to placebo showed that anti-IL5 treatment reduced tenascin and procollagen III deposition in airway walls.⁽⁵⁸⁾ However, similar to what is seen with inhaled

corticosteroids, mepolizumab did not change post-bronchodilator FEV₁ in refractory asthmatics in a separate study.⁽⁵⁹⁾

Observations from the Asthma Phenotype Task Force and the Asthma Clinical Research Network (ACRN)

A recent task force consisting of members from the National Heart Lung, and Blood Institute, the American Thoracic Society, and the American Academy of Allergy, Asthma and Immunology has been charged with defining different asthma phenotypes in order to better our understanding of these asthma subgroups. One of those phenotypes is “asthma with apparent airflow limitation.” The proposed definition of that phenotype has considered many of the issues discussed in this review and is as follows (Asthma Phenotype Task Force, unpublished):

Airway obstruction: FEV₁/FVC ratio below the lower limit of normal for age (8–19 yr: 85%; 20–39 yr: 80%; 40–59 yr: 75%; 60–80 yr: 70% [Expert Panel Report 3, 2007]) and FEV₁ < 90% predicted in a patient taking corticosteroids, after acute administration of a rapid onset bronchodilator. This is defined operationally as follows:

- a. Moderate to high dose inhaled corticosteroid for 4 weeks⁽⁶⁰⁾
OR
- b. Systemic corticosteroids (0.5 mg/kg of prednisone or equivalent) for 2 weeks
AND
- After 4 puffs of albuterol (90 micrograms/puff) (or the equivalent) administered before pulmonary function testing

To gain further insight into the frequency with which asthmatics of different severities display Asthma with Apparent Irreversible Airflow Limitation, we applied this definition, as best as it could be applied, to patients who participated in 7 different ACRN studies. In 3 studies in which patients with mild asthma were studied, the per cent of subjects who displayed asthma with Apparent Irreversible Airflow Limitation was 0% (0/84) in BARGE,⁽⁶¹⁾ 0% (0/122) in SMOG,⁽⁶²⁾ and 4.2% (11/262) in IMPACT.⁽⁶³⁾ In 3 studies in which patients with moderate asthma were studied, the per cent of subjects who displayed asthma with Apparent Irreversible Airflow Limitation was 15.1% (13/86) in PRICE,⁽⁶⁴⁾ 38.7% (12/31) in MICE,⁽⁶⁵⁾ and 43.2% (83/192) in SLIMSIT.⁽⁶⁶⁾ In 1 study in which patients with moderately severe asthma were studied, the per cent of subjects who displayed asthma with Apparent Irreversible Airflow Limitation was 87.4% (153/175) in SLIC⁽⁶⁷⁾ (ACRN unpublished). Therefore, we conclude that irreversible airflow obstruction or limitation is increasingly common as the apparent severity of asthmatics increase.

Alternative Approaches to Preventing Irreversible Asthma

Attempts to treat asthma by targeting a single cytokine or mediator have yielded disappointing results so far. What is apparent is that the mechanisms that modulate the

inflammation and remodeling in asthma are complex and that reductionist approaches like targeting a single cytokine or pathway are not likely to work. Thus, it is not surprising that the most efficacious anti-inflammatory drugs are corticosteroids, which are drugs that have broad effects modulating many inflammatory pathways. Many studies have previously identified potential therapeutic targets in asthma and newer examples in smooth muscle,⁽⁹²⁾ epithelial cells,⁽⁹³⁾ and in novel inflammatory cell networks like the T_H-17 pathway⁽⁹⁴⁾ have recently been described or reviewed. Approaches that more directly target structural elements (e.g. protease-antiprotease networks) may have greater potential than broadly anti-inflammatory approaches, and should be explored. However, it is our opinion that continued attempts to treat or modulate the inflammation and airway remodeling of asthma by selecting single, or narrowly defined targets will not be fruitful and that new systems biology approaches that simultaneously account for the effect of a drug on inflammatory and remodeling signaling networks will be needed. ⁽⁹⁵⁾

Conclusions

Much indirect evidence from longitudinal asthma studies and cross-sectional studies of severe asthma strongly suggests that a subgroup of asthma patients develop a component of irreversible airflow obstruction. In many patients this irreversible component probably occurs early in life. As smoking rates decline, we might expect that this subgroup of patients will comprise an increasing proportion of the population of COPD patients. Unfortunately, as shown in a few randomized clinical trials current medications like corticosteroids appear to be ineffective in preventing the development of irreversible airflow obstruction at least in some patients. Efforts towards understanding the irreversible component of asthma will be aided by the development of a standardized definition of irreversible airflow obstruction similar to that developed for severe asthma.⁽⁶⁸⁾ New, strategies for preventing asthma in the first place as well as new non-corticosteroid treatments for airway wall remodeling are needed.

