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Timothy E. Albertson
Editors

Bronchial Asthma

A Guide for Practical Understanding and Treatment

Sixth Edition

Springer

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Edited by

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Dedication

They asked if the sneezles
Came after the wheezles,
Or if the first sneezle came first.[1]

This text is dedicated towards helping the many millions of people that suffer from asthma and the hope that this book will eventually become an anachronism.

[1]From “Sneezles,” by A.A. Milne, in Now We are Six. New York, E.P. Dutton and Co., 1927.

Preface

It has been nearly 35 years since the first edition of Bronchial Asthma: A Guide for Practical Treatment was published. At that time, virtually every patient with asthma was diagnosed and treated by a specialist. The dramatic changes in health care have necessitated that most evaluations for people with asthma be performed by a primary care specialist and/or physician assistants. Indeed, during this period of time, the number of patients with asthma has increased significantly but yet despite improved therapies, mortality and morbidity have not dramatically improved. We have seen development of both national and international guidelines to treatment approaches, but all too often these treatment approaches are not followed in appropriate fashion, with a resultant decrease in standard of care. Indeed, not only have the medications changed, but so have their deliveries and the use of combinatorial therapies. This textbook will focus on these changes with a broad emphasis on practical issues faced by physicians who face the challenge in the management of their patients. Hence, we will emphasize differential diagnosis, medication, and the use of asthma treatment plans. As in the previous editions, we also continue to define and focus on the special clinical problems of the pregnant patient, the patient undergoing emergency treatment, as well as the common day issues of exercise, athletics, recreational drug use, and especially self care. We also note and discuss the use of medications as well as their side effects. The overall goal is to improve physician and also patient education. At the end of the day, the book will be successful only if it helps our patients.

The authors and contributors have done their best to ascertain that there are no errors but, of course, in a text such as this, there are likely omissions, differences of opinion, and even errors. For these, we apologize.

Finally and especially, this sixth edition would not have been possible without the incredible enthusiasm and dedication of Nikki Phipps. Our sincere appreciation for her work.

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I Clinical Definitions

1 The Clinical Definitions of Asthma

Howard David Pettigrew, MD, Christopher Chang, MD, Suzanne S. Teuber, MD, and M. Eric Gershwin, MD, MACP

Contents

KEY POINTS

- Asthma is a heterogeneous disease, presenting in many forms.
- There is no pathognomonic test for asthma, and the diagnosis is based on clinical presentation.
- Ancillary tests and procedures can only assist in making the diagnosis, and should be taken in context with the clinical history and physical.
- Radiographs are particularly not helpful in defining asthma, due to the lack of specificity.
- The development of asthma is dependent on the interaction between multiple genetic and environmental factors.
- The hallmark of asthma is airway inflammation.
- The concept of airway remodeling in asthma is poorly defined and still incompletely understood.
- Asthma in children can be triggered by allergies, viral upper respiratory infections and exercise.
- The onset of asthma can occur at any age, but it more frequently begins in childhood.
- Asthma in the elderly presents a unique problem as other diseases of the lung and other organs can exist concurrently.

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INTRODUCTION

It is believed that the term "asthma" was coined by Hippocrates around 450 BC. The term literally means "panting," from the Greek. Descriptions of the clinical presentation of those affected with asthma appear in medical literature throughout history. In ancient times, asthma had been described as follows:

> *If from running, gymnastic exercises, or any other work, the breathing becomes difficult, it is called Asthma; and the disease Orthopnoea is also called Asthma, for in the paroxysms the patients also pant for breath. (The Extant Works of Aretaeus, the Cappadocium),*

and more recently, in the words of Thomas Willis in his Pharmaceutice Rationales in 1679, as possessing the following features:

> *an Asthma, either meerly pneumonick, preceeding altogether from the passages bringing in aire being obstructed, or not enough open; or it is meerly convulsive, which only arises by reason of a defect or fault in the motive organs…The ancient Physicians, and for the most part hitherto the Moderns have only acknowledged the first kind of Asthma, judging the next cause, and almost the only cause of this Disease, to be the straitness of the Bronchia…The straitness of the Bronchia, including the first kind of an Asthma, is supposed to come to pass by an obstruction, as often either thick humours and viscous, or purulent matter or bood extravasated, are forced in upon them.*

It is interesting to note that even in these early descriptions, the critical clinical components that we now use to make a diagnosis of asthma were already well-documented, including observations of panting, increased work of breathing, the association with exercise, obstructed airways, and the presence of "humors and viscous." It also described asthma as being a defect in the "straitness" of the bronchi, perhaps implying an irregularity in air flow, a concept that is mirrored in our modern day understanding of airway obstruction.

THE HETEROGENEITY OF ASTHMA

Asthma is one of the most common, if not the most common, chronic disease in children. It is estimated that over 5% of the global population has asthma, which translates to a staggering 350 million people worldwide *(1)*. It is more common in developed countries, where incidence rates can run as high as 20%. The incidence has also been increasing, first in developed countries, and now in developing nations. Mortality rates of asthma show no significant improvement despite the development of new drugs and strategies to treat asthma. Yet for a disease that affects so many people, there is no single diagnostic test available, and the ability to make a diagnosis depends solely on the clinical skills of the modern day physician. It is a huge challenge. We recognize now that asthma is not one disease, but a heterogeneous group of disorders. Making a diagnosis of asthma involves a thinking process that incorporates so many factors, both genetic and environmental, that patients are frequently misdiagnosed. Two people can present to the physician with an identical clinical presentation, and only one will leave with a diagnosis of asthma. How is this possible? The answer can be found in the realization that clinical symptoms that we commonly attribute to asthma are not pathognomonic of the disease, and many other conditions can cause symptoms such as cough, wheezing, or respiratory distress.

The clinical definition of asthma has changed over the years, as our knowledge of the pathophysiology improves. Modern pathological and laboratory techniques have allowed

us to study the diseased airways in asthmatics. The early descriptions noted above describe an "obstruction," and even as recently as 30 years ago, our belief was that asthma was a condition primarily of bronchoconstriction. We now know that bronchoconstriction is more likely a result or epiphenomenon of changes that occur at the cellular level that lead to inflammation of the airways, characterized by smooth muscle hypertrophy, increased vascular permeability and mucous production. These are the known histological events of inflammation, which then lead to the hallmark physiologic features of inflammation – heat, erythema, swelling, and drainage. All of these have been shown to occur in the asthmatic airway. The clinical results of these inflammatory changes are cough, wheezing, respiratory distress, inadequate oxygenation of blood and clearance of carbon dioxide, respiratory acidosis and potentially, death. If the changes are chronic, then there can be permanent damage to the structure of the airway epithelium, a process loosely known as "airway remodeling," leading to the development of an irreversible process more closely resembling chronic obstructive pulmonary disease or emphysema.

A current definition of asthma, based on what we expect to happen as a result of these cellular events that ultimately lead to the symptoms of asthma, may be as follows:

> *Asthma is a recurrent respiratory illness of varying severity resulting from inflammation of the airways, which can cause bronchoconstriction and mucous production, leading to cough, wheezing and dyspnea, that if untreated, can be potentially fatal.*

THE DIFFERENTIAL DIAGNOSIS OF ASTHMA

Because of the numerous ways that asthma can present, there is a vast differential diagnosis. One of the ways to approach this is to study the differential diagnosis of individual common asthma symptoms separately, such as cough, wheezing, and respiratory distress. For example, what is the differential diagnosis of a cough? Asthma certainly is high on the list, but other possibilities can include infectious diseases, such as viral respiratory infections, bacterial pneumonia, tuberculosis or fungal infections, neoplasms, foreign body inhalation, sinusitis, gastroesophageal reflux and many others. Of course, a more complete history and physical will help to rule out diagnoses until one has no other possibility left other than asthma. Similarly, a differential diagnosis for wheeze can include asthma, but also congestive heart failure, transmitted sounds of upper airway congestion or obstruction, tracheal anomalies, vascular rings, vasculitides and vocal cord dysfunction. Respiratory distress could be a result of a chronic lung condition, hypersensitivity pneumonitis, acute respiratory distress syndrome, smoke inhalation, congestive heart failure, respiratory muscle weakness, or a metabolic problem. Again, sorting out the clinical history and physical to come up with the most likely diagnosis depends on the clinical skills of the physician. Table 1 provides a more complete differential diagnosis.

DEFINING ASTHMA BASED ON LABORATORY, PROCEDURES, AND RADIOGRAPHY

In view of the heterogeneity of clinical phenotypes that carry a diagnosis of asthma and of the vast number of conditions in the differential diagnosis that may be related to the symptoms and signs of asthma, the question arises as to whether or not there is a single test or group of tests that will definitive establish asthma as the correct diagnosis.

Table 1
Differential Diagnosis of Asthma

Asthma
Infectious diseases
Viral
Bacterial
Fungal
Mycobacterial
Immunodeficiency disease
Gastroesophageal reflux
Congestive heart failure
Cystic fibrosis
Vascular anomalies (vascular rings, slings, etc.)
Hypersensitivity pneumonitis
Subglottic stenosis
Vocal cord dysfunction
Laryngotrachaelmalacia
Wegener's granulomatosis
Lung neoplasms
Churg-Strauss syndrome
Alpha-1-antitrypsin deficiency
Allergic bronchopulmonary aspergillosus

We currently use many of these tests to evaluate patients with the symptoms characteristic of asthma, or to monitor the severity of the condition. These tests may range from measurement of lung function by spirometry or complete pulmonary function tests including diffusion capacities, to measurement of inflammatory markers such as nitric oxide (FeNO) or eosinophil cationic protein, to evaluation of the lung by conventional or advanced radiographic imaging techniques. The role of each of these tests will be discussed individually, but unlike using a potassium level to identify hypokalemia, for example, none of these tests will by themselves definitively establish a diagnosis of asthma.

Spirometry

Children with asthma often have decreased forced expiratory volume in 1 s divided by forced vital capacity (FEV1/FVC) ratios, when compared to children without asthma *(2)*. Multiple large studies have provided tantalizing clues and have reinforced the accepted notion that the cellular and structural abnormalities of asthma are cultivated early in life.

In the Melbourne Asthma Study, children with a history of wheezing were randomly selected, along with a control group, at 7 years of age in 1962. Within the initial wheezing group, a subgroup of children with severe wheezing was additionally formed at 10 years of age in 1965. These groups have been followed at 7-year intervals since. The last published review comprised data up until 1999, when the participants were on average

42 years of age *(3)*. Throughout the study, the individuals who were initially classified as having mild or severe asthma continued to have consistently decreased FEV1/FVC ratios when compared to the control group. Interestingly, these individuals' decreased FEV1/FVC ratios were established at 7–10 years of age and remained decreased at 42 years of age. Of note, the respective decreased FEV1/FVC ratios were at their lowest at the 10 years of age mark, and did not worsen (relative to the control group) with progression to adulthood despite continued symptoms of asthma. In the second cohort asthma study, the Dunedin Multidisciplinary Health and Development Study, 1,139 children were enrolled at birth and followed at 2- to 5-year intervals, from 9 to 26 years of age *(4)*. A total of 613 individuals were able to provide respiratory assessment at every time point. Persistent wheezing individuals (those reporting wheezing at all survey time points) and relapse wheezing individuals (those reporting wheezing at two or more consecutive survey points, followed by one or more survey points without wheezing, and finally reporting wheezing at all subsequent follow ups) had reduced FEV1/FVC ratios in comparison to children without wheeze. Similar to the Melbourne Asthma Study, this reduction was initially seen at 9 years of age when the initial FEV1/FVC evaluation was preformed. In all groups, there was no difference in the slopes of change in FEV1/FVC ratio as would be expected with increasing age. Interestingly, the reduced FEV1/FVC ratios of the persistent and relapse wheezing individuals, in relation to the nonwheezing and mild wheezing individuals, generally followed the same trend showing very little deterioration, from 9 to 26 years of age. Both studies contribute to the hypothesis that the insult, which results in reduced FEV1/FVC ratio in asthmatic individuals, occurs at a very young age.

The Childhood Asthma Management Program (CAMP) has provided further data to define the time of onset and progression of pulmonary obstruction in children with asthma. Strunk et al. have reported that children, enrolled in CAMP, with mild to moderate asthma have airway obstruction at 6 years of age and increased airway obstruction at 18 years of age *(5)*. The study included 1,041 children with mild to moderate asthma from CAMP, compared with 5,415 children without asthma, from the Harvard Six Cities Study (H6CS). Strunk et al. used FEV1/FVC ratios, a reliable assessment of airway obstruction, and found that in male children with mild to moderate asthma FEV1/FVC was −7.3% at 6 years of age and −9.8% at 18 years of age compared to age- and sex-matched controls *(5)*. Female children with mild to moderate asthma had FEV1/FVC of −7.1% at 6 years of age and −9.9% at 18 years of age compared to age- and sex-matched controls *(5)*. The findings are significant for showing over 70% of obstruction existed before 6 years of age and a progression of obstruction from 6 to 18 years of age. This disagrees with the Melbourne Asthma Study and the Dunedin Multidisciplinary Health and Development Study, and may be due to an increased number of participants. The Melbourne Asthma Study had 372 participants with asthma and 105 control participants without asthma, while the Dunedin Multidisciplinary Health and Development Study had a total of 613 participants finishing their study.

The change in FEV1/FVC ratio in asthmatics begins in childhood and is persistent throughout life. Measurement of spirometry can therefore be a very useful test to help to establish the diagnosis of asthma, but is not absolutely confirmatory as other conditions can lead to airway obstruction as well.

Challenge Tests

Methacholine Challenges

Methacholine or histamine challenge tests have long been considered to be the "gold standard" for the diagnosis of asthma. These tests are conducted by a trained technician and the response in pulmonary function to escalating doses of methacholine is measured. The doses of methacholine used generally ranges from 0.02 to 25.0 mg/mL, and are usually given in doubling doses. The most recent ATS recommendations define two different methodologies: the 2 min tidal breathing method and the 5 min dosimeter method. Dosing starts low, at about 0.03 mg/mL, and increase to a maximum dose of 16.0 or 32.0 mg/mL. Spirometry is performed after each incremental dose is administered, and a 20% drop in FEV1 at any time signifies a positive test. The PC20 FEV1 is the provocative concentration of methacholine that will result in a 20% drop in FEV1. If this drop occurs at a low dose, such as 2 mg/mL, then this is a positive test for asthma, but if there is no drop or the drop occurs at a very high dose, e.g., 32 mg/mL, then this indicates a negative test for asthma. If a drop occurs, the patient should be given bronchodilators to ensure that pulmonary function returns to normal.

While the methacholine challenge test is considered a better "diagnostic" tool for asthma than many other sources of information, tests or procedures, such as history and physical, IgE levels, eosinophil counts, and pre- and post-bronchodilator spirometry, there are confounding factors that can affect the accuracy of methacholine challenge testing to the diagnosis of asthma. These include cigarette smoking, viral infections, exposure to occupational sensitizers or allergens, exercising or the use of bronchodilators, or consumption of foods that can facilitate bronchodilation such as caffeine, prior to the test. Moreover, the test is dependent on the proper technique in performing spirometry; otherwise, the test results will not be valid. Therefore, even methacholine challenge testing cannot be deemed to be 100% diagnostic for asthma, but should be viewed as a very valuable tool in helping to establish the diagnosis of asthma, while taking into context the clinical presentation of the patient. Methacholine challenge testing is indicated when the probability of asthma as the correct diagnosis is assessed to be between 30 and 70% *(6)*.

Exercise Challenges

Exercise is a common trigger for asthma in children and teenagers, and once the patient is old enough to perform spirometry accurately, an exercise challenge test can be done to establish the diagnosis of EIA or EIB. A protocol for performing exercise challenge testing is presented in the chapter on the pediatric asthmatic.

Measurement of Inflammation

Since airway inflammation is now known to be a universal characteristic of asthma, it would be logical to expect that some way of measuring inflammation could be useful in establishing a diagnosis of asthma. Indeed, there are surrogate markers of inflammation that are available in clinical practice at this time. The question is how specific and sensitive these tests are in diagnosing asthma. Are they useful in defining the patient with asthma? Current indirect measures of inflammation, also quaintly known as

inflammometry, include fractional exhaled FeNO, eosinophilic cationic protein (ECP), analysis of sputum and spirometry, which has already been discussed.

FeNO

Fractional exhaled FeNO measures the inhaled levels of a product of inducible FeNO synthase (iNOS). iNOS is upregulated in inflammatory conditions and leads to an increase in measurable FeNO in exhaled air. In fact, there are FeNO measurement devices produced by several manufacturers for clinician office use. However, how valuable is FeNO analysis in the diagnosis of asthma? This has been a very controversial topic because there are other conditions that can cause an increase in FeNO, including viral infections or atopy. FeNO is perhaps a better tool for assessing and monitoring the status of the moderate or severe persistent asthma whose condition changes based on exposure to triggers and adjustment of medications. FeNO is therefore not a "gold standard" for the diagnosis of asthma by any means. It can, however, be of some benefit when taken in context of the individual patient, as long as one is aware of the limitations of these measurements.

Eosinophil Cationic Protein (ECP)

Eosinophils are effector cells in inflammatory disease such as allergies and asthma. Eosinophils can be activated to lead to the production of inflammatory mediators, such as ECP and eosinophil-derived neurotoxin. But many other mediators are released as a result of eosinophil activation that can contribute to asthma. Eosinophil cationic protein has been investigated as a marker for airway inflammation in asthma. It was demonstrated that serum ECP is elevated in patients who are undergoing an acute asthma exacerbation, when compared to stable asthmatics or controls. As in the case of FeNO, ECP appears to be more useful as a tool to monitor asthma status, rather than providing any significant value into the diagnosis of asthma. This is probably true for measurement of sputum eosinophils as well.

Radiographs

Conventional radiography does show abnormalities in asthmatics. However, the abnormalities, including overinflation, are not specific for asthma and therefore radiographs are not helpful in establishing a diagnosis of asthma. However, radiographs can be helpful in identifying other conditions in the differential diagnosis, such as in the child with wheezing secondary to a foreign body inhalation.

HISTOLOGICAL DEFINITIONS OF ASTHMA

Generally, in asthma these changes include increased smooth muscle mass, subepithelial fibrosis, gland enlargement, neovascularization, and epithelial alterations. In turn, this remodeling leads to airway wall thickening/airway narrowing, bronchial hyperresponsiveness, hypersecretion of mucus, and airway edema. Saglani et al. have recently reported compelling findings in children between the ages of 3 months and 5 years *(7)*. Endobronchial biopsies were taken from 16 "confirmed wheezers" (video questionnaire), 14 "reported wheezers," and ten controls (nonasthmatic children presenting with stridor). "Confirmed wheezers" had significantly thicker reticular basement

membrane and significantly greater eosinophilic inflammation, compared to controls. Prior to this study, Saglani et al. examined endobronchial biopsies in 53 infants between 11.5 and 12.4 months of age *(8)*. Infants with decreased specific airway conductance with bronchodilator reversibility and infants with decreased specific airway conductance without bronchodilator reversibility were compared with age-matched controls. Interestingly, no difference was found in reticular basement membrane thickness or inflammatory cell number. Taken together, these studies suggest the possibility that there may be a "developmental window of susceptibility" *(9)* for asthma between infancy and 5–6 years of age. This age is of particular interest because it typically is the period of time when the usual trigger for wheezing in children is respiratory infection, likely caused by viruses. It has been proposed that this typical wheezing pattern seen in some children may be due to an inappropriate inflammatory response to normally innocuous viral infections. This inappropriate response could possibly lead to airway remodeling and subsequent asthma.

It should be clear by now that asthma can present in many ways and represents a heterogenous collection of diseases. Some of the more common phenotypes will be discussed below, but the challenge of the new age of medicine is to find ways to customize patient management based on genetics or pharmacogenetics for the individual patient with asthma.

ASTHMA PHENOTYPES

Cough-Variant Asthma

Perhaps one of the most difficult of patients is the one who presents simply with a cough that will not go away. These patients may be of any age, and do not have a history of wheezing, nor have they ever presented with wheezing. They do, however, have a persistent cough, and a history of it being difficult to treat. In the absence of a wheeze, can one make a diagnosis of asthma? Cough variant asthma may result from "twitchy" airways, which can result from inflammatory changes as a result of a viral respiratory infection or of allergic exposure.

Asthma in Children

Prematurity and Asthma: The Transient Wheezer

Transient wheezers are used to describe a group of children who wheeze during infancy, but the wheezing generally resolves by age 3. The wheezing can be triggered by viruses, and can present as bronchiolitis in infancy. Risk factors include maternal smoking, prematurity, and low birth weight. There is no association with atopy.

On the other hand, chronic lung disease of prematurity, also called bronchopulmonary dysplasia (BPD) *(10)*, can lead to abnormalities in lung function that persists into adulthood. Interestingly, the severity of disease is inversely correlated to birth weight and gestational age, and leads to the concept of a "developmental window of susceptibility" *(9)*. Northway et al. have reported that 68% of individuals with a history of BPD, when measured as adolescents and young adults, had airway obstruction (decreased forced expiratory volume in 1 s, force expiratory flow between 25 and 75% of vital

Table 2
Pathogens Detected from Patients with Asthma Exacerbations

Pathogen	*%Detected in exacerbations*
Adenovirus	<1
Coronavirus	26–40
Human metapneumovirus	7
Influenza	2–9
Parainfluenza	3–9
Respiratory syncytial virus	1–12
Rhinovirus	34–75
M. pneumoniae atypical bacteria	18–46
C. pneumoniae atypical bacteria	2–12

Adapted from Newcomb and Peebles *(48)*.

capacity, and maximal expiratory flow velocity of 50% of vital capacity), compared to age-matched controls without a history of BPD *(11)*. Further, Doyle et al. have reported on a group of 147 survivors (mean age to 18.9 years) of low birth weight (<1,500 g), 33 (22%) of whom suffered BPD *(12)*. 42.4% of individuals who suffered low birth weight and BPD (16.4% of those with low birth weight alone) had reduced airflow lung function (FEV1/FVC ratio <75%) *(12)*.

Viral Infections and Asthma: The Nonatopic Wheezer

One of the most common triggers for asthma in children is viral infection. It is believed that many of the approximately 11 million asthma exacerbations that occur each year in the United States are triggered by viral infections *(13, 14)*. Reverse transcriptase polymerase chain reaction (rtPCR) techniques have demonstrated that up to 80% of asthma exacerbations in children and 76% of asthma exacerbations in adults are due to viral respiratory infections *(13, 15, 16)*. Viruses associated with asthma exacerbations include respiratory syncytial virus (RSV), rhinovirus (RV), human metapneumovirus (hMPV), influenza, parainfluenza, and coronavirus (Table 2) *(13)*. Interestingly, wheezing and infections by RSV, RV or hMPV early in childhood have been associated with the development of asthma later in childhood *(13, 17–20)*. This may reflect the previously mentioned potential "developmental window of susceptibility" *(9)*, when a specific infection results in the development of asthma. It is important to note that this does not prove causality, and there may be factors that convey common susceptibilities for developing asthma and viral infections early in life.

RSV is an enveloped, single-stranded, negative-sense riboxynucleic acid (RNA) virus of the family *Paramyxoviridae*, which is usually spread by droplets, fomites, or close contact. RSV usually causes upper respiratory tract infections, but in some infants, it causes lower respiratory tract infections, leading to bronchiolitis or pneumonia. Bronchiolitis due to RSV is the most common cause of wheeze in infants and young children *(13, 21)*. Studies of children hospitalization for RSV bronchiolitis with wheeze have reported an increased risk of wheeze or asthma at least through the preteen years. Sigurs et al. prospectively studied 47 children who had been hospitalized for RSV bronchiolitis, and compared them with a group of 93 sex, age, family history for reactive

airway disease or atopy, and generally living environment-matched controls *(22)*. At 13 years of age, the children who had previously suffered RSV bronchiolitis had more than a fourfold greater chance of developing wheeze/asthma (43 vs. 8%) *(22)*. Stein et al. prospectively studied 888 children who had a history of lower respiratory tract infections due to various agents within their first 3 years *(23)*. Of this group, 207 children had a history of lower respiratory tract infection due to RSV. These children had a significantly increased risk of wheeze at 6 years of age, but this risk declined at 11 years of age, and was not significant at 13 years of age *(23)*. Additionally, at 11 years of age, force expiratory volume in 1 s (FEV1) was measured in 110 of the children with a history of lower respiratory tract infection due to RSV. When compared to controls, these children had FEV1s which were significantly reduced, but normalized when treated with salbutamol.

The pathophysiology of RSV infection's association with asthma is unresolved, but it is known that RSV infection is mucosa-restricted and that it induces airway epithelium to recruit inflammatory cells through the production of multiple chemokines. These include fractalkine, growth-regulated oncogene alpha (Gro-α), Gro-β, Gro-γ, interleukin 8 (IL-8), interferon-inducing T-cell alpha chemoattractant, macrophage inflammatory protein 1α (MIP1α), MIP1β, monocyte chemoattractant protein (MCP-1), and regulated on activation normal T-cell expressed and secreted (RANTES) *(24, 25)*. IL-8 is not only a chemoattractant for neutrophils, but also a potent angiogenic factor and an effective proinflammatory mediator.

RVs are nonenveloped, single-stranded RNA viruses of the family *Picornaviridae*, which have also been implicated in lower respiratory tract infections, wheezing and the development of asthma *(13, 19, 20, 26, 27)*. Kusel et al. studied 263 infants from birth until 1 year of age, and found that RV was the most common pathogen found in upper and lower respiratory tract infections *(20)*. Khetsuriani et al. studied 65 children with acute asthma exacerbations, and found that 63.1% were due to respiratory viruses, and that 60% of these were due to RV *(27)*. Papadopoulos et al. studied 119 infants admitted for bronchiolitis, and found 73.7% had viral etiology on rt-PCR *(28)*. Only 29% of these viral-induced cases were due to RV, but the presence of RV increased the risk of severe disease by fivefold *(28)*. Lemanske et al. prospectively studied 285 children at high risk for developing allergic respiratory disease, from birth to 3 years of age, and found that when viral etiology was considered, RV-induced wheezing illness in the first year was the strongest predictor of subsequent wheezing in the third year (odds ratio: 6.6) *(19)*. Similarly, Jackson et al. prospectively followed 259 children in a high-risk birth cohort, who had at least one parent with respiratory allergies and/or a history of asthma diagnosed by a physician *(26)*. They performed nasal lavages during wheezing illnesses, from birth to 6 years of age, and found that wheezing due to RV at 3 years of age was strongly associated with a diagnosis of asthma at 6 years of age (87%: 26/30) *(26)*.

There is also a strong association between RV infection and asthma exacerbation in adults with asthma. Venarske et al. studied a cohort of 101 adults upon hospital admission for asthma exacerbation *(29)*. Over the 4-year sampling period, 21% had RV infection, found by rtPCR at admission, as opposed to 1.3% at 3-month follow-up after hospital discharge *(29)*. In this study, RV infection was also significantly associated with smoking and nonuse of inhaled corticosteroids *(29)*. Experimentally, Grunberg et al. have shown similar actions of RV infection in individuals with mild atopic asthma *(30)*.

Intranasal infection with RV16 (a major subgroup of RV) in adults with mild atopic asthma resulted in significant symptoms of asthma, significant symptoms of common cold, and significantly decreased FEV1 at 2 days postinfection, when compared to placebo-infected controls with mild atopic asthma *(30)*.

Some studies have provided insight into the pathophysiology of RV infection's association with asthma exacerbation and possible development of asthma. Grunberg et al. have reported elevated IL-8 levels in the nasal lavage of atopic, mild asthmatic individuals after infection with RV16 *(31)*. Interestingly, increased IL-8 levels on day 2 post-RV16 infection significantly correlated with increased airway responsiveness (histamine provocation) on day 4 post-RV16 infection *(31)*. de Kluijver et al. found increased IL-8 levels in the nasal lavage of asthmatic individuals, but not nonasthmatic individuals after RV16 infection *(32)*. Additionally, he found that the pro-inflammatory mediator IL-1β was produced in both asthmatic individuals treated with placebo and asthmatic individuals treated with budesonide and then infected with RV16 *(32)*. Interestingly, the anti-inflammatory IL-1 receptor antagonist (IL-1ra) was increased only in the asthmatic individuals treated with budesonide and then infected with RV16 *(32)*. Nonasthmatic individuals had significantly elevated baseline IL-1ra levels when compared to placebo-treated asthmatic individuals who were infected with RV16 *(32)*.

Message et al. have reported that atopic asthmatic individuals, infected with RV16, have increased bronchial hyperreactivity (histamine provocation) and increased eosinophilic lower airway inflammation *(33)*. Message et al. also found that atopic asthmatic individuals infected with RV16 had decreased levels of IFN-γ and IL-10, while having increased levels of IL-4, IL-5, and IL-13 in CD4+ T cells from bronchioalveolar lavage fluid *(33)*. This may suggest that mechanisms of impaired Th1, augmented Th2, or IL-10 immunity are involved in the pathogenesis of virus-induced asthma exacerbation *(33)*.

hMPV is a recently isolated, single-stranded, negative-sense RNA virus, closely related to RSV, which is also of the family *Paramyxoviridae*. hMPV has been found to cause severe disease requiring hospitalization in children, especially between 6 and 12 months of age, and in adults, including the elderly with comorbid conditions *(34–37)*. Foulonge et al. prospectively studied 589 children under the age of 5 who were admitted to the hospital with respiratory tract disease *(36)*. While the leading viral cause of respiratory tract disease was RSV, 8.5% (50/589) were found to have hMPV *(36)*. Williams et al. prospectively studied 101 individuals who were admitted to the hospital for asthma exacerbation, and found 6.9% (7/101) had hMPV on rtPCR from nasal washings *(37)*. Considering hMPV's close association with RSV, it is not surprising that Jartti et al. studying 132 children admitted for acute expiratory wheezing, found elevated IL-8 concentrations in nasal secretions *(18)*.

The atypical bacteria, *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, are well known to cause respiratory tract infections, but recently they have also been associated with chronic asthma, as well as asthma exacerbations *(13, 38–41)*. Using serological testing (immunofluorescence or enzyme-linked immunoassays) in a prospective study of 100 adults hospitalized for asthma exacerbation, Lieberman et al. found that 18 (18%) had evidence of acute infection with *M. pneumoniae* compared with only 3 (3%) of control patients without asthma *(41)*. Further, using PCR on pulmonary lavage fluid or lung biopsy specimens from 55 individuals with chronic stable asthma, Martin et al. found that 25 had positive PCR for *M. pneumoniae*, while 6 had positive PCR for *C. pneumoniae (39)*.

Only 1 of 11 control individuals had positive PCR for *M. pneumoniae* *(39)*. Interestingly, individuals with chronic asthma and positive PCR for either *M. pneumoniae* or *C. pneumoniae* had significantly increased numbers of mast cells *(39)*.

More research will be beneficial to determine if *M. pneumoniae* and *C. pneumoniae* are underlying causes of chronic asthma and/or asthma exacerbations, or if they persist independent of asthma.

Allergies and Asthma: The Atopic Wheezer

The incidence of allergies in children with asthma is about 70%. Lombardi et al. studied 360 children from the Tucson Children's Respiratory Study who had not previously been diagnosed with asthma at 6 years of age *(42)*. Positive skin prick testing at the age of 6 was found to be a significant and independent predictor of subsequent development of both persistent and incident asthma from 6 to 11 years of age (hazard ratio = 3.7, 95% confidence interval 1.8–7.4; $p < 0.001$) *(42)*. More interesting, Lowe et al. prospectively studied a birth cohort of 498 children from the National Asthma Campaign Manchester Asthma and Allergy Study who completed both skin prick testing (dust mite, dog, and cat) and body plethysmographic measurement of specific airway resistance at 3 years of age *(43)*. Through multivariate analysis, they found that children sensitized to an allergen without exposure to that allergen and nonsensitized children exposed to an allergen had normal airway resistance *(43)*. Yet, children who were sensitized to a particular allergen and exposed to that allergen had increased airway resistance *(43)*.

Similar results were reported by Illi et al. when they prospectively studied 1,314 children (499 with risk factors for atopy) from birth in 1990 until 13 years of age *(44)*. Children sensitized to perennial allergens (house dust mite, dog, and cat dander) on ImmunoCAP (Phadia, Freiberg, Germany), and exposed to high levels of the respective allergens within the first 3 years of life, had significantly reduced lung function (FVC and maximal expiratory flow at 50% [MEF50], measured by body plethysmograph) at school age, when compared to nonsensitized children or sensitized children who were exposed to less allergen *(44)*. Interestingly, sensitization and exposure to perennial allergens at older ages had weaker effects, and sensitization and exposure to seasonal allergens (mixed grass and birch pollen) were not significantly relevant *(44)*. In this same study, 90% of nonatopic children with wheeze lost their symptoms by school age and had normal lung function at puberty *(44)*. Previously noted, Jackson et al., who found an association of wheezing due to RV at 3 years of age and a diagnosis of asthma at 6 years of age, also found an association of aeroallergen sensitization and asthma at 6 years of age. Prospectively following 259 children in a high-risk birth cohort (one parent with respiratory allergies and/or a history of asthma diagnosed by a physician), they found that aeroallergen sensitization independently increased the risk of asthma at 6 years of age *(26)*.

Overall, common aeroallergens reported to be associated with asthma include house dust mite, cockroach, and cat allergens *(45, 46)*. It is theorized that individuals develop allergen-specific immunoglobulin epsilon (IgE) through a tendency of increased T helper type-2 (Th-2) T-cell responses or decreased Th-1 T-cell responses against common environmental antigens.

Asthma in the Elderly

Asthma in the elderly has become an increasing problem, in part because of the growing population that is living longer than ever. According to studies conducted between 1991 and 1996 in developed countries of the Western hemisphere, the average prevalence of asthma in patients 65 years and over ranged from 6.1 to 8.4%. The incidence of late-onset asthma, defined as asthma occurring after age 65, is between 60 and 100/100,000. Symptoms of asthma in the elderly are similar to those in other age groups, with wheeze, phlegm and cough being the most common. Asthma in the elderly is associated with a female predominance and less atopy or allergic diseases. Asthma in the elderly presents special management issues as it is often accompanied by other respiratory diseases, as well as other nonrespiratory chronic diseases of the elderly.

Exercise-Induced Asthma

Exercise-induced asthma or bronchospasm describes patients who wheeze or experience bronchoconstriction upon exertion. The exertion necessary to trigger such attacks usually involves significant aerobic activity, but there are exceptions to this. Testing for EIA has already been discussed. This condition is very common in adolescents and can exist in patients with or without conventional asthma. The prognosis is usually good and these patients can go on to perform at the level of the "Elite" athletes.

Samter's Triad

Samter's triad includes asthma, aspirin sensitivity, and nasal polyposis. When rhinosinusitis is present, it is also known as aspirin-exacerbated respiratory disease or AERD. The defect appears to involve the arachidonic pathway. Aspirin and other NSAIDs block production of prostaglandins, shunting precursors to the leukotriene pathway, and leading to the overproduction of leukotrienes, a potent mediator of inflammation. This condition can lead to severe asthma exacerbations when patients are exposed to aspirin, and can even include anaphylaxis or urticaria. Treatment is by aspirin desensitizations, and there are standard protocols available for performing aspirin desensitization safely and with optimal effectiveness. Why aspirin affects some patients in this manner but not others is unknown.

Brittle Asthma

The first description of "brittle asthma" was by Sir John Floyer in 1698. These patients tend to have rapid swings in their condition, leading to sudden deterioration in respiratory status. These patients may have an exaggerated morning dipping of PEFR based on diurnal variation, and can present in two ways. Type 1 brittle asthma has a maintained hypervariability in PEFR, while type 2 patients experience sudden attacks of airway obstruction. While the triggers for brittle asthma have not been delineated, proposed risk factors include female gender, food intolerances, psychological disorders, a reduced perception of airway compromise, atopy, reduced total lung capacity, reduced hypoxic drive, and the presence of neutrophil-associated airway inflammation *(47)*.

While one would expect that there is a higher risk of death in this group of patients with sudden deterioration of asthma, this has not been proven.

Occupational Asthma and Hypersensitivity Pneumonitis

Occupational asthma is used to describe asthma that is caused by an exposure to a stimulus that is present only in the workplace. These triggers may vary widely from animals in laboratory workers to wood dust in lumbar yard workers and hairsprays in cosmetologists. There are over 400 agents that have been attributed to occupational asthma. It is estimated that up to 15% of adult asthmatics may fall into the category of occupational asthma. Specific criteria exist for the diagnosis of occupational asthma, and establishing this diagnosis can frequently take months of observation and data collection. Aggravation of pre-existing asthma by a workplace trigger does not constitute occupational asthma. Proper diagnosis is critical, as this impacts worker's compensation decisions in many countries that have these labor systems in place.

Hypersensitivity pneumonitis can also present with symptoms and signs of asthma. This differs from occupational asthma in that the exposure does not have to be solely in the workplace. Examples of hypersensitivity pneumonitis include farmer's lung, malt worker's disease, humidifier lung, baker's asthma, and pigeon fancier's disease. Though clinical symptoms may be similar to asthma, the alveoli are affected in hypersensitivity pneumonitis, and a type III or type IV hypersensitivity plays a more significant mechanistic role than in asthma.

SUMMARY

Based on the information we have learned regarding the pathophysiology of asthma, we can now appreciate that asthma is in fact a potpourri of diseases which vary in clinical presentation and severity. In our analysis of the various phenotypes of asthma, we attempt to isolate common themes or features that will allow us to simplify the definition of asthma. These features can include clinical findings or histological abnormalities, and would certainly include characteristics of an inflammatory disease. The involvement of cellular and humoral elements of the immune system in asthma can also vary widely from patient to patient. There is clearly a genetic element in asthma, as the incidence of asthma in children born to parents with asthma is greatly increased. A unifying definition of asthma, as we know asthma to be in the present day, may look something like this:

> *Asthma is a heterogeneous group of disease characterized by inflammatory changes in the airway, leading to bronchial obstruction, which results in respiratory symptoms and signs of varying character and severity. Asthma is typically but not universally recurring in nature, and is under the influence of genetic, immunologic and environmental factors that are not all known at the present time.*

Asthma is a clinical diagnosis helped by ancillary procedures. We use clinical acumen, good history taking and physical examination, family history, environmental history along with pulmonary function testing, chest radiographs, spirometry, peak flow measurements, asthma control tests, methacholine challenge tests and markers of

inflammation to form a complete picture that we can use to establish a diagnosis of asthma. These are all addressed in more detail in subsequent chapters.

It there is one common theme in asthma, it is that asthma is an inflammatory disease. But the physiological response to such inflammation can also vary from patient to patient, and the diagnosing asthma can sometimes be confusing, especially in the young child when wheezing can be from so many other conditions.

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2 The Genetic Bases of Asthma

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Contents

KEY POINTS/TAKE-HOME MESSAGES

- Numerous genetic, environmental, and hormonal factors underlie the pathogenesis of asthma leading to an abnormal antigen–antibody reaction inducing a vago-vagal axon reflex-mediated bronchoconstriction.
- Asthma has a complex and largely undefined genetic background. Similar to most complex diseases, its heterogeneous phenotype is thought to result from the interaction between multiple genes and environmental factors.
- It has been estimated that 73% of asthma determinants are genetic. Moreover, genetic variation is also thought to account for approximately 60–80% of the inter-individual variability in therapeutic response to medical treatments.
- Epigenetics seems to explain the corticosteroid resistance in patients with COPD.
- Over 25 genes have been hypothesized to be involved in asthma pathogenesis. However, the data reported in genome-wide linkage studies, candidate gene association studies, and, more recently, genome-wide association studies do not support a substantial role of single genes in the development of asthma.
- Future research should be planned to explore gene–environment and gene–gene interactions to unravel the etiology of this complex condition.

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INTRODUCTION

Asthma is characterized by acute clinical symptoms such as bronchoconstriction, bronchial inflammation and cough due to increased smooth muscle contractility, epithelial secretion, and tissue remodeling ultimately leading to airway thickening. Numerous genetic, environmental, and hormonal factors underlie the pathological antigen–antibody reaction inducing a vago-vagal axon reflex. The biochemical mechanisms involved in asthma exacerbations include a disequilibrium between two opposite second messenger systems in the airways, favoring the PLC–PKC over the cAMP cascade.

Asthma has a complex and largely undefined genetic background. Similar to most complex diseases, its heterogeneous phenotype is thought to result from the interaction between multiple genes and environmental factors. The concordance of asthma in monozygotic twins is 65%, significantly higher compared to 25% in dizygotic twins *(1)*, thus supporting a necessary but not sufficient genetic component in the individual predisposition to the disease and it has been calculated that 73% of asthma determinants are genetic. Moreover, genetic variation is also thought to account for approximately 60–80% of the inter-individual variability in therapeutic response to medical treatments. One of the major obstacles in these studies is represented by the wide clinical variability of asthma in terms of severity, age of onset, confounding factors (such as tobacco smoke), and treatment response. Asthma is probably the most common chronic disease in children of developed country; then, significant effort has been invested in the search for its genetic predisposition factors. Unfortunately, there has been independent replication only for a few study findings, mostly due to the lack of statistical power, differences in study design, and demographic differences of the studied populations resulting in different genetic background or environmental factor exposure *(2, 3)*. Genome-wide linkage studies, candidate gene association studies, and, more recently, genome-wide association studies (GWAS) have been used to investigate the genetic basis of asthma over the past decades. Several chromosomal regions were found to be linked to asthma and related disorders, and a number of genes within these regions seem to be biologically relevant in the pathogenesis of the disease.

In general terms, the proteins encoded by the reported genes are mostly transcription factors, and cytokines or receptors involved in Th2 polarization, chemokines and chemokine receptors playing a role in inflammatory cell recruitment into the airways, chloride channels responsible for hypersecretion, proteins regulating allergic reaction through IgE, leukotrienes, prostaglandins, and major histocompatibility proteins or proteins involved in reactive oxygen species scavenging and tissue remodeling (Table 1). These findings will be critically discussed in the present chapter and we will illustrate the possible functional implications of the reported associations, while further details on the pathogenesis and treatment issues can be found in other chapters of this book.

THE CASE OF ATOPIC DERMATITIS

The first atopic manifestation is thought to be atopic dermatitis, being the skin the first site of sensitization, thus making dermatitis an ideal companion for asthma in this discussion. Generally, during the first years of life, a progression from atopic dermatitis to asthma and allergic rhinitis develops and no individual risk factor is sufficient to explain

Table 1
Major Genetic Associations Reported in Asthma and the Relative Protein Function

Gene	*Chromosome*	*Protein function*
IFNG	12q14	Cytokine involved in Th1 response
STAT6	12q13	Transcriptional factor regulating Th2 response
IL-4R	16p12	Cytokine receptor involved in Th2 response
IL-13	5q31	Cytokine involved in Th2 response
ADAM33	20p13	A disintegrin and metalloprotease (ADAM) metallopeptidase domain 33
GPRA	7p14	Neuropeptide S receptor 1
DPP10	2q14	Dipeptidyl-peptidase
PHF11	13q14	PHD finger protein 11
CD14	5q31	Myeloid cell-specific leucine-rich glycoprotein
TLR4	9q33	Protein recognizing pathogen-associated molecular patterns (PAMPs) that are expressed on infectious agents (i.e., bacterial LPS)
TLR2	4q32	Protein recognizing PAMPs that are expressed on infectious agents (i.e., gram-positive bacteria and yeast)
TLR9	3p21	Protein recognizing unmethylated CpG dinucleotides in bacterial DNA
CARD15	16q21	Caspase-recruitment domain containing protein 15 (CARD15), cytosolic receptor involved in bacterial recognition by antigen-presenting cells
TGFB1	19q13	Cytokine involved in fibrogenesis
ADRB2	5q31	β-2-Adrenergic receptor
NOS	12q24	Nitric oxide synthase
SPINK5	5q32	Serine peptidase inhibitor, Kazal type 5
GST (T1,M1,P1)	22q11,1p13 11q13	Glutathione *S*-transferases (GST)
PDE4D	5q12	Lung-expressed phosphodiesterase implicated in airway contractility
ORMDL3	17q21	Transmembrane protein anchored to endoplasmic reticulum
GSDML	17q21	Gasdermin protein regulating apoptosis in epithelial cells
DENND1B	1q31	Protein interacting with TNF-α receptor and expressed by natural killer and dendritic cells

these alterations in global atopic disease prevalence *(4)*. Differences in the prevalence between urban and rural populations or farming communities have been attributed to the risk of atopy, including diet, hygiene, infections, allergens, and air pollution, in combination with genetic factors. Exposure to household pets, livestock, unpasteurized milk, and endotoxins during childhood are associated with a reduced incidence of allergic manifestations, although the data are inconsistently reported overall *(4)*. Nevertheless, there is convincing evidence that demonstrates a clear correlation between increased microbial

exposure and reduced allergic sensitization. In recent studies comparing geographically distinct but genetically related pediatric populations in Finland and Russia, a significant, dose-dependent reduction in the risk of atopy associated with microbial cell content and prevalence of enteroviruses has been demonstrated *(5–7)*.

The mechanisms by which allergen exposure through the epidermis could initiate systemic allergy and start the so-called "atopic march" *(4)* and predispose individuals to asthma have been elucidated during the past years. There is evidence implicating a primary inherited epithelial barrier defect resulting from *filaggrin* gene null mutations as a major predisposing factor in a subset of patients with atopic dermatitis and, secondarily, to the development of asthma *(8)*. Other less known epithelial defects, such as *SPINK5*, also may have a role *(9)*. Proinflammatory factors derived from keratinocytes and other epithelial cells have also elicited considerable interest, including thymic stromal lymphopoietin, which has been shown to stimulate mast cells to produce Th2 cytokines *(10)*. These data suggest potential molecular targets for preventing allergen sensitization associated with epithelial barrier disruption and halting the progression of atopic dermatitis and other atopic diseases.

GENOME-WIDE LINKAGE STUDIES

Prior to the GWAS era, several genome-wide linkage studies or candidate gene association studies were performed to identify gene and chromosomal regions linked to asthma. Nevertheless and as previously mentioned, differences in study design, studied population origins, low statistical power led to various results. Genome-wide linkage studies reported that the regions and genes more consistently associated with asthma are cytokine cluster on chromosome 5q, *INFG* (INF-γ) and *STAT6* on 12q, and *IL-4R* (IL-4Rα) on 16p *(3)*.

Serum INF-γ levels have been found to be significantly lower in patients with atopic asthma. IFN-γ plays an important anti-inflammatory role in asthma, as it suppresses tumor necrosis factor (TNF)-α signaling in atopic patients, and expression of IL-6, IL-8, and eotaxin induced by exposure to TNF-α. It also induces inflammatory genes such as vascular endothelial growth factor (VEGF), and the expression of IL-17 receptor *(11)*. The increased acetylation of the nuclear factor κB (NF-κB) p65 subunit as a result of TNF-α signaling is considerably reduced by IFN-γ. These findings suggest that IFN-γ suppresses the expression of some, but not all, pro-inflammatory genes induced by TNF-α by interfering with the transcriptional activity of NF-κB, possibly through changes in acetylation levels of the key regulatory proteins. Based on this background, the single nucleotide polymorphism (SNPs), T–A, at the 5′ end of the CA repeat of the human *IFN*-γ gene (+874T/A) directly affects the level of IFN-γ production and the A874 allele correlates with a low production of IFN-γ *(4)*. This polymorphism seems to coincide with a putative NF-κB binding site that could have functional consequences for the transcription of the human *IFN*-γ gene, with the result that the polymorphism could directly influence the level of IFN-γ production.

STAT6 is critical for Th2 cytokine signaling *(12)*. Multiple sequence variants of the *STAT6* gene have been identified, some of which are associated with atopic phenotypes in diverse populations *(12)*. Seven dinucleotide GT repeat variants were identified in the noncoding exon 1 of *STAT6*. Case–control association analysis of 214 white British

subjects demonstrated significant association with asthma of an allele with a 13GT repeat sequence (GT13), whereas the GT16 allele showed an inverse association with asthma. Furthermore, individuals with the GT13 allele had a higher level of IgE compared with individuals with the GT16 allele. Transient transfection assays of different alleles revealed significantly higher transcriptional activity with the GT13 allele compared with the GT16 allele in in vitro cell lines. Moreover, the GT13 allele had significantly decreased binding stability compared with the GT16 allele in a reciprocal competitive assay. These findings suggest that the GT repeat polymorphism of the *STAT6* gene contributes to susceptibility to atopic asthma and total serum IgE levels, and that variation in the length of the GT repeat sequence influences the regulation of promoter activity *(12)*.

Linkage studies followed by positional cloning have identified novel genes involved in asthma susceptibility including *ADAM33* on chromosome 20p, *GPRA* on chromosome 7p, *DPP10* on chromosome 2q, and *PHF11* on chromosome 13.

ADAM33 is a member of the ADAM (a disintegrin and metalloprotease) family. ADAM proteins are involved in cell adhesion, cell fusion, cell signaling, and proteolysis *(13)*. These proteins have the capacity to shed cytokines, growth factors, or their receptors from the cell surface and the remodeling of extracellular matrix components. The enzymatic activity of ADAM33 can be inhibited by tissue inhibitor of metalloproteinase-3 and -4 (TIMP-3 and -4, respectively) as well as several small molecules. This suggests that ADAM33 is involved in pulmonary defenses and tissue remodeling. In fact, a crucial pathological feature of chronic respiratory diseases such as asthma is airway inflammation and remodeling leading to airflow obstruction. A truncated, soluble form of ADAM33 containing the catalytic domain caused rapid induction of endothelial cell differentiation in vitro and angiogenesis ex vivo and in vivo, thus suggesting its possible involvement even in lung vascular remodeling in COPD. Genome-wide screening revealed that chromosome 20p13 was significantly linked to asthma and airway hyperresponsiveness in 460 families with asthma from the UK and the USA *(14)*. This genomic region contains the gene *ADAM33*. Since the first report of an association between *ADAM33* polymorphisms and asthma in two Caucasian populations from the UK and the USA, a number of replication studies have been published with differing results *(14)*. The differences in the association results may be due to phenotypic and environmental heterogeneity between cohorts. Additional studies demonstrated that SNPs within the *ADAM33* locus are associated with accelerated decline of lung function in the general population and in patients with asthma. The *ADAM33* gene is expressed in airway smooth muscle cells and fibroblasts in the lung, suggesting that it is not only important in the development of asthma but also in disease progression, possibly through airway remodeling *(13)*. These latter findings suggest a function of *ADAM33* related to lung growth and repair in general rather than solely associated with asthma. Recent studies revealed that SNPs within *ADAM33* confer susceptibility to COPD in the general population and are associated with airway inflammation in COPD.

GPRA, G-protein-coupled receptor for asthma susceptibility, also known as G-protein-coupled receptor 154, *GPR154*, located on chromosome 7 was identified as an asthma candidate gene by positional cloning in Finnish and French Canadian populations *(15)*. *GPRA* has two main isoforms with alternatively spliced 3′ exons (371 amino acids for isoform A and 377 amino acids for isoform B) and distinct tissue distribution

patterns. Expression patterns of the GPRA-B pulmonary isoform are different between asthma patients and healthy controls *(15)*. Moreover, levels of the GPRA-B isoform are increased in airway smooth muscle cells and epithelial cells in asthma patients compared to healthy controls. These data suggest that GPRA plays a role in asthma pathogenesis. *GPRA* single nucleotide polymorphisms (SNPs) and haplotypes have been associated with asthma or atopy in several studies, but not in others. In the studies in which associations have been found, however, the SNPs and haplotypes related to asthma and atopy are inconsistent across populations. Thus, the role of genetic variation in *GPRA* in asthma and atopy remains inconclusive.

CANDIDATE GENE ASSOCIATION STUDIES

Over the past years, candidate gene association studies identified several candidate genes with a few of these results being replicated in subsequent works.

Some of the candidate genes are involved in innate immunity such as TLRs, *CD14*, *CARD15*. The development of allergic disease may be influenced by bacterial and viral infections *(2)*. Thus, genes involved with the innate immunity response are obvious candidates for the understanding of the protective effects of exposure to microbial agents on allergy and asthma. Indeed, several SNPs in genes encoding pattern recognition receptors such as *CD14* and toll-like receptors (TLR) have been associated with atopic sensitization and asthma. Gene–environment interactions were found between ten SNPs in *CD14*, *TLR4*, *TLR2*, and *TLR9* and living in the country during childhood, which was presumed to represent higher exposures to various microbial agents *(3)*. Of note, these observations follow the hygiene hypothesis that has been proposed for numerous immune-mediated conditions *(3)*. Main effects and gene–environment interactions were stronger in subjects who were atopic than in those who were nonatopic. In particular, an association has been found between the *TLR2/+596* polymorphism and asthma and between *CD14/−260* SNP and asthma.

Since TLR2 is involved in the recognition of microbial motifs of a wide range of Gram-positive microorganisms, mycobacteria, and yeast, the exposure to these microorganisms is likely to occur more frequently in rural compared to industrialized areas. A lower expression of TLR2 on the surface of innate immune cells in carriers of the *TLR2/+596C* allele would be associated with a lesser protective effect of environmental exposures to TLR2 ligands on asthma *(16, 17)*. On the other hand, TLR9 is a receptor for bacterial CpG DNA motifs and the studies investigating *TLR9* SNPs in relation to allergy or asthma have reported inconsistent associations. However, significant gene–gene interactions with the *TLR2/+596* SNP were demonstrated, showing effects of two *TLR9* SNPs on asthma in *TLR2/+596 TT* subjects *(16, 17)*. Interestingly, TLR9 and TLR2 have different ligands and these observations may cumulatively reflect an interactive effect of multiple microbial exposures to determine asthma onset.

Genetic variants of the caspase-recruitment domain containing protein 15 (CARD15) that might result in inappropriate immunomodulation are not only associated with autoimmune diseases *(18)*, but also with atopic disorders. CARD15 is a cytosolic receptor involved in bacterial recognition by antigen-presenting cells. Subjects carrying the T allele at rs1077861 manifest a decreased risk of developing asthma, whereas the

presence of an A allele at rs3135500 is significantly associated with an increased risk *(19)*. In addition, a *CARD15* haplotype revealed to be protective against the development of asthma *(19)*.

Other candidate genes involved in inflammation include specific cytokines and chemokines, and also the respective signaling pathway such as mediators involved in IL-4/IL-13 signaling. IL-4 and IL-13 are pleiotropic, proinflammatory cytokines produced by activated T cells as part of an immune response to allergen exposure. The genes for IL-4 and IL-13 lie in a cytokine cluster on chromosome 5q31, a locus previously linked to several asthma phenotype. IL-4 and IL-13 are characterized by structural and functional similarities, as well as a common receptor component, IL-4Rα, located on chromosome 16p11. IL-4 plays important roles in T cell development, eosinophilic inflammation, and IgM–IgE isotype switching in B cells. IL-13 is a Th2 cytokine found to be overexpressed in the lungs of patients with asthma and in murine models of the disease *(20)*. Studies of the 5q31 locus reported significant associations between genetic variants in *IL-4* and *IL-13* genes and asthma or asthma-related phenotypes in some populations *(20–22)*. It has been reported an association between the *IL-4* C-589T allele and asthma severity in whites but not in African-Americans. Similarly, other nine SNPs in the *IL-4* gene have been found to be significantly associated with asthma or total serum IgE in whites *(21)*. It has also been reported an association between asthma-related phenotypes and polymorphisms in both the *IL-13* and *IL-4Rα* genes, as well as evidence of gene–gene interaction between *IL-13* C-1112T and *IL-4Rα* C+22656T (S478P) SNPs. In another study, a significant gene–gene interactions has been reported between the *IL-13* R130Q and *IL-4Rα* Ile50Val (A+4679G) polymorphisms for asthma risk in a Chinese population. Moreover, a significant gene–gene interaction was found between the *IL-13* (A-646G) and *IL-4Rα* (A-4679G) SNPs for baseline lung function among African-American subjects with asthma *(22)*.

Interestingly, additional candidate genes are involved in lung function, growth, and development such as *TGFB1*, *ADRB2*, *NOS1* and *3*, and *SPINK5*. Polymorphisms in the transforming growth factor-β1 (TGF-β1) gene have been implicated in susceptibility to asthma, but a large number of studies have reported inconclusive results. A meta-analysis performed to investigate the association between polymorphisms in the *TGF-β1* gene and asthma susceptibility suggested that the −509C/T polymorphism in the *TGF-β1* gene may be a risk factor for asthma *(23)*. On the other hand, β-2-adrenergic receptors (β(2)AR) participate in the physiologic responses of the lung, including bronchodilation and bronchial protection, through mechanisms such as ciliary clearance, fluid accumulation, and mediator release from mast cells and basophils. Thus, these receptors may also play an important role in the pathophysiology of asthma. The gene encoding β(2)AR, *ADRB2*, is extremely polymorphic, but it appears that, for asthma, *ADRB2* polymorphisms are not etiologically involved *(24)*. However, they might affect disease severity and clinical response to both acute and chronic administration of β(2)-agonists. Finally, genes involved in the response to environmental exposures to pollutants and tobacco have been also found to be associated with asthma such as *GSTM1*, *GSTP1*, and *GSTT1*. Oxidative stress in the lungs has been implicated in the pathogenesis of asthma. Sources of oxidant injury are reactive oxygen and nitrogen species generated by activated inflammatory cells and bronchial epithelial cells and inhalation of atmospheric pollutants,

notably tobacco smoke and oxidant gases, including ozone, sulfur dioxide, and nitrogen oxides. These are countered by enzymatic and nonenzymatic antioxidants, including dietary antioxidants, such as flavanols, vitamins C and E, and glutathione, a major protective antioxidant in the lungs that also has a role in regulation of inflammatory responses. The enzyme family of glutathione-*S*-transferases (GST) has the general function of conjugating glutathione with electrophilic substances that are capable of generating free radicals, thus leading to detoxification of their effects. Genetic polymorphisms associated with reduced activity of GST are therefore of interest in the study of asthma susceptibility. Two common deletion polymorphisms of *GSTM1* and *GSTT1* genes have been associated with asthma in children and adults *(25)*. The Val allele of the *GSTP1* Ile105Val polymorphism, associated with reduced glutathione activity, has been reported to be either protective or associated with increased risk of asthma. A recent meta-analysis does not support a substantial role of *GST* genes on asthma phenotypes in either children or adults, although small effects cannot be excluded and it is possible that these genes act on airway disease through interaction with environmental exposures or other genes *(25)*. Future studies on larger populations are warranted to evaluate *GST* genes in addition to other antioxidant genes or to air pollution and tobacco smoke exposures or the possible association of *GST* genes with asthma severity are needed to provide evidence on gene–gene interactive effects on asthma.

One final and fascinating hint for the etiology of asthma comes from a rare condition. The mutation of *SPINK5* causes Netherton syndrome, a rare recessive skin disease that is accompanied by severe atopic manifestations including atopic dermatitis, allergic rhinitis, high serum IgE, hypereosinophilia, and asthma. The SNP −206G>A of the *SPINK5* promoter is significantly associated with atopy, atopic dermatitis, asthma, and total serum IgE *(26)*. Moreover, the A allele at −206G>A has a significantly higher transcriptional activity than the G allele. Electrophoresis mobility shift assay also showed a significantly higher binding efficiency of nuclear protein to the A allele compared with the G allele.

GENOME-WIDE ASSOCIATION STUDIES

GWAS involving large cohorts of patients and controls have recently been performed in a growing number of complex diseases and, more specifically, identified novel asthma-associated gene regions. The first GWAS in 2007 identified several markers on chromosome 17q21 specifically associated with nonatopic childhood-onset asthma *(27)*. The study examined over 317,000 SNPs in 994 patients and 1,243 controls from UK and Germany, and, subsequently the results have been confirmed in Northern Europeans, North Americans of European ancestry, Puerto Ricans, Mexicans, Japanese, and Chinese, but not in African-Americans *(3)*. Combining gene expression levels with the associated SNP genotype a significant asthma association was found with the transcripts of *ORMDL3*, a transmembrane protein anchored to endoplasmic reticulum, and of *GSDML*, a gasdermin protein regulating apoptosis in epithelial cells. Another GWAS included 359 North American of European ancestry asthmatic patients and demonstrated a significant association between asthma and variants of the *PDE4D* gene, mapped on chromosome 5q12 and coding for a lung-expressed phosphodiesterase involved in airway contractility *(28)*. Ten independent studies attempted to replicate this

association, but only in Caucasian cohorts a weak association between asthma and two out of seven *PDE4D* SNPs was reported *(3)*. Further, a recent GWAS, together with the previously reported association with 17q21 locus, demonstrated a novel asthma locus on 1q31 in two independent cohorts of 793 and 917 patients with asthma of North American of European ancestry, but not in African ancestry patients *(29)*. The locus contains the gene *DENND1B* which is expressed by natural killer (NK) and dendritic cells and is possibly involved in the TNF-α pathway. Interestingly, in the patients of African ancestry 17 SNPs at 1q31 locus have been found to be associated with asthma but at each SNPs the alternative allele was associated with asthma compared to the discovery set. Finally, a GWAS has been conducted on 935 African-American, 929 African Caribbean, but no significant associations were determined *(30)*.

EPIGENETICS

The incomplete concordance between monozygotic twins and the reported associations observed in subgroups of patients with asthma clearly suggest that additional factors are needed to determine disease onset. Accordingly, epigenetics (i.e., DNA methylation and/or various post-translational modifications of histones mediated by acetyltransferase/deacetylase enzymes) appears as an ideal link between the environment and genomics and may thus play an important role in the expression of multiple inflammatory genes in asthma *(31)*. Moreover, epigenetics seems to explain the corticosteroid resistance in patients with COPD.

Gene expression is determined by a balance between histone acetylation which activates transcription and deacetylation which switches off transcription. An altered expression of inflammatory genes and an elevated acetylation of histone-4 were found in patients with asthma; moreover, the degree of histone acetylation seems to correlate with disease severity *(32)*. It has been observed that in the lung tissue of patients with asthma the increased acetylation of histones associated with inflammatory gene hyperexpression is not secondary to an increase in histone acetyltransferase activity, but due to decreased histone deacetylase activity. These mechanisms are particularly interesting in consideration of the fact that the anti-inflammatory activity of corticosteroids is partly due to epigenetic mechanisms and is directed to suppress NF-κB regulated genes including several of the inflammatory genes hyperexpressed in asthma *(31)*. After diffusing across cell membrane, corticosteroids bind their receptor and translocate into the nucleus where the receptor has to be acetylated to bind the glucocorticoid receptor recognition element sited in the promoters of the steroid-sensitive genes. However, it is also necessary that the corticosteroid receptor is deacetylated by histone deacetylase 2 (HDAC2) to inhibit NF-κB. In peripheral blood mononuclear cells and alveolar macrophages of patients with asthma and corticosteroid resistance, HDAC2 has been found to be markedly reduced *(32)*. Further, the corticosteroid resistance of COPD bronchoalveolar macrophages is reversed by overexpression of HDAC2. The mechanisms resulting in HDAC2 reduction in COPD are based on the inactivation, ubiquitination, and degradation of the enzyme by oxidative and nitric oxide-mediated stress. The formation of peroxynitrite, which nitrates tyrosine residues on HDCA2, and the activation of PI3k-δ by oxidative stress, which leads to phosphorylation of HDCA2, are the main mechanisms underlying corticosteroid resistance in COPD. In addition, corticosteroids

switch on corticosteroid-responsive genes, such as MKP-1, via acetylation of K5 and K16 on histone-4, and it has been reported, in some asthma patients, that acetylation of histone-4 K5 fails to occur. Besides the role of histone acetylation and deacetylation in the regulation of inflammatory genes, histone methylation seems also to be involved; moreover, corticosteroids seem partially act through this mechanism in inhibiting inflammatory genes *(33)*.

Interestingly, it has been proved that theophylline can selective activate HDCA2 in macrophages of COPD patients, and ultimately counteract and reverse corticosteroids resistance. These data have been reproduced in murine models and in smokers asthma patients. Theophylline is effective in accelerating COPD exacerbation recovery and to reduce inflammatory mediators. The mechanism of action of theophylline at molecular level seems to be via inhibition of PI3κ-δ *(34)*.

CONCLUSIONS AND FUTURE DIRECTIONS

This summary of the observed genetic associations in asthma clearly illustrate our incomplete understanding of the susceptibility to this complex condition. The mechanisms involved in the genetics of asthma are illustrated in Fig. 1. Similar to other multifactorial diseases, GWAS were welcomed as the solution to our knowledge gaps but have so far failed to prove conclusive or to report associations that may be used in the clinical workup of patients or first-degree relatives of patients. Indeed, reported associations include potential candidate genes that fit well within the current pathogenesis theories. On the other hand, we submit that the upcoming availability and accessibility of next-generation sequencing and genome-wide epigenetics tools may report additional associations (possibly with rare variants) or complementary mechanisms for transcription regulation. Further, given the potential for interactions between the genes found to be asthma-related and environmental toxins known to cause oxidative damage to the lungs, future research should be planned to explore gene–environment interactions. Large studies with accurate measurement of the environmental exposure are needed in order to reach adequate power to detect such interactions. Failure to account for environmental exposures might partly explain not only the heterogeneity of results across studies, but also the overall negative findings. Strong environmental effects on asthma phenotypes could mask modest genetic effects and, more importantly, gene–environment interactions could make the effects of genes become substantial only in the presence of oxidative exposures and not detectable at a population level. Passive smoking, ambient air pollution and endotoxin or other pathogen-associated molecules are good candidates for gene–environment interactions in asthma. Variation in exposure to these environmental factors across studies is likely to have happened given the diverse geographical setting of the studies included, and gene–environment interactions might partly explain the large heterogeneity observed. Moreover, there is evidence that antioxidant supplementation can modify these gene–environment interactive effects, so that the nutritional status of the study population could represent an additional source of heterogeneity. The evaluation of gene–environment interactions is problematic due to the lack of power of statistical tests for interactions and the high measurement error present in the assessment of most environmental exposures.

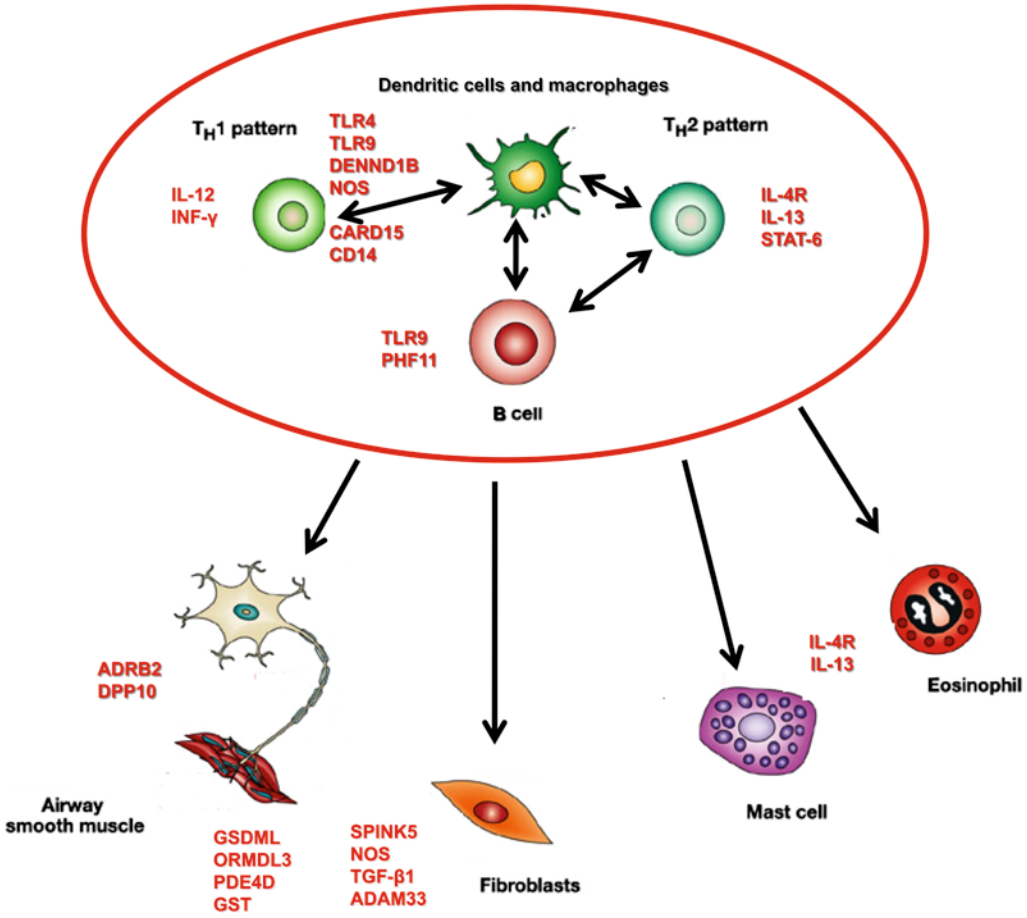

Fig. 1. The functional role of the majority of asthma-associated genes in the pathogenesis of the disease.

In fact, despite the strong biological rationale, results from the literature on gene–environment interactions in asthma remain inconclusive. Standardization of methods for environmental exposure assessment and full reporting of the interactions tested will allow the pooling of data across studies and to reach adequate power to detect interactions.

Similarly, further research should evaluate possible gene–gene interactions. Moreover, the contribution of ethnicity, childhood *vs.* adult asthma, and age at onset should be considered. Differences in asthma definition may also have played a role in generating the observed heterogeneity. Asthma diagnosed by a physician, self-reported doctor-diagnosed asthma, and self-reported history of asthma differ in sensitivity and specificity. Moreover, asthmatic individuals identified through questionnaire in a population-based study may have lower severity than patients recruited at a clinic.

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II Diagnosis and Patient Management

3 The Use of the Pulmonary Function Laboratory in Diagnosing Asthma

Michael Schivo, MD, MAS, Amir A. Zeki, MD, Nicholas J. Kenyon, MD, MAS, and Timothy E. Albertson, MD, MPH, PhD

Contents

KEY POINTS

Dynamic lung measurements

- Spirometry measures airflow rates, some volumes, and the timed VC; it cannot measure RV, FRC, or TLC.
- A reduced FEV_1 and FEV_1/FVC ratio are the best measures of airflow obstruction.

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- PEFR is a good measure of airflow obstruction in trained subjects who have established a baseline "personal best" PEFR; in untrained subjects PEFR varies depending on technique.
- Reductions of the $FEF_{200–1,200}$ or $FEF_{25–75\%}$ are good measures of small airways obstruction when the FEV_1 and FEV_1/FVC ratio are normal, but they are subject to considerable variation based on the quality of the FVC.
- Flow–volume loops can demonstrate intra- or extrathoracic obstructions; a common mimic of asthma is vocal cord dysfunction which may show up as a variable extrathoracic obstruction (i.e., a flattened inspiratory limb of the flow–volume curve).
- The volume–time curve is used to assess the quality of the FVC, and the flow–volume curve is used to assess the quality of the start of the FVC.
- Pneumotachometers are the most commonly used spirometers, and they must be frequently calibrated to maintain accuracy.

Static lung volume measurements

- Static lung volumes measure RV, FRC, and TLC, values not measured by spirometry.
- Plethysmography is the best method of lung volume measurement when evaluating obstructive lung diseases such as asthma.
- Lung volumes which may be increased in asthma include the RV and FRC; occasionally TLC is increased in severe asthma.
- Lung volumes which may change after bronchodilator administration include RV and FRC; this is known as isovolumetric shift.
- Airway resistance (Raw) and conductance (Gaw) are two measures which can aid in asthma diagnosis and may be better than FEV_1 in detecting early disease.
- Severe distal airway narrowing and increased upper digestive tract air may cause plethysmography to overestimate lung volumes; severe airflow obstruction may cause the gas dilution technique to underestimate lung volumes.

Arterial blood gases

- ABGs reflect gas-exchange between the lungs and the blood.
- ABGs in a mild asthma exacerbation will show a respiratory alkalosis (i.e., high pH and low $PaCO_2$).
- ABGs in a severe asthma exacerbation will *appear* normal or show a respiratory acidosis (low pH and high $PaCO_2$); a normal ABG or respiratory acidosis in a severe exacerbation is an ominous sign that requires ventilatory assistance, intensive care unit monitoring, and intensive therapy.

Quality control

- All machines (spirometers, lung-volume equipment, and blood gas analyzers) must be frequently calibrated.
- Trained technicians must assess for patient effort and acceptable maneuvers; this information must be noted on the PFT results.

Pulmonary function tests in asthma

- Asthma usually manifests as a decrease in the expiratory flow rates.
- A reduced FEV_1 is most often seen, but the midexpiratory flow rates ($FEF_{25–75\%}$, V_{max50}, or V_{max25}) may be reduced when the FEV_1 is normal.
- In the case of normal flow rates, plethysmography may detect increased airway resistance (Raw) or an elevated RV/TLC or FRC; these values may reduce after bronchodilator use (isovolumetric shift).

- Airflow obstruction should reverse after bronchodilator use; if it does not, chronic obstruction may be present, there may be bronchodilator resistance, or spirometry cannot detect the effect and lung volumes should be used.
- DLCO is normal or elevated in asthma.
- Mild asthma should present with a respiratory alkalosis on ABG; if the ABG is normal or a respiratory acidosis is present during an exacerbation, the patient requires aggressive care.
- Reference standards of lung function are derived from population studies. They account for age, ethnicity, gender, and height. Interpretation of lung function depends on accurate comparison to these referent populations.

Bronchoprovocation testing

- Indications for bronchoprovocation testing (BT) are suspected asthma without supportive pulmonary function tests (i.e., minimal obstruction and no bronchodilator response).
- A negative methacholine challenge (MCh) BT is highly sensitive and rules out asthma
- A positive MCh BT supports a diagnosis of asthma when present with compatible clinical features.
- Subjects should avoid bronchodilators and inhaled corticosteroids 24–48 h prior to BT, providing it is safe to do so.
- Subjects should avoid vigorous exercise for >4 h prior to exercise BT.

INTRODUCTION

This chapter aims to provide the general clinician with a good understanding of available tests in the pulmonary function laboratory to help characterize asthma. It focuses on how tests are defined and performed, their limitations, their interpretations, and how to use them to follow asthma over time. Bronchoprovocation testing is also discussed, and utilization of arterial blood gas tests to help make acute triage decisions is reviewed. The key elements pertinent to each topic are listed in the "Key Points" at the beginning of this chapter.

DEFINING THE COMPARTMENTS OF THE LUNG

The lung is divided into four volumes and four capacities. A "volume" is a compartment which cannot be further subdivided, and a "capacity" is composed of two or more volumes. Convenient reference points are maximal inspiration and maximal expiration. The resting point at which the inward recoil of the lungs matches the outward recoil of the chest wall is called the functional residual capacity (FRC), and this is found at the end of a normal breath.

The four volumes are illustrated in Fig. 1 below and are defined as follows:

1. Tidal volume (V_T): amount of air that is inhaled with normal, quiet breathing.
2. Inspiratory reserve volume (IRV): additional amount of air which can be inspired following a normal inspiration up to the total lung capacity. The IRV is a rarely used value.
3. Expiratory reserve volume (ERV): additional amount of air which can be exhaled after reaching the end of a normal breath. In other words, ERV is the volume of air exhaled from the end of a normal expiration to the point of maximal expiration.

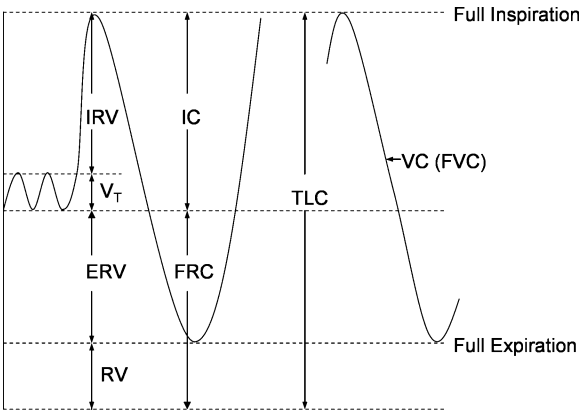

Fig. 1. Lung volumes and capacities. There is considerable variation in both healthy and disease states. *IRV* inspiratory reserve volume; V_T tidal volume (at-rest comfortable breathing); *ERV* expiratory reserve volume; *RV* residual volume (cannot be exhaled); *IC* inspiratory capacity; *FRC* functional residual capacity (balance point or resting level); *TLC* total lung capacity; *VC* vital capacity; *FVC* forced vital capacity. Note, FVC is a dynamic measurement.

4. Residual volume (RV): volume of air left in the lungs after maximal expiration. This volume cannot be expelled.

The four capacities are also illustrated in Fig. 1:

1. Total lung capacity (TLC): entire amount of air in the lungs. It is comprised of all four volumes.
2. Inspiratory capacity (IC): amount of air which can be inspired from the resting level (i.e., the end of a normal expiration) to the maximal inspiration (TLC). It is comprised of the V_T and the IRV.
3. Functional residual capacity (FRC): amount of gas remaining in the lungs after a normal expiration. It is the sum of the volumes ERV and RV. FRC is the balance or resting point of the lungs. It contributes to the maintenance of near constant O_2 and CO_2 arterial blood levels by keeping alveoli and airways open for maximally efficient breathing. Consider, for example, if FRC was zero and each breath completely filled and then emptied the lungs. This would lead to wide swings during the respiratory cycle in O_2 (gained on inspiration) and CO_2 (expelled during expiration). A stable FRC above zero prevents these swings. FRC also functions to keep alveoli and airways open preventing atelectasis (closure of alveoli which causes shunting) and easing the work of breathing (inflating an open alveolus requires less work than inflating a completely closed one). Conversely, if the FRC is too large it can make CO_2 elimination difficult leading to CO_2 retention (hypercapnea) and, if severe enough, can cause low arterial O_2 (hypoxemia). This is often seen in advanced obstructive lung disease with air-trapping and hyperinflation.
4. Vital capacity (VC): amount of air which is measured from maximal inspiration to maximal expiration. It is comprised of the IRV, V_T, and ERV. Usually the VC is measured as a forced maneuver (dynamic) where a subject inhales to maximal inspiration and forcibly exhales to maximal expiration; this is the forced vital capacity (FVC). It can be considered a measure of a subject's ability to change the size of the thoracic cavity, and this ability is influenced by respiratory muscle strength and innervation, chest wall and lung elasticity, and airway patency. Of note, a static VC as measured by nitrogen washout or body plethysmography (discussed later) should always be equal to or larger than the dynamic FVC measured by spirometry.

DYNAMIC LUNG MEASUREMENTS: SPIROMETRY AND FLOW–VOLUME TRACINGS

Spirometry is a measure of airflow rates, volumes, and a timed vital capacity. It is represented in two forms: the volume–time plot and the flow–volume plot. Each expresses abundant information, and a basic understanding of each will enable detection of obstructive lung disease. Uniquely, the volume–time tracing allows assessment of the FVC maneuver for acceptability. The flow–volume loops give a graphic representation of larger intrathoracic and extrathoracic airway patency. Most spirometers now have software that reports both tracings.

The forced expiratory spirogram is illustrated in Fig. 2; this is the volume–time plot. A subject breathes at a normal volume which is recorded as the V_T. They are asked to breathe all air out until they reach RV then to fill their lungs to maximal capacity, TLC. This enables measurements of the ERV, IRV, IC, and IVC. The subject then blows air out of their lungs as quickly and completely as possible to maximal exhalation. This generates the FVC curve. The FVC curve is divided into forced expiratory volumes (FEV) based on time: at 1 s, FEV_1; 2 s, FEV_2, etc. The ratio of FEV_1/FVC is an index of airflow obstruction, and it is expressed as a percentage. Most subjects should be able to exhale a large percent of their FVC in the first second of the maneuver. Subjects with airflow obstruction, however, may exhale a lower percent of their FVC in the first second, and this is conceptually how the FEV_1/FVC ratio is used. Predicted normal reference standards are available *(1)*. When proper technique is used according to the American Thoracic Society guidelines, the above measurements are generally reproducible and reliable. Submaximal effort or poor technique may lead to erroneous data, though often this can be easily identified. Technician involvement is crucial to ensuring proper technique and compliance by the patient (Fig. 2).

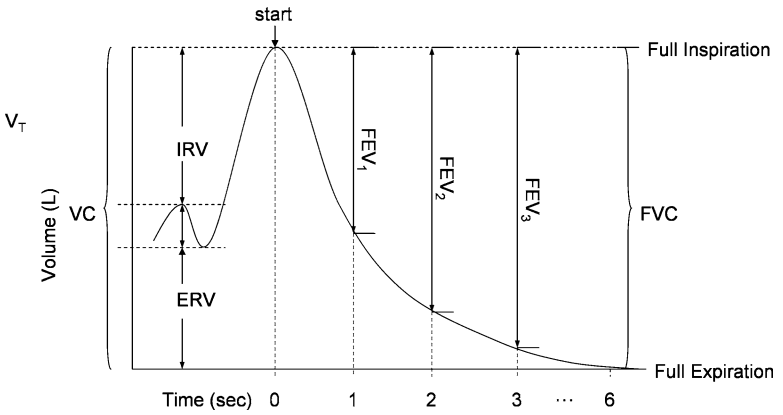

Fig. 2. Spirometry illustrating lung volumes, forced maneuver, and forced expiratory volumes. The forced vital capacity (FVC) begins at the start (noted above graph) after a full inspiration. At each second after the forced maneuver, a volume is shown. At about 6 s, the full FVC is noted. *VC* vital capacity; *IRV* inspiratory reserve volume; V_T tidal volume; *ERV* expiratory reserve volume; FEV_1 forced expiratory volume at 1s; FEV_2 at 2s; FEV_3, at 3s.

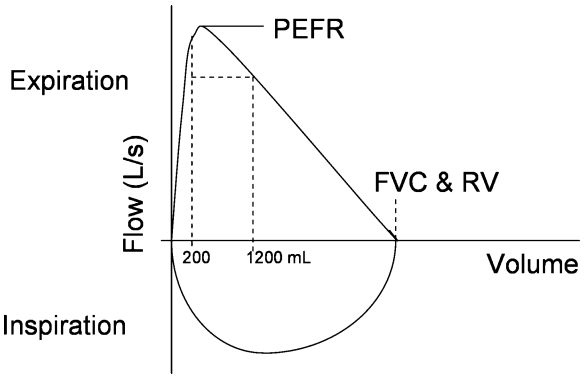

Fig. 3. Flow–volume loop illustrating the peak expiratory flow rate (PEFR). The initial upswing of the expiratory limb is highly effort-dependent, and the downswing is effort-independent. Note that the PEFR is at the cusp of the effort-dependent and -independent portions of the expiratory limb. Also, the range between the initial 200 and 1,200 mL of the forced vital capacity (FVC) straddles the effort-dependent and -independent portions. This implies that both the PEFR and the forced expiratory flow from 200 to 1,200 mL ($FEF_{200–1,200}$; not shown here but implied between the 200 and 1,200 mL volumes) are subject to considerable variability. *RV* residual volume.

Peak Flow and Forced Expiratory Flow from 25 to 75% of the FVC

In addition to the FEV_1 and FEV_1/FVC ratio, specific flow rates allow identification of airflow obstruction. A commonly used value is the peak expiratory flow rate (PEFR; Fig. 3). As flow rates are highest early in the FVC, PEFR allows for an instantaneous measure of maximal effort. When subjects are motivated and trained to perform PEFR properly, it can be used to detect changes in airflow obstruction and monitor for impending asthma exacerbations. Trained subjects identify a "personal best" PEFR when they are healthy and their asthma is controlled. Following this, "zones" of PEFR are identified which correspond to 80 and 50% of the personal best. The PEFR measurement is useful because it can be done by patients ≥5 years old at home and can identify worsening lung function even when symptoms are minimal *(2)*. However, because of its effort-dependence, PEFR is a less reliable measure of obstruction than FEV_1 due to variations in technique, effort, and training *(3)*. The forced expiratory flow from 200 to 1,200 mL ($FEF_{200–1,200}$) below maximal inspiration is another rate which has been used by subjects with asthma trained to perform the FVC properly (Fig. 3). The initial 100 mL of flow are omitted as they are the part of the FVC maneuver where a subject must overcome chest wall inertia. $FEF_{200–1,200}$ is also subject to variability and effort-dependence rendering it less reliable than FEV_1.

The forced expiratory flow from 25 to 75% of the FVC ($FEF_{25–75\%}$) is another flow rate utilized to identify obstruction (Fig. 4). The $FEF_{25–75\%}$ is more reproducible than the $FEF_{200–1,200}$ because it measures flow over the middle 50% of the FVC. This portion is much less effort-dependent than the first 25% of the FVC, and therefore the $FEF_{25–75\%}$ is more reproducible than the PEFR and $FEF_{200–1,200}$. Despite this the $FEF_{25–75\%}$ is not as reproducible as the FEV_1, and it is somewhat dependent on effort. Consider the situation

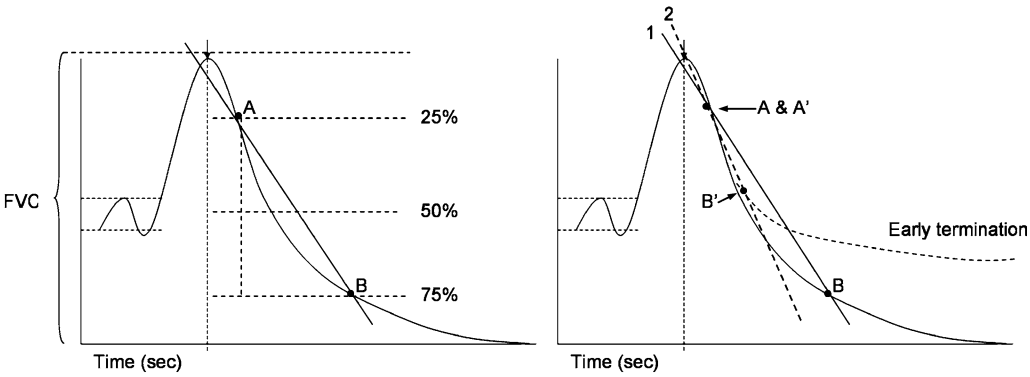

Fig. 4. Measurement of forced expiratory flow from 25 to 75% ($FEF_{25–75\%}$) of the forced vital capacity (FVC) and how the $FEF_{25–75\%}$ changes depending on the FVC maneuver. The *left graph* shows points A and B on the expiratory curve representing where 25 and 75% of the FVC have been exhaled (i.e., the middle 50% of the FVC). The vertical distance between A and B is a volume, and the horizontal distance is time. Taking the volume over time between A and B, we obtain a flow, $FEF_{25–75\%}$. This calculation is subject to considerable variation depending on the effort of the FVC maneuver. The *right graph* shows how the slope between A and B changes when an FVC maneuver is stopped early (*dashed curve*). The new points A′ and B′ along line 2 represent the 25 and 75% points of the new (smaller) FVC. The flow rates of the early part of the two FVC curves are identical, but the terminal portions change causing the $FEF_{25–75\%}$ to change. Unless two FVC maneuvers are within 5% of each other or the expiratory times are the same, the $FEF_{25–75\%}$ cannot be used to compare pre- and post-bronchodilator responses or to note the therapeutic response over time.

illustrated in Fig. 4. The volume–time curve on the left describes the $FEF_{25–75\%}$ (i.e., the change in volume over the change in time: flow). If the FVC maneuver is terminated early, as in the curve on the right, the $FEF_{25–75\%}$ assumes a steeper slope (line 2) resulting in a more rapid flow. This indicates that although decreased $FEF_{25–75\%}$ values can represent airflow obstruction, they cannot be directly compared unless the FVC maneuvers are *identical* (within 5%).

The $FEF_{25–75\%}$ represents flows in the middle 50% of the VC. This corresponds anatomically to the medium to small airways where smooth muscle constriction and mucosal inflammation may be most pronounced. Early studies demonstrated that a reduced $FEF_{25–75\%}$ with a normal FEV_1 suggests pathology in the small airways *(4)*, though reproducibility issues prevented firm recommendations on the use of $FEF_{25–75\%}$. A recent retrospective study examines $FEF_{25–75\%}$ in children who are monitored after an asthma exacerbation *(5)*. It suggests that a persistent abnormal $FEF_{25–75\%}$ when FEV_1 and FEV_1/FVC have normalized indicates suboptimal asthma control and the need for more intensive therapy. Though the role of $FEF_{25–75\%}$ is continuously changing, it remains a valuable parameter to assess small airway function (Fig. 4).

Flow–Volume Curves

Flow–volume curves (seen in Figs. 3, 5, and 6) more directly assess flow rates than the volume–time tracings. These can be used to visually assess airflow obstruction and are a valuable tool for noting large intra- and extrathoracic obstructions (Fig. 5).

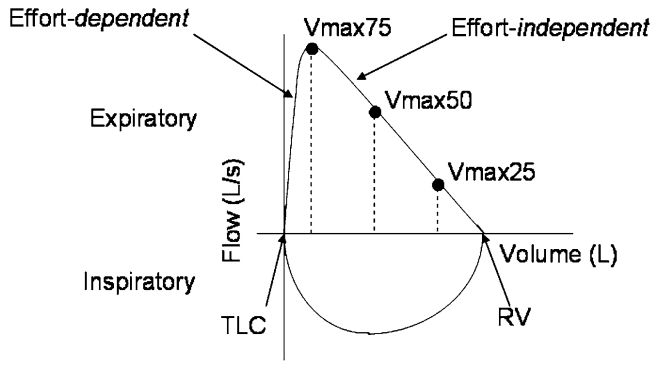

Fig. 5. Flow–volume tracing illustrating the expiratory and inspiratory flows; maximal flows at 75, 50, and 25% of the vital capacity (VC); and the effort-dependent and -independent portions of the expiratory limb. Effort-dependence indicates that subject effort greatly affects the shape of the curve. Effort-independence indicates that the flow pattern cannot be modified by a subject's effort. Note that the maximal flows V_{max75}, V_{max50}, and V_{max25} exist along the effort-independent portion of the expiratory limb. *RV* residual volume; *TLC* total lung capacity.

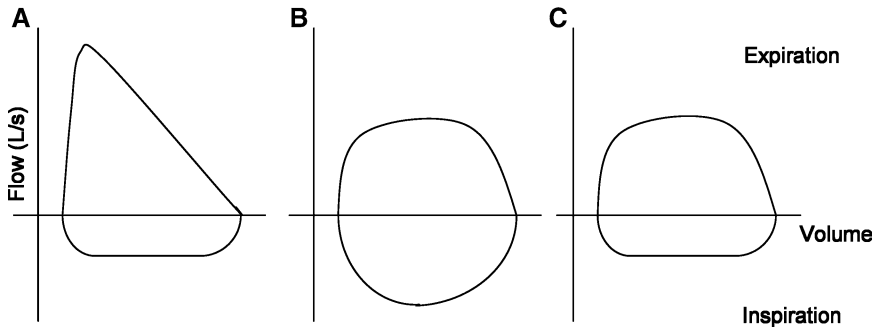

Fig. 6. Flow–volume loops demonstrating a variable extrathoracic obstruction (**A**), a variable intrathoracic obstruction (**B**), and a fixed, large airway obstruction (**C**). A variable extrathoracic obstruction commonly seen in subjects undergoing a workup for asthma is vocal cord dysfunction (VCD). In VCD, the vocal cords paradoxically close (adduct) during inspiration creating a stridorous sound which is often confused with the wheezing heard in asthma.

Briefly, flows on the *y*-axis are plotted dynamically over volumes on the *x*-axis, as noted above in Fig. 5. In our examples the FVC maneuver begins at the left-most intersection of the axes, corresponding to maximal inspiration and TLC. Flows above the *x*-axis are expiratory, and flows below are inspiratory. The maximal flows at different parts of the VC are plotted to demonstrate convenient points at which flows may change depending on the degree of airflow obstruction. These are noted as V_{max75}, V_{max50}, and V_{max25}, respectively, though these values are rarely used clinically. Both effort-dependence and independence are noted. Effort-dependence occurs at the initial part of the FVC maneuver corresponding to the larger airways and higher lung volumes where cross-sectional area is increased and flows are higher. Subjects can significantly modify this portion of the flow–volume tracing depending on their effort.

The effort-independent portion corresponds to smaller airways and lower lung volumes where cross-sectional area is decreased. Flow in these areas depends more on airway resistance and wall friction and less on subject effort. It is in the independent portion of the expiratory limb where obstructive lung pathology will result in decreased flows, reduced maximal flows in the 50 and 25% VC range (V_{max50} and V_{max25}), and the characteristic concavity seen on the flow–volume expiratory limbs (*see* section "Measurements in Asthma" and Fig. 8).

The flow–volume curves can be used to identify larger airway obstructions: intrathoracic (below the level of the vocal cords), extrathoracic (vocal cords and above), and fixed (either above or below the vocal cords causing airflow obstruction with both inspiration and expiration). Characteristic flow–volume patterns are seen in Fig. 6 below.

Limits of Spirometry

As previously mentioned, several spirometric measurements may be misleading if there is variability in effort or lung volumes. The FEV_1 is probably the most reproducible of all measures as most people can generate a maximal effort for 1 s. This is why FEV_1 has remained a consistently utilized test of airflow obstruction. Problems with FEV_1 interpretation may occur if the exact start of exhalation is difficult to identify. The FVC can vary depending on the effort and completeness of exhalation. This may be difficult for subjects with significant airflow obstruction to reliably perform. An incomplete FVC can result in diminished values of all flows beyond the initial flow parameters; PEFR and FEV_1 may be preserved but $FEF_{25–75\%}$, $FEF_{200–1,200}$, V_{max50}, and V_{max25} are diminished if the FVC is terminated early (*see* Fig. 4 for the $FEF_{25–75\%}$ example). The $FEF_{25–75\%}$ and $FEF_{200–1,200}$ are good measures of flow in the small airways, but as discussed they are subject to considerable variability depending on the quality of the FVC. In addition, the $FEF_{25–75\%}$, V_{max50}, and V_{max25} all depend on the volume of air in the lungs at the time of the measurements. This results in significant inter- and intrasubject variability.

Technicians and physicians can recognize poor efforts in both the volume–time and flow–volume tracings. The volume–time tracing is used to note the quality of the FVC. Most adults should be able to maintain an FVC maneuver for >6 s. In those who cannot maintain the FVC for 6 s, the technician accepts an FVC if there is <0.025 L change for >1 s *(6)*. Unacceptable maneuvers may present as an FVC tracing which plateaus then decreases (double dip) or one that stops before a plateau. The flow–volume curve is used to note the quality of the start of exhalation. The slope between the start of the FVC and the PEFR should be steep and quick. If this slope is slow and there is considerable time to reach the PEFR, the effort is poor. The American Thoracic Society and European Respiratory Society have published full criteria to determine the acceptability of spirometric maneuvers *(6)*. If these criteria are followed, spirometry is highly reproducible.

Classes of Spirometers

There are two types of spirometers: volume displacement and pneumotachometer. Volume displacement spirometers use a bell or bellows attached to a rolling seal or inverted pail which move in direct correlation to the volume of air displaced during inspiration and expiration. These machines require infrequent calibration but they are bulky and contain several moving parts which may break. Consequently, volume

displacement spirometers are rarely used. Pneumotachometers are small, light, portable, and rely on few moving parts. In general, airflow moves a turbine at the mouthpiece which is converted to an electronic signal by a sensor. The device plots this signal as a flow–volume and/or a volume–time tracing. Pneumotachometers require frequent calibration, are subject to electronic drift, and may accumulate moisture and particles in the mouthpiece which can alter flow. Currently, they are the most commonly used spirometers either independently or in-line with a plethysmography box. When calibrated properly, pneumotachometers are very precise and accurate, and most are coupled with advanced software which provides instant analysis and an eye-pleasing display.

STATIC LUNG VOLUME MEASUREMENTS

Although less frequently used to identify asthma, static lung volume measurements are valuable tools in assessing for hyperinflation, airway resistance, and volumetric shifts after bronchodilator use. Because spirometry cannot determine RV, FRC, and TLC, static lung volume measurements are used to obtain these values. Additionally, static lung volumes can also measure VC which can be compared to the dynamic FVC measurement to determine if dynamic airflow obstruction is present. In lung volume assessment, the measurements are static so flow rates cannot be determined. In obstructive lung disease, both hyperinflation and an increased airways resistance can be seen. In these circumstances, static lung volume measurement will show an increase in RV and FRC (and occasionally TLC) and airway resistance (Raw). Response to bronchodilator can be seen if there is a decrease in FRC and RV after administration; this is known as isovolumetric shift. Bronchodilator response is also seen if Raw decreases.

Methods of Lung Volume Measurement

Lung volumes are measured in two general ways: thoracic gas volume and gas dilution volumes. Thoracic gas volumes are measured by a body plethysmograph (generally available in hospitals or larger offices) or by radiological techniques. Gas dilution methods utilize a nonreactive gas which does not cross the alveolar-capillary membrane to determine the volume of distribution. Common gases are helium, neon, methane, or nitrogen. In general, both methods are accurate in normal subjects, but in obstructive lung disease the gas dilution method may underestimate the lung volume as the gases may not distribute evenly into all areas of the lung.

Body plethysmography is a very accurate method to measure lung volumes. Subjects sit in an enclosed cabinet (a body box) and breathe through a mouthpiece. V_T, IRV, ERV, and VC are measured, then the mouthpiece closes simulating a closed glottis. The pressure in the cabinet is known, and pressure differences are measured when a subject inspires against the closed mouthpiece. Because plethysmography directly measures pressure differentials, areas of obstructed lung in which gas flow is impaired do not affect the measurement. Plethysmography can also measure Raw and its reciprocal, airway conductance (Gaw). Raw and Gaw can be used to assess response to therapy. Disadvantages to plethysmography are size of the unit, cost, and the need for frequent calibration. However, the accuracy of the information (especially in obstructive lung disease) and the ability to perform spirometry with the same equipment greatly offset the drawbacks.

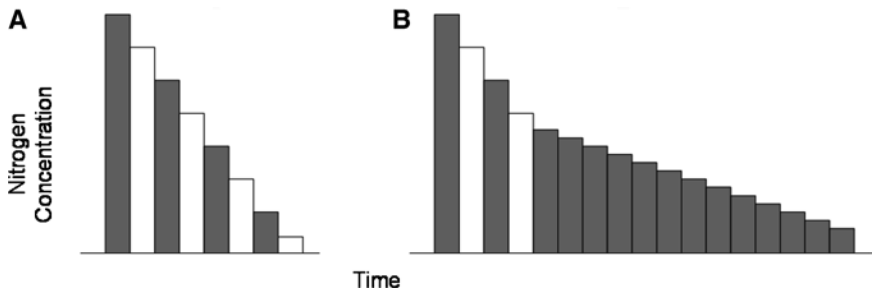

Fig. 7. Nitrogen washout technique for lung volume measurement. As nitrogen (N_2) comprises approximately 80% of air, it can be used as a tracer gas for determining lung volumes. A subject breathes 100% oxygen starting at functional residual capacity. The concentration of N_2 is measured at each breath and a declining graph is formed. The original lung volume is determined by measuring the time it takes for all of the N_2 to be washed out. In normal subjects, the decline of N_2 concentration is linear (**A**). In subjects with airflow obstruction, the decline is nonlinear (**B**).

The radiological method of measuring thoracic gas volume is performed by taking posterior–anterior and lateral chest radiographs (CXRs) *(7)*. This method approximates the total lung capacity by measuring the lungs as a series of ellipses and subtracting the ellipsoid volumes of the hemidiaphragms and mediastinum. To determine RV, a simultaneous spirogram is taken to determine VC. This method is seldom used and few studies compare its accuracy to that of the more commonly used plethysmography.

Gas dilution volume measurements are available at most hospitals and clinics with a pulmonary function laboratory. Usually, the measurement is performed with a tracer gas (helium, neon, or methane) as the determination of alveolar volume during a single-breath carbon monoxide diffusing capacity measurement (*see* Sect. "Diffusing Capacity"). Alternately, a rebreathing technique is used where a concentration of tracer gas is inspired and rebreathed for several breaths. The concentration is then reassessed and volumes are derived based on the change in concentration. A common variant of the rebreathing method is the nitrogen washout. Air is comprised of approximately 80% nitrogen. This serves as the tracer gas in the lungs, and a subject is given 100% oxygen for several breaths starting at FRC. The dilution of the nitrogen in the lungs is measured after each breath, and the lung volumes are determined based on the concentration of "washed out" nitrogen and the time to washout with corrections for the residual nitrogen in the lungs *(8)*. This method can also graphically represent airflow obstruction as seen in Fig. 7 below.

Quality of Lung Volume Measurements

As discussed above, gas dilution techniques are associated with underappreciation of lung volumes in obstructive lung disease. As airflow is heterogeneous and exhalation in certain parts of the lung can be delayed, the distribution of gases is also uneven. Furthermore, gases may become trapped in certain areas of the lung if regional obstruction is severe. As plethysmography measures pressures, it is affected far less by regional airflow obstruction. However, if airflow obstruction is severe the pressure in the distal airways may not equilibrate with the mouth leading to a falsely elevated measure of

lung volume. Also, if there is excessive volume in the gastrointestinal tract (as might be seen in subjects with a large hiatal hernia), plethysmography may overestimate lung volumes. Having subjects perform a slow pant, e.g., <1 pant/s, may help equilibrate pressures between the distal and proximal airways.

Airway resistance and conductance (Raw and Gaw), as measured by plethysmography, are adjuncts to diagnosing asthma. When FEV_1 fails to demonstrate a positive bronchodilator or bronchoprovocation response, Raw and Gaw may change *(9)*. In fact, Raw may correlate more with mid-expiratory flows such as the $FEF_{25–75\%}$ than FEV_1, and thus be able to detect small airway narrowing before FEV_1 *(10)*. In this way Raw and Gaw are more sensitive than FEV_1 in detecting asthma and reversibility, but they are much less specific.

DIFFUSING CAPACITY

The single-breath carbon monoxide diffusing capacity (DLCO) is used to measure the lung's ability to transfer carbon monoxide (CO) from the alveoli to the hemoglobin in the circulating red blood cells. In the pulmonary function laboratory, a solution of 0.3% CO is mixed with 10% helium (or neon or methane) and inspired by a subject. After a 10 s breath hold at TLC, the gas is exhaled and analyzed. The helium promotes even distribution of the CO and is theoretically inert. Its concentration is measured both before and after inhalation to determine lung volume, which in normal subjects equals TLC and in obstructive lung disease will underestimate TLC. The inspired:expired helium ratio is used to determine the expected alveolar volume and dilution of the CO, and this is compared to the measured concentration of CO. This is used to determine the volume of CO which enters the blood, and this generates a calculated DLCO. Normal values are available and cutoffs for pathology are used based on confidence intervals or absolute values.

The main utility of the DLCO in assessing obstructive lung disease is to differentiate between chronic obstructive pulmonary disease (COPD) and asthma *(11)*. In COPD (i.e., due to prolonged smoking), a reduced DLCO in COPD is often associated with a loss of alveolar-capillary units and a reduced overall pulmonary capillary blood volume. In contrast, asthma is often associated with a normal or elevated pulmonary blood volume, and hence DLCO would be normal or increased.

ARTERIAL BLOOD GASES

Arterial blood gases (ABG) are essential in evaluating subjects with asthma during exacerbations. The ABG is a measure of pH, the partial pressure of carbon dioxide (mmHg $PaCO_2$), and the partial pressure of oxygen (mmHg PaO_2). The bicarbonate level is calculated based on the Henderson–Hasselbach equation. An ABG is generally obtained from a radial or femoral artery, and it is analyzed in a blood-gas laboratory or by a certified, hand-held meter. In most healthy adults, pH is 7.40, $PaCO_2$ is 40 mmHg, and PaO_2 is 100 when breathing room air at sea level. If a subject with asthma has an exacerbation and begins to breathe quickly, the initial ABG perturbation is a fall in $PaCO_2$ and an increase in pH – a respiratory alkalosis. As airflow obstruction progresses and/or the subject begins to fatigue, the $PaCO_2$ begins to increase and the pH falls – a respiratory

Table 1
Using Blood Gas Values to Make Triage and Management Decisions in Mild and Severe Asthma Exacerbations

	Normal	*Mild exacerbation*	*Severe exacerbation*
Symptoms	None	Mild SOB Wheezing Increased RR	Severe SOB Wheezing or decreased air movement Accessory muscle use
$PaCO_2$ (mmHg)	40 – normal	30 – low	45 – **high**
pH	7.40 – normal	7.48 – high	7.36 – **low**
PaO_2 (mmHg)	100 – normal	90 – normal	80 – **low**
General Triage Decision	N/A	Bronchodilators Steroids Treat underlying process	**Ventilation (NIV or IMV)** **Intensive care unit** Intensive bronchodilators, steroids, etc

Note that the blood gas values in the normal and severe exacerbation columns are similar; however, normalizing values in a severe exacerbation is an ominous sign portending respiratory failure and warranting intensive care (*bolded*). The $PaCO_2$ and pH values in the severe exacerbation column are actually high and low (*bolded*), respectively, given the clinical situation. Note, the values reported are examples only; actual values may vary considerably. *N/A* not applicable; *NIV* noninvasive ventilation; *IMV* invasive mechanical ventilation.

acidosis. It is at this point where the situation becomes ominous as respiratory failure is imminent. *In fact, when the pH reaches 7.40 and the $PaCO_2$ rises back to 40 in a person with a severe asthma exacerbation, they are demonstrating a loss of normal gas exchange and have already begun to have respiratory failure.* Only after the $PaCO_2$ significantly rises does the PaO_2 begin to fall (*see* Table 1).

QUALITY CONTROL

The value of any study is dependent on good quality control. Patient effort is critical, and having trained technicians to direct patients and identify and correct poor efforts is essential to a well-functioning pulmonary function lab. In addition, technicians must regularly and properly calibrate machinery, troubleshoot machine malfunctions, and stay current with the proper guidelines. Spirometers must be frequently calibrated with certified syringes. Plethysmographs must be assessed for accurate lung volume measurements and good pressure seals. Gas dilution and DLCO units must be assessed for gas linearity to detect leaks and improper air mixing. ABG machines require calibration on a regular basis with known analytes and blood solutions. It is a good idea for each lab to have one or two permanent employees measure their own lung function weekly. This will serve as an internal standard when questionable values arise on the machinery. As discussed previously, the American Thoracic Society and European Respiratory Society have published guidelines on spirometry technique, calibration standards, DLCO measurements, and lung volume measurements *(6, 12, 13, 14)*.

PULMONARY FUNCTION MEASUREMENTS IN ASTHMA

Much of the information that follows has been covered in the prior sections. This section serves to put all of the previous information together as a convenient reference and to highlight the important points.

Spirometry and Flow–Volume Studies

When bronchospasm is present, expiratory flow rates are usually decreased (*see* Fig. 8). The most important values to assess for obstruction are the FVC, FEV_1, and the FEV_1/FVC ratio. Occasionally the FEV_1 and FEV_1/FVC ratio are normal, especially in mild disease. In these circumstances the flows in the smaller airways ($FEF_{25–75\%}$, V_{max50}, and V_{max25}) may be decreased, or all flows may be normal. If some obstruction is present, it is often reversible with a bronchodilator. If the obstruction is not reversible, it may be because the subject took a bronchodilator medication prior to testing, there is a component of irreversible obstruction, the bronchodilator has reached maximal effectiveness, or the response is seen in the smallest airways and not reflected on spirometry. In the latter case lung volume measurement, Raw, and Gaw may be better able to assess bronchodilator response. Figure 8 below illustrates spirometric changes with increasing airflow obstruction.

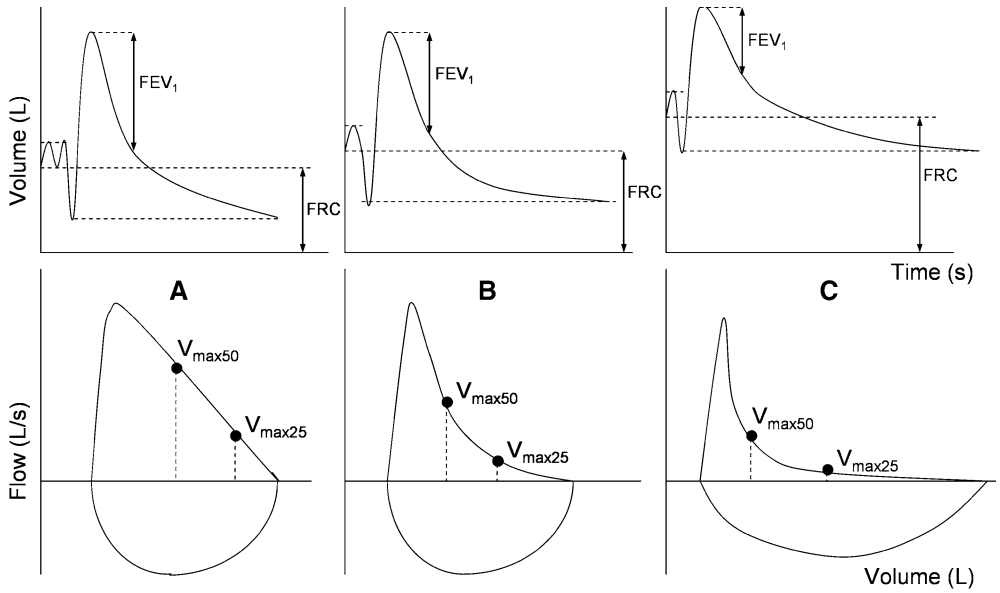

Fig. 8. Volume–time (*upper*) and flow–volume (*lower*) spirometric tracings showing normal curves (**A**), mild to moderate obstruction (**B**), and severe airflow obstruction (**C**). In the volume–time tracings, functional residual capacity (FRC) increases and forced expiratory volume in 1 s (FEV_1,) decreases with worsening obstruction. The time to complete the forced vital capacity also increases with worsening obstruction. In the flow–volume tracings, flow abruptly decreases in the effort-independent portion of the expiratory limb as obstruction worsens. This corresponds to decreased maximal flows at 50% vital capacity (VC) and 25% VC (V_{max50} and V_{max25}). Also, volume increases in severe obstruction. Note, spirometry is not able to measure FRC; it is illustrated for didactic purposes only.

In severe asthma, VC may be decreased (see Fig. 2-1-8, volume–time tracing). This can result from progressive air-trapping which effectively increases the RV or inspissated mucous plugs which physically block areas of lung. When the VC is decreased, the FEV_1/FVC ratio may be artificially increased as the reduced VC (FVC) begins to match the already diminished FEV_1.

Lung Volume Measurements

As previously discussed, the RV, FRC and TLC may be increased in severe asthma. Airway resistance parameters (Raw and Gaw) may also be altered. When FEV_1 and FEV_1/FVC are normal and asthma is suspected, pre- and post-bronchodilator responses may best be seen on lung volume, Raw, and Gaw measurements. A shift from an elevated RV and FRC to lower values indicates a positive bronchodilator response; this is called an isovolumetric shift.

Diffusing Capacity

The DLCO may be normal or elevated in asthma. If it is decreased, alternate diagnoses such as COPD, pulmonary vascular disease, or interstitial lung disease should be considered.

Arterial Blood Gas Measurements

The ABG in itself is not useful to diagnose asthma, but it can be extremely helpful to identify patients with asthma exacerbations who may have gas exchange abnormalities. Table 1 below illustrates the progressive gas exchange abnormalities as asthma exacerbations become more severe. The critical values to focus on are the $PaCO_2$ and pH. Oxygenation generally becomes affected after respiratory failure has occurred and the $PaCO_2$ is elevated. An oxygen defect in the face of hyperventilation (i.e., a low $PaCO_2$) should prompt evaluation for a pneumonia, inspissated mucous plug causing atelectasis, or a pulmonary embolism.

Interpretation of Results

All results obtained from pulmonary function tests must be compared with reference values to determine the presence and degree of abnormality. As each pulmonary function laboratory serves its own unique population, ideally each lab should have its own reference standards. This, however, is impractical, and published reference values utilizing national datasets are available. The most recent widely used dataset is from the third National Health and Nutrition Examination Survey (NHANES III) assessing nonsmoking subjects of Caucasian, African-American, and Mexican-American ancestry, ages 8–80 *(15)*. Analysis of this dataset demonstrated that age and height can be used to assess expected lung volumes and spirometric measurements. The NHANES III data also applies to a broader population of subjects than prior studies which looked at mostly healthy Caucasian groups of European ancestry *(16, 17)*. Newer datasets have been analyzed including adult Chinese Asians in Hong Kong *(18)*, Asian Indians living in the United States *(19)*, and aging adults *(20)*. Each of these investigations reveals that different ethnic populations have different "normal" lung measurements, and they underscore the need for better characterization of lung function based on ethnicity and sex.