Abbreviations

BHR	bronchial hyperresponsiveness
ASM	airway smooth muscle
FEV₁	Forced expiratory volume in the first second
FVC	Forced Vital Capacity
RBM	reticular basement membrane

Glossary List

Airway Remodeling	Airway remodeling is triggered by long-term, untreated airway inflammation. Over time, the airways undergo structural changes which can be permanent if not adequately treated and severely impair lung function. These structural changes include
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thickening of the airway wall, increased mucous production, and increased vascularization in the airways.

Line: 50

Allergic Sensitization

Sometimes referred to as type 1 or IgE mediated hypersensitivity. Occurs when the immune system is exposed to allergens leading to the production of IgE antibodies. Subsequent allergen exposure cross-links the IgE antibodies, which are bound to Fcε receptors on mast cells and basophils, leading to the release of histamine and other mediators which cause allergic symptoms.

Line: 138

Bronchial Hyperresponsiveness (BHR)

Also referred to as airway hyperreactivity. An exaggerated constriction of the bronchioles or small airways in response to physical, chemical or pharmacologic stimuli. Sometimes referred to as a bronchospasm suggesting that airway smooth muscle plays an important role. Typically assessed by a bronchial challenge test using methacholine or histamine. BHR is a hallmark in asthma and chronic obstructive pulmonary disease (COPD).

Line: 33

Bronchodilator

Pharmacologic agents used to dilate the bronchi and bronchioles, thereby decreasing airway constriction and facilitating airflow. Bronchodilators are classified as either short-acting or long-acting based on their ability to provide quick relief from acute bronchoconstriction or control and prevent symptoms, respectively. β₂-agonists (short- and long-acting), anticholinergics (short-acting), and theophylline (long-acting) are three types of commonly prescribed bronchodilators.

Line: 72

Chronic Obstructive Pulmonary Disease (COPD)

COPD is the chronic obstruction of airflow in the airways that worsens over time and increases in persistence. Often COPD is associated with chronic bronchitis or emphysema. The decreased airflow is most commonly associated with loss of lung elasticity, inflamed airways, and increased mucus production. Proper diagnosis of COPD requires pulmonary function tests.

Line: 44

Corticosteroids

A class of hormones synthesized from cholesterol within the adrenal cortex. Glucocorticoids are anti-inflammatory by preventing phospholipid release, decreasing eosinophil action and a number of other mechanisms. Mineralocorticoids control

	<p>electrolyte and water levels, mainly by promoting sodium retention in the kidney. Synthetic glucocorticoids are used in the treatment of inflammation in asthmatics.</p> <p>Line: 210</p>
Cross Sectional Study	<p>A cross-sectional study is an epidemiologic study that measures variables within a specified population at a single point in time. These studies are used to establish the prevalence within a specified population without distinguishing between newly occurring and long-established conditions.</p> <p>Line: 67</p>
FEV₁	<p>Forced expiratory volume in the first second is the volume of air that can be forced out in one second. FEV₁ is typically measured by a spirometer during a pulmonary function test to diagnose respiratory conditions such as asthma, cystic fibrosis, and COPD.</p> <p>Line: 34</p>
Forced Vital Capacity (FVC)	<p>Maximum volume of air which can be exhaled or inhaled by a patient with maximal effort during a pulmonary function test with a spirometer. The ratio of FEV₁/FVC provides a clinically useful measurement of airflow limitation and respiratory disease.</p> <p>Line: 34</p>
Longitudinal Study	<p>A chronological epidemiologic study that measures variables within a specified population at repeated intervals over time. These studies are often used to establish correlations between disease onset and severity.</p> <p>Line: 102</p>
Morbidity	<p>Refers to a diseased state, disability, or poor health due to any cause. Rates of morbidity are of two types; the prevalence rate refers the number of individuals suffering from a specific condition at a specific time, and the incidence rate refers to the number of individuals suffering from a particular condition over a period of time.</p> <p>Line: 156</p>
Phenotype	<p>The physical, physiological and behavioral traits of an individual produced by the interaction of the genetic makeup and environmental influences.</p> <p>Line: 25</p>
Reticular Basement Membrane (RBM)	<p>Also known as the lamina reticularis, is a network of Type III collagen fibers and macromolecular components that varies in thickness and is connected to the basal lamina. The abnormal</p>

thickening of the RBM in asthma is thought to result from the accumulation of collagen referred to as subepithelial fibrosis.

Line: 35

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Table 1

Unanswered questions in airway remodeling

Does the failure of an airway to undergo full bronchodilation upon acute treatment with a beta-agonist mean that airflow obstruction is irreversible?
Does the failure of lung function to normalize after corticosteroid treatment mean that airflow obstruction is irreversible?
Are airway injury-repair mechanisms, at least in part, distinct from inflammatory mechanisms?
Do medications that effectively treat inflammation treat abnormal injury-repair mechanisms or do medications that treat inflammation even alter the natural history of asthma?
When (during what ages) do the changes that lead to irreversible airflow obstruction occur as asthma evolves?
What clinical features, physiologic parameters or biomarkers can predict the development of irreversible airflow obstruction?