When deciding on cutoff points for lung function, the 95% confidence interval of the distribution of lung measurements is often used. If it assumed that all lung measurements fall in a Gaussian (i.e., normal) distribution, "abnormal" is determined as the lowest 2.5% of values which fall outside the low end of the distribution (each 2.5% represent the tails of the normal curve, making a total of 5%). This translates to a 5% chance that a subject with normal lung function will fall outside the reference range and be considered "abnormal." By statistical convention, this 5% chance of an error is acceptable (the false positive or Type I error rate). The American Thoracic Society and European Respiratory Society advocate this interpretive strategy *(1)*. Other strategies used include fixed cutoff points, such as an FEV_1/FVC ratio of 0.7 *(21)*. This may yield falsely low numbers of subjects with lung pathology if they are young, and falsely high numbers of subjects with lung pathology if they are older (>40 in men and >50 in women *(21)*). The best interpretive strategy is probably a combination of using confidence intervals and fixed values depending on subject age.

TESTS OF BRONCHODILATOR RESPONSE

When airflow obstruction is noted, then next important step is to determine if it is reversible. The most common way to assess for reversible obstruction is to use a short-acting β_2-(beta-2)-agonist such as albuterol as an inhaled or nebulized dose after initial pulmonary function tests are performed. Since albuterol's onset of action and time to peak response are short, pulmonary function tests are performed 15–20 min after bronchodilator administration. Long-acting bronchodilators are less often used. It is important that subjects try to avoid bronchodilators for 12–24 h prior to pulmonary function testing as this might confound identification of a response. In some situations, however, it may not be safe for subjects to abstain.

Criteria for Determining a Significant Bronchodilator Response

Determination of a significant spirometric response depends on several general considerations. First, changes in spirometry should be compared to referent values, and those above the 95% confidence interval should be considered statistically significant. Unfortunately there are not many large studies like the NHANES III available for comparison. The American Thoracic Society and European Respiratory Society (ATS/ERS) have utilized existing reference values and made general recommendations (21, *see* Table 2); this concept was also discussed in the subsection "Interpretation of Results." Next, to accurately compare pre- and post-bronchodilator spirometry, the pre- and post-bronchodilator efforts must be equivalent. Last, the lack of a significant spirometric response *does not* equate to the lack of a clinical response. As an example, a subject with very severe airflow obstruction pre-bronchodilator (FEV_1 0.5 L) may only have a 100 mL change in FEV_1 post-bronchodilator (FEV_1 0.6 L), but this may be clinically significant (i.e., the subject feels better). The 100 mL change is less than the required 200 mL change for a significant bronchodilator response, though the percent change from 0.5 to 0.6 L is 20%. In this situation, the subject has a clinical response though he lacks a statistically significant spirometric response. Results of a bronchodilator test must be individualized and take a specific subject's clinical information into consideration.

Table 2
Guidelines on Interpretation of Significant Spirometric Responses After a Bronchodilator Challenge *(21, 14)*

Spirometric responses after bronchodilator challenge	
Parameter	*Post-bronchodilator response*
FEV_1 [a]	>200 mL increase *and* >12% increase from baseline
FVC[a, b]	>200 mL increase *and* >12% increase over baseline
$FEF_{25–75\%}$ [c]	>44 increase over baseline

[a] Either a response in the FEV_1 or FVC category satisfies the requirement.
[b] FVC can only be used if the expiratory time ratio post/pre <1.10 because a prolonged post-bronchodilator FVC may be due to an increased expiratory time and not due to a change in flow.
[c] Alternative parameters include a change in the $FEF_{25–75\%}$, though this is highly variable and requires that the FVC maneuvers be equivalent (FVC ratio of post/pre between 0.96 and 1.04) and the expiratory times be equivalent (expiratory time ratio post/pre >0.9) *(14)*.

Considerable variation exists in determining what constitutes a significant bronchodilator response. The most widely accepted criteria are listed in Table 2. These criteria assess changes in FEV_1, FVC, and $FEF_{25–75\%}$ from baseline pre-bronchodilator levels *(14, 21)*. Other criteria have looked at percent changes of expected values, though these methods are not the most widely used.

There are times when a bronchodilator does not result in a change in the FEV_1, FVC, or $FEF_{25–75\%}$, but a subject has a positive response in their airway mechanics. In these situations, measuring static lung volumes pre- and post-bronchodilator may be helpful. A positive lung volume response would be a decrease in Raw and FRC and an increase in VC (not FVC but VC). This is termed isovolumetric shift and is most often seen in subjects with severe asthma *(22)*. As detailed before, a lack of bronchodilator response may also be seen in subjects who took medication before testing, if subjects are refractory to medications, if irreversible obstruction exists, or if mucous plugging with atelectasis exists.

BRONCHOPROVOCATION CHALLENGE TESTING

Bronchoprovocation testing (BT) is used when a subject suspected of having asthma has pulmonary function tests which do not help confirm the diagnosis. It is also used in settings when occupational asthma is suspected and a particular agent is thought responsible. Airway smooth muscle contracts to noxious stimuli in all people when exposed to high enough concentrations. When the degree of responsiveness exceeds what is noted in normal subjects, it is called airway hyperresponsiveness (AHR). AHR is commonly seen in asthma, but it is not specific to asthma as AHR is also seen in other disorders (congestive heart failure, cystic fibrosis, allergic rhinitis, recent upper respiratory tract infections, and COPD). In asthma, however, the level of AHR is often exaggerated compared to these other situations making it a very sensitive test. Thus, a negative BT virtually excludes active asthma as a cause of breathlessness. A positive test is helpful to make a diagnosis of asthma but only in the context of compatible clinical features.

Table 3
Contraindications to Methacholine Challenge Testing. Adapted From the American Thoracic Society Guidelines for Methacholine Challenge and Exercise Testing – 1999 *(24)*

Absolute	*Relative*
• Severe airflow limitation (FEV <50% predicted or <1 L) • Myocardial infarction or stroke in past 3 months • Uncontrolled hypertension ◦ SBP>200 ◦ DBP>100	• Moderate airflow limitation (FEV_1 <60% predicted or <1.5 L) • Inability to perform acceptable spirometry (may perform plethysmography) • Current use of cholinesterase inhibitor medication (for myasthenia gravis) • [a]Recent bronchodilator use (including caffeine) just prior to testing

[a]Recent bronchodilator use is a relative contraindication as it may confound the results of the test by preventing an accurate assessment of the degree of bronchoconstriction. Bronchodilator use prior to testing may also render a subject less responsive to bronchodilators given to reverse methacholine-induced bronchoconstriction.

Several agents are used to conduct BT. For nonspecific testing, the most commonly used agents are methacholine or histamine. These directly act on the smooth muscles and airway microvasculature to cause bronchoconstriction. Other direct agents include leukotrienes and prostaglandins *(23)*, though these are rarely used outside research settings. Guidelines for administration of methacholine, technician training, and interpretation are summarized in the 1999 ATS statement *(24)*.

Methacholine (MCh) is the most commonly used nonspecific BT in the United States. When the clinical pretest probability for asthma is 30–70%, a MCh challenge test has a very high sensitivity and negative predictive value *(25)*. Briefly, subjects start a BT with baseline pulmonary function tests. If moderate to severe obstruction is present on initial spirometry, MCh testing is not continued (for a list or absolute and relative contraindications to BT, *see* Table 3). If baseline spirometry shows mild to no obstruction, MCh is given in sequentially higher doses followed by spirometry after each dose. If the FEV_1 falls by ≥20% after a MCh dose, and this reduced FEV_1 persists, the test is terminated. The MCh concentration at which the FEV_1 falls by ≥20% is called the PC20. A test is considered positive if the PC20≤4 mg/mL, borderline from 4 to 16 mg/mL and negative at >16 mg/mL. If a PC20 is <1 mg/mL, the test demonstrates moderate to severe AHR *(24)*. These interpretations are only valid if each spirometric maneuver is of good quality and the obstruction resolves after a bronchodilator is administered. A sample positive methacholine challenge test is shown in Fig. 9.

At times subjects cannot perform spirometry to note changes during BT. In these situations, airway resistance (Raw) and specific conductance (sGaw) can be measured by plethysmography. If a reduction in Raw or sGaw of 45% is noted to BT, the test is considered positive *(24)*. Comparisons between spirometry and plethysmography for detecting AHR are limited, but a recent study suggests that plethysmography may be more sensitive than spirometry to detect AHR (9) possibly due to Raw being independent of sex and height (Table 3 and Fig. 9).

Other BTs involve nonselective exercise testing and selective testing with specific compounds. These are generally performed in specialty centers, but familiarity with

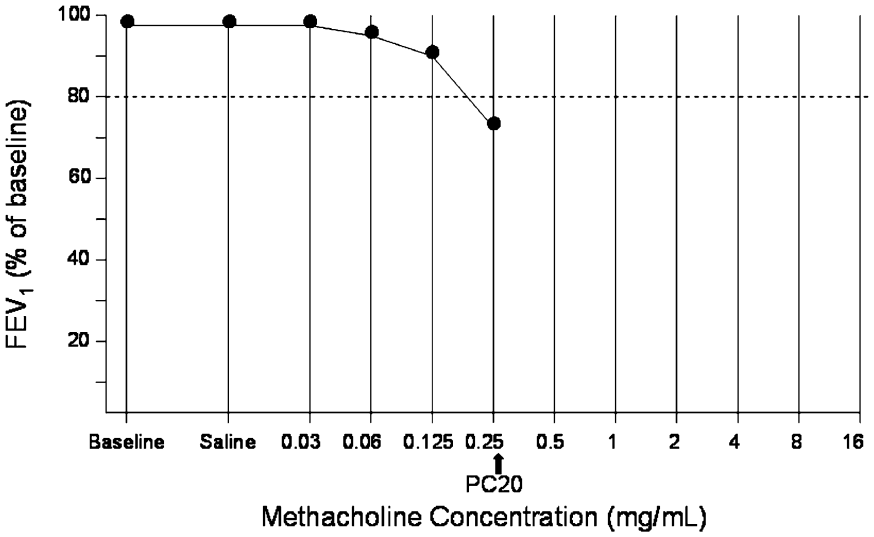

Fig. 9. Methacholine bronchoprovocation testing. This figure represents the 2-min tidal breathing protocol: baseline FEV_1 is obtained and repeated using nebulized saline. This is followed by increasing concentrations of methacholine. At each level, the subject breathes nebulized drug for 2 min by quiet breathing. An FEV_1 is obtained 30–90 s afterwards (optimally the FEV_1 is repeated two to three times). Increasing concentrations of methacholine are used until a decrease of 20% or more in the FEV_1 is seen (*dashed line*). The methacholine dose required to cause the 20% decline is the PC20 (*black arrow*). Once PC20 is reached, the test is terminated. Doses <1 mg/mL are positive for moderate to severe bronchial hyperreactivity (AHR); 1–4 mg/mL mild AHR; 4–16 borderline AHR; and >16 normal AHR.

their use may be important. In asthmatics, exercise can elicit bronchoconstriction through airway cooling and evaporation which lead to mast cell activation, sensory nerve triggering, and prostaglandin and leukotriene release *(26)*. Some subjects develop asthma symptoms only with exercise – exercise-induced bronchoconstriction (EIB). When testing for EIB, baseline spirometry is performed followed by an exercise regimen on a cycle or treadmill. The goals of exercise are a target heart rate of 80% maximum or ventilation of 40–60% maximum voluntary ventilation (calculated as $FEV_1 \times 35$). The test should span from 4 to 8 min, and spirometry is obtained every 5 min over the 30 min following exercise. The test is positive for EIB if the FEV_1 declines by 15% *(27)*.

Specific compounds may be used in BT to evaluate for occupational asthma and asthma due to specific exposures (i.e., aspirin-induced). These tests are less sensitive than the nonselective MCh test, but they are much more specific. Agents used include specific aeroallergens (pollens and molds), isocyanates, salycylates, other NSAIDs, and a variety of food additives. These tests are mainly performed at specialty centers.

Misinterpretation of Bronchoprovocation Testing

Several things can confound BT interpretation. Recent bronchodilator or inhaled corticosteroid use can offset the bronchoconstricting effects of MCh or exercise. Subjects should suspend their respiratory medication use for 24–48 h prior to testing provided it is safe to do so. Also, exercise performed within 4 h of an exercise test may make the airways unresponsive to EIB and elicit a false-negative result during exercise testing.

Subjects should not perform vigorous exercise prior to testing. When determining the response to specific compounds during an evaluation to occupational asthma, a positive result is specific but a negative result does not rule out occupational asthma. Compound selection may be very difficult and pinpointing the exact agent responsible for causing occupational asthma may be near impossible.

EVALUATION OF ASTHMA: THE THERAPEUTIC REGIMEN AND PROGRESSION OF DISEASE

The National Heart Lung and Blood Institute has published guidelines on the management of asthma that involve a step-wise escalation and de-escalation of therapies *(2)*. The guidelines recommend periodic assessment of asthma control after changing therapies which include objective lung function testing. The pulmonary function laboratory can be used to document longitudinal changes in lung function, and it can be used to identify subjects who are not controlled despite a seemingly optimal mediation strategy. For example, subjects with severe asthma may not perceive a loss of asthma control until their lung function is dangerously poor *(28)*. Despite their lack of symptoms, spirometry may demonstrate a progressive FEV_1 decline and prompt more aggressive therapy. Additionally, identification of irreversible airflow obstruction in asthmatic subjects may alert a clinician that chronic airway remodeling has occurred and the therapeutic regimen needs intensification. Just as several blood pressure readings are more helpful than a single one, serial lung function tests provide a robust assessment of disease course in asthma.

LABORATORY INDICATIONS FOR HOSPITALIZATION DURING AN ACUTE ASTHMA EXACERBATION

As discussed in several prior sections, an acute exacerbation of asthma can be a life-threatening event. The combination of spirometry (often as a peak expiratory flow rate, PEFR) and arterial blood gas monitoring can help with triage decisions. Specifically, if the PEFR is 50% of the patient's personal best, the FEV_1 is <1 L, the $PaCO_2$ is normal or elevated (≥ 40 mmHg), hypoxemia is present, the patient will likely require hospitalization and close monitoring. *See* Table 1 for more information.

CONCLUSION

The aims of this chapter were to familiarize the clinician with the role of the pulmonary function testing laboratory in the diagnosis and management of asthma. As asthma is an extremely common disease cared for by many clinicians and ancillary healthcare providers, a good understanding of available tests is indispensable. By the end of this chapter, the healthcare provider should be able to identify: the key tests to diagnose and monitor asthma; the major spirometric and lung volume abnormalities which suggest asthma; causes of misinterpretation of pulmonary function tests; the components of a bronchodilator challenge; the gas-exchange abnormalities on arterial blood gas which signify impending respiratory failure; and the utility of the lab in assessing disease control and course over time.

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4 Diagnosis and Management of Allergic Disease

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Contents

KEY POINTS

- Airborne allergens and viral respiratory infections are the most important environmental factors for the development, persistence, and severity of asthma.
- Sensitization and exposure to the dust mite and *Alternaria* are important factors in the development of asthma.
- Exposure to the cockroach allergens in the inner-city dwellings is a major cause of allergen sensitization and a risk factor for the development of asthma.
- An allergic reaction in the airways, caused by the natural exposure to the allergens, has been shown to lead to an increase in inflammatory reaction, increase in bronchial hyperresponsiveness, and increased eosinophils in the bronchoalveolar lavage.
- Important allergens involved in the development of asthma appear to be inhaled.
- Chronic asthma is largely associated with exposure to the allergens that occur indoor (dust mite, cockroach, cat, and dog).
- Food allergens are not a common cause of allergic asthma.
- Cat allergen can be transferred from place to place on the clothing of people living in a home with a cat.

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- Effective allergens avoidance requires a multifaceted approach.
- Controlled studies of immunotherapy have demonstrated reduction in asthma symptoms caused by exposure to grass pollens, cat, house dust mite, ragweed, *Cladosporium* and *Alternaria*.
- Treatment of allergic rhinitis with intranasal glucocorticoids in patients with asthma may reduce morbidity.

INTRODUCTION

The association of asthma and allergies has long been recognized. Many recent studies have confirmed that sensitization among genetically susceptible populations to certain indoor allergens such as dust mite, animal dander (cat and dog), cockroach, and to outdoor molds such as *Alternaria* is a risk factor for developing persistent asthma *(1)*. For asthmatic children and adults, chronic exposure to household allergens is associated not only with a higher risk of respiratory symptoms and increased medication use, but also with impaired lung function, increased risk of respiratory viral infections, and increased risk of hospitalization for asthma *(2)*. Sensitization to the outdoor allergens such as grass and ragweed pollens has been associated with seasonal asthma and a rise in emergency department visits and hospitalizations due to acute asthma exacerbations.

It is widely accepted that the importance of the inhalant sensitivity as a cause of asthma declines with advancing age. Work place exposure to the allergens such as laboratory animals, chemicals, and dust can also induce asthma. This effect should be distinguished from aggravation of preexisting asthma. Determination of sensitivity to a perennial allergen is usually not possible by history alone. Allergy skin testing or in vitro-specific serum IgE tests are helpful in determining the presence of a sensitivity to a specific allergen.

Effective environmental control and allergen avoidance requires a careful multifaceted approach by the patient and family. Allergen immunotherapy should be reserved for patients whose symptoms occur all year long or during a major portion of the year, or in whom controlling symptoms with pharmacologic management is difficult. The risks of developing a systemic reaction from an allergy shot is increased in patients with asthma.

THE ROLE OF ALLERGIES IN ASTHMA

Youth Risk Behavior Survey (YRBS) provides a national source for self-reported asthma prevalence among U.S. high school students *(3)*. The findings in this report indicate that 18.9% of high school students reported lifetime asthma and 16.1% had current asthma. Among students with current asthma, 37.9% reported having had an asthma episode or attack during the 12 months preceding the survey. In the 2003 National Health Interview Survey (NHIS), parents reported that 14.5% of their children aged 14–17 years had lifetime asthma, 8.9% had current asthma, and among students with current asthma, 57.0% had had an asthma episode or attack during the preceding year.

The role of allergy in the epidemiology, pathophysiology, and treatment of asthma has been increasingly appreciated in the last several years. According to the data from

the European Community Respiratory Health Survey (ECRHS), International Study of Asthma and Allergies in Childhood, and other such studies, it is obvious that asthma prevalence is increasing worldwide and is generally more common in the Western Countries as compared to the developing world. This appears to correlate with a perceived increase in allergies over the same time period, in the same geographical regions. As a result of the findings in the international asthma prevalence patterns, recent research has focused on exposure to allergens, environmental tobacco smoke (ETS), air pollution, and other factors that may contribute to the development of asthma.

Both allergic rhinitis and asthma are heritable conditions, and are defined to some extent as conditions that result from gene-environmental interactions. It is loosely estimated that the risk of an offspring developing asthma is 50% if one parent has asthma, and 75% if both parents have asthma. Intuitively, this may help us understand why there is an increasing incidence of asthma in the developed world. Allergies are also heritable, and various theories have been presented to explain the link between asthma and allergies. The role of early exposure to foods and animal dander in either the protection from, or conversely, the development of, allergic hypersensitivity is proposed in the "hygiene hypothesis," but recent evidence has shown that the hygiene hypothesis is not as straightforward as once previously believed.

ALLERGIC RHINITIS AND ASTHMA LINKS

The Atopic March

The atopic march describes a phenomenon commonly seen in atopic individuals. Atopy defines a genetic predisposition to developing allergies. In these patients, early exposure to food allergens leads to the development of atopic dermatitis. Clinically this presents as eczema, frequently very early in life. About 1/3 of these patients have demonstrable food-specific serum IgE levels. Eczema resolves in about 50% of patients by 5 years of age. Children who are atopic may also develop allergic asthma, followed somewhat later by allergic rhinitis. Total serum IgE levels are higher in children who have eczema. With age, these IgE levels generally fall. Allergic symptoms can continue along with asthma and eczema through childhood into adulthood in some patients (Fig. 1).

The One Airway Hypothesis

In the last several years, numerous epidemiological and clinical studies have confirmed the previous observation of the links existing between the upper and lower airways. This has been referred to as the single-airway, one airway, unified airway, or "one airway, one disease" theory. This hypothesis has been used to explain the asthma-rhinitis link. In patients with allergic rhinosinusitis or allergic rhinoconjunctivitis, bronchial involvement, including spirometric defects, bronchial hyperreactivity, or both, may be found. Early bronchial involvement in patients with allergic rhinitis may easily be detected by performing simple spirometry. Based on this theory, the inflammation seen in the nasal passages is identical to that seen in the bronchial airways. A strategy combining the treatment of both allergic rhinitis and asthma appears to be optimal. Intranasal corticosteroids for the treatment of rhinitis may reduce the

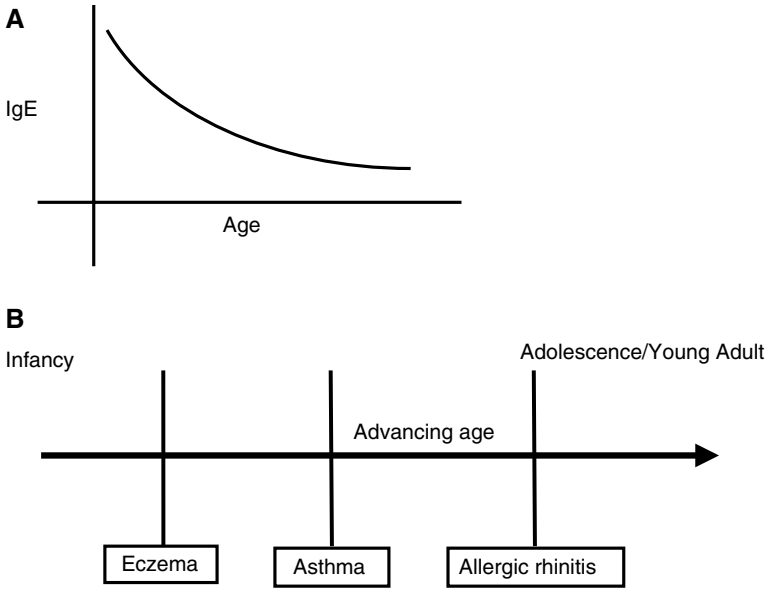

Fig. 1. The atopic march (**A**) Schematic representation of serum IgE levels as a function of age in atopic children (**B**) Clinical manifestations of atopy as a function of age (the atopic march).

morbidity in asthmatics. A future therapeutic strategy that involves integrated treatment of the two diseases will help decrease the burden of asthma in patients with allergic rhinitis *(4)*.

The Hygiene Hypothesis

The hygiene hypothesis was proposed to explain the observation that children born and raised in European farm environments tend to have lower rates of allergic sensitization and asthma. It is also frequently used to explain why people living in developed countries have higher rates of allergic sensitization and asthma. The theory is that with modernization comes better hygienic conditions and less infection. With less infection to deal with, the immune system undergoes a paradigm shift from a predominantly Th1 system to a system skewed towards Th2 associated immunological characteristics, including the development of allergies. Studies have been done to determine if owning a pet, such as a cat or dog, will lead to less sensitization. The results of these studies are somewhat controversial. Moreover, if infection and poor hygiene is supposed to protect against infection, why is it that asthma and allergies appear to be more prevalent in the poorer sections of urban areas? Thus, while the hygiene hypothesis has been a popular theory in recent years, it is clear that this is not the complete answer.

Thunderstorm Asthma

Thunderstorm asthma is a phenomenon that has been reported in conjunction with grass pollen allergy *(5)* or mold (particularly *Alternaria*) spore allergy *(6)*. While the mechanism is still not completely clear, it is postulated that large-scale thunderstorms

result in the release of high levels of respirable particles and that the condition develops in atopic individuals who have existing hyperreactive airways. Other conditions that are necessary appear to be a mature thunderstorm with strong downward drafts and dry, cold outflows. The thunderstorms gather up mold spores or pollen grains into a cloud base, whereupon rupture of the particles is more likely, and then the downdrafts push the respirable particles down and out ahead of the rain, leading to a concentration of allergenic particles in the respirable zone. The rupture of the pollen grains leads to smaller particles which potentially can penetrate deeper into the airways. Thunderstorm asthma is often observed to occur simultaneously in a large number of sensitized individuals who are outdoors during the period of highest exposure.

Dry Air Spora and Asthma

When wind speeds are high and humidity is low, there are some species of fungi whose spores can be detached and dispersed easily. Fungi that contribute to dry air spora include *Cladosporium, Alternaria, Dreschlera, Epicoccum, Curvularia, Pithomyces,* and Smuts. In dry, windy conditions, the spores remain airborne for a longer period of time and can contribute to development of allergic rhinitis and asthma. Spores tend to sediment as a function of size, weight, impaction, and rain. Allergies and asthma can be increased in conditions that favor the dispersion and continued suspension of fungal particles. Conversely, humid conditions can result in a predominance of "damp-air" spora, consisting of a concentration of spores primarily of the *Ascospores* genus that are in a band of air low to the ground. Other factors that can affect the type and number of spores include climate, temperature, season, and time of day. There is a diurnal variation in which fungal spores tend to be present in higher concentrations later in the day. Ballistic dispersion is another way that spores can be dispersed that is based upon the impact of rain drops on the easily fractured spore apparatus, the spores being released into the air within tiny water droplets.

Climate Change, Allergies, and Asthma

The role of climate change in allergies and asthma is not yet clear. Air pollution, which can be a direct trigger for asthma, may also impact the incidence of allergies and asthma by impacting changes in climate. Climate change is known to have a wide range of ecological effects, including changes in vegetation, insect propagation, animal habitats, the food chain, ocean flora, and the type and number of sea dwelling creatures. All of these can lead to changes in environmental exposures, including aeroallergens, pollutants, and microbials, and may even impact early sensitization patterns in atopic individuals.

COMMON ALLERGENS

Important allergens for asthma in children and adults appear to be inhaled. Food allergens are not a common cause of asthma and are more likely to involve pulmonary symptoms when they occur in the context of anaphylaxis. Inhalant allergens causing asthma can be classified into indoor and outdoor allergens. A simplistic view of this distinction is that indoor allergens, including animal dander, dust mite, cockroach, and molds (Table 1), generally lead to year-round symptoms, while outdoor allergens, including grass, tree, weed pollens, and outdoor mold spores (Table 2), lead to more

Table 1
Indoor Allergens Associated with Asthma and Allergic Rhinitis

Class	*Species*	*Allergens*	*Comments*
Dust mite	*Dermatophagoides Pteronyssinus*	*Der p1 , Der p2, Der p3*	*D Pteronyssinus and D farina* are the two most common species of house dust mite associated with asthma. Requires optimal humidity 55–75% and optimum temperature 65–80°F (18°C)
	Dermatophagoides farinae	*Der f1, Der f 2, Der f3*	
	Blomia tropicalis	*Blo t 5*	
	Euroglyphus maynei	*Eur m 1*	
Cat	*Felis domesticus*	*Fel d 1 (major allergen)*	Found in cat pelt, saliva, basal squamous epithelial cells, and sebaceous gland secretions. Male cats have higher level than do female cats. Antigens are found as small aerosolized particles
		Albumin	Minor allergen
Dog	*Canis familiaris*	*Can f 1*	Is detected in the dog coat and saliva. Amount produced by the different breeds vary, but no breed is known to exist without antigen
		Albumin	Minor allergen
Cockroach	German cockroach (*Blatella germanica*)	*Bla g 1 and Bla g 2*	Allergens are derived from the bodies and feces
		Bla g 1	
	American Cockroach (*Periplaneta americana*)	*Per a 1*	Allergens are found in high concentration on the floors, carpets, counters, and other flat surfaces especially in the areas where food is stored or discarded
	Oriental Cockroach (*Blatella orientalis*)		
Rodents	*Ratus norvegicus*	*Rat n 1A, Rat n 1B*	Major problem in lab workers
	Mus muscularis	*Mus m1, Mus m 2*	Prealbumin and Euglobulin
	Guinea Pig, Gerbil, and Hamster	Not well characterized	Both rat and mouse allergens are detected primarily in the urine and are readily airborne
			Major source for other rodents is probably urine

Rabbit	Rabbit	Allergens have not been well characterized	Major source seems to be saliva and fur
Fungi	*Aspergillus* *Penicillium* *Cladosporium*	Few fungal antigens have been characterized to determine their precise chemical nature *Asp f 1* *Alt a 1*	Prevalent in the humid climate, shaded, and unkempt buildings
Plants	Plants and plant products	Pollens	Outdoor pollens can enter the indoor environment during the peak allergy season by way of ventilation, open doors, and windows, and on the clothing and pets (dogs). Indoor plants are usually not highly allergenic
Birds		Avian proteins in feather extracts may be contaminated with dust mite	Indoor exposure from the feather pillow, comforters, and quilts Occupational exposure in the egg processing and bird breeding plants not uncommonly results in occupational asthma

Table 2
Outdoor Allergens

Class	*Scientific name*	*Common name*	*Zone*
Trees	*Olea europa*	Olive	Western United states
	Quercus alba	Oak	US, Mexico, South America, Southern Europe
	Platanus Occidantalis	Sycamores	Eastern US, Mexico, Canada
	Betula verrucvosa	White Birch	Northwest and Eastern US, Scandinavia
	Alanus gultinosa	Black alder	Northwest and rocky mountains US, and Scandinavia
	Acer negundo	Box elder	Eastern US, Canada, Mexico
	Juglans californica	Walnut	Western North America
Grasses	*Cynodon dactylon*	Bermuda grass	Common in Europe and North and South America and Southeast Africa
	Agrostis alba	Red top grass	Canada, US, Europe
	Dactylic glomerata	Orchid grass	US, UK, France, Germany, and Canada
	Phalum pratensis	Timothy grass	US, Canada, Europe
	Lolium perenne	Rye grass	US, Canada
	Poa pratensis	Blue grass	US, Canada, Europe
Weeds	*Ambrosia*	Ragweed	Eastern US
	Plantago lanceolata	Plantain	US
	Salsola kali	Russian thistle	Warm barren soils
	Artemisia gnaphaloides	Mugwort	Mexico, Canada, US

seasonal allergens. It should be noted that depending on geographic location, there may be significant exceptions to this. A sample of allergen sources is illustrated in Fig. 2.

Indoor Allergens

Common Pets

All warm-blooded animals including pets (cat, dog) and rodents produce dander, urine, feces, and saliva that can cause allergic reactions. There is recent evidence that exposure to cat allergens can be significant in homes and even in schools and offices that do not have these animals. In the United States, it has been estimated that there are >105 million cats and dogs. The transfer of allergens from one person's clothes to another in the office or school environment has been documented. When taking a history, the degree of exposure to a pet is frequently underestimated by patients, either consciously or subconsciously, thus making the diagnosis and treatment of pet-related allergic and asthma problem more difficult. Pets not only cause acute allergic reaction, they are also responsible for chronic allergic inflammation, thus leading to persistent nasal, eye, and asthma symptoms. Sensitization to cats appears to be more common than dogs. Cat ownership is associated with high prevalence of asthma *(7)*. As mentioned above, it has been demonstrated in some studies that exposure to cats in the home at a young age may be associated with decreased sensitivity to cat.

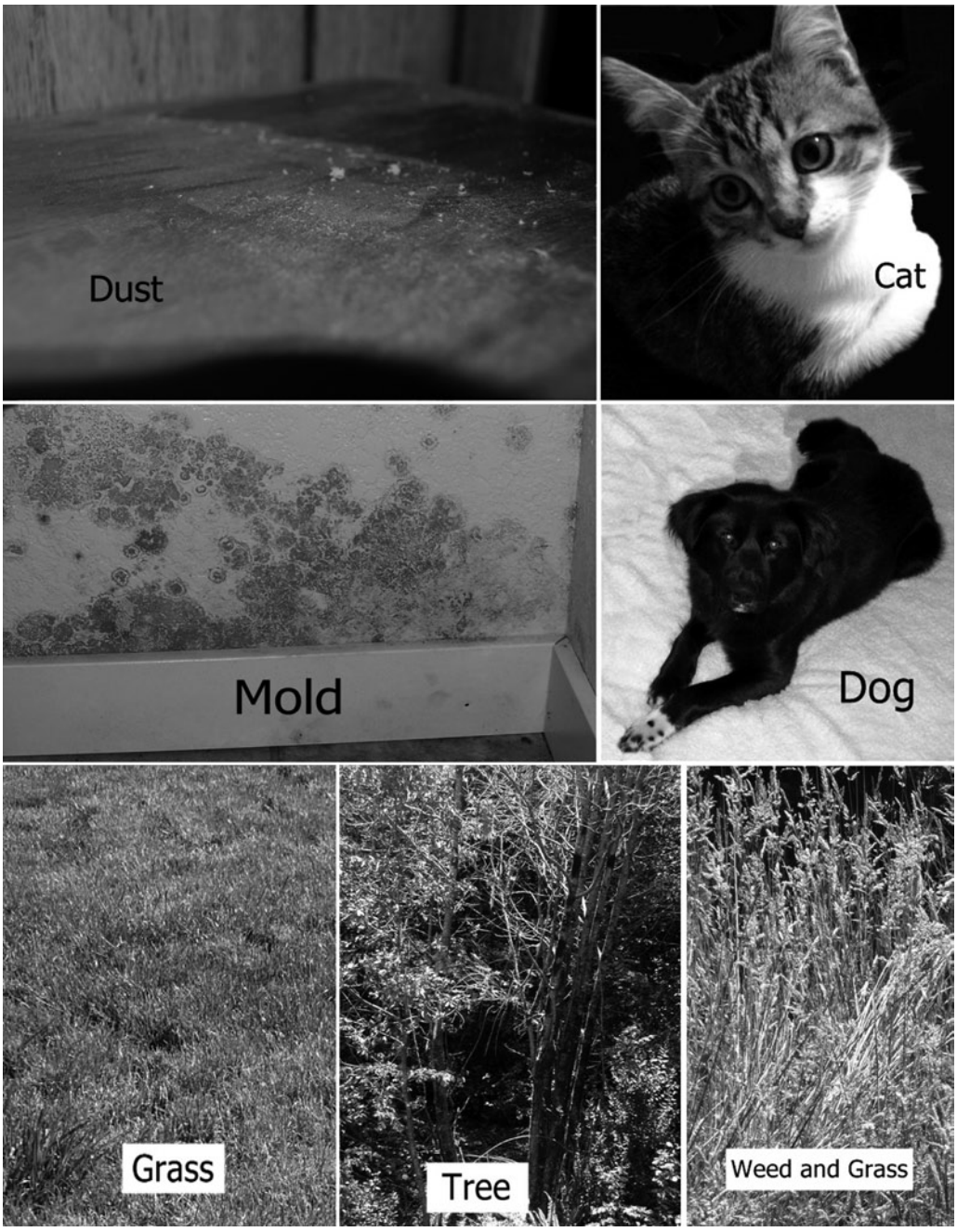

Fig. 2. Potential sources of common allergens.

Laboratory Animals

Approximately one third of the laboratory workers who are exposed to laboratory animals (rat and mice) develop allergic sensitization to these animals and approximately one third of these have symptomatic asthma. Those with a history of atopy and who

have the greatest exposure to the animals (such as cage cleaners and handlers) are most likely to become sensitized and develop asthma *(8)*. In some cases, the allergy or asthma can be so severe that continued exposure can be detrimental to the individual's health, and a change of occupation may be recommended.

Nontraditional Pets and Animals

With the rise in adoption of nontraditional pets into the US households, many cases of allergy to the exotic animals such as iguana, rodents, gerbil, rabbit, hamster, ferret, and monkey have been reported *(9)*. Therefore, clinicians should query patients for contacts with all types of household animals. Allergy to horses is also being reported more frequently. Most patients allergic to horses develop nasal and eye symptoms, but life-threatening asthma exacerbations have also been reported.

Dust Mite

In most temperate climates of the world, house dust mites are major source of multiple allergens. Mite allergens are highly sensitizing and exposure can induce allergic rhinitis, asthma, and atopic dermatitis in both children and adults. House dust mites belong to the suborder Astigmata and family Proglyphidae. Thirteen species have been found, but three are very common in homes around the world and within the United States and are major sources of allergens. These three species are *Dermatophagoides pteronyssinus, Dermatophagoides farinae, and Euroglyphus maynei*. *D pteronyssinus* and *D farinae* are the most prevalent mites found in the homes around the United States and worldwide. *Blomia Tropicalis* or the storage mite can be the prevalent mite in the subtropics.

The allergens associated with the dust mite fecal matter are enzymes that originate from the mite digestive tract. Other sources of mite allergens may be derived from mite saliva, body fluids, and disintegrated body parts after its death. A higher level of *Dermatophagoides pteronyssinus* antigen (Der p 1) has been associated with the asthma severity and is an independent risk factor for allergic asthma *(10)*. Epidemiological data suggest that exposure to dust mite antigen early in life is an important risk factor in the severity of asthma. Chronic exposure to house dust mite can have adverse effects on respiratory health of asthmatics.

Cockroach

Exposure and sensitization to cockroach allergen is associated with an increase in asthma morbidity in the inner cities in the United States and many other countries of the world including Central America, Europe, Japan, Thailand, and India. In the United States, the prevalence of cockroach allergy ranges from 17 to 41% in various studies involving both children and adults in inner-city populations. Exposure of children with a family history of atopy to cockroach antigens early in life contributes to recurrent wheezing and physician-diagnosed asthma. In the United States, high levels of cockroach allergens have been associated with low socioeconomic living conditions. Like dust mite, early exposure to the cockroach allergens is a significant predictor of sensitization and wheezing in the first year of life *(11, 12)*.

Indoor Molds

It is estimated that approximately 10 % of the population have IgE antibodies to common molds and about half of this population will at some point develop allergic disease and asthma as a consequence to the mold exposure. Association of asthma

symptoms upon exposure to the indoor molds is less clearly established. Exposure to the outdoor molds such as *Alternaria alternata* has been linked to the presence, persistence, and severity of asthma.

Allergic Bronchopulmonary Aspergillosis (ABPA) is a well-recognized entity that affects individuals with asthma and cystic fibrosis. The most common offending agent is *Aspergillus fumigatus.* Exposure to *A. Fumigatus* can occur from an indoor or outdoor source. Exposure to molds can also result in hypersensitivity pneumonitis, direct infection from the organism especially in the immune compromised host, and toxic irritant effects from mold by-products *(13)*.

Outdoor Allergens

Pollens

Pollens were among the first allergens identified. The capacity of the pollens to sensitize is universal, but the nature and number of pollens vary according to the geography, climate, and temperature (Table 2). Size of pollen grains generally varies from 10 to 100 μm, but there are exceptions. The predominant range of size of pollen grains explains why most deposition of pollen grains occurs in the eyes and nostrils causing allergic rhinitis and conjunctivitis. Some pollen allergens can, however, be carried on smaller particles, or the allergenic particle can be a fragment of the intact pollen grain, leading to both allergic rhinitis and asthma. As noted above, this is a significant mechanism in cases of asthma attacks that occur during thunderstorms.

In general, grass pollens are dispersed in early spring once the rainy season is over. But in the Pacific Northwest of the United States and Canada, the climate is favorable for a longer season and grasses may be responsible for cases of perennial allergic rhinitis. Grasses generally do not pollinate in very hot temperatures. Tree pollen seasons vary from region to region. Some curious pollination patterns exist, such as the pollination of mountain cedar in the south and southwest United States. However, in general, most trees pollinate in early spring and the fall. Weed pollens (especially ragweed) reach their peak levels in late summer and early fall. Exposure to tree pollens is usually associated with allergic rhinitis, while grass and ragweed pollens are associated with allergic rhinitis and asthma. Asthma symptoms usually begin after the development of persistent symptoms of allergic rhinitis *(14)*.

Outdoor Molds

Allergy to outdoor molds is also an important cause of asthma. Important molds include *Alternaria, Cladosporium, Penicillium, Aspergillus, and Helminthosporium.* The more important sources of allergen containing particles are the hyphae and not the spores (Table 3). *Alternaria* is one of the major aeroallergens in many parts of the world. Allergic sensitization to *Alternaria* has been linked to the airway hyperresponsiveness in children and is associated with persistence and severity of asthma. In addition to the effect of IgE-mediated mechanisms, molds can also produce chronic inflammatory changes through a variety of other mechanisms.

Other Outdoor and Indoor Occupational Allergens

Exposure to a large number of low molecular weight chemicals has been reported to result in an allergic response. Sensitivity to such chemicals may result in dermatologic,

Table 3
Common Outdoor Allergenic Molds

Spores Name	*Class*	*Grows on*	*Disease associations*
Alternaria	Fungi imperfecti	Plants	Allergic asthma
Cladosporium	Fungi imperfecti	Plants, decaying wood products	
Aspergillus	Fungi imperfecti	Soil, hay, and fruits	Asthma, ABPA, sinusitis
Penicillium	Fungi imperfecti	Soil, fruit, cheese	Rhinitis
Epicoccum	Fungi imperfecti	Soil, vegetables	Rhinitis
Mucor	Zygomycetes	Soil, animal waste	Rhinitis
Helminthosporium	Fungi imperfecti	Grain plants	Rhinitis

respiratory, or systemic disease. Generally, such exposure occurs in the industrial and manufacturing setting and not in the home or usual office environment. Anhydrides (used in plastic manufacturing), isocyanates (used in paint manufacturing factories), and ultrafine particles such as those found in diesel exhaust have been known to cause an asthmatic response *(15)*.

FOOD ALLERGIES AND ASTHMA

It is generally accepted that food allergies are not a common cause of asthma. However, food-induced anaphylaxis is a well-known condition, and respiratory symptoms can commonly be a component of anaphylaxis. Allergies to foods are more common in young children. The persistence of a food allergy is dependent, in part, on whether the antigenic determinant is presented as a linear or conformational epitope. Linear epitopes, such as those seen in peanut allergy, tend to lead to more persistent allergies. However, if the primary allergenic determinant is a conformational epitope, then children may "outgrow" their allergies. An example is milk allergy that develops in infancy. About 50% show resolution of their milk allergy by age 5, and an even greater percentage by adulthood.

DIAGNOSTIC TESTING

Skin Testing

In addition to a careful history and physical examination, skin testing is an important tool in the diagnosis of allergic disease. Skin testing to allergens is indicated to provide evidence of allergic sensitization to a specific trigger. The skin tests can be rapidly and efficiently performed in an office setting. High sensitivity and low cost make skin testing a very favorable option for the patient and the allergist. The number of skin tests should be determined on the basis of patient's age, history, environment, geographic location, and occupation. It is important to have an in-depth knowledge of local aeroallergens and their cross-reactivity with other botanically related species for proper interpretation of the test results and appropriate recommendations for environmental control

Table 4
Pros and Cons of Allergy Skin Testing

Pros	*Cons*
1. Easy to perform	1. Medications (antihistamines, β-blockers, and tricyclics) must be withheld
2. Quick results (results available within 15–20 minutes)	2. Cannot perform the tests if patient has skin disease or dermatographia
3. Less discomfort	3. Appropriate techniques must be applied
4. Easy to interpret the results	4. Little standardization of antigens
5. More specific and correlate better with the symptoms	5. Quality control is difficult
6. May perform more tests at one time	6. Rare systemic allergic reactions specially after intradermal testing
7. Low cost	7. Intradermal testing has decreased specificity and a higher incidence of false positives
8. Intradermal testing may be done which provides greater sensitivity	

and immunotherapy. The advantages and disadvantages of skin testing are outlined in Table 4.

The two types of skin testing methods used today include prick (epicutaneous) testing and intradermal or intracutaneous testing. Results are recorded as a wheal (central area of swelling) and flare (surrounding erythema) response. A positive and negative control should always be done. The positive control is usually done with a 6.0-mg/ml of histamine base, and the negative control can be saline, or glycerine, or the diluents used in the extracts. For better clarity and standardization, the size of the wheal and flare should be recorded in millimeters. Any test where the wheal is 3 mm greater than the negative control is generally considered to be positive.

Intradermal tests are usually performed when the prick tests are negative. They are more sensitive and less specific when compared to the skin prick tests. Systemic reactions can uncommonly occur with skin prick tests. On the other hand, intradermal testing has a higher risk of associated systemic reactions. Therefore, they should be reserved for those patients who test negative on skin prick testing *(16, 17)*.

Skin Prick Testing Devices

One must also be familiar with the skin testing devices used for skin testing as there are variable responses to the different devices used. The evolution of the skin test device begins back in 1865, when Charles Blackley first used a lancet dipped in allergen extract to perform the first skin prick test. Over the years, new devices have been introduced, and many have come and gone. Many of the early ones were single test devices, and they varied in the degree of skin penetration and angle of penetration. Techniques have also varied, from a puncture action to a prick action or twisting action. Some devices, when used in a certain way, have had increased sensitivity, but with that usually came decreased specificity. In many instances, false positives may be due to the nonspecific reaction of skin to the trauma of the test.

More recent additions have including devices that are capable of administering several tests per device. This has been welcomed by patients because this decreases the time required to administer the tests and seems to be associated with less discomfort to patients. The multiple test devices also can be used with greater ease in pediatric patients. Although pain may be greater for a single application of the device, the fact that the multiple skin test devices require fewer applications may make the skin testing experience overall more tolerable. A list of devices that have been used over the years is shown in Table 5. Currently, the most commonly used devices include the Morrow Brown needle, the GreerPick, and the Duotip, and the multiple test devices include the Multitest, Multitest II by Center Laboratories, and the Comfort Ten by Hollister-Stier. There were frequent studies done in the 1980s and 1990s to compare the sensitivity and specificity of skin test devices *(18–20)*. More recent studies are relatively uncommon, with the three notable studies having been done in 2005 *(21)* , 2006 *(22)*, and 2007 *(23)*.

In Vitro Testing

In vitro-specific IgE tests are an alternative to skin testing. The sensitivity of in vitro tests is lower than that of skin testing, but in vitro tests are steadily improving. In vitro tests are designed to measure allergen-specific IgE, and the presence of allergen-specific IgE is interpreted as positive sensitization to the allergen tested. However, there are limitations to these in vitro-specific IgE tests and interpretation of the results should include consideration of the patient's history. The total IgE level may also impact the correct interpretation of an in vitro test. Highly elevated total IgE levels may be associated with numerous false positive results *(24)*. The relative pros and cons of in vitro-specific IgE testing are outlined in Table 6 *(25)*.

Radioallergosorbent test (RAST) was developed in 1967 and was the first serological assay to detect allergen-specific IgE. RAST was a radiolabeled antibody detection system that used allergen bound to a cellulose solid phase to bind specific antibody from human serum *(26)*. Newer in vitro-specific IgE assays have since replaced the older RAST. The term "RAST" is still informally used by many healthcare practitioners, although none of the FDA-approved in vitro-specific IgE test systems that remain in use have a radiolabeled analyte and the use of this outdated term is discouraged. It should also be mentioned that the term "RAST" is often used by nonallergists to order specific IgG or IG4 tests, but these "IgG-RASTS" have no relevance to allergy, and in fact, have no clinical use or value at all.

The three FDA-approved laboratory-based in vitro-specific IgE assays in clinical use are the ImmunoCap system from Phadia (Pharmacia, Uppsala, Sweden), the Hycor-MP system from Hycor-Agilent, and the Immulite system from Siemens Corp *(25)*. Each of these assays uses a variation on the enzyme-linked immunosorbent assay. Briefly, an antigen of interest is coupled to a solid support, which is then incubated with patient serum. Specific IgE in the patient's sample binds to its epitope on the support-bound antigen and remains attached, while serial washes remove unbound material. Subsequently, a second anti-human IgE antibody bearing an enzyme moiety that is capable of cleaving a substrate to a colored product is added and allowed to bind to the IgE that remains bound to the antigen on the support. The enzyme substrate is added, a colored product is generated, and the intensity of the color is measured, with that value being converted to units of specific IgE for reporting to the ordering practitioner.

Table 5
Devices for Epicutaneous Skin Testing

Device	*Manufacturer*	*Construction*	*Tests per device*	*Still in use*	*Comments*
Accuset	ALK-Abello		Single	Yes	Skin penetrated at an angle, with a flick-prick motion
Allergy-Pricker	Hollister-Stier	1.0 mm point and 25 degree inclusive angle	Single	No	Early device, less discomfort than blood lancet but no longer used
Bifurcated needle	Wyeth	Two-pronged needle, easy delivery of vaccine	Single	No	Original designed for smallpox vaccinations. A two-pronged needle similar to the Duotip
Blood lancet	Sydeco	4.0 mm point, base width of 1.8 mm	Single	No	Early device no longer widely used
Comfort Ten	Hollister-Stier	1.2 mm stainless surgical steel lancets	10	Yes	Allows for ten test to be performed simultaneously. Reliability perhaps inferior to multitest or multitest II
Derma-pik	Greer	Six tine applicator	Single	No	May be associated with significant nonspecific reactions due to twist technique. Appears to have been replaced by GreerPick
Duotip test	Lincoln Diagnostics	Two precision points	Single	Yes	Two precision points provide for greater reliability
Duotip test II	Lincoln Diagnostics	Two precision points	Single	Yes	Improved grip and added circular collar for easier use
Greer Pen	Greer		Single	No	
Greer Pick	Greer	Self-loading single site device with a six time applicator	Single	Yes	Can be used with 3 different techniques: Prick, puncture, or scratch
Greer Track	Greer			No	Unfavorable results in head to head study

(*Continued*)

Table 5 (*Continued*)

Device	*Manufacturer*	*Construction*	*Tests per device*	*Still in use*	*Comments*
Morrow brown needle	Morrow Brown Allergy diagnostics	NAS styrene methyl methacrylate	Single	Yes	Excellent track record, standard to which other devices are compared
Multitest	Lincoln diagnostics	copolymer with	8	Yes	Popular device. Reliable results
Multitest II	Lincoln diagnostics	triangular point	8	Yes	Popular device. Reliable results
Phazet	Pharmacia	An allergen lancet with a tip of 1.0 mm coated with freeze-dried allergen	Single	No	Used in the 1980 s. Had a wet method and a dry method
Prick Lancetter	Hollister-Stier	Disposable single-use lancet	Single	Yes	
Quantitest	Panatrex (ALO)	6-prong applicator with 3 faces	Multiple	Yes	
Quintest	Hollister-Stier	Stainless surgical steel tips (1.2 mm)	5	Yes	Linear design for constant pressure
Quintip	Hollister-Stier	Stainless surgical steel tips (1.2 mm)	Single	Yes	Applied by perpendicularly downward pressure (puncture technique)
Sharptest	Panatrex		Single	Yes	Increased pain in 2005 head to head study. Puncture technique
Skintestor OMNI	QTI/Greer	Self-loading multiple skin test device	10	Yes	Appears to give less reproducible results when compared with the Multitest device
Small pox needle	Variable	Usually steel, many different devices	Single	No	Some devices used for smallpox vaccination were tried in allergy skin testing in early years
Stallerkit				No	Limited information available
Stallerpoint	Stallergenes	Disposable methacrylate point	Single	Yes	

Table 6
Pros and Cons of in Vitro Testing

Advantages	*Disadvantages*
1. No risk of systemic reactions 2. Test can be performed if patient has skin disease 3. No need to withhold medications	1. Delay in obtaining the results 2. Lack of visible "proof" for the patients 3. False negative tests cannot be confirmed by a back-up technique (as opposed to skin prick test negative patients who have the option of intradermal tests)

A fourth FDA-approved in vitro-specific IgE assay device (Phadia's ImmunoCap Rapid) was approved in January of 2010 for point-of-care binary determinations of the presence or absence of laboratory evidence for atopy. The device is intended for primary care offices *(27)* and may be a valuable tool for identifying those patients with atopy that may then benefit from further specialty referral.

Knowledge of regional aerobiology is helpful in the selection of in vitro-specific IgE tests. At some laboratories, as well as the ImmunoCap Rapid point of care device, a predefined panel of antigens is available, but practitioners should familiarize themselves with its content to ensure the appropriate coverage. Similarly, healthcare providers should familiarize themselves with the specific assay that their clinical laboratory site uses, as the three immunoassays may measure different epitopes or different populations of specific IgE and the values given by any one assay system cannot be extrapolated to the other two. In the evaluation of wheezing related to a suspect food, for example, values that are intrinsically predictive of clinical allergy have been defined for a limited set of antigens, but these values are only applicable to the ImmunoCap assay system *(28)*. The reasons for these differences remain unclear and may be related to the specific allergen preparation used for the solid support or other factors. While in vitro IgE values are not comparable among different assay systems, they do demonstrate fair reliability within a given assay.

Total Serum IgE Testing

The measurement of total IgE has been standardized against the World Health Organization 75/502 international serum human IgE reference preparation, a globally defined reference marker. However, with the notable exception of evaluation for allergic bronchopulmonary mycoses *(29, 30)*, the measurement of total IgE is of limited utility in the diagnosis of allergic disease and serves a clinical role primarily in the determination of a patient's suitability for omalizumab, as well as the proper dosing regimen. Current joint diagnostic testing guidelines from the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology additionally recommend the measurement of total serum IgE to assist in identifying nonspecific binding in in vitro-specific IgE antibody assays performed on patients with very high IgE levels.

In Vivo Diagnostic Provocation Testing

When a conflict occurs between the clinical history and primary diagnostic tests such as in vivo skin testing and IgE-specific test, provocation challenge tests may be useful to establish the patient's true sensitivities. Bronchial and nasal provocation challenges are the techniques used to identify a relationship between the inhaled allergen and a change in the patient's bronchial and or nasal physiology, respectively.

Bronchoprovocation studies involving the use of methacholine or histamine are particularly useful. Allergen extract can also be administered in increasing doses to elicit bronchoprovocation response. Allergens induce changes in pulmonary functions as a result of direct activation of mast cells in the lungs. A positive provocation response is reported as the concentration of allergen that results in 20% drop in FEV1 from the baseline (PC20). Aeroallergen nasal challenge is also considered a safe technique to establish clinically relevant allergies in asthmatic children *(31)*.

Nasal Cytology

Nasal cytology involves obtaining a smear from the nasal mucosa and to visualize the cells on the smear by conventional microscopy in order to identify the presence of eosinophils. Some patients may not have detectable IgE by in vitro-specific IgE testing, but may still experience exacerbation of allergic rhinitis or asthma when exposed to the suspected allergen. It is possible that the mechanism in these cases involves a non-IgE-mediated pathway, whereby an eosinophil-driven mechanism stimulates the release of other inflammatory cytokines such as eosinophilic cationic protein (ECP) and others. This condition has been described in people with rhinitis as Non-Allergic Rhinitis with Eosinophilia (NARES). Eosinophils and their secreted inflammatory cytokines are also believed to play a significant role in asthma.

CT Scan of the Sinuses

It is also important to understand the comorbidities of allergies and asthma, as patients with rhinosinusitis may have concurrent exacerbations of asthma that will not resolve until the underlying rhinosinusitis is treated. The best way to identify sinusitis is with a limited sinus CT scan. Sinusitis can be acute or chronic, and the differentiation is usually possible by CT scan. Whether the sinusitis is acute or chronic impacts decisions on the selection of antibiotics for treatment and the duration of treatment as well.

Evaluation of the Environment for the Presence of Allergens

It has been proposed earlier in the chapter that a knowledge of local aeroallergen patterns helps to determine exacerbating factors for asthma. This is particularly important in studying those patients who appear clinically to react to mold, and who claim to be exposed to high levels of mold spores either in the home or at work. The use of a trained environmental expert to determine the true exposure is sometimes helpful in these cases. These trained personnel can enter a home, office, or school and perform an indoor aeroallergen evaluation by sampling of the air and obtaining surface or bulk samples. Sometimes, it turns out not to be a mold problem at all, but rather a dust mite or animal allergen. Knowledge of the outdoor environment may be useful as well for those patients with pollen allergies. In very severe allergic patients with asthma, knowing when pollen counts are high will allow them to schedule their outdoor activities accordingly.

MANAGEMENT OF ALLERGIC ASTHMA

Environmental Control

The most important step in the allergen-induced asthma is to advise patients to reduce exposure to the relevant indoor and outdoor allergens to which they are sensitized. Major allergens associated with the risk of asthma differ between individuals based on climate, environment, and social factors. Numerous community studies have shown that asthma is largely associated with the allergens that occur indoor. The major risk for allergic asthma is associated with indoor allergens such as dust mites, and in some arid climates, allergy to the outdoor mold *Alternaia spp.* is an important factor. Allergy to cockroach may be responsible for allergic asthma in large urban communities. Pollen allergy is responsible for seasonal asthma and is associated with hospital admissions and emergency department visits for acute asthma.

Effective allergen avoidance requires a comprehensive and multifaceted approach. Individual steps alone are generally not effective (Table 7). Construction methods have an impact on the incidence of allergies and asthma, especially with the trends towards tighter buildings that began in the 1970 s. These were buildings designed with energy

Table 7
Environmental Control Measures for Control of Allergic Asthma

Dust mite	• Encase the mattress and pillow in the allergen impregnable bedding • Wash the sheets and blankets in hot water weekly • Avoid sleeping on the upholstered furniture • Remove the carpet that is laid on the concrete floor • Remove carpet from bedroom • In children's beds, remove stuffed toys • Reduce indoor humidity to or below 60%
Pets	• If patient is sensitive to animal, removal of the pet from home is the treatment of choice • If removal of animal is not possible, then keep the pet out of the bedroom and keep the bedroom door closed • Isolate the pet from the upholstered furniture as possible • Regular vacuuming and cleaning • Weekly washing of the pet dog and cat will remove large quantities of the allergens • Mouse trap and blocking possible entry points for the rodents into the house
Cockroach	• Avoid leaving food or garbage exposed • Pest management by using poison baits or boric acid. Use of aerosol chemical may be irritant for the asthma patients
Indoor fungi	• Measures to control the water leaks and indoor dampness may be helpful
Outdoor pollens (grass, tree, and weed) and fungi especially *Alternaria*	• Stay indoors during peak pollen season especially mid day when pollen level is particularly high • Use of mask when gardening outdoor • Avoid lawn mowing if allergic to grass pollen • Conduct outdoor activities after the sunrise when pollen level not as high

efficiency in mind, so they were built as an effective barrier, but very poor ventilation. The challenge, of course, is to construct residences and workplaces in which adequate ventilation, energy efficiency, and filtration of dangerous allergens are all optimally achieved in a balanced manner.

Dust Mite

House dust mites require a humid environment and a warm temperature to survive and multiply. In addition, if the amount of human dander due to overcrowding has increased, the chance of mite allergen exposure and sensitization is also increased. Houses with no air conditioning have high humidity and thus a high risk of exposure to the increased level of dust mite allergens. Mite exposure can be reduced through measures that remove or degrade the mites and thus reduce the amount of airborne fecal material, where most of the allergen is detectable. This can be achieved through the use of HEPA air filters in ventilation systems and vacuum cleaners, lowering of the indoor humidity, the use of hot water cycles in washing machines, hardwood floors, and use of the barrier protection in the bedding. Patients should be encouraged to use multiple interventions, because one intervention such as mite impenetrable bedding may not offer any advantage. Regular dusting, vacuuming, and cleaning has not been shown to offer any significant help *(32–34)*.

Cockroach

Exposure to high level of cockroach allergens in the inner-city population in US and around the world has been associated with risk of asthma. Cockroach allergens are found in high levels in the dust in kitchen and other open food storage areas. Environmental control of cockroach allergens involves integrated approach of pest management and efforts by the family to emphasize the cleaning of food debris and good personal and environmental hygiene. The use of an entomologist can be considered, as entomologist-directed abatement strategies have been proven to be superior to pest control companies, although potential at greater cost to the patient. It may take six months of aggressive pest management and cleaning to reduce residual cockroach allergen *(35, 36)*.

Pet Allergen Control

Cat and dog allergens have been shown to produce symptoms in the sensitized individuals even in animal-free homes, whereby the allergens are transferred on the clothing of visitors or inhabitants. After the removal of cat from home, allergen levels drop by 70%; however, clinically significant reduction in the aeroallergen levels may take up to several months. Confining the cat to a noncarpeted area other than the bedroom, use of HEPA filter, and washing the cat frequently have been advocated to achieve significant reduction in the cat allergens *(33, 37)*, but this may not be associated with significant reduction in the symptoms.

Molds

High levels of indoor molds usually occur when there is a water leak inside the home, or when the relative humidity of the home is persistently elevated. Otherwise, levels and patterns of measured mold spore counts should mirror that outdoors, in which case the indoor environment presents no higher risk than outdoor exposure. The first step in reduction of indoor mold exposure is to identify and eliminate the source of moisture

such as water intrusion, or cold and moist surfaces. Dilute bleach solution with detergents denatures fungal allergens and prevents their growth. Use of a dehumidifier in areas of moist climate and good ventilation can help to reduce mold exposure. Visible mold does not necessarily indicate a higher risk to mold allergic patients, because it is the inhaled mold spores or hyphae that are the significant allergens. Visible mold, however, does indicate that there is at least a reservoir for inhalable spores.

Pollens

Pollen counts are generally highest on the sunny, windy days with low humidity. Interplay of various weather factors is complex; therefore, it may not be possible to predict the outdoor level of allergens. When involved in the plant disturbing activity such as gardening and lawn mowing, use of face mask can reduce the exposure to the outdoor pollens and fungi such as *Alternaria (38)* Patients can also reduce the exposure to the outdoor allergens (seasonal allergens and mold spores) by staying indoors in with closed windows in air-conditioned environment. For selected areas, knowledge or daily or weekly variation in pollen and mold counts can be obtained from the website of the National Allergy Bureau (www.aaaai.org/nab).

Immunotherapy

Controlled studies of immunotherapy using single allergens have been conducted in selected patient populations with allergic asthma triggered by grass pollens, cat, house dust mite, ragweed, and the molds *Cladosporium* and *Alternaria.* In general, most studies have demonstrated positive clinical benefits in asthma symptom reduction. A meta-analysis of 75 randomized, placebo-controlled studies has confirmed the effectiveness of immunotherapy in allergic asthma. One study found that degree of benefit is comparable to that achieved in studies with moderate dose inhaled corticosteroids. Only a few studies have been reported on the multiple allergen mixes that are commonly used in the clinical practice. A reduction in asthma symptoms was seen in one study where children were treated with an immunotherapy mix consisting of high doses of all allergens to which the children were allergic.

A typical course of allergen immunotherapy ranges from 3 to 5 years. Rare severe fatal reactions have been reported in patient with allergic asthma. Allergen immunotherapy should be administered in a physician's office or clinic where proper equipment and trained personnel are present on site to treat any life-threatening reactions. In Europe, high-dose sublingual immunotherapy has been demonstrated to be effective in asthma symptom reduction. However, comparative studies suggest that sublingual immunotherapy is less effective than subcutaneous immunotherapy *(39–42)*. The risk of anaphylaxis in oral or sublingual immunotherapy appears to be less than that in subcutaneous immunotherapy.

A Cochrane systematic review recently summarized the world literature on injection immunotherapy for asthma and found that injection immunotherapy reduces medication use and improves symptoms to a degree that may be comparable to that of inhaled steroids. Allergen immunotherapy has been shown to reduce medication use and overall healthcare costs even when poor compliance is achieved *(43)* and may prevent the development of new allergic sensitizations in patients with existing allergy. The formulation of an appropriate immunotherapy regimen to modulate the immune response to

allergens is patient-specific and should be tailored to each patient's sensitivities based largely on in vivo skin testing or in vitro-specific IgE testing.

Types of Extracts for Immunotherapy

Allergenic products or determinants are named according to a system defined by the WHO/ISUS Allergen Nomenclature Subcommittee. The naming scheme is based on the accepted taxonomic nomenclature for the source of the allergen and consists of the first 3 letters of the genus followed by a space, then the first letter of the species, followed by a space, then by a number. Initially, the number is allocated based on the chronological order of discovery of the protein, but these numbers are subsequently reassigned based on protein similarities. An example would be Can f 1 for *Canis familiaris 1*.

Allergen extracts have been available for over a century. Early preparation and manufacturing techniques produced poorly characterized mixes. Composition can vary between allergen extracts as a function of allergen source, storage conditions, and the manufacturing process. Thus, allergen extracts can vary widely from manufacturer to manufacturer, and even between different lots between the same manufacturer. This led to attempts to standardize allergen extracts. This, in turn, led to the development of new units of measurement of allergenicity.

The earliest attempt at standardization assigned 1,000,000 Noon units to 1 g of pollen. The most popular measurement of concentration at the very beginning and also in modern times is the weight/volume ratio (w/v). 1:10, 1:20, and even 1:50 are common weight volume ratios seen in extracts today. Later the protein nitrogen unit (PNU) was introduced, based on the fact that most allergens are proteins, and proteins contain nitrogen. Limitations of both these concentration measurements include the fact that not all proteins are allergenic and allergenicity does not always correlate with protein content. More recently, the allergy unit (AU) and bioequivalent allergy unit (BAU) have been proposed as improved methods for quantifying active allergens. The "intradermal dilution for a 50-mm sum of erythema determines the allergy unit" ($ID_{50}EAL$) system identifies the ability of an intradermal injection of an extract to induce a 50-mm mean erythema diameter. The histamine equivalent by prick testing (HEP) defines the amount of allergen extract needed to induce the same wheal size as a 10 mg/ml skin prick test with histamine and is assigned a value of 1,000 biological units (BU). The BAU (bioequivalent allergy unit) is calculated based on the dilution (D_{50}) that will produce a 50 mm sum of erythema for each of 15–20 allergic subjects tested. A D50 of 14.0 is assigned to 100,000 BAU/ml *(44)*. Units of allergen concentrations are shown in Table 8.

Various laboratory techniques have been used to improve the sensitivity and specificity of allergen extracts used for skin testing, and also to improve stability for use in immunotherapy as well. Extracts can be aqueous, glycerinated, lyophilized (freeze-dried), acetone-precipitated, or alum-precipitated. These preparation techniques may each carry specific benefits. For example, in alum-precipitated extracts, the allergen is bound to alum and forms a complex which acts as a depot and allows for slow release. These extracts can be used for immunotherapy, but not skin testing. The advantages in immunotherapy include less frequent and less severe reactions.

Table 8
Units of Concentration of Allergenic Extracts

Unit	*Calculation*	*Advantage*	*Comments*
Weight/volume	1:10 w/v = 1 g of extract in 10 ml of extraction fluid	Widely used measurement, applies to most allergens	Measures protein concentration with no indication of allergenicity
Noon unit	1:10 w/v = 100,000 noon units		Very early attempt at standardization
PNU (Protein-nitrogen unit)	1 mg protein nitrogen = 100,000 PNU	Standardized by the US FDA	Extracts with the same PNU may vary significantly in the composition and biological potency
BU	1,000 BU = 1 HEP (histamine equivalent by prick testing)	Based on quantitative skin testing	Defined by the ability of the extract to elicit a given skin test reaction
BAU	100,000 BAU/ml = extract with a D_{50} of 14.0 (D_{50} is the dilution necessary to produce a 50 mm sum of erythema in an allergic subject)	Based on quantitative skin testing	Commonly used measure of modern standardized extracts including dust mite, cat, and grass

Pharmacotherapy

The main classes of medications used to treat allergies include the intranasal steroids and antihistamines. Other medications used to treat allergies include cromolyn and the leukotriene receptor antagonists. Most allergy medications are relatively safe and are usually either Class B or Class C for use in pregnancy. Table 9 illustrates the various medications available.

Antihistamines

Antihistamines are available in oral and intranasal forms. The first antihistamines that were developed were all sedating and these include the most commonly used over-the-counter (OTC) antihistamine, diphenhydramine. Other more recently introduced OTC antihistamines were also all sedating until loratadine and cetirizine went OTC a few years ago. Fexofenidine is also available OTC now. The nonsedating antihistamines (sometimes referred to as second- or third-generation antihistamines) are longer acting, have much fewer side effects, and are generally nonsedating. Antihistamines have been associated with a small weight gain in some studies. The third-generation antihistamines are desloratadine and levocetirizine, which are active metabolites of loratadine and cetirizine, respectively. They may offer an additional option for patients whose insurance may cover prescription but not OTC drugs, but they are not significantly more clinically effective than their respective parent compounds.

Table 9
Medications for the Treatment of Allergies

Drug class	*Name of drug*	*Generic name*	*Availability*	*Route*	*Usual adult dosage*[a]	*Dose schedule*	*Age indications*	*Comments*
Antihistamine	Zyrtec	Cetirizine	OTC	po	10 mg	qd	≥2 years	Other variations of these exist, in combination with decongestants, or in liquid or "dissolvable" forms. For dosing information in children, please refer to the manufacturer's prescribing information. Allegra is indicated for seasonal allergic rhinitis
	Claritin	Loratadine	OTC	po	10 mg	qd	≥2 years	
	Allegra	Fexofenidine	Rx	po	180 mg	qd	≥2 years	
	Clarinex	Desloratadine	Rx	po	5 mg	qd	SAR ≥2 years PAR ≥6 months	
	Xyzal	Levocetirizine	Rx	po	5 mg	qd	SAR ≥2 years PAR ≥6 months	
	Patanase	Olopatadine-HCl (0.6%)	Rx	in	2 sprays	bid	≥6 years	
	Astepro	Azelastine HCl (0.1% or 0.15%)	Rx	in	1-2 sprays	bid	≥12 years	
Intranasal steroid	Nasonex	Mometasone furoate monohydrate (50 μg)	Rx	in	2 sprays each nostril	qd	≥2 years	Fluticasone is available in generic form. Ciclesonide is a prodrug, which is enzymatically hydrolyzed to an active metabolite. The most common adverse effects in this class of drugs are headache, epistaxis, candida infections, pharyngeal pain, and nasal ulcerations
	Flonase	Fluticasone propionate (50 μg)	Rx	in	2 sprays each nostril	qd	≥4 years	
	Rhinocort Aqua	Budensonide (32 μg)	Rx	in	2 sprays each nostril	qd	≥6 years	
	Nasacort AQ	Triamcinolone acetonide (55 μg)	Rx	in	2 sprays each nostril	qd	≥2 years	
	Nasalide, Nasarel, generic	Flunisolide (25 μg)	Rx	In	2 sprays each nostril	qd	≥6 years	
	Omnaris	Ciclesonide HCl (50 μg)	Rx	in	2 sprays each nostril	qd	SAR ≥6 years PAR ≥12 years	
	Veramyst	Fluticasone furoate (27.5 μg)	Rx	in	2 sprays each nostril	qd	≥2 years	

Leukotriene pathway modifiers	Singulair	Montelukast sodium	Rx	po	10 mg	qhs	SAR ≥2 years PAR ≥6 months	Potential liver toxicity for zyflo. Montelukast is available in multiple forms for use in pediatrics
	Accolate[b]	Zafirlukast	Rx	po	20 mg	bid	≥5 years	
	Zyflo[b], Zyflor CR	Zileuton	Rx	po	600 mg	qid (bid for Zyflo CR)	≥12 years	
Anti-IgE	Xolair	Omalizumab[b]	Rx	sq	Variable (depends on weight and IgE levels)[c]	Every other week or monthly	≥12 years	Indicated for allergic asthma in moderate-to-severe persistent asthma
Optical medications	Pataday	Olopatadine-HCl (0.2%)	Rx	ou	1 drop each eye	qd	≥3 years	This class of drugs are mast cell stabilizers, inhibit release of mediators such as histamine from mast cells and inhibit eosinophil activation and chemotaxis
	Patanol	Olopatadine-HCl (0.1%)	Rx	ou	1 drop each eye	bid	≥3 years	
	Zaditor	Ketotifen fumarate	OTC	ou	1 drop each eye	bid	≥3 years	
	Optivar	Azelastine HCl (0.05%)	Rx	ou	1 drop each eye	bid	≥3 years	
	Cromolyn	Cromolyn sodium	OTC	in	2 sprays each nostril	qid	≥2 years	Available in various generic forms
	Bepreve	Bepotastine besilate	Rx	ou	1 drop each eye	bid	≥2 years	
	Lastacaft	Alcaftadine	Rx	ou	1 drop each eye	qd	≥2 years	

[a] For pediatric dosing, please refer to manufacturer's prescribing information.
[b] Indicated for use in allergic asthma.
[c] See Chapter on Pediatric Asthmatic for full dosing information.

Intranasal antihistamines are also available. Two are available by prescription, olopatadine hydrochloride and azelastine hydrochloride 0.1 or 0.15%. The dose of olopatadine is 665 μg per spray; two sprays per nostril twice daily for patients 12 years of age and over. The dose of azelastine hydrochloride for seasonal allergic rhinitis is 1 or 2 sprays per nostril once or twice daily for patients 12 years of age or older, and for perennial rhinitis, is two sprays per nostril twice daily. Each spray of azelastine 0.15% delivers 205.5 μg.

Intranasal steroids

Intranasal steroids are considered the first-line medication for the treatment of allergic rhinitis. Similar to inhaled steroids, this class of medication is intended as a controller and must be used on a regular basis in order to appreciate its full benefit. There are several intranasal corticosteroids available, including fluticasone propionate, mometasone furoate, fluticasone furoate, budensonide, flunisolide, and triamcinolone acetonide. The doses are outlined in Table 8. These medications have the benefit of once daily or twice daily use, which improves compliance. There are minimal side effects from the use of intranasal corticosteroids, mostly limited to local effects such as epistaxis, discomfort, or hoarseness.

Cromolyn

Cromolyn is a medication derived from a plant, Khelia (*Ammi visnaga*), which has a long history in the treatment of allergies and asthma. It has not been as widely used recently due to its dosage schedule, which is usually at least 4 times a day. The effect of intranasal cromolyn is inferior to that of intranasal corticosteroids, but some patients seem to derive sufficient benefit.

Omalizumab

Omalizumab is a recombinant DNA-derived humanized monoclonal antibody directed against the Fc portion of the IgE molecule. Binding of omalizumab to IgE prevents IgE from binding to the high affinity receptor (FcεRI) on mast cells and basophils. This decreased binding of IgE on the surface of mast cells leads to the decrease in the release of mediators in response to allergen exposure. A decrease in the number of FcεRI in basophils and submucosal cells in the airways is also observed. The vast majority of patient in clinical trials of omalizumab had moderate-to-severe persistent asthma incompletely controlled on inhaled corticosteroids. In addition, all had atopy and elevated IgE levels. Adding omalizumab to the treatment regimen generally produced significant reduction in asthma exacerbations and is associated with small but significant improvements in lung function.

Omalizumab is administered subcutaneously and may be associated with pain or bruising at the injection site. Urticaria and anaphylaxis have been reported in 0.2% of patients. Malignant neoplasms were reported in 0.5% of the patients compared to the 0.2% receiving placebo, but the relationship to the drug is unknown *(45–48)*.

Other Drugs

Other drugs or treatments are available for allergic rhinoconjunctivitis or sinusitis. Nasal saline washes appear to help with clearance of allergenic particles, and with hydration. Performing nasal saline washes up to four times a day can also help with clearance of mucous or infected material in patients with chronic sinusitis.

BIOMARKERS AND FUTURE DIRECTIONS

The waxing and waning nature of disease activity in asthma renders this disease an ideal candidate for prospective management using biomarkers of activity that may be detectable prior to the development of clinical symptoms. Indeed, a host of potential targets for *in vitro* determination of disease activity and likelihood of drug response has been identified, and the search continues. However, few of these research assays have yet been sufficiently well correlated with disease activity that they are able to serve a defined role in asthma management. With the exception of specific IgE determination to aid in the classification of allergic vs nonallergic asthma, major guidelines have not yet embraced the use of any in vitro biomarker system to guide asthma therapeutics.

The measurement of exhaled nitric oxide as a biomarker for asthma control has now been approved and entered clinical use *(49)*. The biological mechanism underlying the utility of nitric oxide measurement involves inducible nitric oxide synthase (iNOS), an enzyme that is induced under conditions of inflammation and leads to the production of nitric oxide from L-arginine. In vivo, actions of nitric oxide include bronchodilation, vasodilation, neurotransmission, immunomodulation, and host defense. It is stable in exhaled gases and may serve as a noninvasive marker of inflammation, providing an attractive target to noninvasively follow disease course and the response to anti-inflammatory therapy, especially in patients with allergic asthma. However, levels are affected by a host of variables, including age, anthropometric factors, dietary factors, smoking (paradoxically, levels are lower in smokers), medications, gender, and has also been shown to be affected by other maneuvers (such as spirometry) that may be concurrently performed in the evaluation of asthma. Some data have shown that the use of nitric oxide measurements to titrate therapy, as well as other measures such as eosinophil counts in sputum, may result in reduced exacerbations of asthma compared to current standards, and nitric oxide analysis may be among the most likely parameters measured by the clinical laboratory to enter widespread standard use in the diagnosis and management of asthma. Given the number of potential variables, the application of a single scale to define "normal" values may be difficult to achieve for a population, whereas changes in values measured over time in a single patient may have greater clinical utility. A study of the relationship between exhaled nitric oxide levels and exposure to allergen in sensitized patients not taking inhaled steroids revealed significantly higher exhaled nitric oxide levels in asthmatic patients who were both sensitized and exposed to the relevant allergen, compared to those who were sensitized but not exposed. The utility of this observation in the identification of those susceptible to allergen-induced asthma exacerbations has yet to be determined *(50)*.

The measurement of sputum eosinophils as a marker in asthma has been a target of a number of investigations, some of which have demonstrated utility in reducing exacerbations. Furthermore, at least one study has demonstrated the utility of this measurement in defining populations likely to respond to specific pharmacologic management in the form of mepolizumab (an anti-IL-5 monoclonal antibody) *(51)*. However, practical factors associated with sputum collection and analysis may limit the utility of this measure in the management of the general asthma population.

Other pharmacogenetic markers such as single nucleotide polymorphisms (SNPs) have been identified that may yet play a role in determining those patients who will respond better or worse to a specific treatment. Correlation of SNPs with phenotypic

features such as patients with an atopic component to their asthma may help in defining a subset of patients whose asthma control may benefit from treatment of their allergies. As in the case of treatment of HER-related breast cancer treatment with Herceptin, the future may bring a time when only those patients with an identifiable genetic variant may expect to be treated successfully with a specific treatment. This will bring important benefits including reducing the exposure of some patients to side effects of nonindicated medications.

CONCLUSION

The majority of asthma patients, especially children, have allergies as well. Along with viral infections and exercise, allergies are a significant trigger for asthma exacerbations in these patients. It is for this reason that no discussion of the evaluation and treatment of asthma is complete without addressing the allergic phenotype. In patients with allergies, treatment of the allergies may benefit their asthma condition. Identification of a patient's sensitivities and their environmental exposures are important considerations when evaluating these patients. Treatment of allergies and allergic asthma involves four components, avoidance of triggers, pharmacologic intervention, immunotherapy and patient education (Fig. 3). Avoidance is possible for some allergens, but not others. In general, medications to treat allergies are associated with minimal side effects. The overall treatment strategy should be customized for each patient. In the future, studies on pharmacogenetics and biologic markers for allergy phenotypes may help direct care and usher in the era of "personalized medicine."

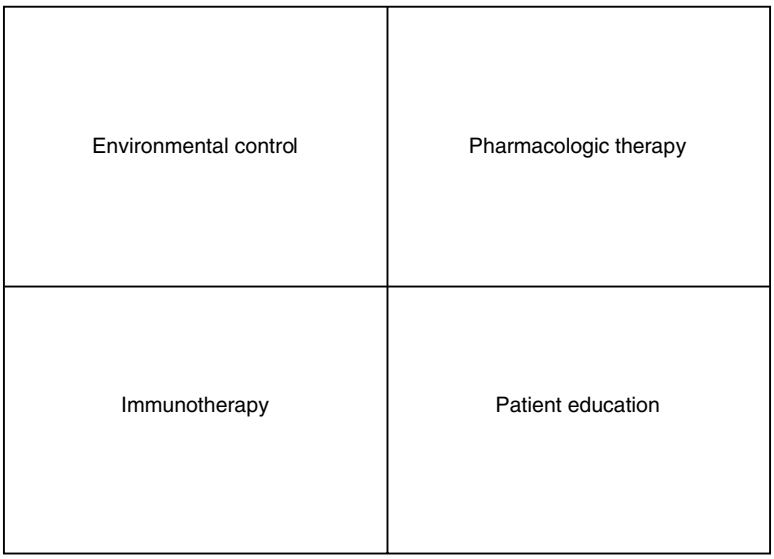

Fig. 3. Strategies to treat allergies.

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5 The Pediatric Asthmatic

Christopher Chang, MD, PhD

Contents

KEY POINTS

- The incidence of asthma has increased dramatically during the past 20 years, with the highest increases in the urban areas of developed countries.
- Asthma treatment goals in children include decreasing mortality and improving quality of life.

From: *Bronchial Asthma: A Guide for Practical Understanding and Treatment, 6th ed.*
Edited by: M. E. Gershwin and T. E. Albertson, DOI 10.1007/978-1-4419-6836-4_5

- Specific treatment goals include but are not limited to decreasing inflammation, improving lung function, decreasing clinical symptoms, reducing hospital stays and emergency department visits, reducing work or school absences, and reducing the need for rescue medications.
- Nonpharmacological management strategies include allergen avoidance, environmental evaluation for allergens and irritants, patient education, allergy testing, regular monitoring of lung function, and the use of asthma management plans, asthma control tests, peak flow meters, and asthma diaries.
- Achieving asthma treatment goals reduces direct and indirect costs of asthma and is economically cost-effective.
- Developing optimal technique in the use of metered-dose inhalers (MDI) in young children is difficult. Ongoing instruction and review may be necessary to ensure good technique. The use of spacers may help.
- Asthma is a chronic disease with a potential psychological impact on the pediatric patient during critical years of development.

INTRODUCTION

The incidence of allergies and asthma in the Western world has been increasing over the past 30 years. However, more recent data suggests that over the past 5–10 years, the overall global trends of asthma incidence have begun to stabilize *(1)*. Urbanization and industrialization has contributed to the increase in developed countries, but the reasons for this are still unclear. Asthma is estimated to be responsible for 1 in every 250 deaths worldwide. Many of these deaths are preventable, and specific issues have been identified that may contribute to this high mortality rate. Factors that contribute to high mortality and morbidity include slow access to care and medications, inadequate environmental control of allergens and irritants, dietary changes, genetic variations, cultural barriers, lack of education amongst patients and providers, insufficient resources, and improper use of health care dollars.

The Global Initiative for Asthma (GINA), initiated in 1989 for the World Health Organization (WHO) and the US National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) periodically establish guidelines for the diagnosis and treatment of asthma (*2, 3*). The most recent significant update to these recommendations appeared in the Expert Panel Review 3 (EPR-3) published by the National Asthma Education and Prevention Program (NAEPP) coordinating committee of the NHLBI of the NIH *(3)*. A historical timeline of these revisions is shown in Fig. 1.

The development of newer medications and delivery devices over the past 25 years has made a significant impact on our ability to decrease morbidity of childhood asthma. Hospitalizations for asthma have clearly decreased as a result of the use of controller medications. Quality of life has been identified as a significant metric to measure asthma treatment success. On the other hand, despite our improved knowledge of the pathogenesis of asthma, newer medications with fewer adverse effects, and increased standardization of treatment protocols, there has been a paradoxical increase in asthma mortality. The reasons for this observation are debatable, but may include lifestyle changes, dietary changes, the increase in obesity rates in the Western Hemisphere, coding anomalies, poor patient and/or caregiver education, and the

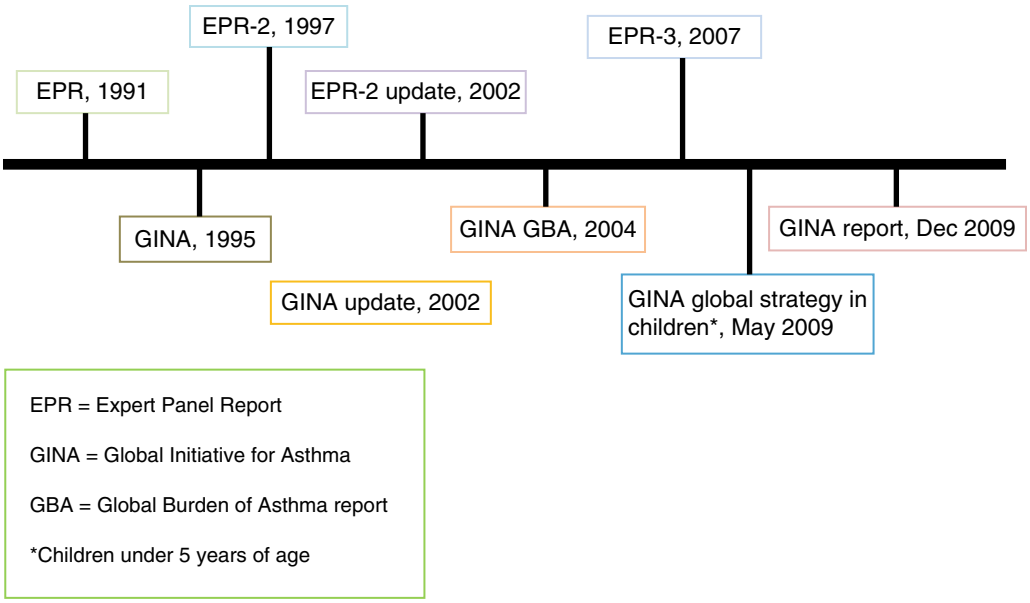


Fig. 1. Historical chart showing recommendations in asthma treatment worldwide.

overall increase in the incidence of allergies and asthma. What is clear, however, is that the development and introduction of new pharmaceuticals is not by itself the answer to improving outcomes in children with asthma. Patient education, environmental avoidance measures, proper use of medications, and immunotherapy are all equally important in the successful treatment of the pediatric asthmatic. The good news is that with our awareness of these factors, mortality has at least stabilized over the past 5 years.

Asthma in children has a unique set of characteristics that merit discussion (Table 1). The diagnosis of asthma in children may be difficult to make in the infant because of the prevalence of viral-associated wheezing in this age group of patients. The impact of viral illness on the development of asthma in later years is addressed later, along with the role of allergies in childhood asthma. Certain medications are not always appropriate for all ages, and devices that are used to evaluate asthma status may not be usable by young children. Exercise-induced asthma (EIA) is particularly important in childhood as physical activity is critical to controlling the epidemic of obesity in developed countries, especially the United States. Lifestyle changes, including the use of television, internet, and other video devices, may play a role in childhood asthma. Finally, the "hygiene hypothesis" has introduced the concept that early exposure to animals, foods, or endotoxin may actually be protective against allergic sensitization. While this is still a controversial issue, it illustrates the complexity of asthma as a heterogeneous disease, with genetic and environmental influences. Indeed, we now know that there is no single asthma gene, rather that there are multiple genetic variants that, under the proper environmental conditions, can result in asthma.

Table 1
Special Considerations for Asthma in Children

The increased significance of allergies in childhood asthma
The role of passive smoking (ETS exposure) in infancy and pregnancy in the development of asthma
The role of respiratory syncytial virus (RSV) and other viral bronchiolitis in pediatric asthma
Genetics (host factors) vs. environmental exposures in childhood asthma
Vocal cord dysfunction (VCD) in teenage athletes with or without concurrent asthma
The increase in obesity in children and its impact on childhood asthma
Gender predisposition for asthma in children is reversed that in adults
Availability of asthma medications and indications in the pediatric age group
The role of immunotherapy in the very young child
The use of biologics in children (omalizumab and new drugs)
Corticosteroids and growth retardation
Exercise induced asthma (EIA) and sports in children

EPIDEMIOLOGY AND THE PREVALENCE OF CHILDHOOD ASTHMA

The prevalence of asthma is now estimated to be more than 300 million worldwide, or about 5% of the global population. The incidence of asthma has been steadily increasing since the 1970s, with the greatest increase occurring in modern, developed countries. Asthma accounts for about 1 in every 250 deaths worldwide. The national prevalence of asthma in different countries varies between 1 and 19% (Table 2). It has been observed that developed countries have the higher incidences, while third world countries have the lower rates, but in recent years, the gap is decreasing due to an increasing incidence of asthma in Asia, South America, and Africa.

The gender predominance is reversed in children from that in adults. In children under the age of 14, there is a 2:1 male to female prevalence of asthma, approximately opposite that in adults. Obesity appears to be a risk factor for asthma. Diet is more complicated, and the initial observation that breast feeding protects against asthma is being challenged. Exposure to Western diets comprising high levels of processed foods with increased levels of *n*-6 polyunsaturated fatty acids, decreased antioxidant levels, and decreased *n*-3 polyunsaturated fatty acids has been associated with the increase in asthma and allergies observed over the past few decades.

GENETICS AND ASTHMA

Asthma is heritable. Children born to asthmatic parents have an increased likelihood of developing asthma themselves. Asthma is polygenic, and multiple phenotypes exist. It is estimated that up to 70% of asthma in children is associated with atopy or allergies. Airway hyperresponsiveness, serum IgE levels, inflammatory mediator expression, and Th1/Th2 balance are four areas that may be influenced by genetics. The genes involved in regulating these processes may differ between ethnic groups. Some of these processes, such as airway hyperresponsiveness and serum IgE levels, may be co-inherited in

Table 2
Asthma Prevalence by Country[a]

Country	*Prevalence (% population)*
Scotland	18.5
Wales	16.8
England	15.3
New Zealand	15.1
Australia	14.7
Republic of Ireland	14.6
Canada	14.1
Peru	13.0
Trinidad and Tobago	12.6
Costa Rico	11.9
Brazil	11.4
United States	10.9
Fiji	10.5
Paraguay	9.7
Uruguay	9.5
Israel	9.0
Panama	8.8
Kuwait	8.5
Ukraine	8.3
Ecuador	8.2
South Africa	8.1
Finland	8.0
Czech Republic	8.0
Columbia	7.4
Turkey	7.4
Germany	6.9
France	6.8
Norway	6.8
Japan	6.7
Hong Kong	6.2
United Arab Emirates	6.2
Spain	5.7
Saudi Arabia	5.6
Argentina	5.5
Chile	5.1
Italy	4.5
South Korea	3.9
Mexico	3.3
Denmark	3.0
India	3.0
Cyprus	2.4
Switzerland	2.3
Russia	2.2
China	2.1
Greece	1.9
Georgia	1.8
Romania	1.5
Albania	1.3
Indonesia	1.1

[a] Selected countries.

Table 3
A Few Selected Candidate Genes for Asthma and Their Impact on Disease or Treatment

Gene	*Target response/asthma phenotype*	*Population/location*
CTLA-4	Response to corticosteroids	European
Arginase 1 and 2	Response to bronchodilators	Netherlands
Glutathione *S*-transferase	With air pollution as interactive risk factors	Italy
ADAM-33	Risk for asthma, elevated IgE, and increased specific IgE to dust mite species	Columbia
IL-4R	Specific asthma phenotype, eczema, and allergic rhinitis	Sweden
DENND1B	Increased susceptibility to asthma (GWAS study)	North America
LTA4H and ALOX5AP	Gene–gene interactions convey variants in asthma susceptibility	Latinos (Mexico and Puerto Rico)
TLR4	Gene polymorphisms convey risk of asthma (IRAK1, NOD1, MAP3K7IP1 gene–gene interactions)	Netherlands
PHF11 and DPP10	Risk for asthma	Chinese, European and Latin American
NOS-1	Increased IgE levels, increase in frequency of asthma phenotype	Taiwanese
ECP	Allergy and asthma symptoms, smoking	From the European Community Respiratory Health Survey (ECRHS)
TSLP	Higher risk of childhood and adult asthma	Japan
RANTES	Higher risk of asthma in subgroup analysis by atopic status	Global

TLR4 Toll like receptor 4; *PHF11* plant homeodomain zinc finger protein 11; *DPP10* dipeptidyl-peptidase 10; *ADAM-33* a disintegrin and metalloprotein 33; *LTA4H* leukotriene A (4) hydrolase; *ALOX5AP* arachidonate 5 lipooxygenase activating protein; *IL-4R* interleukin 4 receptor; *CTLA-4* cytotoxic T-lymphocyte antigen 4; *NOS-1* nitric oxide synthase 1; *ECP* eosinophil cationic protein; *TSLP* thymic stromal lymphopoetin; *RANTES* regulated upon activation, normal T cell expressed and secreted. DENND1B=DENN/MADD domain containing 1B protein.

some individuals, possibly as a result of close proximity of genes affecting both processes (e.g., chromosome 5q).

Genes can also affect an asthmatic child's response to medications. This has been found to be the case for β-adrenergic agonists, glucocorticoids, and leukotriene modifiers. While studies of pharmacogenetics have so far produced more questions than answers, this is an exciting area of research because it promises the capability of generating customized care plans, or personalized medicine, that will match optimal treatment with each individual asthmatic child. Genes that are involved in asthma are now too numerous to count. An example of genes associated with asthma is given in Table 3.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF CHILDHOOD ASTHMA

Making the diagnosis of childhood asthma requires taking a thorough history and doing a complete physical examination on the patient. There are many conditions that may mimic asthma. Some of these diagnoses are age dependent. A complete list of conditions in the differential diagnosis is given in Table 4. Asthma is still a clinical diagnosis, as there is no pathognomonic marker for diagnosing asthma. Taking a good history is critical. A good history includes current or past history of cough, wheezing, viral respiratory diseases, accompanying allergy symptoms or signs, shortness of breath, and sinus problems. The intensity and characteristics of any breathing sounds should be determined. It is also important to obtain an exposure history to attempt to clarify relevant triggers for asthma exacerbations. This can include indoor allergen exposures,

Table 4
Differential Diagnosis of Cough, Wheezing, and Other Bronchial Sounds

Asthma
Foreign body aspiration
Aspiration pneumonia
Bronchopulmonary dysplasia
Heart disease
Infections (may be viral, bacterial, fungal, or mycobacterial)
Pneumonia
Bronchitis
Bronchiolitis
Epiglottitis (stridor, respiratory distress)
Sinusitis
Exposures
Allergies
Smoke inhalation
Toxic inhalations
Hypersensitivity pneumonitis
Gastroesophageal reflux
Genetic disorders
Cystic fibrosis
Iatrogenic
ACE inhibitor related cough
Anatomical abnormalities
Vocal cord dysfunction
Vocal cord anomalies (nodules)
Subglottic stenosis (stridor)
Laryngotracheal malacia (in infants)
Vascular anomalies of the chest
Endotracheal fistulas and tracheal anomalies
Other
Immunodeficiency syndromes
Obesity
Alpha-1 antitrypsin deficiency

outdoor pollens, viral upper respiratory infections and exercise, exposure to foods, and an occupational history of both the child (if old enough to be working) and the parents or caregivers. Exposure to day care is also important and environmental tobacco smoke and pollution exposure should also be documented. A past medical history asking about previous hospitalizations, doctor visits, frequent otitis media, sinusitis or pneumonia, and a complete medication history, including use of nebulizers or inhalers and any other pertinent medications should be elicited. The family history is also important, as asthma has a genetic component.

In addition to taking a good history, a complete physical examination should also be conducted to rule out any other possible diagnoses. While the presence of a wheeze may suggest asthma, foreign body aspiration may also be a possibility if the wheeze is unilateral. The presence of a heart murmur may suggest a coarctation with compression of the trachea. Clubbing of the fingers may be suggested of a more chronic condition such as cystic fibrosis. These are only some of the many observations one may glean from a physical examination that can help in establishing or ruling out the diagnosis of asthma.

Procedures and laboratory tests have a role in the diagnosis of asthma. Allergy testing may be indicated if the history is consistent with an allergic component or trigger. Spirometry should certainly be done, with the response to bronchodilators examined as well. Exercise challenge tests can be done in the child or adolescent who suspects EIA or bronchospasm (EIB). Other tests that may be helpful in monitoring the condition of an asthmatic may be fractional exhaled of nitric oxide (FeNO). A complete blood count, chest X-ray, or sinus CT scan may also be indicated in some cases. Components of a diagnostic scheme and clinical assessment of asthma are shown in Fig. 2.

While we think of wheezing as a hallmark of asthma, it can be present in children without asthma, and absent in those with asthma. In children under 5 years of age, wheezing can be categorized into three groups: transient early wheezing, persistent early onset wheezing, and late-onset wheezing/asthma. These are discussed in more detail later.

TRIGGERS OF ASTHMA IN CHILDREN

Allergens

It is estimated that between 60 and 70% of asthma in children is allergic asthma. Conversely, children with allergies have a 30% chance of having asthma as well. The atopic march describes a commonly seen paradigm in which children who are atopic (genetically predisposed to developing allergies) present early in life with atopic dermatitis, then asthma, and finally allergic rhinitis and conjunctivitis. Common allergens can be categorized into either indoor or outdoor allergens. The outdoor allergens are mostly linked to seasonal allergic rhinitis, whereas indoor allergens are linked to perennial allergic rhinitis. There are geographical differences in the seasonal distribution of pollen allergens. Recently, it has been suggested that climate change may be impacting the prevalence of various outdoor allergens through different mechanisms. In addition, environmental exposures and host factors can lead to changes in an individual's sensitivities throughout life. Certain allergens, such as dust mite, cat and dog dander, and *Aspergillus* are independent risk factors for the development of symptoms of asthma in children under 3 years of age *(4)*.

Fig. 2. Diagnosis and clinical assessment of the asthmatic child – the appropriate parts of the history and physical examination should be performed depending on the circumstances (e.g., is this a new patient with a history of cough presenting to the office as a consult, or is this a patients with known asthma who is in the midst of an asthma exacerbation presenting to the emergency room).

On the other hand, the "hygiene hypothesis" has been used to explain why in some cases, exposure to dogs and/or cats leads to a decrease in allergic sensitization *(5)*. These inconsistencies in studies on allergen sensitivity have not been adequately resolved, and it is likely that other factors, possibly related to the timing of exposure or host factors play a significant role in the effect of allergen exposure on sensitization. In addition to cats and dogs, other pets such as guinea pig, gerbils, hamsters, mice, rats, and rabbits can also trigger asthma attacks in susceptible individuals.

It has been suggested that exposure to endotoxin may play a protective role in allergen sensitization, though this is not universally observed. Cockroach and mouse

Table 5
Common Allergenic Determinants

Determinant	*Source*	*Source scientific name*	*Protein class/function*
Der p 1	Dust mite	*Dermatophagoides pteronyssinus*	Cysteine protease
Der p 2	Dust mite	*D. pteronyssinus*	Serine protease
Der f 1	Dust mite	*D. farina*	Cysteine protease
Der f 2	Dust mite	*D. farina*	Serine protease
Der m 1	Dust mite	*D. microcerax*	Cysteine protease
Blo t 1	Dust mite	*Blomia tropicalis*	Cysteine protease
Fel d 1	Cat	*Felis domesticus*	Salivary glycoprotein
Can f 1	Dog	*Canis familiaris*	Salivary lipocalin proteins
Bla g 1	Cockroach	*Blattella germanica*	Unknown
Bla g 2	Cockroach	*B. germanica*	Aspartic proteinase
Rat n 1	Rat	*Rattus norvegicus*	Major urinary protein
Mus m 1	Mouse	*Mus muscularis*	Major urinary protein
Per a 7	Cockroach	*Periplaneta americana*	Tropomyosin
Lol p 1	Ryegrass	*Lolium perenne*	Unknown
Amb a 1	Ragweed	*Ambrosia artemisiifolia*	Polysaccharide lyase 1 family
Aln g 1	Alder	*Alnus glutinosa*	Pathogenesis-related protein
Bet v 1	Birch	*Betula verrucosa*	Pathogenesis-related protein
Que a 1	Oak	*Quercus alba*	Pathogenesis-related protein
Ole e 1	Olive	*Olea europea*	Unknown
Cyn d 1	Bermuda grass	*Cynodon dactylon*	Expansin family
Art v 1	Mugwort	*Artemisia vulgaris*	Unknown
Dac g 3	Orchard grass	*Datylus glomerata*	Expansin family

allergen have both been found to play a significant role in allergic sensitization in children living in inner city environments *(6)*. Both early and late phase reactions have occurred in places where cockroach infestation is a problem, such as highly populated urban areas in warm climates.

Food allergens can be a significant cause of allergic sensitization in children, especially in the younger age range. Foods are typically associated with eczema in infants and toddlers, but eczema is a feature of atopy, and the earliest manifestation of the "atopic march." These patients can subsequently develop asthma or allergic rhinoconjunctivitis as they grow older.

In order to treat allergic asthma effectively, it is therefore important to identify a child's current allergic sensitization patterns. This can be done by skin testing or by a blood test that measures specific IgE. There are advantages and disadvantages to both forms of testing. Skin testing is more sensitive and specific, although the blood test methodology is improving. The blood test can be done if there are contraindications to skin testing, such as in the very young child who may not be able to tolerate skin testing, a patient on antihistamines or β-blockers, or a patient with a severe rash. Available now are "multitest" devices that facilitate skin testing and make it possible to perform in the very young child. A list of common environmental allergens is given in Table 5.

While food allergens can also trigger asthma, these are less likely triggers, and testing for food allergens is not as sensitive or specific as environmental allergens. A complete discussion on the role of allergies in asthma can be found in chapter 4 on the diagnosis and management of allergies.

Irritants

Most air pollutants are irritants, although some can have immunomodulatory effects. The most extensively studied airborne pollutant is environmental cigarette smoke. Gaseous irritants include nitric oxide, sulfur dioxide, formaldehyde, ozone, and other volatile organic compounds (VOC). Airborne particulates can vary in size, ranging from course particulates to fine particles, to ultrafine particles or nanoparticles. The smaller the particle, the greater the penetration into the airway. Particles greater than 10 μm in diameter are generally cleared in the upper airway. Although these larger particles can indirectly trigger early or late phase asthma reactions by virtue of their action in the upper airways, fine and ultrafine particles present a more significant problem due to their deeper penetration into the smaller airways *(7)*. Recently, evidence has surfaced that these ultrafine particles indeed possess effects on inflammatory cells such as neutrophils or eosinophils that can lead to asthma symptoms. This can occur through several different mechanisms and are reviewed extensively elsewhere *(7)*.

Exercise-Induced Asthma or Bronchospasm

Exercise is a common trigger for asthma in children. However, exercise is essential to the physical and psychological development of all children. Lack of exercise also promotes obesity, which has been linked to asthma *(8)*. Therefore, we no longer recommend that children with asthma stop exercising. In fact, exercise can help to build lung reserve. With proper control of asthma using controller medications, a patient with EIA can almost always participate in regular cardiovascular training without adverse effects. Asthma can even be managed successfully in the elite athlete. The severity of a patient's EIA can be evaluated using an exercise challenge test. Historically, the methodology of exercise challenge tests has been very inconsistent, but recently the American Thoracic Society (ATS) has proposed a set of criteria that should be met in order to ensure an accurate and valid test *(9)*. These criteria and a typical protocol are illustrated in Fig. 3.

Viral Respiratory Illness and Asthma

The link between viral respiratory infections and asthma has been well established *(10)*. In infants, the most well-known viral respiratory illness associated with wheezing is respiratory syncytial virus (RSV). However, rhinovirus is the more common virus in children *(11)*, and wheezing can be associated with other viruses as well, including parainfluenza virus, influenza virus, metapneumonia virus, adenovirus, coronavirus, and picornavirus. Rhinovirus is the major pathogen associated with hospital admissions for asthma in children *(12)*.

Transient early wheezing develops in infancy and usually resolves by 3 years of age. Risk factors include low birth weight, prematurity, maternal exposure to tobacco smoke, male gender, and upper respiratory viral infections. A second phenotype is that of the atopic wheezer. These are school age children who have a history or family history of atopy. Their wheezing may or may not be triggered by a viral infection, but they have a

A) An exercise challenge protocol

Equipment needed:

1. Spirometry equipment
2. Exercise challenge protocol
3. Exercise challenge result sheet
4. Stethoscope
5. Pulse oximeter
6. Calculator
7. Printer
8. Treadmill or place to run

C) Guidelines/criteria for exercise challenge testing:

1. >= 10-15% decrease for + test
2. Pulmonary medications withdrawn prior to test
3. No vigorous exercise 4 hours before testing
4. 4 hours separate sequential exercise challenges
5. Treadmill testing with target intensity reached within 2-4 minutes
6. HR = 80-90% predicted or minute ventilation = 40-60% predicted maximum
7. Target HR or minute ventilation maintained for 4-6 minutes
8. Relative humidity <50%
9. Air temp = 20-25oC
10. Use nose clip to ensure smooth air flow
11. Post-exercise spirometry up to 15-20 minutes post exercise
12. Use of higher of minimum 2 FEV1 values

Protocol:

1. Prepare pre-printed results form. Enter demographics
2. Listen to the child's lungs for wheezing – chart results
3. Record pulse and oxygen saturation
4. Have child perform spirometry three times. Record results
5. Have child run for 6 minutes. Heart rate should reach 85% maximum heart rate.
6. Auscultate child's chest
7. Record pulse and oxygen saturation
8. Perform spirometry one time (0 minutes after exercise). Immediately calculate % change in FEV1. Record result. If FEV1 decreases > 12% compared to pre-exercise test, skip to step 13
9. After 2 minutes, repeat step 8
10. After 5 minutes, repeat step 8
11. After 10 minutes, repeat step 8
12. After 15 minutes, repeat step 8
13. Auscultate child's chest. If child is not wheezing, is not in respiratory distress and FEV1 did not at anytime drop >12% compared to pre-exercise levels, then test is finished
14. Administer a unit dose bronchodilator nebulization treatment
15. After completion of the treatment, wait five minutes and repeat spirometry 3 times. Record results.
16. Auscultate child's lungs

B) Exercise challenge test results sheet- sample

Date: _____ Patient name: _____ DOB: _____

Test performed by: _____

How to calculate %change:
(post FEV1-best pre FEV1) x 100% = % change

Event	*Time*	*O2 Saturation*	*Pulse*	*FEV1*	*%change*
Pre					
0 min post					
2 min post					
5 min post					
10 min post					
15 min post					
After neb treatment (if indicated)					

Fig. 3. (**A**) An exercise challenge protocol. (**B**) Exercise challenge test results sheet – sample. (**C**) Guidelines/criteria for exercise challenge testing.

strong probability of continued wheezing into adolescence or adulthood. It is in this group that one would be able to detect chronic inflammatory changes in the airways. A third category, persistent early onset wheezing, includes preschool aged children and is usually not associated with a family history of asthma or atopy, but instead is associated with acute viral respiratory infections. This group has a better long-term prognosis and symptoms may disappear when they reach school age.

Bronchiolitis in infancy can lead to decreased FEV1 and FEF25–75% in childhood *(13)*. A connection between asthma and RSV bronchiolitis was supported by an observation that there is elevated eosinophil cationic protein (ECP) and leukotriene C4 in the nasal lavage fluid of infants with RSV bronchiolitis *(14)*. It is not clear whether the occurrence of RSV bronchiolitis as an infant significantly increases the risk of developing asthma at a later age, although one prospective study of 47 children hospitalized for RSV bronchiolitis in infancy showed a higher incidence of airway hyperreactivity at age 13 compared to 93 matched controls *(15)*. Continued follow-up of these patients revealed a persistent increase in allergic asthma into early adulthood among patients who had RSV bronchiolitis in infancy *(16)*.

INTERPRETING THE NEW ASTHMA GUIDELINES IN CHILDREN

The new EPR guidelines were released in 2007 *(3)*. These guidelines contain revisions that were aimed at improving the overall care of asthmatics. There are several important changes. Firstly, the main goal of asthma treatment is control of symptoms and disease. A list of specific goals to target control is given in Table 6. Better distinction is made between monitoring asthma control and classifying asthma severity. Severity is defined as the intrinsic intensity of asthma and is still grouped into the original classification of mild intermittent, mild persistent, moderate persistent, or severe persistent. Categorizing severity in this manner is helpful for initiating therapy. Control

Table 6
Treatment Goals in Asthma

Decreasing mortality
Decreasing morbidity and improving quality of life
Fewer nighttime awakenings
Ability to participate in sports with no limitations
Fewer school or work days lost
Reduction of symptoms of cough or wheezing
Reduction in the need for rescue medications
Easy compliance with medications with minimal disruptions in daily life
Reduction in side effects of asthma medications
Reduction in the number and severity of asthma exacerbations
Reduction in emergency or unscheduled office or clinic visits
Reduction in the need for systemic steroids
Prevention of “airway remodeling” and long-term sequelae of asthma
Economic goals
Reducing costs of treating asthma by improving preventative measures

is defined as the response to therapy, in terms of the degree to which manifestations of asthma are kept to a minimum. Therapy should be adjusted periodically in order to maintain control.

The second major change is the focus on impairment and risk. These are the two key domains of control and severity, and provide additional information or parameters to assess response to treatment. Impairment is defined as the extent to which standard goals of asthma treatment are maintained, so this includes the frequency and intensity of symptoms and interference with good quality of life, such as an inability to conduct normal daily activities. Risk can include several parameters – the likelihood of developing an asthma exacerbation, the risk of side effects of medications, and the risk of declining lung function or lung growth.

In order to address the change in focus, the treatment recommendations have also been adjusted. The stepwise approach is still utilized, but now there are six steps, with clearly defined actions, instead of having progressive actions within each step. The treatment recommendations have also been divided into three groups depending on age, a group for children 0–4 years of age, another group addressing children 5–11 years of age, and the third group consisting of adults and children 12 and over. This was done because the evidence for the various treatment modalities may be different between age groups.

Other important recommendations address environmental control, with the recommendation for these actions being present in all age groups. Inhaled corticosteroids are the first-line control drug for all ages. The use of combination inhaled steroid and long acting β-agonists (LABAs) is considered an equal alternative to increasing the dose of inhaled corticosteroids in patients 5 years of age and older. Omalizumab is also recommended in patients with allergic asthma who are 12 years of age and older who require step 5 or 6 therapy. A black box warning for anaphylaxis accompanies omalizumab. The breakdown of the stepwise approach for children under 12 is given in Table 7.

NONPHARMACOLOGIC MANAGEMENT OF CHILDHOOD ASTHMA

An asthma management plan involves approaching the problem from three different angles – environmental control, pharmacologic intervention, and immunotherapy. In addition, objective measurement of asthma status is important, and ongoing monitoring is also of benefit. It is clear that the development of new drugs is only a part of a more comprehensive strategy to treat asthma. In addition to drugs, nonpharmaceutical modes of treatment need to be incorporated into the asthmatic child's treatment plan. Nonpharmaceutical modes of therapy for asthma are discussed below and listed in Table 8.

Environmental Control

Allergen challenge studies have shown that exposure to an allergen to which an asthmatic has been sensitized is likely to bring about an asthma exacerbation *(17)*. Conversely, avoidance of such allergens may lead to resolution of the exacerbation. Thus, allergen avoidance has been recognized as an important part of an asthma management plan. The effectiveness of an allergen avoidance plan requires knowledge of the patient's sensitivities and exposure pattern.