Table 2

Selected Longitudinal Asthma Studies

Childhood Asthma Management Program (CAMP) ^(18;47;69)	RCT with average follow-up 4.3 years, mean age 9 y/o. All groups experienced reduction of FEV1/FVC ratio. A subgroup (25.7% of subjects) experienced >1% loss of FEV1 % predicted/year; this was not modified by treatment.
Coronary Artery Risk Development in Young Adults study (CARDIA) ⁽⁷⁰⁾	Lung function followed in young adults for 10 years. Asthmatics had lower baseline FEV1, and experienced higher rate of loss of lung function than non-asthmatics Smoking accelerated the loss of lung function.
University Hospital of Groningen, Netherlands ^(71;72)	Cohort of asthmatic children followed for 30 years. A small increase in FEV1 % predicted was seen over time though FEV1/FVC ratio seemed to decline.
Beatrijxoord Hospital, Haren, Netherlands ^(17;73;74)	Cohort of 281 adult asthma patients including smokers followed for 26 years. Increased BHR was paradoxically associated with less risk of developing irreversible airflow obstruction. Exacerbations were associated with accelerated loss of lung function.
Copenhagen City Heart Study ^(75;76)	Large, community-based study, asthma was self-reported in 778 adult subjects. Asthma prevalence increased over time. Subjects with asthma experienced accelerated loss of lung function made worse by cigarette smoking.
Denedin, New Zealand ⁽¹⁵⁾	Population-based birth cohort evaluated over 17 years. BHR or bronchodilator reversibility in childhood was associated with relapsed or persistent asthma in adulthood.
Manchester, UK ^(20;21)	Study performed in young children showed that increased airway resistance (sRaw) at age 3 predicted increased sRaw and was associated with persistent wheezing at age 5 suggesting that loss of lung function occurs early in life.
German Multicenter Allergy Study ^(22;77)	Population-based birth cohort. Children with allergic sensitization (especially to perennial allergens) exhibited greater reductions in FEV1 and post-bronchodilator FEV1/FVC ratio than non-sensitized children.
Melbourne Asthma Study ^(19;78–81)	Population-based cohort of children followed for 42 years. Loss of lung function (reduced FEV1 % predicted) was most profound in the severe asthma group. The loss occurred early in life (by age 10) but did not worsen over time in any group.
Tuscon Children's Respiratory Study ^(14;16;82–84)	Population-based birth cohort of 1246 infants was followed for 22 years. Persistent asthma at age 22 was associated with low lung function, BHR and persistent wheezing at age 6.
Copenhagen, DK ⁽⁸⁵⁾	Clinic based cohort of 92 non-smoking patients followed for 10 years. On re-examination, non-reversible airflow obstruction was associated with increasing bronchodilator reversibility at enrollment, and long-term use of oral corticosteroids

Table 3

Selected Severe Asthma Studies

NHLBI Severe Asthma Research Program (SARP) ^(25;28)	Cross-sectional American Study showing that in severe asthma compared to non-severe asthma, forced vital capacity (FVC) was disproportionately reduced and air trapping was more severe. On average, best lung function obtained after bronchodilator challenge remained low in moderate and severe asthma whereas on average it normalized in mild asthma.
The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) ^(86–88)	Large, prospective 3-year cohort study wherein persistent airflow limitation was associated with older age, male gender, duration of asthma and cigarette smoking.
European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) ^(23;89;90)	Cross-sectional multicenter European study wherein asthma severity was mostly defined by medication use. Severe or poorly controlled asthma was associated with less atopy, lower FEV1, less bronchodilator reversibility on average, more air trapping, and sputum neutrophilia. Female sex and higher body weight also were associated with more severe disease.
Royal Brompton Hospital, London, UK ⁽²⁴⁾	Series of asthma patients from clinics classified based on FEV1. In severe asthma patients FVC was lower and there was more air trapping. On average FEV1 was only partially reversible in the severe group.
Montréal, Canada ^(38;39)	Small series of clinic and hospital patients with severe asthma. Patients with chronic persistent airflow obstruction did not differ with respect to sputum cell differential but had a higher proportion of sputum neutrophils plus eosinophils and more smooth muscle hypertrophy in the bronchial wall when compared to subjects with "intermittent (airflow) obstruction." Persistent obstruction was associated with earlier age of onset and longer disease duration.
Leiden University Medical Center, NL ^(27;91)	Series of 152 clinic patients with severe asthma. About half (48.5%) had persistent airflow limitation which was associated with more BHR, and sputum eosinophila when compared to the non- persistent group. Adult-onset asthma was more associated with persistent airflow limitation than early-onset disease.
National Jewish Medical and Research Center, Denver, CO ^(26;33)	Cross-sectional study of subjects hospitalized at a referral center. Though lung function (FEV1 % predicted) was better in children than in adults, children were as likely to require high dose corticosteroid therapy. Lung function impairment was associated with duration of disease only when disease began in childhood.