Table 7
EPR-3 Guidelines for the Diagnosis and Treatment of Asthma in Children[a]

a) 0-4 years of age

Determine severity when initiating therapy

Components of severity		Classification of Asthma Severity (0-4 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	**Symptoms**	<= 2 days/wk	>2 days/wk	Daily	Throughout day
	Nighttime awakenings	< 2x/month	3-4x/month	>1x/wk	Nightly
	SABA use for symptom control (not EIA)	<= 2days/wk	>2days/wk, <1x/day	Daily	Several times/day
	Interference with normal activity	None	Minor	Some	Extreme
Risk	**Exacerbations requiring oral corticosteroids**	0-1/year	>=2 exacerbations in 6m requiring oral steroids, or >= 4 wheezing episodes/year lasting >1day and risk factors for persistent asthma. Exacerbations of any severity can occur in asthmatics in any severity category		
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3 and consider short course of steroids	
		Evaluate level of asthma in 2-6 weeks. Adjust therapy if no clear benefit, reconsider diagnosis			

Once control is achieved, continue to assess control on ongoing basis (approx every 1-6 months)

Components of Control		Classification of Asthma Control (0-4 years of age)		
		Well controlled	Not Well Controlled	Very Poorly Controlled
Impairment	**Symptoms**	<= 2 days/wk	>2days/wk	Throughout the day
	Nighttime awakenings	<=1x/month	>1x/month	>1x/wk
	SABA use for symptom control (not EIA)	<= 2 days/wk	> 2 days/wk	Several times/day
	Interference with normal activity	None	Some	Extreme
Risk	**Exacerbations requiring oral corticosteroids**	0-1/year	2-3/year	>3/year
	Treatment related adverse effects	Can vary from none to very troublesome. Consider in overall assessment of risk		

(Continued)

Table 7 *(Continued)*

Stepwise treatment approach

Intermittent Asthma	Persistent Asthma: Daily Medication If Step 3 or higher is required, should refer to asthma specialist				
Step 1 ***Preferred*** SABA prn	**Step 2** ***Preferred*** Low dose ICS ***Alternative*** Cromolyn or montelukast	**Step 3** ***Preferred*** Medium dose ICS	**Step 4** ***Preferred*** Medium dose ICS + either LABA or montelukast	**Step 5** ***Preferred*** High dose ICS + either LABA or montelukast	**Step 6** ***Preferred*** High dose ICS + either LABA or montelukast Oral systemic corticosteroids

Patient Education and Environmental Control at each Step

- Quick-Relief Medications for All Patients
- SABA as need for symptoms. With viral respiratory infections, SABA q4-6h. Consider short course of oral/parenteral steroids if severe

b) 5-11 years of age

Determine severity when initiating therapy

Components of severity		Classification of Asthma Severity (0-4 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	**Symptoms**	<= 2 days/wk	>2 days/wk	Daily	Throughout day
	Nighttime awakenings	< 2x/month	3-4x/month	>1x/wk	Nightly
	SABA use for symptom control (not EIA)	<= 2days/wk	>2days/wk, <1x/day	Daily	Several times/day
	Interference with normal activity	None	Minor	Some	Extreme
	Lung function	Normal FEV1 between exacerbations FEV1>80% predicted FEV1/FVC>85%	FEV1 =>80% predicted FEV1/FVC>80%	FEV1=60-80% predicted FEV1/FVC=75-80%	FEV1<60% predicted FEV1/FVC<75%
Risk	**Exacerbations requiring oral corticosteroids**	0-1/year	>=2 exacerbations in 6m requiring oral steroids, or >= 4 wheezing episodes/year lasting >1day and risk factors for persistent asthma. Exacerbations of any severity can occur in asthmatics in any severity category		
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3 and consider short course of steroids	Step 3 or 4 and consider short course of steroids
		Evaluate level of asthma in 2-6 weeks. Adjust therapy if no clear benefit, reconsider diagnosis			

Once Control is achieved, continue to assess control on ongoing basis (approx every 1-6 months)

Components of Control		Classification of Asthma Control (0-4 years of age)		
		Well controlled	Not Well Controlled	Very Poorly Controlled
Impairment	**Symptoms**	<= 2 days/wk	>2days/wk	Throughout the day
	Nighttime awakenings	<=1x/month	>1x/month	>1x/wk
	SABA use for symptom control (not EIA)	<= 2 days/wk	> 2 days/wk	Several times/day
	Interference with normal activity	None	Some	Extreme
Risk	**Exacerbations requiring oral corticosteroids**	0-1/year	2-3/year	>3/year
		Consider severity and interval since last exacerbation		
	Reduction in lung growth	Evaluation requires long term follow-up		
	Treatment related adverse effects	Can vary from none to very troublesome. Consider in overall assessment of risk		

(Continued)

Stepwise treatment approach

Intermittent Asthma	Persistent Asthma: Daily Medication If Step 3 or higher is required, should refer to asthma specialist				
Step 1 ***Preferred*** SABA prn	**Step 2** ***Preferred*** Low dose ICS ***Alternative*** Cromolyn, nedocromil, theophylline or montelukast	**Step 3** ***Preferred*** Low dose ICS + either LABA, LTRA or theophylline ***Alternative*** Medium dose ICS	**Step 4** ***Preferred*** Medium dose ICS + either LABA ***Alternative*** Medium dose ICS + either LTRA or theophylline	**Step 5** ***Preferred*** High dose ICS + either LABA or montelukast ***Alternative*** High dose ICS + either LTRA or theophylline	**Step 6** ***Preferred*** High dose ICS + either LABA + oral systemic corticosteroids ***Alternative*** High dose ICS + either LTRA or theophylline + oral systemic corticosteroids

Patient Education and Environmental Control at each Step

- Quick-Relief Medications for All Patients
- SABA as need for symptoms. Intensity of treatment depends on severity of symptoms, up to 3 treatments at 20 minute intervals as needed. Short course of corticosteroids may be required.
- Caution: Increasing use of SABA or use greater than 2 days per week for symptom relief not related to EIA indicates inadequate control and need to step up treatment

The above tables were adapted from NAEPP EPR-3 guidelines

[a]The tables were adapted from NAEPP EPR-3 guidelines.

Table 8
Nonpharmacologic Treatment Modalities for Asthma

Objective measurement of asthma status
Peak flow monitoring
Pulmonary function testing
Spirometry
Environmental control and identifying sensitivities
Allergy skin testing
Environmental exposure assessment
Allergen avoidance
Monitoring and prevention
Asthma diary sheets
Asthma action or management plans
Education
Asthma education
Exercise regimen
Asthma camps for children
Dietary assessment
Tobacco prevention counseling for parents
Internet
Printed material
Special help for children
Use of spacer devices
Small volume nebulizer machines

Avoidance of seasonal allergens, mainly pollens, is difficult without making unreasonable changes to one's lifestyle, because these allergens are windborne and can travel for miles. On the other hand, there are well-established strategies developed for avoidance of indoor allergens. Because we spend up to a third of our time sleeping in close quarters with dust mites, the bedroom should have a high priority when developing an indoor allergen avoidance program. Dust mites require water to survive, and damp environments allow them to reproduce and proliferate. Keeping the relative humidity of the home around 50–55% will help keep dust mite concentrations down. In addition, the uses of mattress and pillow encasings, as well as high-efficiency particulate air (HEPA) filters are additional control measures that may provide benefit. The child with asthma should also not be the one to vacuum as the action of vacuuming can disturb dust mite reservoirs and release these particulates into the breathing zone. Good ventilation and filtration systems in the home can also help to reduce exposure. Additional measures of allergen avoidance are illustrated in Fig. 4.

Avoidance of pet allergen is best accomplished by getting rid of the pet altogether. This is often an insurmountable task because of the emotional attachment that patients, especially children, have towards their pets. If getting rid of the pet is not possible, then at least keeping the pet out of the bedroom may help. Washing the pet regularly is of

Fig. 4. Avoidance measures for common allergens.

questionable benefit. Numerous "denaturing" preparations are also available, but again, their effectiveness is controversial.

Molds are common allergens that originate from the outdoor environment and are particularly prevalent in moist climates. The presence of a high indoor to outdoor mold count ratio is probably indicative of a water leak or at least of excessive humidity indoors. As in the case of dust mites, keeping the relative humidity of the indoor environment at around 50% helps to reduce mold spore exposure. Substrates for mold growth include decaying living material, damp paper or books, or household plants. Removal of these substrates may reduce indoor mold spore levels.

As mentioned earlier, pollens are more difficult to avoid, but patients and their parents can glean information regarding outdoor exposures by accessing the American Academy of Allergy, Asthma and Immunology (AAAAI) National Allergy Bureau

(NAB) website (http://www.aaaai.org/nab). The site contains information on pollen and mold counts derived from counting stations run by certified counters. As of October 2010, there were 85 counting stations throughout the United States, as well as 2 in Canada and 2 in Argentina.

Spirometry in Children

Spirometry provides information on lung mechanics. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), the FEV1/FVC ratio, and peak expiratory flow (PEF) are the four main parameters measured during spirometry. Measurement of spirometry before and after bronchodilation treatment can help determine if there is reversibility of lung function. Because sometimes patient history, especially in children, can be inaccurate, spirometry provides an objective assessment of the child's condition. Spirometry can be attempted at about 4–5 years of age, but at these very young ages, obtaining reliable results depends on the child's ability to follow instructions and their physical coordination. Data on predicted values of spirometry parameters have been obtained by several investigators and are dependent on age, gender, height, and ethnic background. However, as in the case of peak flow measurement, there is significant individual variability, and it is important to establish each child's baseline spirometry. Obviously, as the child grows, this will change, so frequent updates may be needed. While spirometry is not diagnostic of asthma, it serves as a complementary test to the history and physical that can be used to support the diagnosis of asthma.

The Use of Peak Flow Meters in Childhood Asthma

Measurement of peak flow may part of an asthma management plan. Peak flow measurements provide objective evaluation of an asthmatic's condition. With the proper teaching, even a 5 year old can learn to use a peak flow meter effectively (Fig. 5). Usually, peak flow measurements are done in the morning and in the evening, but the peak flow meter can be used throughout the day or night, whenever necessary. Most new peak flow meters are small enough to fit in a pocket or a purse. Traditional peak flow meters are available for children and adults. The low range peak flow meters usually measure up to about 450 L/m, while the high range measure up to 800 L/m. The peak flow zonal system, based on the child's personal best peak flow, is a convenient and simple method for parents and patients to assess how they are doing, whether to administer a breathing treatment, and whether to seek additional help. Electronic versions of peak flow meters are also available. These have the advantage of being able to record and store data that can be analyzed and trended on a computer. Some of the newer electronic versions can also measure FEV1, which is considered to be a more reliable measurement of airway obstruction as it is not as dependent on patient technique or effort. An assortment of peak flow meters and spacers is shown in Fig. 6.

Asthma Diary Sheets and Asthma Assessment Questionnaires

Asthma diary sheets (illustrated in Fig. 7) provide patients with a means to keep track of their symptoms and their peak flows. The recent availability of electronic peak flow meters with memory is an alternative way to monitor a patient's asthma status, which is

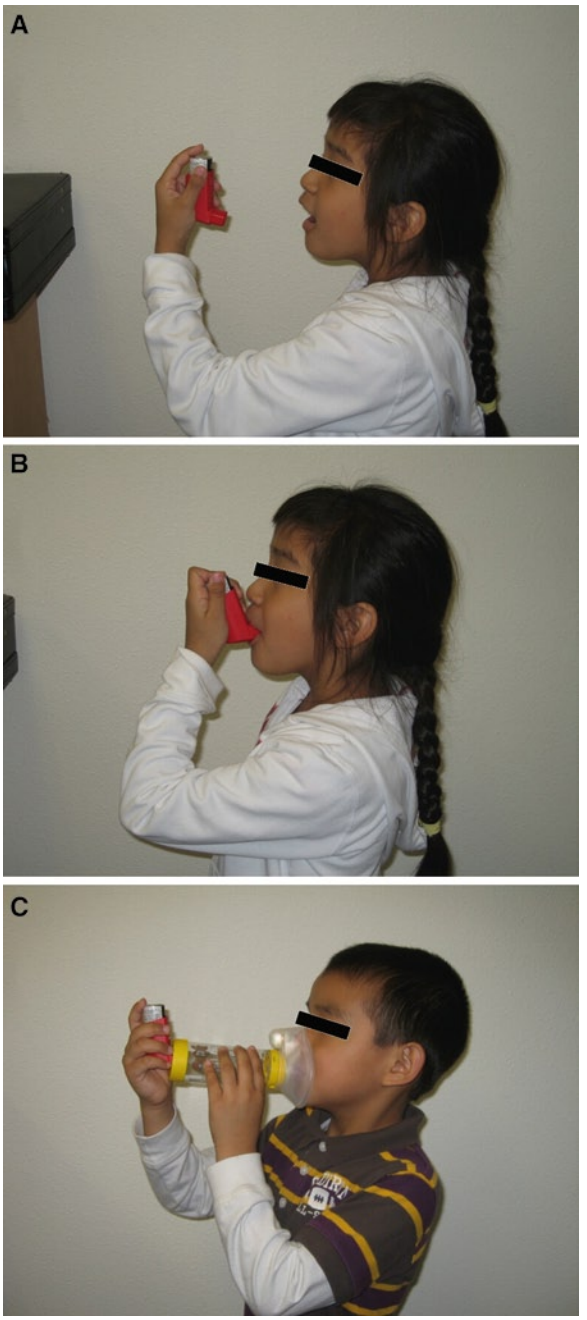


Fig. 5. Inhaler technique. (**A**) Open mouth technique. (**B**) Closed mouth technique. (**C**) Using a spacer and a mask.

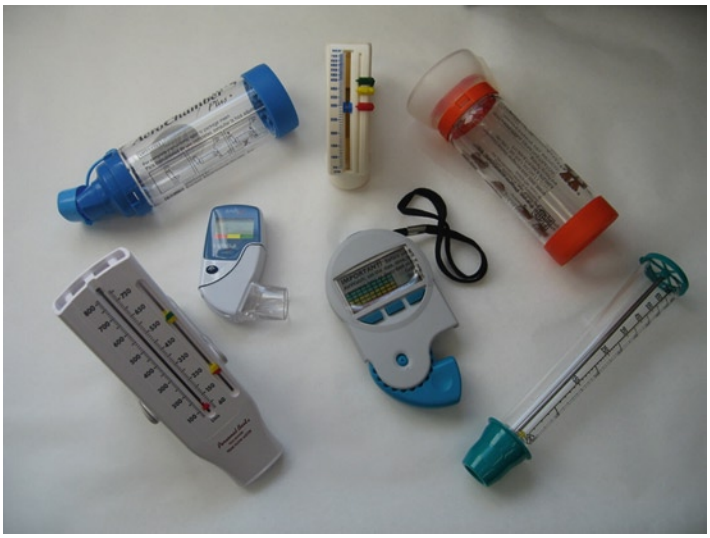


Fig. 6. A sampling of peak flow meters and spacer devices.

similar to monitoring blood pressure with an automatic blood pressure cuff or diabetes with a home glucose monitoring kit. Monitoring of peak flows not only gives a continuous assessment of the patient's condition, but also may help as a reminder for patients to take their control medications, thus improving compliance. Patients should be instructed to bring their asthma diary sheets to their doctor visit, so that their progress can be reviewed. Besides symptoms and peak flows, there is space to record other pertinent information, such as β-agonist use, exposures that are out of the ordinary, addition of new medications, etc.

In addition to home monitoring, patients should complete an asthma assessment questionnaire each time they visit their asthma care provider. The asthma assessment questionnaire is a tool that can be used to evaluate control, impairment, and can also help to identify gaps in patient education. From the asthma assessment questionnaire, a great deal of important information can be obtained, such as whether the patient is compliant with medications, if they are overusing their rescue inhaler, are they having too many nighttime awakenings, is their daily activity restricted, and so on, all of which addresses asthma control. Figure 8 shows an independently developed asthma assessment questionnaire, which has not been validated. Some questionnaires, such as the ACT (Allergy Control Test) or ATAQ (Allergy Therapy Assessment Questionnaire), have been validated and have been distributed for use by physicians and patients.

Asthma Action Plans

The components of an asthma management plan are shown in Fig. 9. Asthma action plans are an important part of successful asthma management. They provide written guidance for parents and patients once they leave the doctor's office or hospital. This is important because sometimes asthma treatment can be complicated for patients, and parents and patients can become overwhelmed with all the instructions about multiple

Week 1								
Date								
		Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Morning	Peak flow							
	FEV1							
	Symptoms							
Afternoon	Peak flow							
	FEV1							
	Symptoms							
Evening	Peak flow							
	FEV1							
	Symptoms							
SABA use								
Regular medications								
New medications								
Exposures								
Comments								
Week 2								
Date								
		Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Morning	Peak flow							
	FEV1							
	Symptoms							
Afternoon	Peak flow							
	FEV1							
	Symptoms							
Evening	Peak flow							
	FEV1							
	Symptoms							
SABA use								
Regular medications								
New medications								
Exposures								
Comments								

Fig. 7. An asthma diary.

medications, how to use a peak flow meter, and what to do in an emergency. The asthma action plan can also serve as a refresher course for patients, who have recently been discharged from the hospital after an admission for an asthma exacerbation. Involving schoolteachers in a child's asthma action plan can also help to improve the overall asthma control and quality of life *(18)*.

Name:_____Date:_____Age:

_____

Date of previous assessment:_____

Asthma control parameters

1	# days in the past week with wheezing, coughing, shortness of breath, chest tightness	
2	# nights in the past week awakening with symptoms listed in (1)	
3	Days in the past week that asthma has restricted physical activity	
4	# asthma attacks since last assessment	
5	# emergency department visits since last assessment	
6	# doctor visits for acute attacks since last assessment	
7	# puffs of rescue medications used in the past week	
8	# school days or work days lost since last visit	
Total score		

How would you characterize your asthma?

Poorly controlled Fair control Good control Well control

Have you been using your peak flow meter? Y_____N_____

Have you been charting your peak flows? Y____N_____

What is your best peak flow?_____Average peak flow?_____

Would like to receive more information on:

Medications

Avoidance or environment control

Immunotherapy

Inhaler technique

Exacerbations

Fig. 8. A sample asthma assessment tool.

An Asthma Action Plan developed for_____ Date: _____ DOB: _____ Gender: M/F

Address: _____ Tel: _____ E-mail: _____

Date of diagnosis: _____ Age at diagnosis: _____ Personal best PF: _____ Date measured: _____

Asthma disease classification: Mild intermittent _____ Persistent: Mild _____ Moderate _____ Severe _____

Pulmonary Function Test: Date: _____ FVC: _____ FEV1: _____ PEF: _____

Known triggers: Exercise _____ Viral infections: ____ Allergies:_____ Other: _____

Allergic triggers: Dust mite Dog Cat Mold Pollen Cockroach Mouse Other: _____

Nonpharmacological intervensions

Avoidance measures (Circle applicable measures): Dust mite proof encasings HEPA filters Relative humidity/temperature gauge

Dehumidifier HEPA vacuum Removal of pet Cockroach abatement Professional cleaning Home remodeling

Medications

Regular control medications: _____

_____

Rescue medications: _____

Health care provider	Telephone number	Pager number

Asthma Exacerbation Management Plan

1. Awareness of increased exposure or condition which may lead to an asthma attack
2. Evaluation of symptoms: a) Respiratory rate, b) Retractions, c) Mental status changes
3. Measure peak expiratory flow (or FEV1)
4. Zonal system for evaluating asthma status

Green zone – all clear No symptoms Normal daily activities Control medications effective	Peak flow above_____	Take regular control medications
Yellow zone – action Increased symptoms Unable to perform certain tasks Increased use of β-agonist	Peak flow between_____and _____	Increase inhaled steroid _____ to _____ puffs per day. Take β-agonist inhaler and measure peak flow. If improved, monitor closely. If not improved, repeat β-agonist, proceed to seek professional help
Red zone – alert Symptoms > 24 hours Difficulty breathing Ineffective relief with β-agonists	Peak flow below	Add oral steroid_____mg/day (_____mg/kg/day). Take β-agonist inhaler or nebulization treatment. If symptoms persist or not improvement in peak flow, proceed to seek professional help

Call 911 or proceed to hospital if danger signs occur, such as lack of response, difficulty breathing or ambulating due to respiratory distress or if lips or fingernails are blue

Fig. 9. An asthma management plan. An asthma action plan must include information on how to assess the child's condition. Known triggers should be listed and the PEF zonal system can be used to provide easy instructions for patients and parents. The form also allows for entering medication doses.

One of the reasons for the persistently high asthma morbidity in the face of newly developed asthma medications is that patients do not usually follow all the instructions to ensure effective asthma control. Written action plans help circumvent this problem, making it easier for patients to be compliant. Besides medication instructions, asthma

action plans can also give instructions on environmental control and avoidance of triggers. Instructions on when to seek professional help is also entered on an asthma action plan.

OBJECTIVE METHODS OF ASSESSING AIRWAY INFLAMMATION

Nitric Oxide

Fractional exhaled nitric oxide (FeNO) is elevated in children with asthma. It has been demonstrated to be a marker of eosinophilic airway inflammation in children with asthma, and it also responds to glucocorticoid therapy *(19)*. Measurement of FeNO may be an effective way of monitoring airway inflammation and bronchial hyperresponsiveness. Recently, increased levels of FeNO have been found to correlate with risk of asthma in children *(20)*. Equipment to measure FeNO is currently available, but this test has not yet been widely adopted, mainly because there is still controversy regarding its value in managing the asthmatic child, but also because insurance companies have been slow to reimburse for this test adequately. As these issues are sorted out, FeNO may yet prove to be a valuable tool to assess airway inflammation.

Eosinophil Cationic Protein

Elevated ECP levels in cord blood are predictive of atopy. ECP is a marker of eosinophil activation. Serum ECP levels correlate with airway inflammation in wheezing children *(21)*. In a retrospective study of 441 patients with respiratory disease, the sensitivity and specificity for asthma was 70 and 74%, respectively. ECP was not predictive for any other respiratory disease *(22)*. When patients with asthma are bronchial challenged with allergen, activation of eosinophils and generation of specific eosinophilic mediators result. Evaluation and continued monitoring of eosinophil and ECP may be a way to assess efficacy of asthma therapy and airway inflammation in children with allergic asthma *(23)*. Both leukotriene receptor antagonists and inhaled corticosteroids have been associated with a reduction in sputum ECP levels in patients with mild to moderate persistent asthma *(24)*. A response of serum ECP levels to glucocorticoid treatment has also been observed *(25)*.

PHARMACOLOGIC MANAGEMENT

Controller Medications

Inhaled Corticosteroids

The beneficial effect of ACTH in the treatment of asthma was shown in 1949 *(26)*. Subsequently, oral corticosteroids were also shown to be beneficial but side effects limited their widespread use. The introduction of inhaled corticosteroids in 1972 heralded a new age in asthma treatment, and inhaled corticosteroids have been the first-line treatment in the control of asthma since then. Corticosteroids work by switching off inflammatory genes through their interaction with the glucocorticoid receptor and recruitment of histone deactylase-2 (HDAC-2). By regulation of transcription of

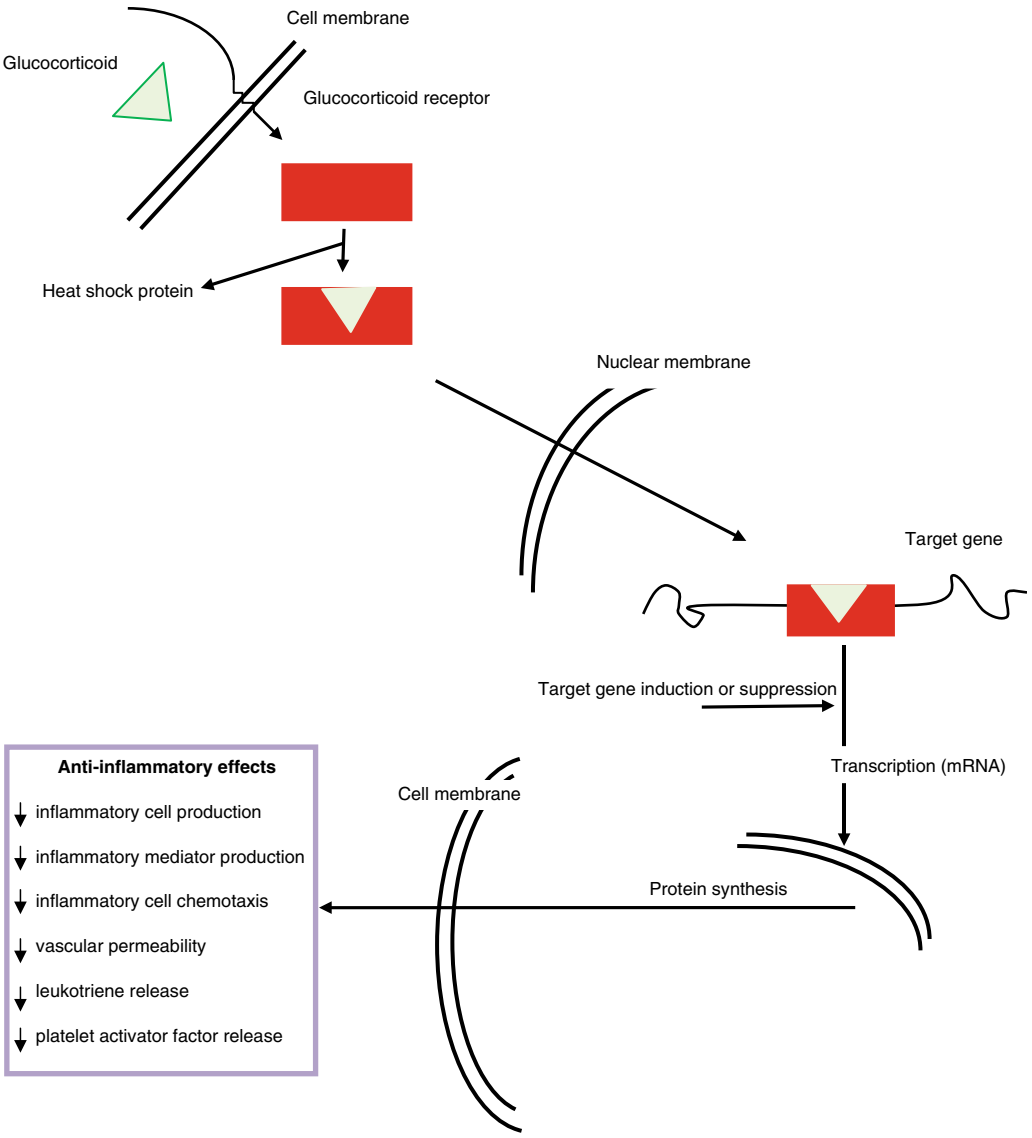


Fig. 10. Mechanism of action of glucocorticoids.

inflammatory genes or their promoters, they exert a number of anti-inflammatory effects (as illustrated in Fig. 10). The relative potency of the various steroids is given in Table 9.

All of the different inhaled corticosteroids can be used in children. Budesonide is also available in nebulized form, in three strengths, 0.25, 0.5, and 1.0 mg. A multicenter study of 481 children demonstrated improvement in daytime and nighttime symptoms when treated with nebulized budesonide. Inhaled corticosteroids are now the first-line drug for treatment of mild, moderate, and severe persistent asthma.

Table 9
Steroid Dose Equivalency

Scientific name	*Dose equivalency (mg)*	*Relative potency*	*Half-life (h)*	*Comment*
Cortisone	25	0.8	8–12	
Hydrocortisone	20	1	8–12	
Prednisone	5	4	12–36	Available in liquid or tablet form
Prednisolone	5	4	12–36	Available in liquid or tablet form
Methylprednisolone	4	5	12–36	Used in ED or hospitalized patients
Triamcinolone	4	5	12–36	
Paramethasone	2	10	36–72	
Dexamethasone	0.75	26.67	36–72	
Betamethasone	0.6	33.34	36–72	

The issue of adverse effects of inhaled steroids in children has been extensively studied. Steroids are associated with numerous side effects (*see* Table 10). Most of these have been attributed to oral or parenteral steroids. In children with asthma, the major concerns regarding inhaled or nebulized steroids have been the effect on growth *(27)*. Studies to determine if inhaled corticosteroids indeed have such an effect are difficult to conduct because asthma itself has been associated with growth retardation *(28)*. Results have therefore been inconsistent; however, the bulk of the evidence suggests that even if there is growth retardation, this is usually reversible, and there is a period of "catch-up" growth. Moreover, even if corticosteroids do indeed affect growth, the extent of growth retardation is minimal. Thus, the risk of growth retardation is small compared to the potential for serious asthma exacerbations. Adrenal suppression in children on inhaled steroids is also not a significant problem. In a study of 14 children on a dry-powder beclomethasone dipropionate inhaler, there was no suppression of the hypothalamic-pituitary-adrenal (HPA) axis *(29)*. The dose of beclomethasone was 12–25 μg/kg/day. Other studies have failed to demonstrate adverse effects on the HPA axis *(30)*. On the other hand, use of high doses of fluticasone has been shown to cause HPA axis suppression *(31)*. It is not known if there is any clinical significance to these observed effects. A list of the available inhaled corticosteroids and their daily dosing regimens in pediatrics is given in Table 11.

Long Acting β-Agonists

LABAs are available either alone or in combination with an inhaled corticosteroid. The two available LABAs currently available are salmeterol xinafoate and formoterol fumarate. Salmeterol xinafoate possesses a long hydrocarbon chain connecting the binding site with the active site of the molecule. Theoretically, this conformation allows repetitive interaction between the active site and the target receptor, as the binding site is firmly attached to an alternate site on the cell membrane and the long chain acts as a

Table 10
Adverse Effects of Asthma Medications

β-*Agonists*	*Inhaled steroids*	*Systemic steroids*	*Anticholinergics*	*Leukotriene pathway modifiers*	*Theophylline*	*Anti-IgE*
Tremors	Dysphonia	Hyperglycemia	Dry mouth	Elevated liver enzymes	Gastritis	Anaphylaxis
Tachycardia	Oral thrush	Hypertension	Blurry vision	Churg–Strauss syndrome	Seizures	
Muscle spasms[a]	Growth retardation[a]	Osteonecrosis	Increased wheezing	Risk of suicide	Tremors[a]	
Hypokalemia	Adrenal suppression[a]	Osteoporosis			Insomnia	
Tachyphylaxis		Cushing's syndrome			Nausea/vomiting	
Hyperglycemia		Adrenal suppression[a]			Tachycardia	
Headache		Moon facies[a]			Hypokalemia	
Hyperactivity[a]		Gastritis[a]			Hypoglycemia	
Increase in asthma mortality[b]		Psychological disturbances[a]			Central nervous system stimulation	
		Acne[a]			Headache	
		Cataracts			Hyperactivity[a]	
		Hirsutism[a]				
		Decreased platelet function				
		Growth retardation[a]				

[a] Of particular importance in children.
[b] Not clearly established, may be related to other confounding issues.

Table 11
Daily Pediatric Doses of Inhaled Corticosteroids

				Mild persistent	*Moderate persistent*	*Severe persistent*
Medication	*Pediatric indication*	*Dose/ actuation (μg)+*	*Dosing frequency*	*Number of actuations/day*	*Number of actuations/day*	*Number of actuations/day*
Beclomethasone dipropionate	5–11 Year	40	Bid	2	2–4	
		80	Bid		2	2
Triamcinolone[a]	6–12 Year	100	Bid to qid	4–8	8–12	8–12
Flunisolide	6–15 Year	250	Bid	4	4	4
Budesonide	6 Year and older	200	Bid	1	2	4
Nebulized budesonide	12 Month to 8 year	Ampules of 250, 500, and 1,000 mg	Bid	1 mg total daily dose		
Fluticasone	12 Year and older	44	Bid	2–4	4–10	
		110			2–4	4–8
		220			2–4	4–8
Fluticasone diskus	4–11 Year	50	Bid	2–4		
		100			1–4	2–4
		250			1–4	2–4
Mometasone furoate	4–11 Year	110	Bid	1	2	4
		220	Bid		1	2

[a] Triamcinolone inhaler is no longer commercially available.
[+] These are suggested doses modified from the package inserts of each drug.

tether. Salmeterol is indicated down to age 4. It used to be available as an MDI and the diskus, but now only the diskus is available. The dose per puff in the diskus is 50 μg and should be taken twice daily. The terminal elimination half-life of salmeterol is 5.5 h. Formoterol is available in an aerolizer, a dry powder device in which a capsule must be punctured in a specialized chamber. A total of 12 μg of drug is contained in one capsule. Formoterol is also dosed twice daily. The mean elimination half-life of formoterol in healthy subjects is 10 h. The structures of salmeterol and formoterol are illustrated in Fig. 11.

The LABAs are not generally considered first-line treatment for persistent asthma and the current recommendation is that it be used as an add-on therapy. Recently, case reports appeared in the literature of asthma-related deaths associated with salmeterol use. The FDA subsequently attached a black box warning on increased asthma-related deaths to the LABA class of drugs. The issue is, however, still under significant debate due to the presence of other confounding variables that may or may not have been taken into account in the studies. The recommendation for the use of LABAs is to discontinue the LABA once the patient's asthma has been stabilized and control of his/her asthma has been achieved. It remains to be seen if there will be adverse consequences of such a recommendation *(32)*.

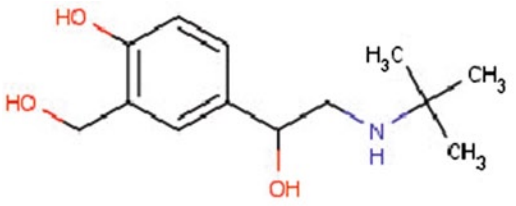
Cromolyn and Nedocromil

These two unrelated compounds have an excellent safety profile. Their chemical structures are illustrated in Fig. 12. Both are mast cell stabilizers, and both also inhibit the activation and release of inflammatory mediators from eosinophils. This appears to be mediated through blockage of chloride channels *(33)*. Both early and late phase reactions to allergen challenge are inhibited. Cromolyn is derived from the plant, *Ammi visnaga*, or bishop's weed. The commercial product can be administered in either nebulized form or by MDI. The dose of cromolyn via MDI is 1 mg/actuation, where as the dose of nedocromil is 2 mg/actuation delivered from the valve and 1.75 mg/actuation delivered from the mouth piece of the inhaler. The dose of cromolyn delivered via nebulizer is 20 mg/treatment. The terminal elimination half-life of nedocromil sodium is 3.3 h. Nedocromil sodium is indicated in children 6 years of age or older. Cromolyn sodium is regularly used in very young children via nebulizer.

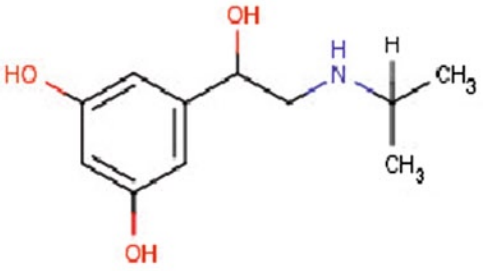
Because of the unfavorable dosing schedule, Cromolyn, a previously widely used medication, has given way to other nebulized anti-inflammatory medications, such as the glucocorticoids. Nedocromil has an unpleasant taste, and along with cromolyn, has fallen out of favor recently.

Leukotriene Pathway Drugs

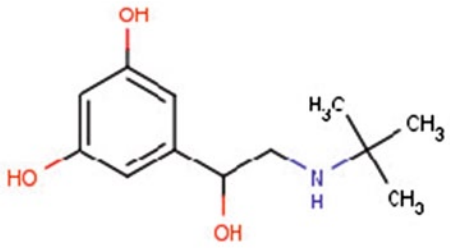
Drugs that block the effects of leukotrienes were first introduced in the early 1990s. Two strategies were used in the development of these drugs, inhibiting their synthesis or blocking their action at the Cys-LT receptor level. Drugs that block leukotriene synthesis, such as zileuton, have been associated with liver toxicity. The leukotriene receptor antagonists have a much better safety profile and dosing schedule, and have been the more widely used medications. The mechanism of action of leukotrienes is shown in Fig. 13.



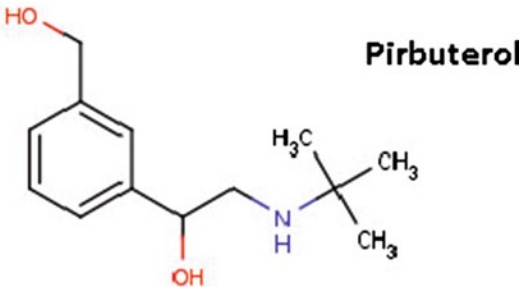
Albuterol



Metaproterenol



Terbutaline



Pirbuterol

Fig. 11. Structure of the β-adrenergic agonists. Comparison of the structures of albuterol and salmeterol helps to explain the long half-life of salmeterol. The long chain connects the binding site to the active site of the molecule. Once bound at the binding site, the long chain is theorized to swing back and forth, allowing the active site to repeatedly come in contact with the receptor site, prolonging the action of the drug.

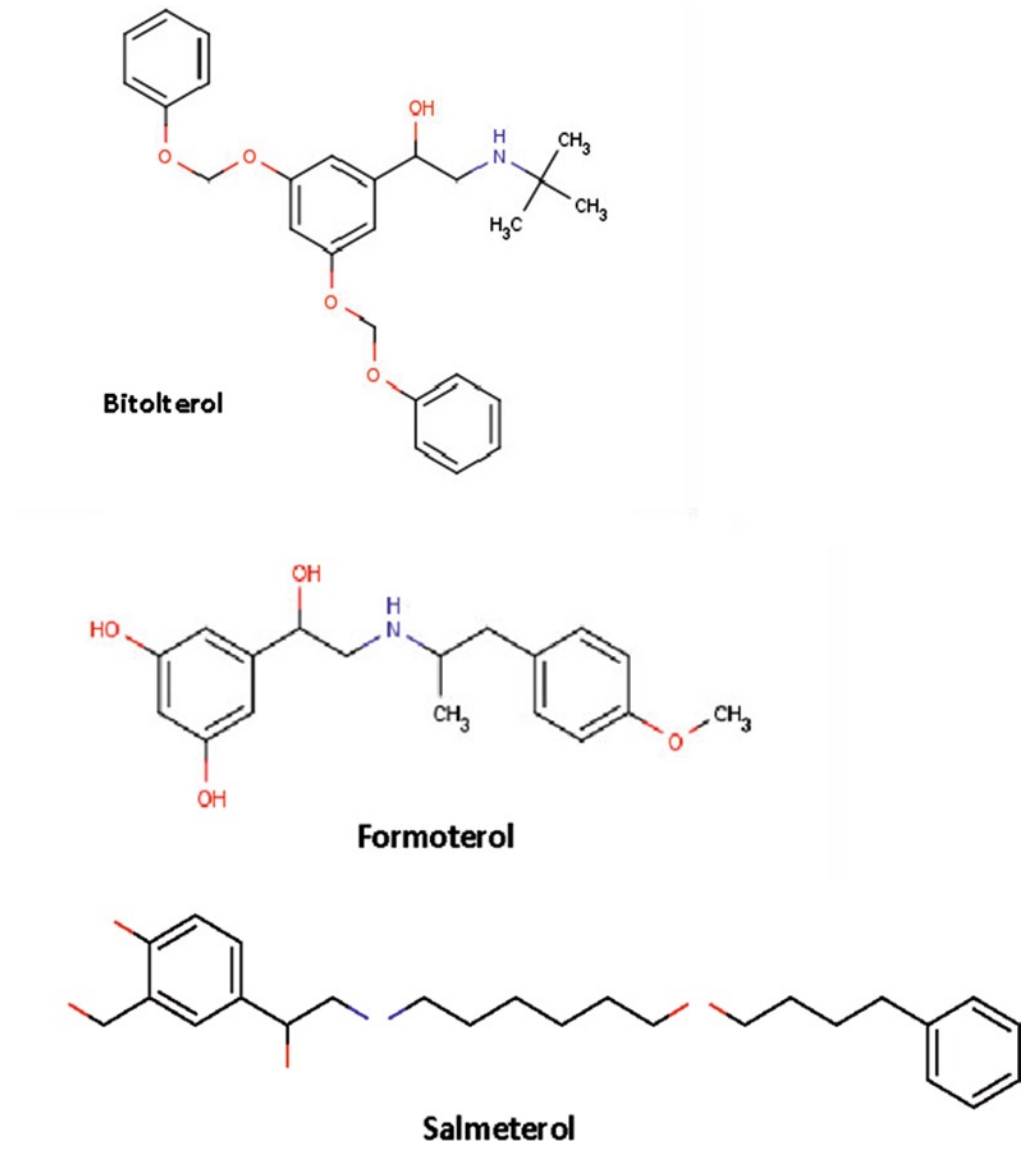


Fig. 11. *(Continued)*

As an inflammatory mediator in asthma, leukotrienes are 1,000 times more potent than histamine *(34)*. The effects of LTC4, LTD4, and LTE4 on the Cys-LT receptor include an increase in mucous production, constriction of bronchial smooth muscle, augmentation of neutrophil and eosinophil migration, and stimulation of monocytes aggregation. In general, side effects of the leukotriene receptor antagonists are mild, with the exception of Churg–Strauss syndrome, a vasculitis associated with peripheral eosinophilia, elevated serum total IgE, patchy pulmonary infiltrates, cutaneous purpuric lesions, and pleural effusions. Leukotriene pathway modifiers can also affect metabolism of theophylline and a number of other drugs.

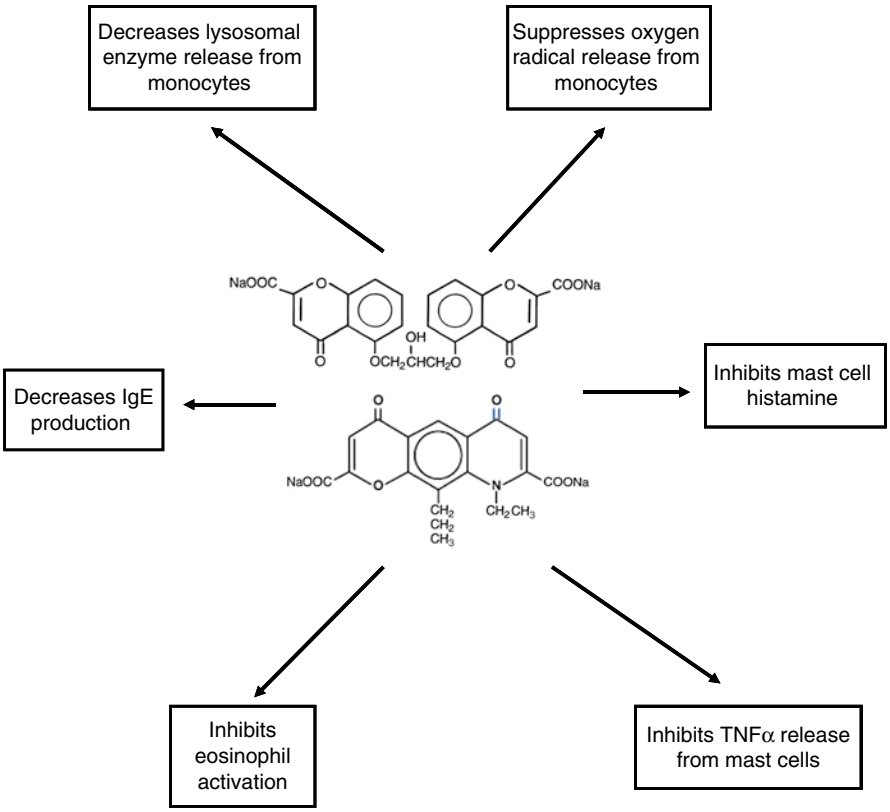


Fig. 12. Structure and anti-inflammatory effects of cromolyn and nedocromil.

Montelukast, the most commonly used leukotriene pathway drug is approved in children 1 year and older for asthma, 6 months and older for perennial allergic rhinitis, and 24 months and older for seasonal allergic rhinitis. Montelukast has been particularly useful in the treatment of cough variant asthma in children *(35)*. Early reports of an association between suicide and montelukast have been re-assessed, and the conclusion is that the risk of suicidal ideation in montelukast use is low. However, it was recommended that patients should be screened for behavioral anomalies including suicide ideation, which are generally more common in adolescents and the elderly.

Antihistamines

Whether to use antihistamines in children with asthma has been a hotly debated topic. The FDA originally had a warning on using antihistamines in asthma which was a class effect, so any newer antihistamines that were introduced all carried the same warning. However, while the first-generation antihistamines had side effects that could potentiate an asthma exacerbation, such as the anticholinergic effects of drying, as well as the

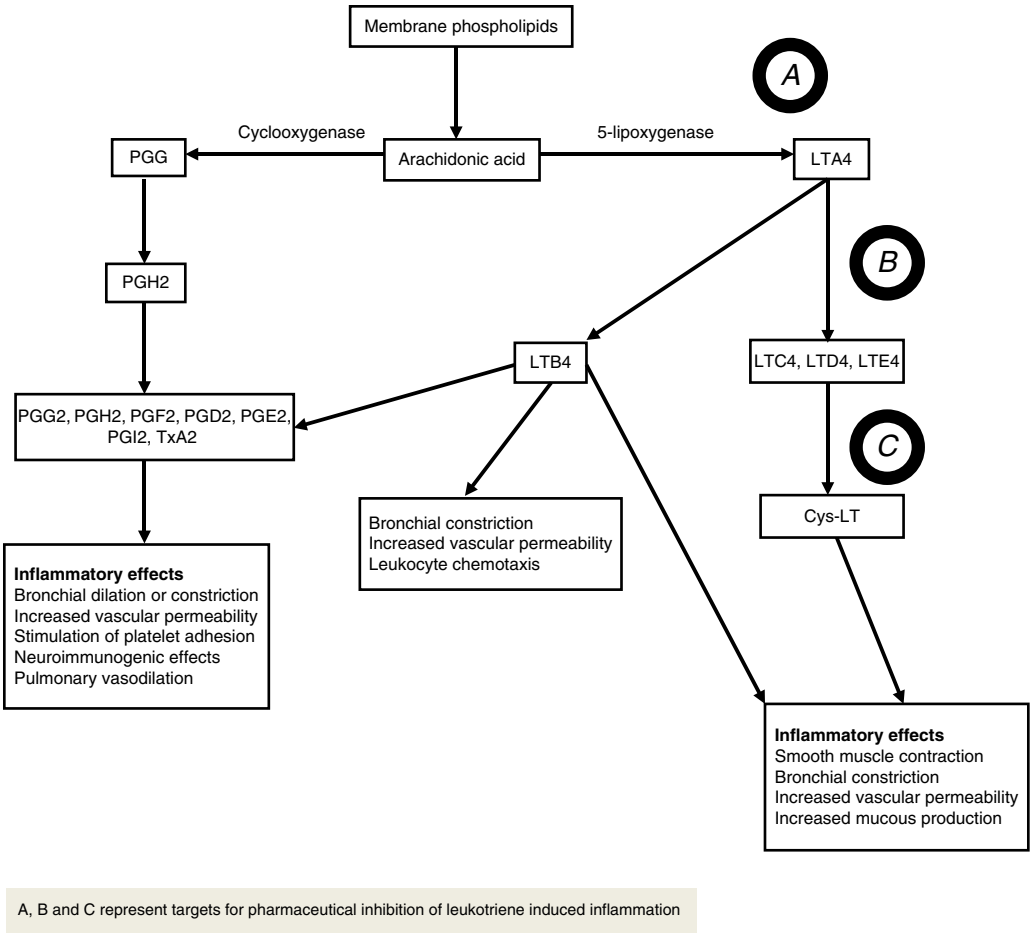


Fig. 13. Mechanism of action of leukotriene pathway modifiers.

sedative effects, the second-generation antihistamines have much less of these adverse effects and should be safe in asthmatics. They should also provide some benefit, especially in children, where the greater proportion of asthma is associated with allergies *(36)*. The currently available second-generation antihistamines in the United States are cetirizine, levocetirizine, loratidine, desloratidine, and fexofenidine. These drugs block the allergic effect of environmental allergens, but cetirizine also inhibits leukocyte recruitment and activation and eosinophil migration *(37)*, and has been shown to decrease late leukocyte migration into antigen-challenge skin blister fluid chambers *(38)*. All three inflammatory cell lines, including neutrophils, eosinophils, and basophils were affected.

Theophylline in Childhood Asthma

Theophylline and aminophylline had their heyday in the 1980s, when almost every child with an asthma exacerbation requiring hospital admission was started on an

aminophylline drip. Similarly, most patients with asthma were placed on theophylline as a maintenance therapy. The use of this class of medications has decreased significantly since then, due to its narrow therapeutic window, and potentially severe side effects (Table 10). Aminophylline is metabolized to theophylline, which is then metabolized to caffeine.

Theophylline acts as a phosphodiesterase inhibitor (Fig. 14). Its efficacy in improving symptom scores and pulmonary function test parameters is similar to inhaled steroids. Therefore, despite the undesirable effects of theophylline, there may still be role for its use as a steroid sparing agent in children with severe persistent asthma, especially those on systemic steroids. Theophylline levels should be monitored regularly every 2–3 months or more frequently if there are dosage changes, signs of adverse effects, or lack of efficacy. A list of factors and agents that influence theophylline levels and their effect is given in Table 12.

Monoclonal Anti-IgE

Omalizumab (Xolair) is a recombinant DNA-derived humanized IgG1a monoclonal antibody, which binds specifically to human IgE. Binding of IgE by omalizumab inhibits both early and late-phase reactions of asthma. Effects of omalizumab include a reduction in serum IgE levels and a decrease in allergen-induced bronchoconstriction *(39)*. Omalizumab is indicated for patients 12 years of age or older who have moderate to severe persistent allergic asthma with a positive skin or blood allergy test, who have IgE levels between 30 and 700 IU/mL. Table 13 shows the dosing schedule for omalizumab. Side effects include malignancies, anaphylactic reactions, and local injection reactions. The high cost of Xolair can be potentially offset by savings in the cost of asthma exacerbations, e.g., hospital costs, outpatient emergency department visits, rescue medications, and indirect costs from loss of productivity by the patient.

Reliever Medications (Rescue Medications)

Short Acting β-Agonists

The mechanism of action of the β-agonists is through activation of the β2-adrenergic receptors on airway smooth muscle cells, which leads to activation of adenyl cyclase. This, in turn, leads to an increase in the intracellular concentration of cyclic adenosine monophosphate (cAMP). cAMP activates protein kinase A, causing inhibition of phosphorylation of myosin and lowering of intracellular calcium concentrations, which then results in relaxation of bronchial smooth muscle. β2-Adrenergic receptors are present in all airways, from the trachea to the terminal bronchioles. Another effect of the increase in cAMP concentration is the inhibition of mediator release from mast cells. Adverse effects of β-agonists include paradoxical bronchospasm, cardiovascular effects, central nervous system stimulation, fever, tremors, nausea, vomiting, and an unpleasant taste (Table 10).

The short acting β-agonist (SABA) used include albuterol, levalbuterol, pirbuterol, bronkosol, isoproterenol, metaproterenol, and terbutaline (Fig. 11). The more recently developed β-agonists are more specific to β2-adrenergic receptors, optimizing the effects on bronchial smooth muscle while reducing cardiac side effects, and have made

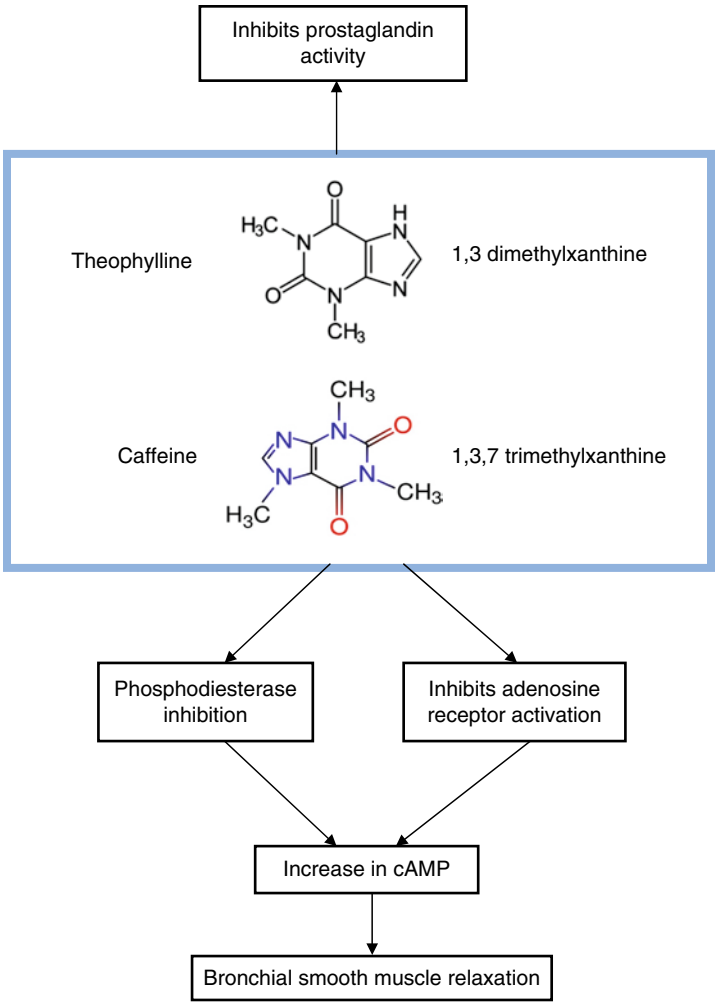


Fig. 14. Structure and bronchodilatory effects of theophylline and known actions of theophylline and caffeine. Actual mechanism for the bronchodilatory effect of methylxanthines is not completely understood. Phosphodiesterase inhibition appears to be the most likely mechanism, but theophylline is known to have other activity, as shown.

older less-specific drugs such as metaproterenol and isoproterenol obsolete. Dosing recommendations for SABA inhalers are given in Table 14. Albuterol, the most commonly used β-agonist, is available as a 0.083% nebulization solution. The use of β-blockers is a relative contraindication in children with asthma. β-Blockers have been associated with worsening asthma *(40)*.

Albuterol is a 50–50 racemic mixture of the stereoisomers R-albuterol (levalbuterol) and S-albuterol. Levalbuterol is available in both inhaler and nebulizer solution form. There are three available doses of levalbuterol, 0.31, 0.63, and 1.25 mg for nebulization. Levalbuterol increases mean FEV1 by 31–37% in children between the ages of 6 and 11 *(41)*. The elimination half life of levalbuterol is 3.3 h compared to 1.5 h for albuterol.

Table 12
Factors Affecting Theophylline Metabolism

Factor or drug	*Effect on theophylline levels*
Antibiotics	
Ketolides	Increase
Ciprofloxacin	Increase
Rifampin	Decrease
Macrolides: erythromycin, clarithromycin	Increase
Antiepileptics	
Phenobarbital	Decrease
Carbamazepine	Decrease
Phenytoin	Decrease
Other drugs	
Aminoglutethimide	Decrease
Disulfiram	Increase
Ticlopidine	Increase
Propranolol	Increase
Cimetidine	Increase
Allopurinol	Increase
Calcium channel blockers	Increase
Methotrexate	Increase
Other factors	
Diet	Increase/decrease
Obesity	Increase
Hypoxia	Increase
Smoking	Decrease
Viral illness	Usually increase
Pediatric and geriatric population	Usually increase

Table 13
Dosing Schedule for Omalizumab[a]

Pretreatment serum IgE (IU/mL)	*Body weight (kg)*			
	30–60	*>60–70*	*>70–90*	*>90–150*
Every 4 weeks dosing				
≥30–100	150	150	150	150
>100–200	300	300	300	See below
>200–300	300	See below	See below	
>300–400	See below			
>400–500				
>500–600				
Every 2 weeks dosing				
≥30–100	See above	See above	See above	See above
>100–200				225
>200–300		225	225	300
>300–400	300	300	375	Do not dose
>400–500	300	375	Do not dose	
>500–600	375	Do not dose		

Adapted from Omalizumab package insert.
[a]Omalizumab is FDA approved in children over 12 years of age.

Table 14
Characteristics of Inhaled or Nebulized Bronchodilator Preparations[a]

Generic name	*Dosage/inhalations or puff*	*Available delivery devices*	*Dosing frequency*	*Max puffs/day*	*Half life (h)*	*Onset of action (min)*	*Time to peak effect (min)*	*Duration of action (h)*
Albuterol	90 μg/puff or 2.5 mg/ nebulization	MDI, D, C, N	2 Puffs q4 h prn, 1 tmt q4 h prn	12	1.5	6	55–60	3
Levalbuterol	0.31, 0.63 or 1.25 mg/ nebulization or 90 μg/MDI puff	MDI, N	2 Puffs q4 h prn, 1 tmt q4 h prn	12	3.3	10–17	90	8
Metaproterenol	630 μg/puff or 15 mg nebulization	MDI, N	2 Puffs q4 h prn or 1 tmt q4 h prn	12	N/A	5–30	60–75	1–2.5
Pirbuterol	200 μg	A	2 Puffs q4–6 h prn	12	N/A	5	50	5
Bitolterol	370 μg	MDI, N	2 Puffs q6 h prn	12	N/A	3–4	30–60	5–8
Formoterol	12 μg	D	2 Puff q12 h	2	10	5	60	12
Salmeterol	25 μg	MDI, D	2 Puffs q12 h	4	5.5	10–20	45	12[b]
Ipratropium	18 μg/puff or 500 μg/ nebulization	MDI, C, N	2 Puffs q6 h prn or 1 tmt q6 h	12	2	15	60–120	3–4

[a] Some of these are no longer commercially available.
[b] Late phase reaction may be inhibited up to 30 h.
MDI Metered-dose inhaler (only HFA available now); *A* autoinhaler; *D* dry-powder inhaler; *C* combination inhaler; *N* solution for small volume nebulizer.

Albuterol is also available in oral form, either as a 2 mg/5 mL syrup or a sustained release 4 mg tablet. The oral dose in children is 0.03–0.06 mg/kg/day in three divided doses (no more than 8 mg/day). Terbutaline is also available orally in 2.5 and 5 mg tablets and is indicated for use in children over 12 years of age.

Anticholinergics

Anticholinergic inhalers are indicated for the treatment of chronic obstructive pulmonary disease (COPD), but may be of some value in the treatment of the asthmatic during an exacerbation. The mechanism of action of ipratropium bromide is through competitive inhibition of M2 and M3 muscarinic cholinergic receptors. This leads to a decrease in airway vagal tone and decreased mucous gland secretion. Bronchoconstriction is also inhibited by anticholinergic agents *(42)*. Ipratropium bromide is available in nebulized form (2.5 mL of a 0.02% solution = 500 μg), or by HFA MDI (17 μg/dose from the mouthpiece). Ipratropium bromide is not well absorbed in the gastrointestinal tract. The elimination half-life of ipratropium bromide is 1 h when taken by MDI or administered intravenously.

Mucolytics

The use of mucolytics, such as *N*-acetylcysteine and *S*-carboxymethylcysteine, in childhood asthma is controversial. Mucolytics exert their action by breaking up the disulfide bonds between mucin chains and allowing for easier clearance of mucous. On the other hand, they can cause bronchoconstriction. Although animal studies have demonstrated that *N*-acetylcysteine can improve gas exchange after methacholine challenge *(43)*, there is currently no clinical indication for the use of mucolytics in the treatment of childhood asthma.

Oral or Parenteral Steroids

Fortunately, the use of systemic steroids in the treatment of asthma has decreased in countries where access to preventative, controller medications is easy and unrestricted. Systemic steroids, administered orally or parenterally on a chronic basis, are associated with a long list of adverse effects, many of which are potentially more serious than the disease they are being used to treat. These side effects are listed in Table 10. One important side effect that is sometimes forgotten is osteonecrosis. While corticosteroid-induced osteonecrosis is more common in autoimmune diseases and transplant patients than in asthma, one should still have a high index of suspicion when treating an asthmatic child who has been on steroids for a long time *(44)*. Generally speaking, a short course of steroids to treat an asthma exacerbation is acceptable from a risk benefit standpoint. In this case, if the corticosteroid course is less than 7 days, no tapering of dose is needed. A tapering schedule should be formulated for those patients in whom steroids are being used for longer than 1 week. If the patient requires multiple courses of steroids, then the possibility of developing serious side effects should be considered.

There are several corticosteroids available to treat asthma exacerbations. These are given in Table 9. Many of the oral preparations have a very bad taste and may need to be disguised in foods in order to be able to administer them to young children. There is also available at least one form in an oral disintegrating tablet (ODT), which will facilitate compliance in young children.

TREATMENT OF EXERCISE-INDUCED ASTHMA

Exercise is a common trigger for asthma, and is particularly relevant in children, as many children are active in sports. SABAs are widely used, whereby the child takes two puffs of an albuterol inhaler prior to exercising. This has the effect of shifting the stimulus–response curve to the right. Inhaled albuterol or terbutaline provides relief for up to 1 h during exercise. Other short-acting bronchodilators that have been used in EIA include fenoterol and bitolterol. Oral bronchodilators have provided longer relief, up to 6 h for albuterol and 2–5 h for terbutaline. Cromolyn and nedocromil have been found to protect against EIA for 120 and 300 min, respectively. Theophylline has also been used in EIA, but the narrow therapeutic window and the lack of benefit observed at lower doses has hindered its widespread use. The use of ipratropium bromide in EIA has not produced consistent results. Controller medications that have played a role in preventing EIA include inhaled corticosteroids and the long-acting bronchodilators salmeterol and formoterol. Leukotriene receptor antagonists have also been shown to be of some value in preventing EIA in children. The data on ketotifen, calcium channel blockers, and antihistamines in the treatment of EIA is conflicting.

INHALATION DEVICES IN CHILDREN

MDIs were first introduced in 1955 to deliver a predetermined amount of drug to the airways. The devices have undergone significant evolution since then and now are the most common device to carry and administer drugs to treat asthma. Dry powder inhalers (DPI) are an alternative to MDIs. While the ability to deliver drug straight to the airways has revolutionized asthma treatment, the use of these devices in children presents some special considerations. The most important of these is the ability of young children to use these devices effectively. Specifically, this is the ability of the child to (1) understand how to use them and (2) be coordinated enough to use them accurately and effectively. MDIs require considerable more coordination than DPIs, although spacer devices do help. If a child is found to be unable to effectively use one of these devices, then it would be much more beneficial to the asthmatic child to continue with the use of nebulizers. A comparison of the various drug delivery devices is given in Table 15. The table also shows the most common age at which these inhalers can typically be used, although it is important to appreciate that there is a significant variability to these ages.

IMMUNOTHERAPY IN CHILDHOOD ASTHMA

Also referred to as hyposensitization, desensitization, or allergy shots, immunotherapy plays a significant role in the treatment of pediatric asthma. Studies done in children who were allergic to dust mite, cat, dog, mold, grass, ragweed, olive tree, and other allergens have demonstrated a beneficial effect of subcutaneous immunotherapy (SCIT). A study of 215 patients with dust mite allergy demonstrated that those patients with an FEV1 greater than 90% were 4 times as likely to benefit from immunotherapy to house dust mite, compared with patients with FEV1 less than 60%. Moreover, patients under the age of 20 years were 3 times more likely to

Table 15
Comparison of Inhaler Devices

	CFC inhalers	*HFA inhalers*	*Autoinhalers*	*Dry powder inhalers (DPIs)*	*Spacer devices*	*Nebulizers*
Availability	No longer available	Widespread	Rare	Increasing	Common	Widespread
Portability	Easy	Easy	Easy	Easy	Some are cumbersome	Smaller devices are available
Ease of use	Difficult	Difficult	No need for coordination	Need for adequate breath actuation	Improves effectiveness of MDI	No coordination necessary
Age range of use	5 Year and older	5 Year and older	4 Year and older	4 Year and older	May allow for use of MDI at an earlier age	Any age
Available for	Not available	SABA, LABA, corticosteroids, ipratropium bromide	SABA (pirbuterol)	LABA, corticosteroids, combination products	N/A	SABA, cromolyn, nedocromil, iptratropium bromide, corticosteroids
Cost/value	N/A	Expensive/good	Expensive/fair	Expensive/good	Moderate/good	Expensive/good
Comments	CFCs no longer available	The standard for MDI devices	Difficult to find	Dose lost if child exhales through device	Improves drug delivery to airways	Most reliable way to deliver drug – less dependent on patient technique

improve than those more than 51 years of age *(45)*. Indications for immunotherapy include clear evidence of symptom–exposure relationship, perennial symptoms, and inadequate control with medications. Recent advances in sublingual immunotherapy (SLIT) may provide another option for hyposensitization in children with allergic asthma.

EMERGENCY TREATMENT OF STATUS ASTHMATICUS

A child may present to an emergency room or urgent care setting in respiratory distress but without a diagnosis of asthma. It is important for the emergency room physician or provider to be able to quickly formulate a differential diagnosis in order to administer the correct treatment. Assessment of respiratory distress involves the evaluation of patient symptoms and signs including heart rate, respiratory rate, retractions, mental status changes, presence of cough or wheezing, pulsus paradoxicus and if quickly available, peak flow measurement and pulse oximetry. A differential diagnosis of asthma is given in Table 4. If wheezing is present, other causes must be ruled out, including foreign body aspiration or bronchiolitis. A chest radiograph may help in this case, and also in identifying potential comorbidities of asthma, such as atelectasis or pneumothorax. An algorithm for the emergency treatment of the pediatric asthmatic is shown in Fig. 15.

A comprehensive initial evaluation of the patient in respiratory distress can be done fairly quickly, and if the respiratory distress is severe, then treatment must be initiated promptly. In an asthmatic in status asthmaticus, a SABA such as albuterol or levalbuterol should be administered quickly, preferably via a small volume nebulizer. If there is time, measurement of peak flow or spirometry done prior to and after the treatment can help to evaluate the effectiveness of the treatment, but one should not delay treatment if the child's condition is serious. If the child appears dyspneic, the patient should be placed on a cardiac monitor that can provide a rhythm and oxygen saturation. Intravenous (IV) access should be established in patients who are in respiratory distress or to maintain hydration status. Parenteral steroids may be initiated for moderate to severe asthma exacerbations. Methylprednisolone 1–2 mg/kg can be given intravenously or intramuscularly. This can be continued every 6 h if the child requires admission. If the child's condition improves quickly and he or she remains stable, the child may be discharged home on a short course of oral steroids (prednisone 1–2 mg/kg/day) with close follow-up and an action plan with detailed instructions. Measurement of peak flow and oxygen saturation should be done prior to discharge.

Epinephrine, although always important to consider, is less commonly used because of the abundance of other medications with lesser side effects. Side effects of epinephrine include tremors, hypertension, tachycardia, neutrophil demargination, and cardiac stimulation. In very severe cases, subcutaneous epinephrine (1:1,000) has been used in the treatment of the asthmatic child. The dose is 0.01 mL/kg to a maximum of 0.3 mL. The dose can be repeated if the response is inadequate. Having an epinephrine autoinjector available obviates the need to measure out the dose and saves time.

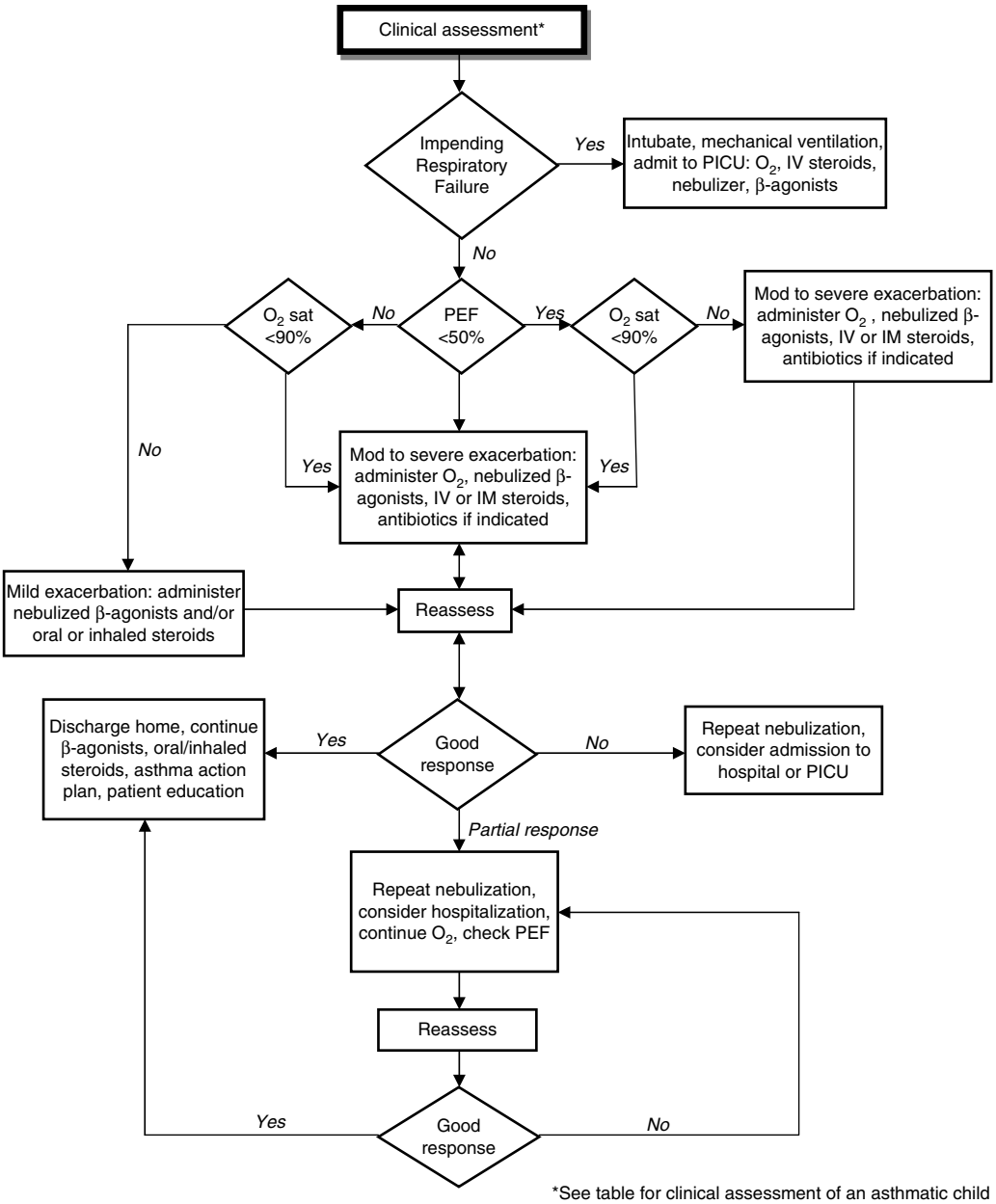


Fig. 15. Algorithm for the treatment of the acute asthmatic child.

Dehydration can be a factor in the successful treatment of the asthmatic child because it results in drying up of bronchial mucous and/or electrolyte imbalances, making the treatment of the asthmatic more difficult. Concomitant infection, such as pneumonia or sinusitis should be treated with antibiotics. Other medications used in

Table 16
Emergency Equipment and Medication Doses in Children

Emergency medications

Age	*Weight (kg)*	*Epinephrine SQ 1:1,000 (mL)*	*Epinephrine IV 1:10,000 (mL)*	*Atropine 0.1 mg/mL (mL)*	*Sodium bicarbonate 0.5 mEq/mL (4.2%) for children <3 month, 1.0 mEq/L >3 month (mL)*
Newborn	3.0	0.03	0.3	1.0	6.0
1 Month	4.0	0.04	0.4	1.0	8.0
3 Month	5.5	0.055	0.55	1.1	11.0
6 Month	7.0	0.07	0.7	1.4	7.0
1 Year	10.0	0.1	1.0	2.0	10.0
2 Year	12.0	0.12	1.2	2.4	12.0
3 Year	14.0	0.14	1.4	2.8	14.0
4 Year	16.0	0.16	1.6	3.2	16.0
5 Year	18.0	0.18	1.8	3.6	18.0
6 Year	20.0	0.20	2.0	4.0	20.0
7 Year	22.0	0.22	2.2	4.4	22.0
8 Year	25.0	0.25	2.5	5.0	25.0
9 Year	28.0	0.28	2.8	5.6	28.0
10 Year	34.0	0.34	3.4	6.8	34.0

Emergency equipment sizes

Age	*Weight (kg)*	*Self-inflating bag size*	*O_2 ventilation mask size*	*Endotracheal tube size*	*Laryngoscope blade size*
Premature newborn	<2.5	Infant	Newborn small	<3.0	0
Newborn	2.5–4.0	Infant	Newborn	3.0–3.5	0–1
6 Month	7.0	Child	Child	3.5–4.0	1
1–2 Year	10–12	Child	Child	4.0–4.5	1–2
2–5 Year	12–18	Child	Child	4.5–5.0	2
5–8 Year	18–24	Child	Child	5.0–5.5	2
8–10 Year	24–30	Child/adult	Small adult	5.5–6.0	2–3

the treatment of the acute asthmatic include nebulized corticosteroids, nebulized cromolyn, leukotriene-receptor antagonists, theophylline or aminophylline, and nebulized anticholinergic agents. The doses of emergency medications and the size of emergency equipment that is used in the pediatric population are summarized in Table 16.

Currently, theophylline is much less commonly used in the treatment of the acute asthmatic. However, if β-agonist nebulization is not effective in resolving respiratory distress, theophylline can be administered first as an intravenous bolus followed by a continuous intravenous drip. Once theophylline is started, the child

should be admitted to the hospital. Each milligram per kilogram of theophylline IV bolus results in about a 2 mg/dL rise in theophylline levels. The therapeutic window of theophylline serum levels is between 10 and 20 mg/dL. Thus, a commonly used bolus of 6 mg/kg results in a level that should fall well within the therapeutic window. An intravenous theophylline drip of 0.8–1 mg/kg/h will result in a steady state serum level. Theophylline levels must be monitored carefully because of the serious side effects that can occur at higher serum levels (Table 10). Another disadvantage of using theophylline is that multiple factors can affect theophylline metabolism, sometimes leading to unpredictable serum levels. These factors are given in Table 12.

The use of leukotriene receptor antagonists in the treatment of an asthma exacerbation has been reported. In a recent study of 201 patients, montelukast administered intravenously led to a significantly improved FEV1 after 20 min when compared to patients who were given placebo *(46)*. The effect lasted longer than 2 h, and patients in the treatment group received less β-agonist and had fewer treatment failures compared to the placebo group. Some success with the use of oral montelukast in the treatment of asthma exacerbations has also been reported *(47)*.

INPATIENT MANAGEMENT OF CHILDHOOD ASTHMA

The decision to admit a child with an asthma exacerbation to the hospital or intensive care depends on several factors. These include the efficacy of treatment in the emergency room and the original severity of the asthma exacerbation. Persistent wheezing and retractions, dyspnea, reduced oxygen saturation, and abnormal blood gas parameters can all be indications for admission. Treatment that has been initiated in the emergency room can also lead to an admission, such as supplemental oxygen, theophylline drip, intubation, IV rehydration, or IV antibiotics. Intubation should not be delayed if the patient is in impending respiratory arrest because resuscitation is more difficult in patients who are in respiratory failure. If intubation is performed, arterial blood gas measurement and chest radiography to document placement of the endotrachael tube must be done.

Oxygen, nebulized steroids, oral or parenteral steroids, leukotriene-receptor antagonists, and theophylline can be continued as indicated, until the patient condition allows for weaning of medications. Oxygen saturation should be monitored either continuously or intermittently depending on the child's status. Particular attention should be paid to hydration status, fever, or signs of adverse effects of medications, such as tremors or electrolyte imbalances from nebulized steroids. Infections should be treated appropriately.

As the child improves, treatment can be weaned and discharge planning initiated. Children should be sent home with an asthma management plan, and instructions to return if conditions worsen. Discharge medications depend on the patient's history of present illness, and past history of asthma. Close follow-up as an outpatient by an asthma specialist is preferable to review ongoing treatment and preventative measures. Table 17 shows pediatric indications for the various asthma medications, according to the manufacturer's prescribing information (PI).

Table 17
Pediatric Indications for Asthma Drugs

Drug name (trade name)	*Category*	*Components (scientific names)*	*Pediatric indication*[a]
Accolate	Leukotriene receptor antagonist	Zafirlukast	5 Years and older
Advair Diskus	Combination (ICS + LABA)	Fluticasone propionate Salmeterol xinafoate	4 Years and older
Advair HFA	Combination (ICS + LABA)	Fluticasone propionate Salmeterol xinafoate	12 Years and older
Albuterol oral syrup	SABA	Albuterol sulfate	2 Years and older
Alvesco	Inhaled ICS	Ciclesonide	12 Years and older
Asmanex Twisthaler	Inhaled ICS	Mometasone furoate	4 Years and older
Atrovent HFA	Anticholinergic	Ipratropium bromide	Not established
Dulera	Combination (ICS + LABA)	Mometasone furoate Formoterol fumarate dihydrate	12 Years and older
Foradil	LABA	Formoterol fumarate	5 Years and older
Intal inhaler	Anti-inflammatory	Cromolyn	Discontinued in US, available still in other countries
Intal nebulization solution	Anti-inflammatory	Cromolyn	2 Years and older
Pro-Air HFA	SABA	Albuterol sulfate	4 Years and older
Proventil HFA	SABA	Albuterol sulfate	4 Years and older
Pulmicort Flexhaler	Inhaled ICS	Budesonide	6 Years and older
Pulmicort respules	Inhaled (nebulized) ICS	Budesonide	12 Months to 8 years
QVAR	Inhaled ICS	Beclomethasone dipropionate	5 Years and older
Seretide Accuhaler	Combination (ICS + LABA)	Fluticasone propionate Salmeterol xinafoate	4 Years and older (Australia)
Seretide MDI	Combination (ICS + LABA)	Fluticasone propionate Salmeterol xinafoate	4 Years and older (Australia)
Serevent Accuhaler	LABA	Salmeterol xinafoate	4 Years and older (Australia)
Serevent Diskus	LABA	Salmeterol xinafoate	4 Years and older (USA)
Serevent Inhaler	LABA	Salmeterol xinafoate	4 Years and older (Australia)
Singulair	Leukotriene receptor antagonist	Montelukast	12 Months and older (for asthma)
Spiriva HFA	Anticholinergic	Tiotropium bromide	Not indicated in children
Symbicort HFA	Combination (ICS + LABA)	Budesonide Formoterol fumarate dihydrate	12 Years and older

(Continued)

Table 17 *(Continued)*

Drug name (trade name)	*Category*	*Components (scientific names)*	*Pediatric indication*[a]
Tilade CFC free	Anti-inflammatory	Nedocromil sodium	2 Years and older
Ventolin HFA	SABA	Albuterol sulfate	4 Years and older
Xolair	Monoclonal anti-IgE	Omalizumab	12 Years and older
Xopenex HFA	SABA	Levalbuterol tartrate	4 Years and older
Xopenex nebulization solution	SABA	Levalbuterol HCl	6 Years and older
Zyflo	Leukotriene receptor antagonist	Zileuton	12 Years and older

[a]These are current pediatric age indications by the FDA or corresponding regulatory agency if drug is available elsewhere.

INTEGRATIVE MEDICINE IN PEDIATRIC ASTHMA

About one third of the population in the United States uses some form of alternative or complementary medicine. Techniques that have been utilized by patients to treat asthma include acupuncture *(48)*, herbal medicines, homeopathy, massage therapy, ayurvedic medicine, yoga, relaxation techniques, breathing exercises, and meditation *(49)* (Table 18). While popular, these modes of therapy have not been well studied, and at the present time, there is no scientific evidence to support their efficacy in the treatment of asthma. Although the majority of these techniques are themselves harmless, using them as a substitute for established asthma management may deny the pediatric asthmatic the proper care that he or she should be receiving. Special warning should be given to herbal medications, which in addition to the lack of evidence for efficacy, may actually be harmful either by themselves or in interaction with concurrent asthma medications. The use of these preparations in children should be especially discouraged until further evidence of safety and efficacy are available.

NATURAL HISTORY AND PROGNOSIS OF CHILDHOOD ASTHMA

Although many patients believe that they have outgrown their asthma, this is never really the case, because asthma is at least partially genetically determined. On the other hand, a child's asthma can vary during their childhood and even into adulthood. Asthma is dependent on having a genetic predisposition and clinically, is modulated by the environment. Environmental modulation can stem from allergenic exposure, exposure to other agents such as endotoxin, irritants, ozone, particulates, and even temperature. Hormones can also play a role in asthma, as suggested by the interesting observation that in pregnancy, women who have asthma have an equal chance of their asthma worsening, improving, or remaining unchanged.

Table 18
Important Cytokines Targets in Asthma

Cytokine	*Cellular expression (with particular relevance to asthma)*	*Cell targets*	*Function*	*New drug or drug target for asthma treatment*	*Results*
IL-3	Activated T-cells	Bone marrow progenitors	Increases lifespan of eosinophils, stimulates differentiation of multiple cell types	None	N/A
IL-4	Macrophages, Th2 cells	Naïve T cells, B cells, T cells	Upregulation of immunoglobulin E synthesis, Th2 lymphocyte differentiation, production of VCAM-1, effects low affinity CD23 IgE receptors	Soluble IL-4 receptors Pitrakinra	Phase II trials show significant improvement in asthma Successful asthma treatment in a monkey model
IL-5	T helper 2 cells and mast cells	Eosinophils, B cells	Stimulates differentiation and activation of eosinophils	Monclonal antibody to IL-5	Blockage of eosinophils, reduces eosinophil numbers
IL-6	T cells, macrophages, fibroblasts	T cells, B cells, liver cells, mature B cells	Downregulation of inflammatory cell infiltration and enhancement of airway remodeling	None	N/A
IL-8	Macrophages, epithelial cells, platelets	Neutrophils, macrophages, endothelial cells, keratinocytes, mast cells	Chemokine, angiogenic factor, may have a role in bronchiolitis, also known as neutrophil chemotactic factor	None	N/A
IL-9	T helper cells	T helper cells, B cells	Th2 cytokine, activity in conjunction with IL-4, IL-1 and IL-3	Anti-IL-9	Inhibits asthma related features in antigen stimulated mice

IL-10	Monocytes, lymphocytes, mast cells, Th2 cells, Treg cells, activated macrophages	T cells, mast cells, B cells	Inhibits allergen-induced airway hyperresponsiveness and inflammation	None	N/A
IL-12	Activated macrophages and dendritic cells	Th cells, Tc cells, NK cells	Immunomodulatory cytokine	R848 (Resiquimod)	Reduces airway inflammation after antigen challenge
IL-13	Th2 cells + many other cell types	B cells + others	Proinflammatory cytokine, Th1/Th2 balance, mediator of allergic inflammation	Anti-IL-13	Antibody to IL-13 suppressed AHR, eosinophil infiltration, proinflammatory cytokine production, serum IgE in mice, poor results clinically
IL-17	Th cells, NK cells, Treg cells, mast cells	Release of cytokines from many cells	Proinflammatory cytokine, chemokines, differentiation of Th17 cells, airway remodeling	Possibly under investigation for asthma	Unknown
IL-19	Epithelial cells, endothelial cells, macrophages, monocytes	NK cells, T cells, B cells, monocytes	Function unknown, may alter balance of Th1/Th2 cells in favor of Th2 cells, increases proportion of IL-4 producing cells	None	N/A
IL-25	Helper T cells, mast cells	Eosinophils (via stimulation of production of IL-4, IL-5 and IL-13)	Inflammatory bowel disease, mucosal immunity	None	N/A
IL-33	Mast cells, bronchial smooth muscle cells, epithelial cells	Helper T cells, mast cells, eosinophils, basophils	Role in atopic dermatitis and asthma, gene	None	N/A

(Continued)

Table 18 *(Continued)*

Cytokine	*Cellular expression (with particular relevance to asthma)*	*Cell targets*	*Function*	*New drug or drug target for asthma treatment*	*Results*
GM-CSF	Macrophages, T cells, endothelial cells, fibroblasts, mast cells	Stem cells	Proinflammatory cytokine, potentially leading to increase in inflammatory cells	None	N/A
Interferon-γ	Th1 cells, Tc cells, dendritic cells, NK cells	Many cell types	Suppresses Th2 activity, activates inducible NOS	None	N/A
TNF-α	Macrophages, T cells + many other cells	Neutrophils, macrophages, T cells, B cells + others	Proinflammatory cytokine, activates neutrophils, stimulates phagocytosis, acute phase reactant	Has been studied extensively in asthma	Generally poor results
ADAM-33	Vascular smooth muscle cells, fibroblasts, lung mesenchymal cells	Unknown	Type 1 transmembrane protein implicated in asthma and eczema	None	N/A
RANTES	Airway smooth muscle cells, mast cells, macrophages	T cells, basophils eosinophils	Chemotactic, leukocyte recruitment	None	N/A
CCR3	Eosinophils, basophils, Th1 cells, Th2 cells, airway epithelial cells	Eosinophils and other inflammatory cells	Eosinophil chemotaxis	None	N/A
CXCR2	Mast cells, human mesenchymal stem cells, endothelial cells	Endothelial cells, neutrophils	Neutrophil and monocytes chemotaxis	None	N/A
Matrix metalloproteinase-12 (metalloelastase)	Lung and alveolar macrophages	Extracellular matrix	Repair cycles influence airway changes in asthma, reduction of levels of chemotactic factors and other proinflammatory cytokines	MMP-12 specific inhibitor	Attenuates early airway response, blocks late airway response

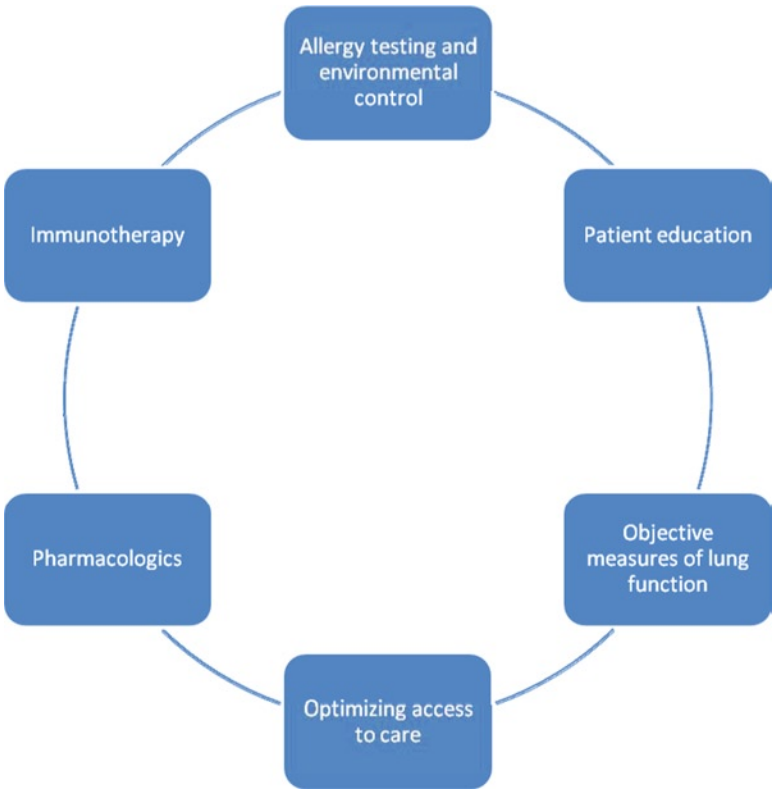


Fig. 16. A comprehensive asthma management program.

What is known, however, is that asthma is an inflammatory disease that results in bronchoconstriction. Successful treatment of the asthmatic means control of the inflammation. Failure to control inflammation results in chronic obstructive lung disease, as in the case of the cigarette smoker. The introduction of inhaled corticosteroids over the past few decades has greatly improved asthma care, and probably will prove to have a beneficial effect on long-term sequelae of asthma. The persistently high mortality from asthma is probably more related to patient and provider education and compliance than anything else. This is why treatment of asthma requires a comprehensive management plan that incorporates all facets of treatment, including environmental control, medications, education, and immunotherapy (Fig. 16). Regular monitoring is important to minimize the morbidity of chronic asthma.

FUTURE DIRECTIONS

New Medications

Targets for new treatment modalities in asthma include IgE, eosinophils, cytokines, chemokines, cell-signaling pathways, adhesion molecules, and inflammatory mediators such as leukotrienes, prostaglandins, and platelet activating factor. The development of airway inflammation is under the control of many biological modulators, many of which are targets of asthma research. Currently, phosphodiesterase-4 inhibitors, peroxisome proliferator-activated receptor-γ (PPAR) agonists, nuclear factor κB, phosphoinisotide-3-kinase γ, lipoxins, and p38 mitogen-activated protein kinase inhibitors are anti-inflammatory drugs that are being investigated in the treatment of asthma. It is unlikely that a single agent will be identified that will be a panacea for the treatment of asthma due to the redundancy of the immune system. A list of biologically active molecules that may have a role in asthma is given in Table 19.

Phosphodiesterase-4 inhibitors are currently being studied in the treatment of asthma. A study of airway responses to allergen challenge in 24 mild asthmatics treated with an inhaled phosphodiesterase-4 inhibitor showed an inhibition in the fall of minimum and weighted FEV1 compared to placebo *(50)*. Other phosphodiesterase-4 inhibitors are also under investigation.

Platelet activating factor has been associated with EIA and allergen-induced asthma. Inhibition of platelet activation diminishes the late phase reaction of asthma *(51)*. Several medications currently used to treat asthma, including the glucocorticoids and ketotifen, normalize platelet survival times *(52)*. Platelets also secrete platelet-factor 4, platelet-derived growth factor (PDGF), arginine-glycine-aspartic acid, thrombospondin, transforming growth factor-α and -β, 5-hydroxytryptamine, thromboxane A2, 12-hydroxyeicosatetranoic acid, β-lysin, adenosine diphosphate, and platelet derived histamine releasing factor, all of which may play a role in airway inflammation.

Platelets possess low-affinity receptors for IgG and IgE on their surface, and release adhesion molecules and inflammatory cell chemoattractants such as RANTES *(53)*. Cromolyn sodium *(54)*, nedocromil sodium *(55)*, and cetirizine *(56)* can all inhibit IgE-induced platelet activation. Platelet activation is associated with increased airway eosinophils. Despite the numerous inflammatory effects of platelets, and the potential for new drugs, there are currently no available platelet-related drugs for the treatment of

Table 19
Integrative Medicine and Asthma

Acupuncture
Herbal medicines
Homeopathy
Yoga
Ayurvedic medicine
Massage therapy
Relaxation techniques
Breathing exercises

asthma. Interestingly, the recent furor over vitamin D has led to the identification of vitamin D as an inhibitor of thrombin and PDGF-induced airway smooth muscle proliferation *(57)*, suggesting that improvement in nutrition in young children may lead to normalization of vitamin D levels, and a decreased incidence of asthma.

Other targets for the future treatment of childhood asthma include the prostaglandins, specifically PGD2, a tyrosine kinase inhibitor (masitinib), and a number of potential cytokine-based therapies targeting Th2 cytokines such as IL-4, IL-5, IL-9, IL-13, IL-17, and TNF-α *(58)*. Other drugs that are continually being developed for asthma are anticholinergics and new glucocorticoid agents. There are many other potential targets that have not been mentioned here that are beyond the scope of this chapter.

New Forms of Immunotherapy

SLIT has been used in Europe for several years. Early experience in the United States suggests that it is of comparable efficacy to SCIT, but with significantly diminished side effects or risk of anaphylaxis. One potential drawback of SLIT compared to SCIT is the lack of supervision associated with self-administration of oral or sublingual extracts. Better patient education may circumvent this objection, however, and SLIT may yet become widely used in the treatment of asthma. The other potential road block with SLIT is the absence of an established regimen for prescribing SLIT in polysensitized individual. A study of 51 polysensitized children with allergic rhinitis and/or mild to moderate asthma treated with SLIT for 1 year showed an improvement in symptoms of allergic rhinitis severity and classification, nasal, ocular and bronchial symptoms, and medication use. While the majority *(42)* of these children was treated with a single allergen, seven were treated with two or more extracts and experienced benefit as well *(59)*. Studies on the efficacy of SLIT have been done for dust mite, *Olea*, grass pollen, and others.

Other novel forms of immunotherapy include the development of allergen vaccines based on allergen-derived T cell peptides, recombinant allergens, and hypoallergeneic allergen derivatives. Another new chimeric Fc-γ allergen protein immunotherapy is being evaluated for cat and peanut allergy. Studies of these new forms of immunotherapy are still in the early phases and are not currently used clinically.

GENETICS-BASED THERAPIES IN ASTHMA

Asthma is a polygenic disease with a great deal of heterogeneity. Multiple genes have been identified that convey risk of asthma. The list of asthma genes continues to grow. Single nucleotide polymorphisms (SNPs) have been found that play a role in asthma severity or response to medications. A current goal is matching the asthma phenotype with an existing drug or a drug in development to maximize the response in an individual patient.

The ability to perform Genome Wide Associations Studies (GWAS) provides a technology to rapidly analyze and compare genomes of many people to determine variations associated with specific diseases. Identification of genes that may play a role in multiple diseases or conditions has also been made possible, as in the analysis of the relationship between obesity and asthma *(60)*. This has opened the door to an infinite amount of research on asthma genetics.

CHILDHOOD ASTHMA AND HEALTHCARE SYSTEMS

Delivery of care for allergies and asthma is highly dependent on the existing health care system within each country. There are clearly advantages and disadvantages to socialized medicine vs. fee for service medicine. Every country has its own health care system, and outcomes vary as a result of the efficiency and effectiveness of delivery of care.

In the United States, the issue of whether asthma should be managed by a generalist or a specialist has always been hotly debated. Multiple studies have shown that management by an asthma specialist (especially allergists) leads to reduced morbidity and mortality and improved quality of life. Treatment by a specialist leads to fewer hospitalizations, fewer exacerbations requiring emergency care, better quality of life, and better outcomes. However, the availability of financial resources, and more important, the failure to properly allocate such resources can be such an economic burden that optimal systems of healthcare are not implemented. As a result of this, many asthmatic children receive the bulk of their care from generalists and even mid-level practitioners, even in those cases where referral to a specialist may be indicated.

Unfortunately, in today's healthcare climate, generalists are being asked to see more and more patients and they simply do not have the time to formulate a comprehensive asthma treatment program as illustrated in Fig. 16. Asthma educators who may be nurses or even medical assistants who are specially trained may help, but no financial resources are actually devoted to this form of medical care. Too many patients with asthma are not well controlled and eventually end up in an urgent care or emergency department, at many times the cost of prevention. A list of recommendations for referral to a specialist is given in Table 20. These should be considered the very minimum requirements for referral to a specialist.

Table 20
Indications for Referral to a Specialist

Children requiring step 3 care of higher (step 2 for children under 4 years of age)
Children on or those who may be candidates for immunotherapy
Uncontrolled patients not meeting goals of therapy within 3 months of after initiation of treatment
Children who have had a life-threatening asthma exacerbation
Children in whom symptoms are atypical or if the diagnosis has not been established
Children with comorbid or complicating factors, including chronic sinusitis, nasal polyps, gastroesophageal reflux, allergic rhinitis, allergic bronchopulmonary aspergillosis, etc.
Children in whom additional diagnostic testing is needed, such as allergy testing, pulmonary function tests, rhinolaryngoscopy, provocation challenge or bronchoscopy
Children who require systemic corticosteroids on a chronic basis or who have more than two steroid bursts in 1 year
Children who have been hospitalized for asthma
Children with EIA or other special circumstances
Children and/or parents who require or desire counseling on issues related to compliance, environmental evaluation and control, medication usage, device usage, peak flow meter usage, or any other additional asthma education
Children who may have an unusual exposure which may be provoking or contributing to asthma

SUMMARY

Since our last edition, the treatment of asthma in children has become more standardized, at least amongst allergy and asthma specialists. Inhaled corticosteroids have become the first-line medical treatment of asthma in all age groups. There is still debate on the preferred add-on therapy, the options being increasing the dose of steroids, adding a leukotriene receptor antagonists, or adding a LABA, but all of these options are acceptable, and should be tailored and customized for each individual child with asthma. Future research may be able to identify which treatment might be preferred based on the patient's pharmacogenetics, but we have not yet reached this point. Environmental control has become a mainstay in asthma treatment, and new modes of immunotherapy have contributed to a significant less morbidity over the past two or three decades. Hospitalization rates of asthmatic children have decreased, drugs with high rates of side effects such as theophylline have been replaced, and quality of life has improved. Most children with asthma are able to enjoy very normal lives, compete in sports at a high level and have very few missed school or work days, as long as they are compliant with their asthma management plan.

There is continual ongoing improvement in the educational component of asthma. The development of the internet has facilitated the availability of multiple resources for physician, provider, ancillary staff, parents, and patients (Table 21). Publications for children to make it easier for them to understand their disease are now ubiquitous. With better education comes better compliance, and hopefully, better outcomes.

Some problems remain. Mortality has not decreased significantly since the last edition. One of the main remaining issues is related to patient education and compliance. It is now not a matter of availability of education materials, but acceptance and

Table 21
Asthma Resources for Physicians, Patients and Parents

World Allergy Organization	http://www.worldallergy.org
American Academy of Allergy, Asthma and Immunology (AAAAI)	http://www.aaaai.org
American College of Allergy, Asthma and Immunology (ACAAI)	http://www.acaai.org
World Health Organization (WHO)	http://www.who.org
American Lung Association	http://www.lungusa.org
American Thoracic Society (ATS)	http://www.lungusa.org
Asthma and Allergy Foundation of America	http://www.aafa.org
National Technical Information Service	http://www.ntis.gov
National Asthma Education and Prevention Program (NAEPP)	http://www.nhlbi.nih.gov/about/naepp/
National Heart, Lung and Blood Institute (NHLBI)	http://www.nhlbi.nih.gov
Allergy and Asthma Network/Mothers of Asthmatics	http://www.aanma.org
Center for Disease Control	http://www.cdc.gov
Global Initiative for Asthma (GINA)	http://www.ginaasthma.com
National Allergy Bureau (NAB)	http://www.aaaai.org/nab
Kidshealth	http://www.kidshealth.org

utilization. Another main issue, which may become even more of a problem in the face of cost-cutting measures associated with a variety of health care reform ideas, involves the access to specialist care. There is also some concern that health care reform in the United States may lead to an overall reduction in access to care to any healthcare provider, let alone the asthma specialist.

From a scientific standpoint, the future of pediatric asthma is bright. Research is ongoing to better understand the pathophysiology of asthma, and in doing so, developing new pharmaceuticals to treat asthma. Knowledge of the genetic basis for asthma and how children react to asthma medications will help guide us in developing a personal care plan for the treatment of each child with asthma. Hopefully, this will lead to further improvements in the outcomes of asthmatic children.

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6 The Adult Asthmatic

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Contents

It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.

—Sir William Osler (1849–1919)

KEY POINTS

- Asthma is a clinical syndrome characterized by reversible airflow obstruction, abnormal airway hyperresponsiveness, chronic small airways inflammation, bronchial smooth muscle hypertrophy, and adverse airway remodeling.
- Different asthma subphenotypes exist reflecting the true clinical and pathological heterogeneity of this disease. Given the diverse definitions of asthma, we highlight the practical difficulties in diagnosing asthma, and discuss treatment options to help patients achieve asthma control and avoid acute exacerbations.
- Adult-onset asthma or late-onset asthma can have their roots in childhood and remain unrecognized or clinically silent.

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- Severe asthma or chronic severe asthma since childhood can mimic the airway physiology of COPD, but differs by the absence of emphysema or reduced carbon monoxide diffusion capacity.
- The phenotypic manifestation of asthma in the individual patient can change with age and evolving comorbidities.
- Successful asthma treatment requires patient education and participation, and adherence to medications via the step-up or step-down approach of the NIH-NAEPP asthma treatment guidelines, to better personalize asthma care.
- Long-acting β-agonists should only be used with a controller medication such as inhaled corticosteroids given the potential for increased risk of asthma-related deaths.
- A new paradigm of predefined "clusters" of asthma subphenotypes may help reduce heterogeneity in asthma study populations, thereby improving chances of finding treatment responders.

ABBREVIATIONS

FEV_1	Forced expiratory volume in the first second
AOA	Adult onset asthma
LOA	Late-onset asthma
GERD	Gastroesophageal reflux disease
NAEPP-EPR3	National Asthma Education and Prevention Program – Expert Panel Report 3
COPD	Chronic obstructive pulmonary disease
CS	Corticosteroid
ICS	Inhaled corticosteroid
LABA	Long-acting β-agonist
SABA	Short-acting β-agonist
CDC	Centers for disease control
HRT	Hormone replacement therapy
CI	Confidence interval
NSAID	Nonsteroidal anti-inflammatory drug
COX	Cyclooxygenase
LT	Leukotriene
GOLD	Global obstructive lung disease
cys-LT	Cysteinyl leukotriene
BMI	Body Mass Index
RANTES	Regulated upon activation normal T-cell expressed and secreted
GWA	Genome-wide association
NO	Nitric oxide
NOS	Nitric oxide synthase
AHR	Airway hyperresponsiveness
FE_{NO}	Fraction of exhaled nitric oxide
EBC	Exhaled breath condensate
PEF	Peak expiratory flow
LTRA	Leukotriene receptor antagonist
PC_{20}	The provocative concentration or dose of methacholine that causes a 20% decrease in baseline FEV_1
FDA	Food and drug administration

SARP	Severe Asthma Research Program
ACRN	Asthma Clinical Research Network
PPARγ	Peroxisome proliferator-activated receptor-gamma
PDE4	Phosphodiesterase 4
BDP	Beclomethasonedipropionate
FP	Fluticasone propionate
MDI	Metered dose inhaler
DPI	Dry powder inhaler
TNF	Tumor necrosis factor

INTRODUCTION

Asthma in adults is a clinical syndrome that is largely allergic in nature, which manifests reversible to partially reversible airway obstruction. Asthma is underdiagnosed and undertreated in the United States, especially in those who are >40 years of age or older. Despite the reduction in asthma mortality since 1996, morbidity and healthcare resource utilization associated with asthma continue to increase. Forty to sixty percent of asthma patients do not achieve asthma control, and the basics of asthma care are missing for large segments of the population, including African Americans, Native Indians, Hispanics, and Asians. The annual cost for asthma is nearly $15 billion with 80% of the direct costs directed at only 10–20% of asthmatic patients. The inability to bring about well-controlled asthma in every patient by applying the current NIH-NAEPP guidelines should draw attention to disease heterogeneity and the urgent need to reconsider old paradigms with new ideas.

Atopic, adult-onset asthma (AOA) represents the most prevalent asthma phenotype in clinical practice. However, many patients diagnosed with nonatopic asthma as adults do not fit neatly into categories or guideline definitions, and do not respond to treatments in a predictable manner. The abnormal airway hyperresponsiveness (AHR) in asthma is thought to emanate from chronic small airways inflammation, mucus production, and structural airway remodeling which ultimately leads to air-trapping. However, reversible or partially reversible bronchoconstriction no longer distinguishes asthma from other airway disorders such as COPD. It is increasingly evident that asthma is actually a syndrome of multiple different phenotypes that contribute variably to disease heterogeneity and severity.

Several international groups have defined asthma broadly (Table 1) and provided recommendations to treat disease physiology, e.g., FEV_1, not necessarily the patient living with the disease. Patient phenotypes and subphenotypes (or clusters) exist (Table 2) that confound treatment goals, as indicated by the recognition that poor responses to ICS are not uncommon. Some argue that while the atopic, T_h2 paradigm of immune dysregulation is useful, it does not encapsulate the incredible heterogeneity in asthma, thus calling for a re-evaluation of how we conduct clinical trials *(1)*. Instead, subtypes of asthma may be defined functionally or pathologically by specific molecular mechanisms or by a distinct treatment response. Recently, five distinct clinical subphenotypes or "clusters" of asthma have been described, possibly representing different pathophysiologic mechanisms, thus creating an opportunity to develop individualized novel therapies *(2)*.

Table 1
Definitions of Asthma

- Expert Panel Report 3-National Asthma Education and Prevention Program *(33)*: "Asthma is a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation." Classified clinically as Intermittent or Persistent (Mild, Moderate, Severe)
- Global Initiative for Asthma (GINA) Definition – 2008 Update *(69)*: "Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment."
- American Thoracic Society (ATS) Workshop on Refractory Asthma 2000 *(70)*

Table 2
Asthma Phenotypes

- Nocturnal asthma, exercise-induced asthma, cough-variant asthma, childhood asthma, occupational asthma, asthma in the elderly, seasonal asthma, and aspirin-induced asthma (GINA 2008 Update) *(69)*, and asthma-COPD overlap syndrome *(9)*
- Intrinsic (nonallergic) vs. Extrinsic (allergic) *(71)*
- Eosinophilic (+) and (−) severe asthma *(72)*
- Asthma based of sputum inflammatory subtypes: eosinophilic, neutrophilic, mixed granulocytic, and pauci-granulocytic *(73)*
- Refractory asthma *(70)*
- High vs. Low Th2 asthma subphenotypes *(74)*
- Five asthma clusters *(2)*

In this chapter, we provide an overview of the changing approach to adult asthma highlighting new genetic and immunologic mechanisms, controversies, emerging biomarker technologies, new treatments (including bronchial thermoplasty), and investigational therapies. We aim to inculcate in the clinician an appreciation for the disease heterogeneity inherent to asthma and the opportunities this creates for novel management strategies.

DEFINITIONS

AOA implies the development of asthma in adulthood and is defined as asthma in an adult 18 years of age or older at the time of diagnosis. Late-onset asthma (LOA) is defined as asthma in a person 65 years of age or older at the time of diagnosis. The time of asthma onset in a patient's life is but one of several risk factors associated with AOA. It more often reflects when asthma symptoms are first recognized in the medical record, rather than when the pathophysiologic disturbance first began. Clinicians diagnose asthma by its phenotype or clinical appearance (Tables 1 and 2). Asthma can be viewed as a general set of symptoms (or syndrome) representing distinct diseases that express a common appearing clinical phenotype. To complicate matters further, birth cohort and cross-sectional studies of young children with wheezing have uncovered links between

Table 3
Normal Physiologic Changes in the Lungs Associated with Aging

- Increased air-trapping leading to hyperinflation
- Decreased lung elastic recoil
- Decreased chest wall compliance → ↑FRC, ↑RV
- Increased restriction from kyphosis, e.g., secondary to osteoporosis and vertebral compression fractures
- Loss of height → ↓FEV1, ↓FEV1%, ↓VC, ↑FRC, ↑RV. No change in TLC
- Decreased respiratory muscle strength
- Impaired respiratory reflexes
- Impaired perception of respiratory workload reduces mental cognition or awareness

FRC functional residual capacity; *RV* residual volume; *VC* vital capacity; *TLC* total lung capacity.

lung function and immune responses in early life and the subsequent development of persistent wheezing and chronic airflow obstruction seen in adulthood, such as asthma and COPD *(3)*.

Much of what is currently understood about asthma comes from the scientific study of selected animal models and asthma patients beginning in early childhood. However, AOA vs. LOA can be recently acquired in adulthood or represent various stages of long-standing disease. Atopic adults can carry the genotype of childhood asthma asymptomatically into adulthood only to have the phenotype finally expressed because of a powerful trigger, e.g., specific aeroallergen(s) or viral infection. The majority of AOA could have started as mild childhood asthma that was never appropriately diagnosed or was clinically silent. Alternatively, longstanding AOA beginning in young adulthood can lead to chronic persistent airway obstruction and be easily mistaken for COPD caused by cigarette smoking. The majority of AOA, even if first recognized in adulthood, represents chronic persistent asthma that began early in childhood. Aging itself can cause obstructive patterns to emerge on pulmonary function testing, where incomplete reversibility with bronchodilators becomes more often the rule rather than the exception in AOA (Table 3).

The majority of mild childhood asthma cases enter clinical remission, but persistence of severe disease from very early childhood into adulthood is also responsible for the development of asthma in adults. In this latter group of patients, chronic asthma is linked to persistence of atopy even though in later years some older adults lose their positive skin tests to specific allergens. However, it is very important to recognize that many adults diagnosed with AOA do not have evidence of atopic disease. They still present with the same asthma syndrome or clinical phenotype as their atopic counterparts, but probably through different mechanisms of disease.

The NIH-NAEPP-EPR3 divides asthma patients arbitrarily into the following age groups: children 0–4 years of age, children ages 5–11 years of age, whereas youths ≥ 12 years of age and adults are combined together. Using age to discriminate asthma, however convenient, disregards the phenotypic heterogeneity of adult asthma. While allergic asthma remains a chronic eosinophilic bronchitis with bronchial smooth muscle hypertrophy and mast cell infiltration, clinicians today recognize heterogeneity in asthma responses to controller treatments, with highly variable responses to ICS and the antileukotriene drugs. Between 25 and 46% of asthmatics do not respond to or improve their asthma control with ICS *(4)*.

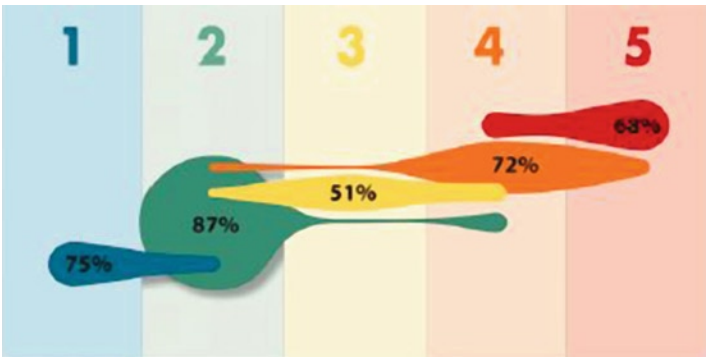

Fig. 1. The five clusters are represented by the numbers 1–5 above. Based on the tree analysis per Moore et al, 80% of subjects were assigned to the correct cluster of asthma severity, as follows: *Cluster 1*: 75% with mild atopic asthma. *Cluster 2*: 87% mild-to-moderate atopic asthma. *Cluster 3*: 51% late-onset non-atopic asthma. *Cluster 4*: 72% severe atopic asthma. *Cluster 5*: 68% severe asthma with fixed airflow. Considerable overlap in severity and cluster group exist which confirms and mirrors the clinical experience with asthma (adapted from Moore et al. *(2)*. Reproduced with permission).

The Severe Asthma Research Program (SARP) has recently defined five distinct clinical asthma subphenotypes *(2)* that will hopefully change future research by providing more homogenous cohorts to study. Cluster analysis was used to identify five groups or clusters of asthmatics, where age ≥ 12 years old was considered "late-onset": Cluster 1 includes those with early onset atopic asthma, normal lung function, on two or fewer controller medications, and have minimal health care utilization. Cluster 2 consists of subjects with early onset atopic asthma and preserved lung function, but increased medication requirements and health care utilization. Cluster 3 is composed of mostly older obese women with late-onset nonatopic asthma, moderate reductions in FEV_1, and frequent oral corticosteroid use to manage exacerbations. Cluster 4 includes asthmatics with severe airflow obstruction and bronchodilator responsiveness but who differ in their ability to attain normal lung function, and have a very early age of asthma onset in childhood (not adolescence), atopic status, and use of oral corticosteroids. Cluster 5 is similar to Cluster 4, but consists of more women (63%) with later-onset disease (69% late-onset), less atopy (66%), and longer duration of disease (Fig. 1).

Although some overlap does exist amongst these clusters, the divergent phenotypic characteristics described in this analysis suggest disease mechanisms very different from atopy and IgE-mediated inflammation (i.e., T_h2 immune responses) that may determine the variable clinical responses to NIH-NAEPP treatment schemes. It is of great interest to ascertain whether specific biomarkers for each asthma cluster exist to promote more effective diagnosis and treatment. The interaction between possible genomic differences and the environment (e.g., viral infections, aeroallergens, and common air pollutants) within the aforementioned five clusters can be studied from childhood to adulthood to better define their respective natural history.

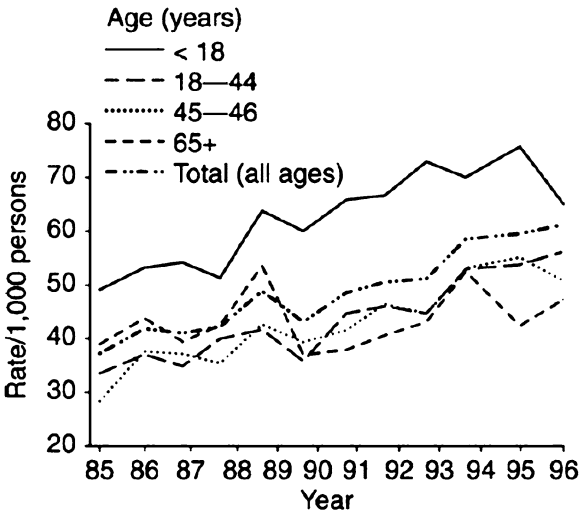

Fig. 2. Trends in asthma prevalence in the United States by age, where the greatest increases are seen in children. Years are from 1985 to 1996 (adapted from Braman *(5)*. Reproduced with permission).

EPIDEMIOLOGY

Approximately 24.6 million Americans suffer from asthma (CDC, 2009 http://www.cdc.gov/nchs/fastats/asthma.htm), 71% of whom are adults. For adults this accounts for 12.3 million office visits, 504,000 hospitalizations, and two million emergency department visits per year. Although mortality rates have declined overall since the 1980s and 1990s (now estimated to be 3,447 annually (CDC, 2007)), death rates are still high for children and adults alike. The mortality from adult asthma in the United States is approximately 1.1 deaths in 100,000 (CDC, 2007).

The prevalence of asthma in older adults (≥65 years of age) ranges from 3 to 17% and continues to rise over time (Fig. 2) *(5)*. More recently, the prevalence of asthma in older adults is reportedly between 6 and 10%, where women predominate in the age group 64–75 years. However, asthma prevalence is similar between men and women after age 75 years *(6)*. New cases of asthma continue to arise throughout life, and the 5-year age-specific and sex-specific incidence of newly diagnosed asthma in adults ≥ 65 years of age is estimated to be 103 per 100,000 people, where two-thirds of asthma deaths occur in people aged 65 years or older. However, these studies can underestimate the true prevalence and incidence of asthma. The DIDASCO Study used screening spirometry to detect COPD and doubled the number of patients with COPD in their clinic population *(7)*. Similar results can be realized in undiagnosed asthma patient populations in primary care settings.

Significant overlap between asthma and COPD exists (Fig. 3), known as the *asthma-COPD overlap syndrome*. The degree of overlap can vary considerably with the community, region, and country and the prevalence of cigarette smoking and air pollution. In Melbourne and Victoria, Australia, 50% of adults with asthma had chronic bronchitis and 73% of adults with chronic bronchitis had asthma in a 2002 survey *(8)*. Similar prevalence numbers were seen in a large cohort from the United States and United Kingdom, which also included overlap between emphysema and asthma (51.9%) *(9)*.

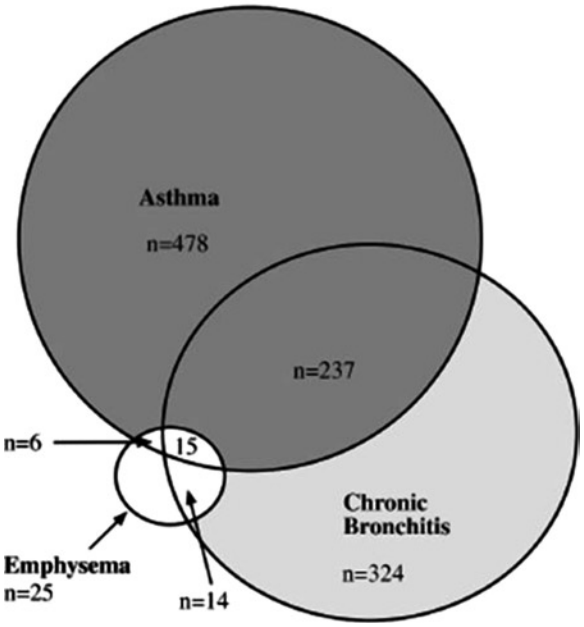

Fig. 3. Number of patients reporting asthma, chronic bronchitis, and/or emphysema. Considerable overlap exists amongst these common respiratory ailments (adapted from Abramson et al. *(8)*. Reproduced with permission).

RISK FACTORS AND SYNDROMES

Several risk factors and predisposing conditions affect the development of asthma in adults. Pregnancy, infections, occupational exposures, and aspirin-induced asthma are not addressed in this chapter, but have equal significance, and are covered in other chapters of this book. Stress, socioeconomic status, sleep disorders and chronobiology, and diet are also risk factors pertinent to asthma not covered below in order to focus our discussion on atopy, gender, hormone replacement, tobacco smoking, GERD, and obesity.

Atopy

Atopy is the manifestation of the environmental and genetic predisposition to develop an immunoglobulin E (IgE)-mediated response to common allergens. Atopic children generally remain atopic to varying degrees when they enter adulthood. AOA can persist clinically with exacerbations despite changes in skin test reactivity. Little is known regarding the true prevalence of atopy in elderly asthmatics. Bochenska-Marciniak et al. investigated the prevalence of atopy using skin prick tests in 274 asthmatics 60 years and older *(10)*. They found the prevalence of atopy ranged between 40% in those with LOA (defined in the study as asthma that developed before age 40) and 57% in all others groups that experienced asthma at an earlier age. Eight percent of patients with early onset asthma (defined by the investigators as asthma that developed before age 30) and 4% of LOA had negative skin prick tests for allergens. Dust mite,

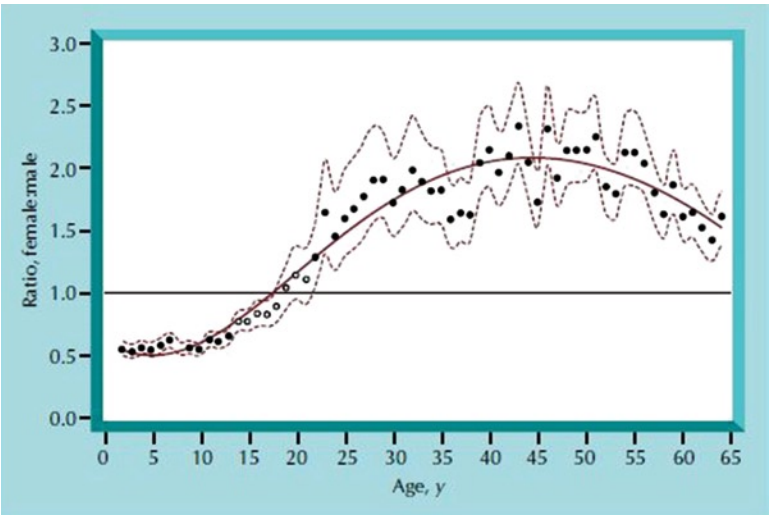

Fig. 4. The ratio of female-to-male asthma with increasing age. The dashed lines represent the 95% confidence intervals. With increasing age, the ratio of females with asthma increases relative to males (adapted from Melgert et al. *(75)*. Reproduced with permission).

feathers, grass, and tree pollen were the most common allergens that caused a positive skin prick tests in the study. More recent studies suggest that specific serum IgE decreases with age in those with allergic rhinitis or asthma, and this cannot accurately reflect atopy *(11)*. However, in a smaller study of elderly asthmatics, atopy was common (74.7%) *(12)*.

Gender

Epidemiologic studies indicate that women have a higher risk of developing AOA than men (Fig. 4), and they suffer more severe disease than men. There is strong evidence that sex hormones are major determinants of some of these differences. Postmenopausal women who take estrogen hormone replacement for 10 years or longer are more likely to develop asthma than women who have never used estrogen. Women with asthma are more likely to have a severe attack immediately before or during their menstrual period, perhaps related to levels of estradiol. The FACET study found women are at higher risk and experience more severe asthma exacerbations than men *(13)*. In the SARP cohort, a unique subphenotype (Cluster 3) of mostly older, obese women with late-onset, nonatopic asthma, with moderate reductions in FEV_1, and frequent oral corticosteroid use was identified confirming decades of clinical observations that match these characteristics *(2)*. The preponderance of women with this subphenotype (71%) compared to older obese men suggests that gender is important in disease pathogenesis.

Siroux et al. found a relationship between eosinophils, IgE, and atopy with (i) asthma according to gender and age-of-onset, and (ii) hormone-related events *(14)*. Using data from the Epidemiological Study on the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness, and Atopy, adults and children with asthma were recruited in chest clinics ($n=313$) and first-degree relatives of patients with asthma ($n=214$) were

compared with nonasthmatic controls ($n=334$) and first-degree relatives without asthma ($n=595$). Among asthmatic women, eosinophilia was significantly associated with perimenstrual asthma independent of age, smoking, and asthma severity (eosinophils/mm^3: 330 vs. 194; $p=0.01$). In women without asthma, IgE level was significantly decreased (by 50%) and the incidence of atopy decreased with menopause. Furthermore, IgE levels were increased with oral contraceptive use, independent of age and smoking. Comparing both genders, the increase of eosinophil counts was significantly greater in women with childhood-onset asthma than in women with AOA or in men in general. No interaction between gender and asthma was observed for eosinophils in children and for IgE level and atopy in children and adults *(14)*.

Hormone Replacement

Previous randomized clinical studies have suggested that hormone replacement therapy (HRT) can mediate the development of asthma and COPD. However, we now know that estrogen or HRT increases the risk of AOA in women, but not COPD. HRT increases postmenopausal asthma incidence twofold in women treated for 10 years or more.

The longitudinal Nurses Health Study initiated in 1976 was a prospective cohort study of more than 121,000 female registered nurses age 30–55 years who became menopausal. Barr et al. found a link between HRT use and the development of new asthma in nurses *(15)*. HRT users had an 80% higher risk of developing asthma than did those women who never used HRT. During 546,259 person-years of follow-up, current use of estrogen alone was associated with an increased rate of asthma (multivariate rate ratio 2.29; 95% CI 1.59–3.29) compared with those who never used hormones. The effect was similar among women who took conjugated estrogen only and among those who received the combination of estrogen and progestin. Asthma risk increased with higher doses of estrogen and with longer duration of estrogen use. In contrast, rates of newly diagnosed COPD were the same among hormone users and nonusers (multivariate rate ratio 1.05; 95% CI 0.80–1.37).

It should also be recognized that asthma severity has been linked in younger patients perimenstrually to the reproductive hormones and to the use of oral contraceptives, the state of pregnancy, and onset of menopause regardless of whether HRT is used *(14)*.

Tobacco Smoking

Tobacco smoking has been linked to COPD and difficult-to-control asthma in adults. The similarities between the clinical definitions of asthma and COPD (GOLD 2009 http://www.goldcopd.com) are incontrovertible, e.g., airway obstruction reversibility (albeit incomplete and occasionally absent) after bronchodilator treatment, and the presence of airway inflammation. The early diagnosis and proper treatment of different reversible obstructive airway disorders is therefore a challenge in adults and begs for the development of more specific biomarkers besides lung function to separate asthma from COPD.

Asthmatic smokers experience an excessive and more rapid decline in FEV_1 compared to nonsmokers. In developed countries, approximately 25% of adults with asthma are active cigarette smokers. Asthma and active cigarette smoking combine to increase severe symptoms, accelerate decline in lung function, and impair short-term therapeutic responses to corticosteroids.

Cigarette smoking modifies inflammation associated with asthma by stimulating cys-LT production. In a study comparing subjects with asthma and COPD who smoked, smoking significantly affected urine leukotriene E4 (LTE4) levels but only in asthmatic patients (mean ± SD: 164 ± 48 vs. 87 ± 26.3, $p < 0.0001$ for smokers) indicating a different underlying cys-LT inflammatory process in this phenotype *(16)*. The mechanisms of corticosteroid resistance in asthmatic smokers are unexplained, but could be due to alterations in airway cellular inflammation (e.g., increased neutrophils or reduced eosinophils), changes in the glucocorticoid receptor-α to -β ratio (e.g., over-expression of glucocorticoid receptor β), and increased activation of pro-inflammatory transcription factors (e.g., nuclear factor-κB or reduced histone deacetylase activity). Thus, every effort should be made to encourage asthmatics to stop smoking.

GERD

Gastroesophageal reflux disease (GERD) is a trigger of asthma that is clinically silent in 50% of asthmatics who have GERD. Although GERD is epidemiologically associated with asthma, it is an unproven epidemiologic risk factor for AOA. Patients with AOA also have a higher prevalence of hiatal hernias. Asthma medications such as β_2-agonists and theophylline can aggravate GERD by reducing lower esophageal sphincter pressure. Adults over age 19 with AOA and GERD are at higher risk for hospitalization with poorly controlled asthma. However, in a recent clinical trial of esomeprazole to treat poorly controlled asthma in subjects with asymptomatic GERD, there was no reduction in the episodes of poor asthma control and no improvement in secondary outcomes such as pulmonary function, airway reactivity, overall asthma control, symptom scores, nocturnal awakening, or quality of life *(17)*. In patients with symptomatic GERD, they should be treated for this indication whether or not it impacts their asthma.

Obesity

Nearly 33% of Americans are obese (BMI >30) and more than half of the country is overweight (BMI 25–30). The obesity epidemic has shadowed the asthma epidemic since the 1970s. In the Nurses' Health Study, after controlling for diet and physical exercise, BMI >30 directly correlated to an increased incidence of asthma. An independent relationship between obesity, nocturnal GERD, habitual snoring, and the onset of respiratory and asthma symptoms in adults was found in the European Community Respiratory Health Survey *(18)*.

Obesity is an inflammatory state with increased levels of leptin and cytokines including tumor necrosis factor-α (TNFα), transforming growth factor-β1 (TGFβ1), IL-6, IL-8, and C-reactive protein (CRP). There is significant overlap between adipocyte immune function, and T-lymphocytes and macrophages. In women, obesity increases estrogen levels which are also linked to mast cell activation.

Obesity and asthma may be linked via the same candidate genes, which could explain the parallel growth of both epidemics. Polymorphisms in specific regions of chromosomes 5q, 6p, 11q13, and 12q (each of which contains one or more genes encoding receptors relevant to asthma, inflammation, and metabolic disorders), including the β_2-adrenergic receptor gene *ADRB2* and the glucocorticoid receptor gene *NR3C1,* could link asthma and obesity *(19)*. Whether all obese adult asthmatics fall into the subphenotype identified as Cluster 3 in the SARP study remains to be determined *(2)*.

GENETIC AND IMMUNOLOGICAL INSIGHTS

Genetic Insights

Complex gene–environmental interactions likely play a role in shaping the final asthma subphenotype and its clinical presentation. Over 100 genes are associated with asthma, with smaller subsets of these genes found across different groups of asthmatics. Many of these genes are linked to immune system functions or to modulation of the inflammatory response. Genetic associations in both the adult and pediatric population have been reported. Genetic predisposition includes genes found on chromosomes 5, 6, 11, 12, and 14. If genotyping can establish an earlier diagnosis of asthma, then appropriate and individualized therapeutic interventions can be initiated in a timely manner.

A functional polymorphism in the RANTES gene promotor is associated with the development of LOA *(20)*. Regulated upon activation, normal T-cell expressed and secreted (RANTES) is an important CC chemokine involved in asthmatic inflammation. It is a potent chemoattractant for T-cell lymphocytes, eosinophils, basophils, monocytes (that become macrophages), and mast cells.

Hizawa and colleagues noted the -403A and -28G alleles of the RANTES promoter region exhibit significantly enhanced promoter activity in gene reporter constructs *(20)*. They investigated the genetic influence of these alleles on the development of asthma using case-control analysis in 298 Japanese patients with asthma and 311 control subjects. The -28G allele was significantly associated with LOA (odds ratio 2.033; 95% CI 1.379–2.998; corrected $p < 0.0025$), but was not associated with the other two asthma subgroups. The -403A allele was not associated with any of the asthma subgroups. Further evidence of the importance of the -28G allele was a significant increase in the production of RANTES in vitro in individuals who carried this allele conferring susceptibility to LOA.

Gene polymorphisms in the *ADAM33* asthma susceptibility gene on chromosome 20p13 have been associated with an accelerated decline in lung function in asthmatics and the general population *(21)*. Polymorphisms in *T-bet* (TBX21 or T-box 21) on chromosome 17q21, which modulates helper T-cell type 1 (T_h1) lineage development, are associated with AHR in asthmatic children and adults in another cohort *(22)*. Polymorphisms in the *GPRA* (G protein–related receptor for asthma) gene on chromosome 7p are also associated with asthma, AHR, and allergic predisposition in children *(23)*. Genetic variations in the gene that encodes arginase-1 have been associated with bronchodilator responses in children in the Childhood Asthma Management Program (CAMP) cohort *(24)*. Polymorphisms in the promoter region of the gene encoding chitinase 3-like 1 (CHI3L1) were associated with atopy and increased levels of YKL-40, a potential biomarker of asthma severity and structural airway remodeling *(25)*.

Several genome-wide association (GWA) studies have expanded our understanding of novel genes in asthma. The innate immunity gene encoding the CD14 protein has been associated with asthma in an adult rural population and also determined gene-by-environment interactions in the cohort *(26)*. In another large GWA study, asthma was associated with eosinophilia and the genetic loci *IL1RL1, WDR36, IL33,* and *MYB (27)*. Some of these genes modulate T-cell functions with correlates in animal models.

The gene *IL33* encodes interleukin-33 which is expressed in high levels in the airways of severe asthmatics *(28)*.

Genotype-specific responses are clinically relevant. Polymorphisms at the 16th amino acid residue of the β_2-receptor gene are associated with adverse effects of β_2-agonist use in asthmatic patients. Patients with the Arg/Arg genotype improved when β_2-agonist therapy was withdrawn and replaced with the anticholinergic drug ipratropium bromide. Patients with the Gly/Gly genotype had better control of their asthma with regular albuterol use. It is estimated that one-sixth of the asthma population in the United States have the Arg/Arg genotype and the prevalence is present in approximately 20% of African Americans and 15% of Caucasians. Israel et al. in the BARGE Study suggest that patients with the Arg/Arg genotype benefit from discontinuing albuterol as their rescue bronchodilator and could use ipratropium bromide instead *(29)*.

Immunological Insights

The immunological basis of asthma and the role of T-helper cell 1 (T_h1) and T_h2 immune pathways are well established. The IL-17-producting T-cells (T_h17) and regulatory T-cell (T_{reg}) types have recently emerged as key players in asthma pathogenesis. It is generally accepted that T_h1 cells antagonize the effects of T_h2 cells in asthma and vice versa. Similarly, T_{reg} cells (implicated in immune tolerance and autoimmunity) also inhibit T_h2 cell responses in asthma. The T_h2 cytokines IL-4 and IL-13 are important in both human and animal models of allergic asthma. Aeroallergen-induced activation of airway dendritic cells leads to subsequent B- and T-cell activation, which in turn leads to recruitment of mast cells, eosinophils, macrophages, and neutrophils. Ultimately, these same processes and increased production of pro-inflammatory chemokines and cytokines promote airway remodeling in various resident cell types (Fig. 5).

Beyond adaptive immune responses to allergens (i.e., antigen-dependent), the innate immune response which is antigen independent has emerged as a major mechanism in asthma pathogenesis and is an area of burgeoning research (Fig. 6). However, little is known about the impact of aging on both adaptive and innate immunity, and how this relates to the clinical manifestations of AOA.

With aging, airway cell populations and their mediators can change in AOA and affect disease progression. The bronchial eosinophilic inflammation orchestrated by mast cells and $CD4^+$ T-lymphocytes in childhood asthma extends into early adulthood. However, eosinophils and neutrophils become increasingly more important with AOA and in severe persistent asthma in adults. This relationship was explored by Wenzel and her colleagues to determine whether phenotypic differences exist between early onset severe asthma (before age 12), as compared with LOA (after age 12), and whether the presence or absence of eosinophilia influences these phenotypes. Differentiating severe asthma by age at onset and presence or absence of eosinophils identifies phenotypes of asthma which could benefit subsequent genetic and therapeutic studies. The presence of eosinophils in either age at onset group was associated with worse lung function. LOA was associated with the highest numbers of lung eosinophils, however, only early onset severe asthma was associated with a lymphocytic/mast cell inflammatory process. Finally, subjects with LOA without eosinophils had no subepithelial basement membrane fibrosis *(30)*.

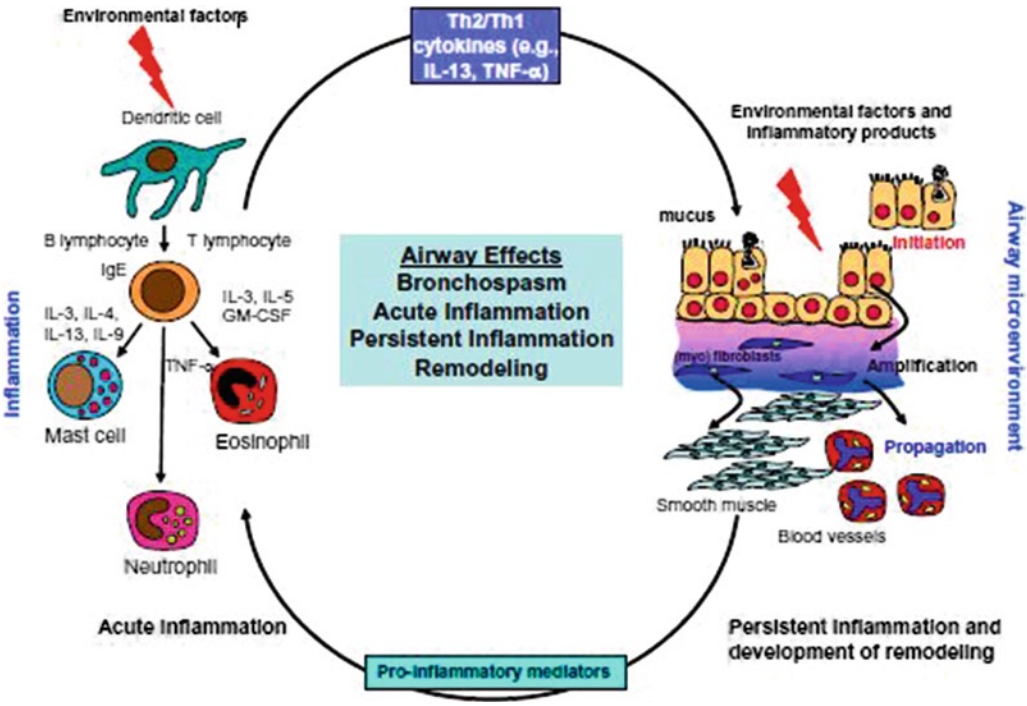

Fig. 5. Chronic inflammation and adverse airway remodeling lead to the clinical syndrome of asthma. The Th1 and Th2 cytokine responses are shown, as well as the changes that take place in airway resident cells leading to remodeling and airway hyperreactivity (adapted from Holgate et al. *(76)* and EPR3 2007 *(33)*. Reproduced with permission).

DIAGNOSIS

One of the hallmarks of asthma is reversible airflow obstruction. A significant bronchodilator response is commonly seen in children with asthma after administration of albuterol, with FEV_1 improving by at least 200 mL and 12%. The same criteria have been applied to adults; however, many older patients have reduced expiratory flow rates due to aging (Table 3). Lung volumes can also improve but often are not measured after bronchodilator challenge. Total lung capacity (TLC) and residual volume (RV) can *decrease* and inspiratory capacity (IC) can *increase* significantly after bronchodilator administration in patients with asthma or COPD. This can occur in the *absence* of any significant improvement in expiratory flow rates (Fig. 7). Examination of flow-volume loops before and after bronchodilator treatment can readily disclose this phenomenon, or a decrease in TLC or functional residual capacity (FRC) by ≥500 mL or ≥15% from baseline (as measured by plethysmography).

Aging causes an annual decline in lung function and this may confound the differentiation between asthma and COPD. The normal decline in FEV_1 is approximately 25–35 mL per year. From age 25 to 39, the decline is approximately 20 mL per year; age >45 years, 35 mL per year. Therefore, loss of spirometric lung function increases with age, emphasizing the need to consider the individual's current age when evaluating lung function and not just the age of asthma onset.

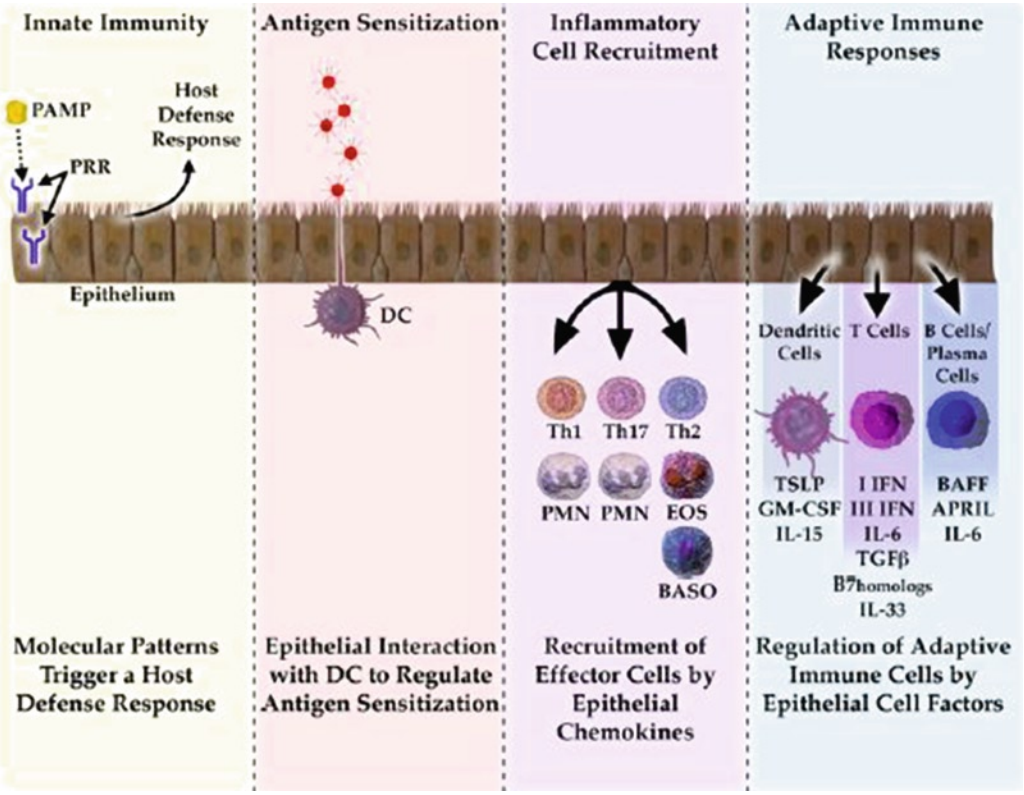

Fig. 6. The role of the adaptive and innate immune responses in asthma. These two arms interact via T-cells and T_{reg} cells beyond the initial trigger by epithelial and dendritic cells. This then leads to the adaptive immune responses and the recruitment of various inflammatory cells from the blood stream and into the airway compartment (adapted from Schleimer et al. *(77)*. Reproduced with permission).

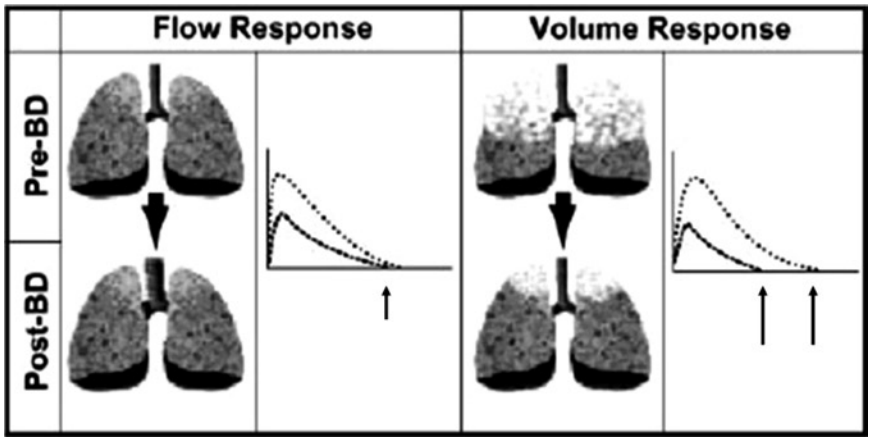

Fig. 7. Responses to bronchodilator therapy can have two responses. On the *left*, a predominantly expiratory flow response is seen. On the *right*, a predominantly volume response is seen (the *two arrows* show an increase in lung volume postbronchodilator, with a shift of the expiratory limb to the right). The *white areas* in the volume response lungs representing air-trapping behind high-resistance peripheral airways (adapted from Sciurba *(78)*. Reproduced with permission).

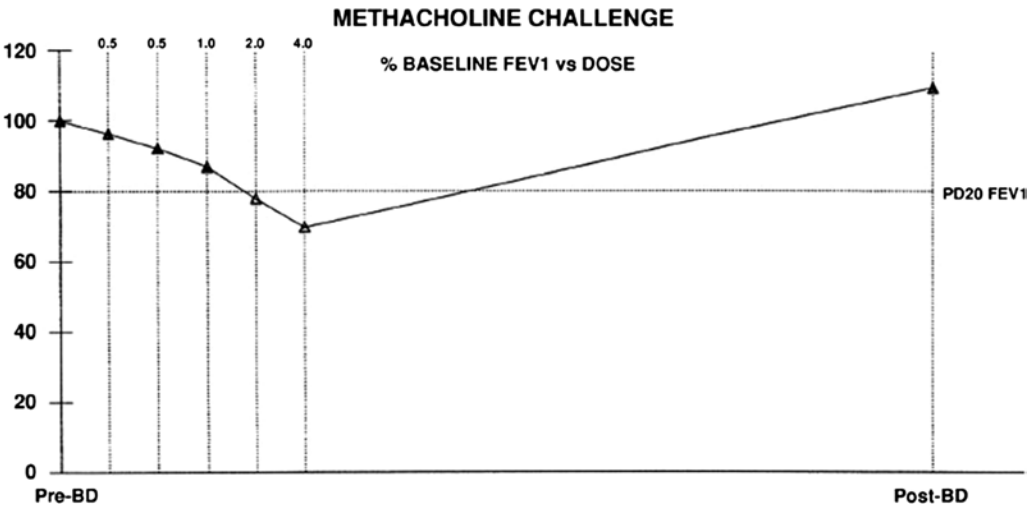

Fig. 8. A positive methacholine bronchial challenge test with a drop in FEV1 of >20% from the subject's baseline.

Bronchoprovocation challenge tests detect the presence of nonspecific AHR in patients with a normal spirometry and chest X-ray. AHR is defined as the degree to which expiratory flow rates decline after response to a nonspecific trigger (e.g., methacholine, histamine, cold air, mannitol, exercise, or adenosine-5′-monophosphate). The methacholine PC_{20} is the provocative challenge or dose of methacholine that causes a 20% decrease in a patient's baseline FEV_1 measured after inhaling normal saline. Methacholine bronchial challenge is used primarily to rule out AHR in the clinical setting of normal pulmonary function tests. However, it can be used to detect AHR in AOA, particularly in the elderly. When the methacholine challenge test is negative (i.e., normal FEV_1 response), a diagnosis of AOA can be excluded in most cases. A positive test confirms the presence of AHR but is not specific for asthma (Fig. 8).

Exhaled Nitric Oxide

Exhaled nitric oxide has emerged as a possible new adjunctive test in the diagnosis of asthma. Several studies have evaluated this with and without sputum eosinophils and spirometry. However, the exact relationship between the fraction of exhaled nitric oxide (FE_{NO}) and the underlying pathophysiology of asthma is unclear. In one prospective study evaluating 160 patients with obstructive airways disease, nearly half (46.9%) were found to have asthma, 15.6% had COPD, 5% with asthma-COPD overlap syndrome, and 32.5% did not have airflow obstruction *(31)*. The diagnosis of asthma could be ruled-in with an FE_{NO} >46 parts per billion (ppb) and ruled-out with an FE_{NO} <12 ppb. However, in a large study from New Zealand (n=528) there was a wide range of FE_{NO} levels in normals and asthmatics not on ICS. At a 20 ppb cut off, sensitivity and specificity were poor (sensitivity 49%, specificity 61%), and a higher cut-off of 50 ppb improved the specificity at the expense of sensitivity *(32)*.

The FE_{NO} testing can be done in conjunction with the standard history and physical, spirometry, sputum eosinophil counts (if feasible), and chest X-ray. The FE_{NO} has clear limitations with respect to helping establish an asthma diagnosis, but in current clinical practice FE_{NO} is also used to assess underlying airway inflammation, monitor disease activity, and identify corticosteroid responsiveness.

Biomarker Technologies

The collection and analysis of exhaled breath condensate (EBC) is a recent development in the world of asthma. The EBC contains water vapor, respiratory droplets, particles, and thousands of molecules released from the lung. Many biomarkers of airway inflammation have been reported in the EBC. Amongst the compounds measured there are markers of oxidative stress (8-isoprostane, hydrogen peroxide), leukotrienes (B4, cysteinyl), nitrosothiols, chemokines (e.g., eotaxin-1), cytokines (e.g., IL-6), isoprenes, and airway pH amongst many others. Although at present it is unclear whether EBC will have the ability to distinguish between asthma and COPD, or to help diagnose asthma, it is an active area of research with significant promise.

TREATMENT

The current NIH-NAEPP-EPR3 (2007) guidelines *(33)* focus on achieving and maintaining asthma control using an individualized treatment plan to minimize the patient's *impairment* and *risk* of acute exacerbation. It utilizes a step-wise approach which directs step-up or step-down asthma therapy based on disease control rather than disease severity.

Comorbid conditions should be suspected and treated when AOA becomes difficult to control in adults, e.g., GERD, rhinosinusitis, infection. Given recent concerns about drug safety, it is vital to carefully determine and monitor the safety and effectiveness of each drug used. Below, we highlight areas of particular interest to the adult and elderly asthmatic.

Inhaled Corticosteroids

Inhaled corticosteroids (ICS) remain the single most effective therapy for adult patients with asthma. It is the first-line treatment for asthmatics; however, it is increasingly evident that predicting ICS response is difficult where neither sputum eosinophils nor FE_{NO} are predictive of improvement. Only lung function, specifically FEV_1 and FEV_1/FVC were predictive of a favorable response *(4)*. For those unable or unwilling to take ICS, the use of leukotriene modifiers/receptor antagonists is an alternative. Long-acting β_2-agonists (LABA) are the preferred add-on treatment for patients with persistent asthma who have not adequately responded to an ICS alone. The LTRAs are effective as an alternative to LABA (as an add-on treatment to ICS), and more recently tiotropium was proved efficacious and comparable to salmeterol *(34)*. However, since the long-term effects of LABAs on acute exacerbations and survival remain unclear, the FDA has mandated a Black Box Warning regarding LABA use in asthma.

Marked and variable responses to ICS should be expected in AOA, and particularly in LOA. Szefler et al. in the NIH ACRN compared the relative beneficial and systemic effects of two ICS, beclomethasone (BDP) and fluticasone (FP) *(35)*. A 24-week,

parallel, open-label, multicenter trial examined their benefit–risk ratio in persistent asthma ($n=30$). Benefit was assessed by improvements in FEV_1 and PC_{20}; risk of side effects was assessed by overnight plasma cortisol suppression. Maximum FEV_1 response occurred with the low dose for FP and the medium dose for BDP (as metered dose inhalers (MDI)) and was not further increased by treatment with FP-dry powder inhaler (DPI). Near-maximum methacholine PC_{20} improvement occurred with the low dose for FP-MDI and the medium dose for BDP-MDI. Both BDP-MDI and FP-MDI caused dose-dependent cortisol suppression.

Responsiveness to ICS treatment was found to vary markedly among subjects. Good (>15%) FEV_1 response, in contrast to poor (<5%) response, was found to be associated with high exhaled nitric oxide, high bronchodilator reversibility (25.2% vs. 8.8%), and a low FEV_1/FVC ratio (0.63 vs. 0.73) before treatment. Near-maximal FEV_1 and PC_{20} effects occurred with low-to-medium doses for both ICSs. High-dose ICS therapy did not significantly increase the aforementioned efficacy measures, but it did increase systemic effects (as measured by overnight cortisol secretion). Significant intersubject variability in responses occurred with both ICS. It is possible that higher doses of ICS are necessary to manage more severe patients or to achieve goals of therapy not evaluated in this study, such as prevention of asthma exacerbations. Beyond sole dose titration, reducing the frequency of inhaler use, i.e., once vs. twice daily, may also have a role in asthma management.

Inactivation of histone deacetylase-2 (HDAC2) results in corticosteroid resistance in both asthma and COPD. Unlike patients with asthma, those with COPD are poorly responsive to corticosteroids, providing little clinical benefit except during acute COPD exacerbations. In both diseases, multiple inflammatory genes are activated, which results from acetylation of core histones around which DNA is wound. This acetylation opens up the chromatin structure allowing gene transcription and synthesis of inflammatory proteins to proceed. Corticosteroids recruit HDAC2 to the actively transcribing gene, which reverses this process and switches off inflammatory gene transcription. Cigarette smoking and oxidative stress, leading to a pronounced reduction in responsiveness to corticosteroids, can impair HDAC2 function. High doses of ICS (as defined by the NIH-NAEPP) combined with one or two other long-term controllers or systemic corticosteroids (20 mg every other day) can be a viable alternative in very severe AOA or refractory asthma, but evidence-based data for their efficacy are lacking.

A departure from the traditional use of the combination inhaler ICS/LABA as daily scheduled controller is the use of the ICS/LABA also as an "as needed" reliever. Several studies have shown fewer asthma exacerbations, better lung function, and better asthma control with as needed extra puffs of budesonide/formoterol combination than either one alone *(36)*. This regimen is popular in Canada and Europe but is prohibited by the FDA in the United States. Repeated and high doses of ICS have also been studied in the setting of acute asthma, but we do not recommend this be part of the asthma action plan in AOA.

Inhaled β_2-Agonists

Tolerance to β_2-agonists treatment after regular use in AOA has been reported in a meta-analysis of 22 studies in patients who take either β_2-agonists or placebo regularly for at least 1 week *(37)*. Patients who took β_2-agonists regularly for at least 1week were less responsive to the effects of subsequent doses of β_2-agonists than were patients who

took placebo. Regular users developed tolerance to the effects of β_2-agonists with respect to both bronchodilation and inflammation. Regular users demonstrated more airway inflammation than those who took placebo. It is unclear whether taking β_2-agonists "as needed" is worse than not taking any β_2-agonists at all. It is unclear whether a similar phenomenon occurs with LABAs since previous NIH Asthma Clinical Research Network (ACRN) studies suggested that the return of airway inflammation was due in large part to the withdrawal of ICS *(38)*.

The FDA has determined through a comprehensive review and their own meta-analysis of available studies that LABAs as a class of drugs (i.e., salmeterol, formoterol) increase the risk of asthma-related deaths and issued a Black Box Warning to alert physicians and patients that LABA use without the concomitant use of an asthma controller, such as ICS, is contraindicated in asthma treatment. The FDA has relied on the SMART study which demonstrated a small but significant increase in the relative risk of asthma-related deaths *(39)*. However, when baseline ICS use was taken into account in this study, these differences were not statistically significant across all study groups (i.e., total population, Caucasians, African Americans). The United States is the only country with a FDA-mandated Black Box Warning with no similar edict in Europe, Canada, or other countries *(39)*. Despite the increased prescription and use of LABAs (used in combination with ICS), asthma mortality has declined by more than 33% since 1996. It is important that physicians, patients, and all healthcare providers not minimize the risk of asthma-related deaths from LABAs when used alone without ICS. The FDA has recommended stopping use of LABAs once asthma control is achieved with ICS. However, there is no clear evidence whether this approach would increase the risk of asthma exacerbations or not.

The BARGE study (Beta-Adrenergic Response by Genotype) recently raised concerns over the clinical significance of β_2-receptor polymorphisms and lung function *(29)*. It indicated that even "as needed" albuterol use is not safe in patients with the Arg/Arg genotype. Previous retrospective studies suggested that regular albuterol use produces adverse effects in Arg/Arg patients. Israel et al. argue that we need to carefully evaluate the bronchodilator response of asthma patients to β_2-agonists before prescribing long-term therapy and rescue treatments *(29)*. Some have speculated that anticholinergics can be a safer alternative in the long term. However, only albuterol was used in the BARGE study as an intervention, and ipratropium bromide was used the "as needed" inhaler in order to avoid confounding and additional use of albuterol. Whether the effects are observed with other SABAs or LABAs is not yet known, nor are the consequences of having the Arg/Arg genotype with more severe asthma, or the interaction and effect of combining β_2-agonists with ICS.

Omalizumab

Omalizumab (anti-IgE) is a monoclonal antibody that prevents binding of IgE to high-affinity receptors on basophils and mast cells. Busse et al. showed that for asthmatics with a total serum IgE $\geq$ 30 IU/mL to $\leq$ 700 IU/mL, omalizumab injection every 2 or 4 weeks (depending on baseline IgE level) resulted in significantly lower asthma exacerbations, a reduction in beclomethasone dose, improved asthma symptoms and lung function, and reduction in rescue β-agonist use *(40)*. It can be considered for adults and adolescents 12 years and older with moderate-to-severe persistent asthma who are

positive for perennial aeroallergens and whose symptoms are inadequately controlled with ICSs and LABAs. Omalizumab should be considered for patients with very poorly controlled asthma (step 5) before choosing to add oral corticosteroids (step 6, NIH-NAEPP EPR3 2007) *(33)*.

In early 2007, the FDA issued and began requiring a Black Box Warning be added to omalizumab. Despite the consistent benefits of omalizumab and the inclusion of this drug in steps 5 and 6 of the NAEPP-EPR3, concerns have been raised over potential adverse effects (e.g., malignancy and anaphylaxis). Anaphylactic and urticarial reactions have been reported in 0.1% of cases, and postmarketing analyses indicate that anaphylaxis occurred in approximately 0.2% of all treated patients.

Physicians must be trained and fully equipped to handle anaphylactic reactions in the clinic and that patients be informed and prepared to recognize and initiate emergency self-treatment for anaphylaxis outside the clinic setting. Anaphylaxis can develop after any dose of omalizumab, even if there was no adverse reaction to the first dose given. Anaphylaxis can be delayed up to 24 h after a subcutaneous dose.

Malignancies occurred in 0.5% of all patients who received omalizumab and 0.2% in the placebo group, more than two times the rate. Epithelial or solid organ cancers were the predominant type of cancer, more than hematologic malignancies. The effect of longer drug exposure or use in patients who are at increased risk for cancer is unknown since most patients treated with omalizumab were observed for only 1 year.

Montelukast

The three leukotriene modifiers are montelukast, zafirlukast, and zileuton, all available as oral tablets for the treatment of asthma. Leukotriene modifiers comprise two classes of compounds: the 5-lipoxygenase inhibitors (e.g., zileuton), and the leukotriene receptor antagonists (LTRA) which block the cys-LT1 receptor (e.g., montelukast and zafirlukast). In smokers, those with exercise-induced bronchospasm, and aspirin-induced asthma, these agents may be helpful. The antileukotriene drugs improve symptoms and reduce exacerbation rates in some patients with moderate asthma and poor control on ICS. In clinical trials, adding montelukast to inhaled budesonide in patients with moderate asthma significantly improves asthma control *(41)*. In a large, multicenter clinical trial ($n = 1{,}490$), the addition of montelukast to fluticasone in asthmatics whose symptoms remained uncontrolled is noninferior to treatment with fluticasone and the LABA salmeterol *(42)*.

Sims et al. evaluated whether montelukast or formoterol provides additive effects to asthmatics not controlled on ICS by studying patients homozygous for the Gly/Gly-16 genotype who were considered to be genetically susceptible to β_2-receptor downregulation *(43)*. In genetically susceptible patients with the homozygous Gly/Gly-16 genotype, montelukast, but not formoterol, conferred sustained anti-inflammatory properties in addition to ICS, which were dissociated from changes in lung function after 2 weeks. Therefore, assessing lung function alone can deprive potentially beneficial anti-inflammatory effects of montelukast when used as add-on therapy.

In March 2008, after reviewing postmarketing reports, the FDA and Merck announced a possible link between the use of montelukast and behavioral and/or mood changes including suicidality and depression. Postmarketing adverse events for montelukast in 2007 included tremor, depression, and suicidality, where anxiety was included later in 2008.

This safety review was extended to all leukotriene modifiers, including zafirlukast and zileuton. Based on a 2009 FDA updated communication, the incidence of suicidal ideation was less than 0.01% for all leukotriene modifiers.

However, montelukast is an effective drug and is indicated for the treatment of asthma in all age groups according to NIH-NAEPP-EPR3. We feel that patients should not discontinue montelukast or other leukotriene-modifying medications, including zafirlukast and zileuton, and they should not stop taking LABAs without notifying their health care provider. Until further information is available from the FDA and the NIH-NAEPP, health care providers should monitor their patients regularly for worsening asthma control, particularly those taking LABAs, and monitor for suicidal thinking and changes in behavior in patients who are taking montelukast.

Allergen Immunotherapy

Allergen injection immunotherapy is the only treatment in current use with the potential for modifying the course of allergic disease, particularly rhinosinusitis. It is considered adjunctive treatment for asthma by the NIH-NAEPP-EPR3 and not a preferred or alternative treatment. For atopic asthma, novel treatment strategies aim at locally targeting inflamed airways. Nebulized monoclonal antibodies and soluble interleukin receptors against T_h2 cytokines have been designed, or alternatively the administration of T_h1 cytokines. Although immunomodulatory strategies provide a promising outlook for the treatment of allergic patients, more studies are needed to address issues of efficacy, safety, and the long-term effects of altered immune responses.

NOVEL TREATMENTS

Tiotropium

Many studies have suggested that blocking airway muscarinic receptors in asthma could have benefit, at least in some subgroup. Peters et al. investigated the effects of a long-acting anticholinergic agent, tiotropium bromide, in the treatment of inadequately controlled asthma *(34)*. In a three-way, double-blind, triple-dummy crossover trial involving 210 asthmatic patients, tiotropium bromide was either added to ICS, the existing ICS dose was doubled, or a LABA was added to ICS. Tiotropium was superior to doubling the ICS dose and noninferior to the LABA/ICS combination, as determined by peak expiratory flows (PEF), FEV_1, the number of asthma control days, and daily symptom scores. Since its effects appear to be similar to LABA/ICS combination, tiotropium can prove to be a viable add-on alternative step-up treatment in uncontrolled asthma.

Mepolizumab

The cytokine IL-5 is one of several important eosinophilic chemotactic peptides known to play a role in human asthma. Mepolizumab is an anti-IL-5 monoclonal antibody that has recently been shown to have benefit in a subset of asthmatics with eosinophilic, severe refractory asthma *(44, 45)*. This anti-IL-5 antibody can lower blood and sputum eosinophils and thereby reduce severe exacerbations. As an add-on therapy to high doses of ICS/LABA or chronic oral corticosteroids in patients with severe asthma who have persistent sputum eosinophilia and frequent exacerbations, the mepolizumab group had fewer exacerbations (relative risk 0.57; $p=0.02$), the primary outcome

variable. There was no significant change in lung function parameters as was seen with the omalizumab clinical trials suggesting that immunomodulators are likely to decrease risk than to alter traditional indicators of control (symptoms or lung function).

Antifungal Therapy

As with the macrolide antibiotics, the role of antifungal therapy in asthma is emerging as a potentially viable alternative treatment. The effects of itraconazole in the Fungal Asthma Sensitization Trial (FAST) improved the Asthma Quality of Life Questionnaire (AQLQ) score of asthmatics as compared to placebo *(46)*. Those who maintained therapy to 32 weeks (61%) continued to increase and improve their AQLQ score. The group that received itraconazole also demonstrated an improvement in morning peak flow (20.8 L/min, $p=0.028$), improvement in rhinitis score ($p=0.013$), and decrease in total serum IgE level ($p=0.001$). This study was not designed to uncover the underlying mechanism of action, thus either the antifungal or immunomodulatory effect of itraconazole could have accounted for the observed clinical benefits. Interestingly, based on their high baseline IgE levels (212 IU/mL itraconazole group, 245 IU/mL placebo group) these asthmatics would have also qualified for treatment with omalizumab raising the question: is there any added benefit to treatment with both omalizumab and itraconazole in the allergic asthmatic with fungal sensitization?

Antibiotics

For over a decade there has been growing interest in the use of macrolide antibiotics such as azithromycin or clarithromycin, for the treatment of both pediatric and adult asthma. Clarithromycin has direct anti-inflammatory effects with reductions in airways IL-8 and neutrophils counts, as well as improvements in quality-of-life scores *(47)*. In another study, clarithromycin when added to inhaled fluticasone improved AHR but did not improve asthma control *(48)*. Azithromycin has been studied in children and adults with mixed results. The tetracycline antibiotics also have anti-inflammatory properties and in a small clinical trial, the addition of minocycline resulted in a 30% reduction in mean daily prednisone use compared with placebo ($p=0.02$), and improved lung function, and symptoms in those with moderate and severe asthma *(49)*. It is the authors' perspective that data are still lacking for a clear indication for antibiotic use in asthma.

Bronchial Thermoplasty

Bronchial thermoplasty represents a departure from past approaches to treating severe adult asthma. This highly novel treatment entails applying radio frequency energy (near 60°C) to 3–10 mm airways in three staged bronchoscopies (right lower lobe, left lower lobe, bilateral upper lobes). The rationale is that heat treatment can ablate sections of smooth muscle bundles and reduce airway smooth muscle mass. In April of 2010, bronchial thermoplasty was approved by the FDA for the treatment of severe persistent asthma in patients 18 years or older (18–65 age group) whose asthma is not well controlled with ICSs and LABAs, after the results of the pivotal AIR2 trial were published *(50)*. In that trial, 79% of the subjects in the thermoplasty group versus sham bronchoscopy group noted improvement in their asthma questionnaire score, which was the primary outcome. The Alair® Bronchial Thermoplasty System delivers radiofrequency energy to the airways via

a bronchoscopically directed catheter, reducing smooth muscle mass and providing the first potentially permanent treatment for asthma. While it has been demonstrated to improve quality of life symptoms and asthma control *(50)*, its primary effect is likely a reduction in bronchospasm.

Bronchial thermoplasty has undergone substantial animal and human studies. Healthy dogs treated with bronchial thermoplasty with radiofrequency ablation (RFA) at 65°C and 75°C, but not 55°C, had significant reduction in the degree of airway diameter narrowing in response to bronchoscopically administered methacholine. This has been shown in preclinical models, but the mechanism of effect in humans is not well known yet. Corresponding airway histology revealed a significant reduction in airway smooth muscle. A preliminary human study of eight subjects who underwent bronchial thermoplasty prior to medically necessary, elective lobectomy, revealed similar histologic findings of reduction in airway smooth muscle *(51)*.

Following two open-label clinical trials demonstrating improvement in asthma control *(52, 53)*, the first human, sham-bronchoscopy-controlled clinical trial (AIR2) demonstrated the effectiveness of bronchial thermoplasty in the treatment of asthma *(50)*. Two hundred and ninety seven patients with severe persistent asthma not adequately controlled on high dose ICS and LABAs were randomized in a double-blind, 2–1 fashion to bronchial thermoplasty or sham-bronchoscopy control. The primary effectiveness end-point, change in Asthma Quality of Life Questionnaire (AQLQ) score at 6, 9, and 12 month follow-up, was significantly higher in the treatment vs. the sham bronchoscopy group. The treatment group also had fewer severe exacerbations; emergency department visits; and days missed from work, school, or daily activities compared to the sham control group. Adverse events were higher in the treatment group during the treatment phase with an increase in respiratory adverse events, with the majority of symptoms occurring within 1 day of a procedure and resolving within 7 days with standard treatment *(50)*. Preliminary 5-year follow-up data has demonstrated stability of respiratory adverse events, hospitalization and emergency room visits for respiratory events and spirometry *(54)*.

While relatively large clinical trials suggest that bronchial thermoplasty helps control respiratory symptoms in severe asthma and potentially offers the first permanent treatment for asthma, postapproval clinical experience is limited. Although very promising, novel, and an exciting new treatment for asthma, bronchial thermoplasty has not yet been fully tested on a large-scale commercial basis and its future is yet to unfold. Bronchial thermoplasty is performed at only a few clinical centers of excellence, including the University of California, Davis.

INVESTIGATIONAL THERAPIES

Beyond the development of new even longer acting β-agonist inhalers or new varieties of glucocorticoids with selective receptor activation, research in the areas of TNF, phospholipase A2, and IL-4Rα receptor blockade (e.g., pitrakinra) is ongoing. Cytokine therapies and chemokine antagonists are also under development for asthma, as are peroxisome proliferator-activated receptor (PPAR)γ agonists, phosphodiesterase (PDE)4 inhibitors, kinase inhibitors, adhesion molecule blockade, and spleen tyrosine kinase (Syk) inhibitors *(55)*. Many of these are still in the realm of preclinical studies, but it is

likely that some of these drugs will move into clinical trials. Vitamin D deficiency in asthma may play a role in disease pathogenesis, where it may modulate the role of T_{reg} cells and influence other manifestations of atopy. In both children and adults with asthma, vitamin D deficiency was associated with decreased lung function, increased atopy, and worse asthma severity *(56)*. These studies suggest that replacement of vitamin D in such patients may improve asthma symptoms and outcomes.

The PDE4 inhibitor roflumilast, administered as an oral drug over a 4-week clinical trial to treat COPD, reduced sputum eosinophils and neutrophils, IL-8 and other markers of inflammation, and improved postbronchodilator FEV_1 with a mean difference between treatments of 68.7 mL (95% CI, 12.9–124.5; $p=0.018$) *(57)*. A study in asthma using an oral PDE4 inhibitor MK-0359 also showed some benefit in airway function, day and nighttime symptoms, quality of life scores, and rescue medication use, but at the expense of greater gastrointestinal side effects *(58)*.

The statin drugs used to treat hyperlipidemia and cardiovascular disease also have pleiotropic immunomodulatory and antiproliferative effects *(59)*. Beyond cholesterol-lowering, the statins also inhibit small G-proteins which are important cell signaling molecules that modulate inflammation and cell proliferation. Epidemiologic studies have linked statin use with improvements in asthma and COPD *(60–62)*. Several small clinical trials in asthma have had mixed results, where statin use reduces sputum inflammatory markers (e.g., LTB4) and leukocyte counts, but without clear clinical benefits *(63–65)*. However, a recent double-blinded study where simvastatin (10 mg daily for 8 weeks) was given as add-on therapy to low-dose (200 μg) inhaled budesonide in patients with mild asthma showed that simvastatin enhances the anti-inflammatory effect of budesonide *(66)*. Sputum eosinophil counts were significantly reduced by the combined therapy with budesonide and simvastatin compared to budesonide and placebo ($p=0.02$). Although the study was not powered to detect changes in lung function, there was a trend toward higher FEV_1 in the budesonide and simvastatin group compared to budesonide and placebo. Ongoing trials will test whether clinical outcomes will also improve with these drugs as add-on anti-inflammatory agents in asthma (www.clinicaltrials.gov). The statins are a potentially groundbreaking innovation in asthma treatment given their safety profile, widespread use, and ready availability around the world.

THE PATIENT: COMPLIANCE AND SAFETY

Patient safety is paramount in the treatment of the adult asthmatic. Patients must understand their shared responsibility to take prescribed controller medications daily. Adherence with prescribed asthma therapy in the United States is very poor and contributes to the poor control of asthma we see. In a study evaluating the adherence of 48,571 adult asthma patients, <30% took ICS twice daily, <30% took inhaled long-acting β_2-agonists (LABA) twice daily, and <50% took a leukotriene receptor antagonist (LTRA) once a day at 6 and 9 months. There was a statistically significant difference between groups with $p<0.004$ for LTRA vs. ICS and LABA based on medication refills *(67)*. There can be a difference between men and women with respect to their attitudes towards their inhaler medications, where women were found to be more compliant and used their ICS more often than men in a European study of 470 asthmatics who took part in the European Community Respiratory Health Survey (ECRHS) II *(68)*.

β_1-Blockers

Numerous randomized clinical trials of β_1-blockers have shown significant reduction of total mortality in patients with myocardial infarction and congestive heart failure (CHF). Despite the life-saving therapy of β_1-blockers in these diseases, they are often withheld from patients with asthma and COPD because of the fear of triggering acute bronchospasm. Recent meta-analyses in the Cochrane Library show that cardioselective β_1-blockers in normally prescribed dose ranges are well tolerated by these patients without causing acute exacerbations. However, both cardioselective and noncardioselective β_1-blockers can cause bronchospasm at higher dosages and caution is warranted in the setting of glaucoma where a β_1-blocker is prescribed to treat the ocular condition.

β_1-blockers were previously contraindicated in CHF because of their intrinsic negative inotropic effects, but are now an established agent in CHF treatment, partly due to their ability to enhance sensitivity to sympathetic stimulation. Similarly, new evidence has shown that cardioselective β_1-blockers such as atenolol, metoprolol, and betaxolol are safe in patients with asthma and COPD, and can actually be beneficial by enhancing sensitivity to endogenous or exogenous β-adrenergic stimulation manifest as an increased FEV_1 bronchodilator response after albuterol treatment.

Relative contraindications for β_1-blockers include acute COPD exacerbations and severe to very severe stages of COPD (GOLD Stage III and Stage IV) as well as severe persistent asthma. β_1-blockers therapy should be given with low initial doses, preferably using cardioselective drugs. Given their demonstrated benefit in conditions such as CHF, coronary artery disease, and hypertension, cardioselective β_1-blockers should not be withheld from adults with mild-to-moderate asthma or COPD.

CONCLUSIONS

The authors' goal was to emphasize that asthma is a syndrome characterized by phenotypic heterogeneity. We reviewed the challenges in diagnosing and managing adult asthma, the impact of increasing age, and highlighted the importance of an individualized asthma management plan given the variable responses to pharmacotherapy. In the near future, genetic profiling will facilitate making diagnoses and help further define the asthma subphenotypes or clusters of interest. Advanced noninvasive technologies such as EBC analysis and exhaled nitric oxide can help monitor disease activity and could ultimately help distinguish asthma from COPD. Despite emerging novel therapies, patient compliance and drug safety concerns have complicated the care of the asthmatic patient. Adult asthma remains a vastly complex field always in need of novel ideas and better, safer therapies.

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7 The Patient with Asthma in the Emergency Department

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Contents

KEY POINTS

- Peak expiratory flow meters aid in assessing severity and following the progress of patients with acute asthma exacerbations in conjunction with history, examination, and pulse oximetry. Predicted levels must factor in height in pediatric patients.

From: *Bronchial Asthma: A Guide for Practical Understanding and Treatment, 6th ed.*
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- Mild to moderate exacerbations should be treated with albuterol, by nebulizer or metered-dose inhaler with holding chamber, and most patients should receive systemic corticosteroids (CS).
- Severe exacerbations should be treated with high-dose nebulized albuterol, ipratropium bromide, and CS, either by oral or intravenous route.
- Adjunctive therapies such as intravenous magnesium should be considered for patients with ongoing severe airflow obstruction after the first 60 min of standard treatment. Such patients should also receive continuous high-dose albuterol and additional ipratropium bromide and CS as needed. Heliox should also be considered if available.
- Best available evidence suggests no benefit to doses greater than 100 mg of prednisone equivalent per day.
- Other options for very severe exacerbations not responding to standard therapy include ketamine and noninvasive positive pressure ventilation.
- Determination of disposition should start after the first 60–90 min of treatment rather than at the time of initial presentation.
- Discharge from the emergency department should involve appropriate discharge medications, education, a written asthma action plan, and follow-up arrangements.

INTRODUCTION

Patients of all ages present to the emergency department (ED) with respiratory distress and wheezing. Initial evaluation entails assessing the severity of the respiratory distress and determining if an acute exacerbation of asthma is the cause.

Asthma is a common condition that accounts for approximately two million ED visits, 500,000 hospitalizations, and over 4,000 deaths each year in the United States *(1)*. Because it involves both paroxysmal spasmodic narrowing of the bronchial airways and inflammation of the bronchi, it is not surprising that patients experience sudden symptoms requiring prompt medical attention. Although improved medication regimens and step-up treatment plans have been successful in decreasing ED visits, in certain centers, acute asthma may still comprise 10% of all ED visits.

Asthma may be diagnosed for the first time in a patient presenting to the ED, but in the majority of cases, the patient will be aware of the underlying diagnosis of asthma and will communicate it in the field or at triage. This history is often helpful in the initial categorization of the problem and treatment approach, allowing the emergency practitioner to focus on initiating therapy, assessing severity, and identifying a triggering cause and comorbid conditions. Previous work has reported that as many as 30% of patients carrying a diagnosis of asthma may not actually have asthma and requires the ED clinician to remain open to the possibility that the symptoms may be due to another disease entity mimicking an asthma exacerbation *(2)*.

ASSESSING THE SEVERITY OF RESPIRATORY DISTRESS

Rapid initial assessment is required for the expert provision of emergency services and initial treatment should be started coincident with this assessment when suspicion for asthma is high. The universal concept of ABC – airway, breathing, and circulation – must be applied to the patient with severely symptomatic asthma. In respiratory failure, ventilatory support needs to precede detailed history and physical examination.

Table 1
Primary Assessment

Signs of a severe asthma attack in an adult
Severe agitation
Hunched sitting position with arms supporting torso (tripod)
Limited ability to speak
Use of accessory muscles
Cyanosis
Respiratory rate more than 30/min
Signs of a severe asthma attack in an infant
Use of accessory muscles
Supraclavicular and intercostal retractions
Nasal flaring
Paradoxical breathing
Cyanosis
Respiratory rate more than 60/min
Signs of impending respiratory arrest
Lethargy or confusion
Silent chest
Paradoxical thoracoabdominal movement
Bradycardia

The presenting appearance of the patient provides key information (*see* Table 1). Vital signs showing high blood pressure, pulse rate, or respiratory rate are usually indications for aggressive emergency treatment. Limited ability to speak, assuming the tripod position, and using accessory muscles are worrisome for severe exacerbation. Signs of impending respiratory failure include drowsiness or confusion, diaphoresis, paradoxical thoracoabdominal movement, and a silent chest and should prompt preparations for intubation and mechanical ventilation. Vital signs showing low blood pressure and bradycardia signify reduced cardiac output, are indications for immediate resuscitative intervention, and should prompt a search for complications such a pneumothorax and pneumomediastinum.

Pulse oximetry provides a guide regarding severity of exacerbation. Values below 90% on room air are concerning for severe exacerbation. Typically, however, the patient with a more serious condition is administered supplemental oxygen as an urgent treatment, and it is the pulse oximetry on oxygen that is assessed and followed in the ED.

An arterial blood gas (ABG) is a consideration for patients in whom there is incongruity between clinical impression and other clinical information, and may also be used to follow patients who are close to needing ventilatory support. In mild and moderate exacerbations, the ABG usually shows a respiratory alkalosis and does not typically add additional information relevant to clinical care in such cases. Normal or increased CO_2 implies severe disease and impending respiratory failure, although the converse is not necessarily true. Metabolic acidosis should be recognized as a marker of very severe disease.

Table 2
Categorization of Severity of Asthma Exacerbation: Common Clinical Features and Assessment of Lung Function

Severity	*Mild*	*Moderate*	*Severe*
PEFR (% predicted or personal best)	≥70%	40–69%	<40%
Speech	Sentences	Phrases	Words
Mental status	Anxious	Agitated	Distressed
Accessory muscle use	No	Sometimes	Commonly
Oxygen saturation (%)	≥95%	90–95%	<90%

Table 3
Potential Events Antecedent to Asthma Attack

Asthma triggers and exacerbating factors
Infection
Exposures
Allergens
Cigarette smoke
Chemical irritants
Aspirin
Cold temperature
Exercise
Alteration in medication
Out of medications
Change in medications
Steroid dose reduction
Other pulmonary or cardiac conditions

Severity of airways obstruction is further evaluated by auscultating the chest, listening both for the quality and amount of wheezing and airflow. For example, the presence of inspiratory stridor or monophonic wheezing best heard over the neck or central airways may signify upper airway or large airway obstruction. Prolongation of the expiratory phase generally reflects the severity of acute asthma. In mild bronchospasm, the inspiration-to-expiration ratio may be 1:1; in severe bronchospasm, the ratio may be 1:3; a silent chest is a marker of very severe obstruction and impending respiratory failure.

However, studies have indicated that the practitioner cannot always accurately assess the degree of airway obstruction through clinical examination alone. As such, use of indices derived from a forced exhalation by the patient into a measurement apparatus has become a standard technique in EDs. Most commonly, a peak expiratory flow meter is used and yields the index of peak expiratory flow rate (PEFR); less commonly, a spirometer is employed and yields the index of forced expiratory volume in 1 s (FEV1). The advantages of this approach include objectivity and a numerical result to follow over the course of treatment, ideally with a comparison to the patient's historical baseline or predicted reference value (*see* Table 4).

Table 4
Predicted Peak Expiratory Flow Rate for Adults and Children

Table of predicted peak expiratory flow for age and height: adult (L/min)										
	Women (height)					*Men (height)*				
Age (years)	*55″*	*60″*	*65″*	*70″*	*75″*	*60″*	*65″*	*70″*	*75″*	*80″*
20	390	423	460	496	529	554	602	649	693	740
30	380	413	448	483	516	532	577	622	664	710
40	370	402	436	470	502	509	552	596	636	680
50	360	391	424	457	488	486	527	569	607	649
60	350	380	412	445	474	463	502	542	578	618
70	340	369	400	432	461	440	477	515	550	587
Table of predicted peak expiratory flow for height: children										
Height	39″	43″	47″	51″	55″	59″	63″	67″	71″	75″
L/min	110	160	210	260	320	370	420	475	530	570

Adapted from Leiner et al. *(46)* and McElroy *(47)*.

In 2007, the National Asthma Education and Prevention Program (NAEPP) Expert Panel 3 (EPR3) published revised asthma management guidelines that included the addition of a chapter dedicated to the management of acute exacerbations *(3)*. These guidelines defined new PEFR cut points for defining the severity of acute exacerbations and stressed the use of serial measurements to gauge response to treatment. An initial PEFR of less than 40% of either the patient's baseline or predicted indicates a severe exacerbation. PEFR of 40–69% indicates a moderate exacerbation, whereas a PEFR of greater than or equal to 70% is typical of a mild exacerbation. A PEFR of less than 25% identifies a subset of patients at risk for respiratory arrest.

Unfortunately, a PEFR is not obtainable in all patients because of ability or effort. Children younger than 4–5 years of age cannot always be expected to perform this type of maneuver. Testing often cannot be performed by patients with particularly severe symptoms; however, clinical assessment is usually sufficient for accurate classification of severity in this subset of patients.

Most patients have worsening of asthma symptoms for a 2–7 day period prior to presenting to the ED. A subset of approximately 10% have onset of the attack in less than 6 h but tend to respond rapidly to treatment. Death from acute asthma episodes is reported in less than 0.1% of patients with asthma. Approximately, half will suffer an out of the hospital death and half will succumb in the hospital setting. Near fatality has been defined as the occurrence of respiratory arrest and/or coma necessitating emergency tracheal intubation and mechanical ventilation, and the condition is distinguished from those patients who are electively intubated because of fatigue.

Despite research efforts, solid predictors of patients who are at risk for fatal or near-fatal episodes of asthma have not been identified because the associations are neither sensitive nor specific. Many risk factors occur too frequently in the general asthma population and too infrequently in subpopulations who are at risk for a fatal or near-fatal episode to allow precise application. For example, retrospective surveys indicate that 15–30% of asthma deaths occur in patients whose disease is categorized as only mild asthma.

Table 5
Risk Factors for Fatal Asthma Exacerbation

Historical factors
History of intubation for asthma
History of ICU admission for asthma
Multiple hospital admissions for asthma in the past year
Multiple ED visits for asthma in the past year
Use of more than 2 albuterol MDI per month
Use of LABA without concurrent use of ICS
Limited awareness of symptom severity
Social factors
Low socioeconomic status
Poor access to healthcare
Substance abuse
Comorbid factors
Psychiatric Illness
Concurrent nonasthmatic lung disease
Cardiovascular disease

Adapted from Expert Panel Report 3 *(3)*.

Nonetheless, certain historical information is helpful in gauging the seriousness of the attack and has implications for prognosis, response to initial therapy, and disposition. History taking should be focused on identifying risk factors for fatal or near fatal exacerbations. Relevant history includes the severity of previous exacerbations, the types and doses of medications the patient has been using, symptoms of comorbid acute illness such as pneumonia or myocardial ischemia, and chronic conditions such as cardiovascular disease, other chronic lung disease, polysubstance abuse, and psychiatric disease (*see* Table 5). For example, if a patient has previously been intubated for asthma exacerbation, there is an almost 20-fold increase in likelihood this will be required again *(4)*. Although older case-control studies using retrospectively collected data suggest that excess use of short-acting beta-agonists (SABA) was a risk factor, more recent information suggests that patterns of use may be a marker for more severe asthma rather than causal of severe attacks *(5)*. More recently, the chronic use of long-acting beta-agonists (LABA) in patients with asthma has been associated with a small increased risk of asthma-related death and adverse events in a meta-analysis of over 60,000 patients from randomized, controlled trials *(6)*. While an increased risk of death was not observed in the trials that mandated the use of a LABA with an inhaled corticosteroid (ICS), LABA use either alone or with an ICS may identify patients at increased risk of severe exacerbations.

In summary, numerous pieces of information can be gathered and assimilated quickly in the ED to categorize the severity of an acute asthma exacerbation. Attention should focus on identifying patients at risk for fatal or near-fatal exacerbations. Mild, moderate, and severe categories can be assigned based on a combination of signs and symptoms of distress and objective measurement of impairment in PEFR (*see* Table 2). Although this information correlates only loosely with ultimate outcome and disposition for the

acute episode, it provides the basis for decision making for the initial level of monitoring and treatment intensity.

DIAGNOSIS

In the ED, typically the clinician uses a prior diagnosis of asthma or makes the presumptive diagnosis. The ED physician should be able to rely on the prior diagnosis in the following circumstances: patient has a history of bronchospasm from childhood that has been responsive to asthma medications; patient has a positive prior methacholine challenge test. In most other circumstances, the diagnosis would be presumptive, based on evidence for asthma and lack of evidence for other disease processes. In patients with a significant smoking history, distinguishing asthma from other forms of chronic obstructive pulmonary disease (COPD) can be challenging in the acute setting and the two diagnoses may coexist in the same patient.

TRIGGERING AND/OR COMPLICATING FACTORS

Many patients with asthma are able to recognize their own triggers (*see* Table 3). These may have been identified through experience or specific testing. Triggers may include exposure to allergens, such as from grasses, trees, weeds, dust, dust mites, cockroach, fungi, and animals. They may also include exposure to irritants, such as smoke, chemical products, or occupational hazards. Asthma exacerbation may be induced by exercise or exposure to cold. It may be induced by use of aspirin or beta-blocking drugs.

Patients with underlying asthma may have an exacerbation when there is a complicating problem, such as infection, pneumothorax, or arrhythmia. In many settings, the most common precipitant of an asthma exacerbation is infection with a respiratory virus. Bacterial pathogens such as *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae* are less common but may precipitate acute exacerbations and may cause concurrent pneumonia. Bronchospasm frequently increases with active sinusitis.

The clinician must also consider that the basis for the acute exacerbation may be medication noncompliance, medication change, or steroid dose reduction.

DIFFERENTIAL DIAGNOSIS

Other medical conditions can be confused with asthma. Misdiagnoses may be present in up to 30% of outpatients *(2)*, in 1% of general asthma admissions and 10% of intensive care unit admissions.

Upper airway obstruction may masquerade as lower airway obstruction. Especially in pediatric patients, common conditions to be considered include rhinitis and sinusitis and less common conditions to be considered include epiglottitis and retropharyngeal abscess. Foreign body may be present in the upper airway or one of the larger lower airways. A child presenting for the first time with new onset wheezing should have a chest X-ray to evaluate for evidence of foreign body, congenital malformations, or childhood tumors. Angioedema may occur and cause upper airway obstruction.

In the pediatric population, croup and certain congenital and acquired anatomical problems may contribute to medium and large airway obstruction including chronic underlying diseases such as cystic fibrosis, bronchopulmonary dysplasia, and alpha-1 antitrypsin deficiency. The differential diagnosis of wheezing in pediatric patients

should also include aspiration, as a result of gastroesophageal reflux or swallowing disorders, and primary cardiac conditions resulting in congestive heart failure (CHF) from congenital heart disease.

In the adult population, the differential diagnosis includes COPD, bronchiectasis, nonasthmatic bronchiolitis, endobronchial lesions, aspiration, pneumonia, pulmonary emboli, and cardiogenic pulmonary edema. Examples of other conditions associated with wheezing include upper airway obstruction, anaphylaxis, and carcinoid syndrome.

Glottic dysfunction, otherwise known as vocal cord dysfunction (VCD) may be a form of a conversion reaction and is characterized by the paradoxical adduction of the vocal cords. Like in asthma, clinical features may include wheezing and even hypoxemia; however, the blood gas pattern is that of central alveolar hypoventilation, the wheezing is typically monophonic, and there may be stridulous or halting breathing over the neck. Although direct vocal cord visualization for dysfunctional movement and/or ventilation scanning to confirm a normal distribution can be done in the ED, frequently the patient is treated presumptively for asthma and laryngeal assessment is deferred.

TESTING IN THE ED

Patients with mild to moderate acute asthma exacerbation need little in the way of specialized testing. Vital signs and pulse oximetry are routinely monitored. All patients over the age of 5 should have PEFR measured at presentation to aid in assessing the severity of the acute exacerbation. PEFR should be checked sequentially over time starting 30–60 min after initiating treatment to gauge the response to initial therapy, guide the use of adjunctive therapies, and to aid decision making regarding the need for hospitalization. An alternative would be the performance of pulmonary function tests (PFTs) or spirometry, but this equipment is generally not available in EDs and the extra information gathered is typically not germane for emergency care.

When complicating conditions are being considered, additional diagnostic testing is warranted. A complete blood count and differential may be helpful to look for eosinophilia and infection. While mild elevation of the white blood cell count may simply be a nonspecific marker of stress or may reflect catecholamine or steroid treatment, marked elevations with or without bandemia may suggest infection. Measurement of electrolytes, blood urea nitrogen, and creatinine may be helpful to assess for hydration status and may be important preparatory information for certain treatment interventions such as neuromuscular blockers (NMB) or diuretics, or for certain types of diagnostic testing, for example those using radiocontrast media. If applicable, a theophylline level should be checked.

A chest radiograph (CXR) is an option for the first presentation of bronchospasm but would not be expected to show more than hyperinflation. A CXR is indicated when other conditions are suspected, such as pneumothorax/pneumomediastinum, CHF, pneumonia, bullous disease, and fibrotic or interstitial lung disease. A CXR is usually done if the patient is being admitted to the hospital.

Obtaining an electrocardiogram (EKG) is important when there is a question of dysrhythmia or cardiac ischemia. In older patients with suspected or known cardiovascular disease, an EKG should be a routine test when there is a presentation of shortness of

breath, with or without chest pain. Similarly, cardiac enzyme testing should be done in patients at risk for cardiac ischemia presenting with shortness of breath. B-type natriuretic peptide testing may help exclude concurrent acute decompensated CHF when a patient with a history of both CHF and asthma presents with shortness of breath and wheezing. Evaluation for pulmonary embolus (PE) may involve D-dimer testing or chest computed tomography (CT) scanning. In a patient otherwise felt to be low risk for PE, a negative high-sensitivity D-dimer test excludes PE in most patients. CT angiography of the pulmonary arteries in patients with a positive D-dimer or those felt to be at medium-high risk of PE can effectively exclude PE and may also identify other thoracic pathology *(7)*. Sinusitis is frequently a clinical diagnosis in the ED, but with the availability of CT scanning, the sinuses can be more accurately assessed if needed.

The question of the need for microbiology cultures in patients with wheezing is often raised in the ED. Sputum cultures are generally not needed for bronchitis. The high rate of viral infections, the variable quality of the submitted specimens, and the obligatory slow turn-around time do not make them cost-effective for decision making in the ED. When antibiotic therapy is indicated for bronchitis, the choice of drug is typically empiric. Sputum cultures generally also are not needed for community-acquired pneumonia that will be treated on an outpatient basis. For patients with concurrent pneumonia who will be treated in the hospital, however, it is reasonable to obtain sputum and blood cultures both of which should be obtained prior to the administration of antibiotics.

Clinical suspicion for influenza complicating asthma exacerbation should prompt rapid point of care testing for influenza in the ED as the effectiveness of antiviral therapy is thought to depend on early initiation. Confirmatory testing for seasonal as well as pandemic strains should be sent for all patients admitted to the hospital with a positive rapid assay and for those with a negative point of care test and strong clinical suspicion. This may also be helpful in triage when deciding on the most appropriate bed type and location to limit in-hospital spread of infection if there is a suspected outbreak of influenza.

In the pediatric population, viral testing is a consideration. Bronchiolitis, a viral infection of the bronchioles, is usually seen in children younger than 2 years old. Respiratory syncytial virus (RSV) is the most common etiology, occurring November to March, although other etiologies include parainfluenza and *Mycoplasma*. Antigen tests of nasal washings may detect RSV and be helpful in the management of high-risk patients.

TREATMENT OF MILD AND MODERATE ASTHMA EXACERBATIONS

Most patients with mild exacerbations of asthma are managed at home or in the outpatient clinic. If a patient presents to the ED with the features of a mild exacerbation, the first-line medication is albuterol (also known as salbutamol) typically administered by metered-dose inhaler (MDI) with a holding chamber (spacer) (ProAir®, Proventil®,Ventolin®). Nebulized albuterol is an alternative for patients who have difficulty using a MDI. A mild attack is confirmed when the patient experiences a prompt and complete response to initial treatment with SABA with resolution of wheezing, cough, and/or shortness of breath. These patients can often be discharged after

education and scheduled follow-up but with no additional medical therapy. Patients and family members should be given specific instruction in the proper use of inhalers and spacer.

Patients with mild exacerbations who do not have a complete and immediate response to initial therapy with albuterol, and those presenting with features of a moderate exacerbation, should be treated similarly according to the 2007 NAEPP EPR3 guidelines. All patients should have initial and serial measurement of PEFR and all should immediately receive oxygen, a short-acting beta agonist, and systemic CS usually by the oral route.

Supplemental oxygen delivered by nasal cannula or mask should be provided as needed to ensure a peripheral oxygen saturation of at least 90% in most patients. Oxygen saturation should be maintained above 95% in pregnant patients or those with active cardiovascular disease.

Delivery of albuterol may be by MDI with a holding chamber or by nebulizer. Studies of adults and older children with acute asthma have shown that both modalities are effective in providing particles of the optimal 1–5 μm size to the lower airways. This results in no significant differences in the rate of hospital admission, length of time spent in the ED, or PEFR *(8)*. As such, the choice of modality is often determined by the degree of respiratory distress including the patient's ability to time respiratory efforts with the use of an MDI, with more pronounced respiratory distress favoring use of a nebulizer.

The standard albuterol MDI delivers 90 μg of albuterol per puff. The recommended dose of albuterol for mild to moderate exacerbations, when administered by MDI with use of a spacer, is 4–8 puffs given every 20 min as needed for up to three doses in the first hour in children, and every 20 min for up to 4 h in adults *(3)*. Levalbuterol has been added to the EPR3 guidelines as an alternative to albuterol. Whereas albuterol is a racemic mixture of (R)- and (S)- isomers, levalbuterol (Xopenex®) contains only the (R)-enantiomer. The (R)-albuterol has the bronchodilating properties, whereas the (S)-form has preferential pulmonary retention, a longer half-life, and possible pro-inflammatory effects *(9)*. Levalbuterol is delivered by MDI at 45 μg/puff but the number of puffs and timing of administration are otherwise the same as for albuterol. While there are in vitro and preclinical data that might suggest superiority of levalbuterol over racemic albuterol, clinical studies have supported the equivalency rather than superiority of levalbuterol in terms of the degree or bronchodilation, side effects, and rates of hospital admission *(10)*. It may, however, be reasonable to switch to levalbuterol in patients with dose-limiting adrenergic side effects after the first few doses of racemic albuterol.

The nebulizer dosage for children is 0.15 mg/kg (minimum dose 2.5 mg) every 20 min up to three doses and then 0.15-0.3 mg/kg up to 10 mg every 1–4 h as needed. For adults, the dose is 2.5–5 mg every 20 min as needed for three doses and then 2.5–10 mg every 1–4 h as needed thereafter. For levalbuterol, the pediatric dosing is 0.075 mg/kg (minimum dose 1.25 mg) for the first three doses and then 0.075–0.15 mg/kg up to 5 mg every 1–4 h as needed. For adults, the dosing is 1.25–2.5 mg every 20 min as needed for three doses and then 1.25–5 mg every 1–4 h as needed *(3)*. The mode of delivery is typically via a medication reservoir attached to a pipe-like mouthpiece, but for infants and young children, a facemask device can be employed.

Oxygen or compressed air at 6–8 L/min from a wall outlet or tank is connected by tubing to drive the nebulization.

Systemic corticosteroids (CS) are used to counter airway inflammation and hasten resolution of the asthma exacerbation. Because they act through ligand-dependent activation of nuclear receptors, gene regulation, and new protein synthesis, clinical benefits are thought to accrue gradually over 6–12 h.

Systemic CS should therefore be given promptly to all patients with a moderate exacerbation, to those presenting with mild symptoms that do not immediately resolve after initial therapy with albuterol, and to all patients with even mild symptoms who have recently taken systemic CS. CS have been shown to speed the resolution of airflow obstruction, to decrease the rate of hospital admission, and to decrease the rate of relapse and beta-agonist use after discharge *(11–13)*. Emergency physicians must remember to obtain a history of medications taken at home prior to presentation to the ED (e.g., prednisone) and those administered by prehospital providers as these medications may reduce the initial impression of severity.

Oral administration of CS is preferred over the intravenous (IV) route as both routes have been shown in studies to have equal efficacy *(3)* and oral administration can be accomplished without need for IV access. IV administration should be reserved for patients in whom oral absorption may be unreliable, for those unable to swallow, or in case of nausea and vomiting. Current guidelines also reflect evidence suggesting that moderate doses of CS are just as effective as higher doses. For example, a 2001 meta-analysis suggested that low (≤80 mg), medium (>80 and ≤360 mg), or high (>360 mg) dosing of methylprednisolone in the first 24 h resulted in similar therapeutic efficacy and changes in lung function. Although reference manuals often recommend repeat dosing every 6 h, high and frequent doses do not confer a therapeutic advantage *(3, 14, 15)*.

Current guidelines recommend 40–80 mg of prednisone equivalents in one or two divided doses. For patients discharged from the ED, recommendations are for 40–60 mg of prednisone daily, or divided twice daily, for 5–10 days *(3)*. For patients at high risk of nonadherence or for those unable to pay for an outpatient prescription, a 2004 study found no difference in the rate of relapse following discharge from the ED with use of 160 mg depot methylprednisolone compared to an 8-day tapering of a total dose of 160 mg oral methylprednisolone *(16)*. For children, current recommendations are for 1–2 mg/kg in two divided doses in the first 24 h (max 60 mg/day), followed by an outpatient burst of 1–2 mg/kg/day (max 60 mg/day) for 3–10 days *(3)*.

Current evidence does not support the use of increased doses of ICSs as a substitute for systemic CS to treat acute exacerbations. However, patients taking ICS as outpatients can continue their ICS even while on systemic CS. Furthermore, prescribing an ICS at the time of discharge for patients not previously on ICS may reduce the risk of relapse *(17)*.

Finally, serial measurement of PEFR and reassessment of symptoms are key to determining the response to treatment. Typically, repeat measurement of PEFR is performed after 30–90 min of therapy and then every hour thereafter as indicated. Objective evidence of improvement in PEFR provides reassurance that current management is effective and supports gradually tapering the frequency of SABA treatments. Once the patient's PEFR is ≥70% of either baseline or predicted, and the patient is no longer in distress, the PEFR is repeated 60 min later with no intervening therapy to ensure a

sustained response in anticipation of discharge. Alternatively, if PEFR and symptoms are worsening, the clinician should promptly increase the intensity of current therapy, consider use of adjunctive treatments, and carefully assess the patient for signs of impending respiratory failure.

TREATMENT OF SEVERE ASTHMA EXACERBATIONS

Patients with severe exacerbations have a PEFR <40% of baseline or predicted. Because not all patients with severe exacerbation will be able to reliably perform PEFR maneuvers, vital signs and physical exam are important indicators of severity. These patients often have more pronounced respiratory distress including a respiratory rate >30 and use of accessory muscles. Tachycardia is often pronounced with a heart rate >120 and a pulsus paradoxus (the drop in systolic blood pressure during inspiration) >25 mmHg can be seen. Hypoxemia with an arterial oxygen saturation <90% on room air is common.

As such, these patients should be moved to an area of the ED equipped to manage respiratory failure and hemodynamic instability. They should be placed on monitors for continuous recording of the rhythm strip and pulse oximetry, and for frequent recording of the blood pressure. If end-tidal air stream CO_2 monitoring is available, it could be used in this situation to monitor for impending respiratory failure. Supplemental oxygen should be provided to ensure adequate tissue oxygen delivery, waiving concern regarding CO_2 narcosis if there is significant hypoxemia. Intravenous access should be established, preferably at two sites. Intravenous fluids will be needed in most pediatric patients and should be considered for adult patients.

High-Dose Inhaled Bronchodilators

Therapy with high-dose bronchodilators and systemic CS should be started immediately. As with mild-moderate exacerbations, albuterol can be delivered either by MDI with a spacer or by nebulizer with equivalent outcomes so long as the degree of respiratory distress does not compromise the patient's ability to effectively coordinate use of a MDI. A typical dose of albuterol by MDI/spacer would be 8–12 puffs every 20 min up to 4 h and then every 1–4 h as needed thereafter assuming clinical improvement. It is common, however, to deliver albuterol via a nebulizer in patients with significant agitation, respiratory distress, and in the young and old. Initial nebulizer dosing for severe exacerbations can be given with the same frequency as for mild-moderate exacerbations but higher doses per treatment should be considered.

For severe exacerbations with significant respiratory distress, albuterol should be delivered by continuous nebulization. A 2003 meta-analysis of eight trials with over 450 patients concluded that, as compared with intermittent nebulizer treatments, albuterol by continuous nebulizer resulted in greater improvements in lung function, fewer hospitalizations, and no difference in side effects *(18)*. A typical dose by continuous nebulizer would be 15–20 mg delivered by high-volume nebulizer over 1 h. High-dose levalbuterol can be substituted for albuterol either by MDI/spacer or nebulizer and scheduled the same as in mild-moderate exacerbations. Note that levalbuterol has not been studied by continuous nebulizer, however, and should not be used via this mode of delivery.

Ipratropium bromide (Atrovent®) should also be given with the first and subsequent treatments as a large body of evidence has demonstrated improved outcomes in patients with severe exacerbations. A 2005 meta-analysis of data from 32 randomized, controlled trials and over 3,600 patients concluded that the addition of inhaled ipratropium bromide to SABA resulted in greater improvements in lung function and decreased rates of hospital admission *(19)*. This is reflected in the 2007 NAEPP EPR3 guidelines that recommend use of ipratropium in all patients with severe exacerbation. Ipratropium can be given via MDI with a spacer or by nebulizer. If the MDI with spacer approach is being used, eight puffs of ipratropium should be intermixed with albuterol treatments either as two separate MDI treatments or as eight puffs of the fixed combination product Combivent®. MDI treatments should be given every 20 min for three doses and then every 20 min as needed thereafter for up to 3 h. In children, the dose is 4–8 puffs every 20 min as needed up to 3 h *(3)*. Commonly, ipratropium is mixed with albuterol for nebulization with 0.5 mg of ipratropium (0.25–0.5 mg for children) mixed in the same nebulizer with albuterol and administered every 20 min. Ipratropium can also be mixed with albuterol for continuous nebulization. Of note, studies support the use of ipratropium for management of asthma exacerbations in the ED but have not shown benefit when added to SABA for hospitalized patients.

Systemic Corticosteroids

Prompt initiation of systemic CS is critical to effective management of severe exacerbations. As mentioned earlier, when CS are given orally or IV, no difference in lung function or clinical outcomes has been observed even in severe exacerbations, and no additional benefit is derived from doses exceeding 100 mg of prednisone equivalents per day. Patients with severe exacerbations, however, may have difficulty swallowing due to respiratory distress and may have nausea, vomiting, or comorbid conditions that make oral absorption unreliable. Under these circumstances, CS should be given IV. A typical dose would be 60–125 mg of IV methylprednisolone.

Magnesium Sulfate

For patients with severe exacerbations and either suboptimal improvement or clinical deterioration after 30–60 min of therapy with oxygen, inhaled bronchodilators, and systemic CS, adjunctive therapy with intravenous magnesium sulfate should be strongly considered *(3)*. Magnesium sulfate is thought to cause relaxation of bronchial smooth muscle by inhibiting calcium influx into smooth muscle cells and may also have anti-inflammatory effects. Two recent systematic reviews found that IV magnesium sulfate had favorable effects on lung function and reduced hospitalizations both in adults and in children with the greatest benefits realized in those with more severe exacerbations *(20, 21)*. The recommended adult dose is 2 g given IV over 20 min. The recommended pediatric dose is 25–75 mg/kg up to a maximum of 2 g. No significant adverse events have been associated with IV magnesium in these doses and significantly higher doses have been used in other clinical settings with a very favorable safety profile. The low cost, ease of administration, and familiarity of use by most physicians make IV magnesium sulfate a useful adjunct for severe exacerbations.

Magnesium can also be delivered by nebulizer; however, studies are less clear as to benefit with conflicting evidence existing as to both short-term effects on lung function

and clinical outcomes. A large, multicenter trial comparing intravenous to nebulized magnesium sulfate in the treatment of patients with severe exacerbations is ongoing and should shed additional light on the use of this therapy *(22)*.

Heliox

The recent NAEPP EPR3 guidelines now suggest consideration of heliox-driven nebulization for patients with persistent severe symptoms despite standard and other adjunctive therapies *(3)*. Heliox is a mixture of helium and oxygen, typically at a ratio of 80:20 or 70:30 of helium to oxygen. Heliox's lower density compared to air/oxygen mixtures causes less turbulent gas flow most notably in the larger airways, results in improved dyspnea scores, and is thought to reduce the work of breathing by decreasing airway resistance. In some studies, heliox has been reported to potentiate the bronchodilatory effects of beta-agonists when heliox is used to power the nebulizer. These data, however, come from mostly small studies of varying methodologic quality. A 2006 meta-analysis of ten randomized, controlled trials involving almost 550 patients concluded that heliox should not be used in all patients with acute asthma exacerbations but that it may be effective in improving lung function and possibly decreasing rates of admission in the most severely affected patients. There were insufficient data to evaluate the effects of heliox on rates of intubation *(23)*. Helium is insoluble in human tissues and, as such, heliox has no significant safety issues by itself.

If the clinician decides to use heliox, the practical setup is as follows. A commercial mixture of helium and oxygen is used, available in a portable cylinder, often as 80% helium and 20% oxygen or 70% helium and 30% oxygen. Administration is best via a nonrebreathing face mask to minimize mixing of heliox with room air. During administration of inhaled bronchodilators, heliox should be used to power a standard nebulizer. For patients with significant hypoxemia, supplemental oxygen can be provided via nasal cannula, although this increases the density of the gas mixture and may negate any clinical benefit. It should be noted that peak flow readings vary depending on the viscosity of the gas being delivered, and the relatively lower density of heliox would be expected to result in a higher peak flow compared to air unless standardization is done.

ADDITIONAL TREATMENTS FOR SEVERE ASTHMA EXACERBATIONS

The aforementioned therapies are consistent with the recommendations of the 2007 NAEPP EPR3 guidelines and reflect the best available data to guide management of asthma exacerbations. Patients with severe exacerbations who do not respond readily to the therapies detailed earlier present a significant management challenge. The goal of therapy for these patients is focused on averting respiratory failure and, if necessary, managing the complications of intubation and mechanical ventilation as this patient population has a reported mortality as high as 20% *(24)*. Despite an absence of high quality data, smaller randomized studies, case series, and isolated case reports provide a rationale for considering additional therapeutic options.

Parenteral Beta-Agonists

Subcutaneous terbutaline and epinephrine, when not contraindicated, have historically been used as alternatives if the inhaled route were unavailable or failing. Data on

the efficacy of subcutaneous beta agonists are extremely limited and this approach has not been clearly shown to change the course of patients who are not responding to inhaled high-dose albuterol. While epinephrine is generally well tolerated in this setting, deaths have been reported with the use of epinephrine to manage asthma patients with cardiac disease. In pregnant asthma patients, epinephrine may contribute to uterine vessel spasm making terbutaline the preferred agent in this patient population. A typical adult dose of subcutaneous epinephrine for treatment of severe asthma is 0.3 mg every 20 min up to three doses. Subcutaneous terbutaline can be given in adults at 0.25 mg every 20 min for three doses. Intravenous beta-agonists have been tried as well. Randomized controlled trials of intravenous terbutaline have produced conflicting evidence regarding whether the intravenous route or the inhaled route is more efficacious; there is agreement that the intravenous route is associated with more adverse effects such as tachycardia and hypokalemia *(25, 26)*. The conclusion of a meta-analysis of 15 randomized, controlled trials was that evidence is lacking to support the use of intravenous beta2-agonsits in ED patients with severe acute asthma, except possibly for those patients for whom inhaled therapy is not feasible *(27)*. Data on intravenous epinephrine are too limited to draw conclusions.

Methylxanthines

For patients who do not respond to or are not able to take standard emergency treatment medications, intravenous aminophylline, at 5–6 mg/kg bolus and then 0.6–0.9 mg/kg/h has historically been used. A 2000 meta-analysis of 15 randomized, controlled trials comparing the addition of aminophylline to standard therapy with beta-agonists with or without CS, however, showed no difference in pulmonary function or hospital admission but did show a higher rate of arrhythmia and vomiting *(28)*. As such, current guidelines do not endorse the routine use of aminophylline in acute exacerbations *(3)*.

Leukotriene Receptor Antagonists

For patients who are responding suboptimally to standard emergency treatment medications, the addition of a leukotriene receptor antagonist, such as montelukast (Singulair®) or zafirlukast (Accolate®), could be considered. In oral form, these agents have an established role in the chronic management of asthma but their role in the treatment of acute exacerbations is less clear. Randomized, controlled trials of both oral and IV formulations of montelukast added to standard therapies have shown improvements in lung function but did not show a difference in clinical outcomes such as admission rate or hospital length of stay *(29, 30)*. There were no significant adverse events noted in any of these trials, however, making the addition of oral montelukast a reasonable adjunct in severely affected individuals.

Ketamine

Ketamine (Ketalar®) is a rapid-acting dissociative anesthetic derived from phencyclidine that has potent analgesic, sedative, and amnestic properties while preserving respiratory drive and airway protective reflexes. Ketamine is commonly used for conscious sedation during painful procedures and is also used as an induction agent for endotracheal intubation. Research suggests that ketamine acts to relax bronchial smooth muscle by stimulating the release of catecholamines that act on beta2-adrenergic receptors, by inhibiting vagal tone, and possibly by a direct effect on smooth muscle

cells *(31)*. Side effects include tachycardia, hypertension, hypersalivation, nausea and vomiting, increased intracranial pressure, and emergence reactions such as disorientation and hallucinations. The use of ketamine is relatively contraindicated in patients with active cardiovascular disease, increased intracranial pressure, alcohol intoxication, and altered mental status of unknown etiology.

A beneficial effect of ketamine in severe asthma remains to be definitively proven. Two small randomized, placebo-controlled trials of low-dose ketamine infusion have been reported, one in adults and one in children with severe asthma exacerbations. In these trials, no benefit was seen with regard to either lung function or hospital admission *(32, 33)*. Nonetheless, multiple case reports and small case series continue to report anecdotal benefit from ketamine, commonly at higher doses than those used in the controlled trials, with benefits seen in terms of alleviation of bronchospasm, improved oxygenation, and avoidance of intubation and mechanical ventilation. No clear dosing recommendation has emerged from these reports but boluses as high as 2 mg/kg and drip rates as high as 3 mg/kg/h have been reported in children *(34)*.

Noninvasive Positive Pressure Ventilation

Noninvasive positive pressure ventilation (NPPV), also known as noninvasive pressure support ventilation (NIPSV), represents the delivery of mechanically assisted breaths via a patient interface that is external to the body, such as a tightly fitting nasal or facial mask, rather than an internal artificial airway. It is also referred to as bilevel positive airway pressure ventilation (BiPAP®), based on the name of the noninvasive ventilator commonly used, produced by Philips-Respironics. Studies have shown that NPPV is efficacious in acute respiratory failure related to exacerbations of COPD, acute cardiogenic pulmonary edema, and hypoxemic respiratory failure in immunocompromised hosts *(35)*. NPPV is contraindicated when respiratory failure is imminent, in patients with vomiting, and in patients with a depressed level of consciousness.

Improvements in pH and pCO_2 within 1.5–2 h are predictive of the eventual success of NPPV and if they do not occur, invasive mechanical ventilation should be considered. In general, however, a trial of NPPV is a reasonable option for ventilatory support in patients in whom there is a rapidly reversible cause of respiratory failure identified or in patients who are particularly high risk for complications of intubation and mechanical ventilation. Furthermore, barotrauma is uncommon, and adverse hemodynamic effects are unusual. Nosocomial pneumonia and sinusitis are also less common compared with patients who are intubated. For these reasons, NPPV is an attractive therapy for management of severe, difficult to treat asthma exacerbations.

The utility of NPPV in asthma, however, is not well defined and the number of studies addressing its use in patients with asthma with severe respiratory distress is limited. One case series reported an encouraging experience when NPPV was used in 17 patients with asthma complicated by acute hypercapnic respiratory failure; all survived, and 15 did not require intubation with coincident improvements in pH, $paCO_2$, oxygenation, and respiratory rate beginning within 2 h of initiation *(36)*. Another retrospective series of 22 patients with severe exacerbation treated with NPPV in the ICU revealed a subsequent rate of invasive mechanical ventilation of only 14% *(37)*. Two recent small randomized, controlled trials of NPPV in patients with severe exacerbations at risk for respiratory failure have shown improvements in both lung function and rates of admission *(38)* and in decreasing

bronchodilator requirements as well as ICU and hospital length of stay *(39)*. Despite these encouraging preliminary results, the use of NPPV in patients with severe asthma is currently not recommended for routine management of severe exacerbations and should only be used selectively on a case-by-base basis by clinicians familiar with its risks.

MANAGEMENT OF RESPIRATORY FAILURE IN SEVERE ASTHMA

Intubation and mechanical ventilation can be life-saving for patients with severe asthma exacerbations complicated by respiratory failure. The severe airways obstruction and associated dynamic hyperinflation seen in such patients makes these procedures fraught with risks including hypotension, aspiration, barotrauma, hospital-acquired infection, and myopathy.

Patients presenting with respiratory arrest or severe hypopnea should be intubated immediately. Similarly, those in whom the level of consciousness is inadequate to enable inhaled therapies or to ensure airway protection should be intubated. Other indications for immediate intubation include a paO_2 of <60 mmHg despite high-flow oxygen delivered by a nonrebreathing face mask and signs of exhaustion such as paradoxical thoracoabdominal motion and a silent chest. If the patient's status is borderline, however, it may be reasonable to begin a trial of aggressive interventions while at the same time preparing for the possibility of intubation should the patient show signs of worsening respiratory acidosis or any of the above signs of respiratory failure.

Rapid-sequence intubation (RSI) is the standard approach for patients who are obtunded or who are in respiratory arrest. The largest diameter tube possible should be chosen to minimize resistance to airflow and to facilitate suctioning and bronchoscopy.

Commonly used induction agents for RSI include etomidate, propofol, and ketamine. Propofol and ketamine have theoretical advantages in that both are known bronchodilators. Propofol may be preferred for hypertensive patients for both its bronchodilating and vasodilating properties. A typical induction dose of propofol ranges from 1.5 to 3 mg/kg IV. The use of propofol may cause unwanted hypotension in volume-depleted patients especially immediately after initiating positive pressure ventilation. As such, IV fluids should be given rapidly around the time of intubation to ensure adequate cardiac preload. Ketamine may be preferred in patients with hypotension for its bronchodilating properties and because it stimulates catecholamine release. A typical induction dose is 1–1.5 mg/kg IV. Etomidate is the most hemodynamically neutral of the induction agents. The usual dose of etomidate is 0.3 mg/kg.

Paralysis during RSI can be achieved with either depolarizing or nondepolarizing NMB. Succinylcholine is commonly used because of its rapid onset and relatively short duration of action of 5–10 min. The usual dose is 1–1.5 mg/kg IV. Note that succinylcholine is contraindicated in patients with a personal or family history of malignant hyperthermia and in those with hyperkalemia, neuromuscular disorders, increased intraocular pressure, and subacute burns. Alternatively, a nondepolarizing agent such as rocuronium or vecuronium can be used to avoid the risks associated with succinylcholine. These agents, however, last for 30–45 min and pose serious risks if the patient cannot be ventilated or intubated. Sugammadex, an investigational agent capable of rapidly and fully reversing the effects of rocuronium and vecuronium, if approved for use, will greatly improve the safety profile of the nondepolarizing NMB.

Alternatives to RSI include awake nasotracheal intubation, awake orotracheal intubation over a fiberoptic bronchoscope, and orotracheal intubation with sedation but without paralysis. These methods all share in common the advantage of preserving the patient's respiratory effort thus ensuring some residual ventilation. Nasotracheal intubation may be less favorable in asthmatics because of the high frequency of nasal polyps in this population and the smaller size endotracheal tubes typically used. Orotracheal intubation using an induction agent without a NMB allows a standard direct laryngoscopy but avoids the dangers of complete paralysis in the events that the trachea cannot be successfully intubated.

Awake orotracheal intubation over a fiberoptic bronchoscope is another alternative to RSI for nonemergent intubation and is particularly useful for managing known or anticipated difficult airways. This method avoids the need for induction agents and NMB and allows the patient to remain sitting upright. Using topical oropharyngeal anesthesia with atomized lidocaine and light sedation, the endotracheal tube is loaded onto a fiberoptic bronchoscope and inserted through a bite block or hollow oral airway (e.g., Berman® intubating airway) into the oropharynx. The bronchoscope is passed through the cords into the trachea and used as a stilette to pass the endotracheal tube into place. The scope can be used to confirm proper tube placement and is then removed. In addition to avoiding deep sedation and paralysis, this method commonly avoids the increased dynamic hyperinflation and resultant hypotension that often accompanies bag-mask ventilation during a standard direct laryngoscopic intubation. Awake fiberoptic intubation requires patient cooperation and may be limited by severe agitation or coughing; adequate topical anesthesia and low doses of sedatives and analgesics are usually but not always effective. Other complications include laryngospasm and aspiration although these are uncommon. This technique, however, requires a skilled operator familiar with use of a fiberoptic bronchoscope.

Independent of the intubation technique, it is necessary to provide additional sedative and analgesic medications such as propofol or versed, and fentanyl after intubation to ensure patient comfort and to prevent tachypnea, patient-ventilator dyssynchrony, and the resultant dynamic hyperinflation with its associated complications.

The goals of mechanical ventilation following intubation are to ensure adequate oxygenation and ventilation, and to prevent short-term complications such as hypotension and barotrauma by improving dynamic hyperinflation. This is accomplished with a strategy known as permissive hypercapnia in which dangerous plateau pressures are avoided by limiting respiratory rate and tidal volumes, allowing full exhalation between breaths, and permitting some degree of respiratory acidosis. Hypercapnia itself is of little consequence in most patients and a blood pH down to 7.20 is generally safe and well tolerated. Initial ventilator setup should use either a volume-cycled or pressure-limited control mode, should target a minute ventilation of 8–10 L/min, and should limit plateau pressure to <35 cmH_2O. Tidal volumes should aim for 6–8 mL/kg of predicted body weight. The respiratory rate should be set initially to 10–12 breaths/min and the inspiratory flow rate or inspiratory times should be adjusted to provide an expiratory time long enough for full exhalation between breaths. Frequent measurement of ABGs should occur until stability is achieved. Continuous infusions of NMB may be necessary in patients resistant to high doses of sedatives and analgesics, although prolonged use of neuromuscular blocking agents and CS is associated with myopathy and should be

used with caution *(40)*. Inhaled therapies such as continuous nebulizers and heliox should be adapted to the ventilator circuit and oral therapies should generally be converted to the IV route.

Even with permissive hypercapnia, ED clinicians must be prepared to deal with potential complications of mechanical ventilation. Hypotension is common and if present, intravenous fluids should be administered and the patient should be evaluated for tension pneumothorax and pneumomediastinum. If pneumothorax is present, the chest must be vented with a needle or with placement of a chest tube. The possibility of auto-positive end-expiratory pressure (auto-PEEP) from dynamic hyperinflation also needs to be considered; it may be empirically treated by removing the patient from the ventilator for a period followed by either additional sedation and analgesia and/or use of NMB to manage tachypnea and patient-ventilator dyssynchrony.

For the most severely affected and treatment-refractory patient, the ED clinician should be aware of salvage treatments such as the use of inhaled anesthetics and extracorporeal gas exchange as implementation of these modalities often requires consultation with multiple specialists and arranging transfer to other settings such as the operating room or specialized intensive care units. Note that alternative modes of mechanical ventilation that do not allow for a prolonged expiratory time such as high frequency oscillatory ventilation and airway pressure release ventilation are generally thought to be contraindicated in the setting of severe airflow obstruction due to the risk of worsening dynamic hyperinflation. As such, these modes have not been studied in asthma exacerbation and cannot be recommended as rescue strategies.

ADVERSE RESPONSES TO MEDICATIONS USED FOR EXACERBATIONS

Albuterol is the mainstay of therapy for patients with acute asthma exacerbation.

Commonly reported mild adverse effects associated with frequent dosing include tachycardia, tremor, and headache. If continuous high-dose albuterol is administered by nebulizer, tremor occurs in approx 20% of patients *(41)*. Albuterol is also known to cause hypokalemia by shifting potassium intracellularly. Preexisting hypokalemia should be corrected but aggressive replenishment of potassium during albuterol therapy is not recommended. Albuterol in high doses may cause arrhythmias but cause and effect are often difficult to sort out because patients may have concomitant hypoxia and acid–base abnormalities. There are rare reports of lactic acidosis with albuterol administration.

The most common adverse events associated with inhaled ipratropium included tremor, agitation, tachycardia, dry mouth, headache, nausea, vomiting, and dizziness. However, many of the reported side effects are minor and occur during administration of ipratropium for more than 12 weeks rather than in the setting of the acute treatment of exacerbations.

Systemic CS have a large number of known adverse effects but most are seen only with prolonged or repeated use. Short-term use of systemic CS in the treatment of acute exacerbations is generally well tolerated. Common side effects include psychiatric disturbances such as insomnia, agitation, and even psychosis, worsening glycemic control in diabetics, and fluid retention in patients with underlying cardiovascular disease.

Patients should be educated about these side effects and instructed to seek medical attention should they occur.

ADVERSE ASTHMA RESPONSES TO NONASTHMA MEDICATIONS

The practitioner must be aware that certain medications are contraindicated or relatively contraindicated in patients with acute asthma exacerbations. Beta-blockers are in this category. Although cardioselective beta-blockers have been shown to be safe in short-term use in patients with mild-moderate reversible airways obstruction *(42)*, their use is not well studied in acute exacerbation. As such, their use in patients with acute exacerbation should be avoided unless a strong indication exists and no alternative is available. Noncardioselective beta blockers such as propranolol, labetalol, and carvedilol should be avoided in acute asthma exacerbation.

Patients with aspirin allergy or with the syndrome of asthma, nasal polyposis, and aspirin sensitivity should not be given aspirin. There is an approximately 20% cross-reactivity with nonsteroidal anti-inflammatory drugs (NSAIDs). For such patients presenting with acute coronary syndrome or ischemic cerebrovascular accident, an ADP receptor antagonist such as clopidogrel (Plavix®) should be considered as an alternative.

TREATMENTS NOT RECOMMENDED FOR ROUTINE USE IN EXACERBATIONS

Antibiotics should not be given routinely to patients with asthma exacerbation unless there is a high clinical suspicion for concurrent acute bacterial infection such as pneumonia or sinusitis. Some studies suggest that chronic infection with *M. pneumoniae* or *C. pneumoniae* may play a role in acute exacerbations in some patients and research in nonasthmatic airways disease suggests a possible anti-inflammatory effect of macrolide antibiotics. Additional research is needed, however, to define the role of macrolides in asthma exacerbations before their routine use can be recommended.

Aggressive hydration should not be given as a matter of routine unless there is clinical history of poor oral intake, signs and symptoms of intravascular volume depletion, or hemodynamic instability. Careful clinical assessment of volume status should precede aggressive hydration.

Mucolytics should not be given as they have no demonstrable clinical efficacy in acute asthma and are known to induce bronchial irritation and bronchospasm. As mentioned earlier, methylxanthines are no longer recommended for routine use in acute asthma exacerbations but may be considered for use in severe, treatment refractory cases *(3)*.

PREDICTING FATAL OR NEAR-FATAL EPISODES

Near fatality has been viewed as the occurrence of respiratory arrest and/or coma necessitating emergency intubation and mechanical ventilation, and the condition is distinguished from those patients who are electively intubated because of fatigue. Despite research efforts, clinically reliable predictors of patients who are at risk for fatal or near-fatal episodes of asthma have not been conclusively identified. Patient characteristics associated with increased risk include lack of understanding or misinterpretation of the

seriousness of the symptoms, poor medical adherence, and coincident psychiatric illness and/or substance abuse. At-risk patients are also likely to have had multiple ED visits, repeated hospitalizations, admission to the intensive care unit, and a history of respiratory failure. Histopathological findings suggest that the type of acute asthma that leads to death may be a unique entity. Until studies are better able to explain why some patients with asthma die of a potentially reversible disease, ED management needs to focus on rapid evaluation and institution of therapies guided by the best available evidence.

PREDICTING RESPONSE TO THERAPY

Early identification of patients with acute asthma who will require hospitalization or ICU admission would be helpful in the management of ED resources. It is not unusual for patients to be treated for several hours before a disposition decision is made. Additionally, because a substantial number of patients who are discharged from the ED suffer relapse and require a repeat visit within 2–14 days, it would also be helpful to prospectively identify this group.

Accurately predicting the clinical trajectories of individual patients, especially those with moderate or severe exacerbations, has proven difficult in practice. Many studies have attempted to identify factors predictive of response to therapy. There is general agreement that for the majority of patients presenting with acute asthma, there is no single universal parameter in the initial history, physical examination, or bedside testing that reliably predicts response. Similarly, multivariate formulas based on initial information have not been shown to improve predictive accuracy for all-comers.

Numerous studies have shown that repeat assessments, for example after the first hour of treatment, are better at predicting eventual response to therapy than assessments based on presentation. While multiple scoring systems have been published, no one system has proven broadly applicable. As such, repeat assessments focus on a combination of lung function and clinical data including the PEFR measured after initial treatment with inhaled bronchodilators and systemic CS. Although not universally predictive, a PEFR of less than 40% of predicted after initial therapies is associated with an increased need for hospitalization while a PEFR ≥70%, if sustained for 60 min after the last treatment, is typically an indication for discharge home. Other factors predictive of eventual need for hospitalization include ongoing use of accessory muscles and persistent hypoxemia after 1 h of therapy *(43)*. Patients with an incomplete response to initial interventions, such as those with persistent symptoms and PEFR 40–69% of predicted, will usually remain in the ED for ongoing treatment and reassessment. The NAEPP EPR3 guidelines suggest making a decision to admit or discharge these patients within 4 h of initial presentation *(3)*.

DISPOSITION OF THE PATIENT WITH ASTHMA

The ultimate decision to admit or discharge the patient is based on a combination of factors including objective measures of lung function, symptoms and exam findings, and the patient's capacity to continue managing the exacerbation as an outpatient.

Decisions based on PEFR are complicated by several factors. Some patients with asthma have significant fixed airflow obstruction even during asymptomatic periods.

The baseline personal best PEFR for these patients is likely more useful than the percent predicted but often this is not known by the patient or easily accessible in the medical record. In the very young and in a subset of adults not able to perform PEFR testing reliably, PEFR data may be unavailable altogether, necessitating greater reliance on clinical and social factors in decision making. Prior to making a decision about discharge, patients should be reassessed at least 60 min after the last bronchodilator treatment to ensure that gains in PEFR and clinical parameters are sustained.

Some features of the patient's case may prompt caution in decision making around disposition. Frequent ED visits, frequent hospitalizations, a history of intensive care unit admission, and prior intubation should weigh the decision more toward admission. Furthermore, social and socioeconomic factors need to be considered such as the presence of poorly compensated psychiatric illness, substance abuse, limited understanding of asthma, limited access to healthcare, or an inability to pay for medications on discharge. The presence of one or multiple of these conditions may favor a brief admission to facilitate ongoing care.

With few exceptions, patients discharged after successful ED management of an exacerbation should be prescribed a burst of oral steroids. For patients in whom adherence or access may be limited, a depot formulation of intramuscular steroid may be provided. An ICS should be prescribed for all patients previously using an ICS and should be strongly considered in naïve patients to reduce the rate of relapse. ICS should be started on ED discharge and overlapped with systemic CS.

Discussion regarding avoidance of triggers should be undertaken, including counseling and medications for smoking cessation. Patients should be shown proper technique for use of inhalers including use of a holding chamber (spacer). The patient should be provided with a peak expiratory flow meter and instructed in its appropriate use. Outpatient follow-up with the patient's primary care provider or asthma specialist within 1 month should be arranged by ED staff and patients should be instructed to contact their provider within 3–5 days of discharge given the high rate of relapse in this period *(3)*. Patients presenting with a life-threatening exacerbation or recurrent exacerbations should be referred to an asthma specialist.

All patients discharged from either the ED or the hospital should be provided with a written asthma action plan. A systematic review of 36 randomized trials of asthma self-education plans in adults showed significant reductions in hospitalizations, ED visits, and unscheduled visits to the doctor; best results were seen in patients who had written care plans *(44)*. A freely available asthma action plan can be obtained online from the National Institutes of Health *(45)*.

CONCLUSION

The full spectrum of acute exacerbations of asthma is addressed in the ED ranging from mild to life-threatening severity, straightforward to complicated presentations, and immediate to highly refractory responses to treatment. For all asthma cases, the goal is prevention of morbidity and mortality through rapid assessment and initiation of therapy, using the best available evidence to guide management. The provision of high quality care should be team based and focused on both medical interventions and patient education. Healthcare delivery should be coordinated between physicians, nurses, and respiratory therapists as well as social workers and case managers in the

ED. Effective communication must also occur between ED clinicians and both inpatient and outpatient providers to ensure continuity of care and the best possible outcomes for patients with this potentially treatable disease.

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8 The Critically Ill Asthmatic: from ICU to Discharge

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Contents

The best treatment of status asthmaticus is to treat it three days before it occurs.

—Thomas L. Petty, M. D.

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KEY POINTS

- The in-hospital mortality rate for all asthmatics is between 1 and 5%, but for critically ill asthmatics that require intubation, the mortality rate is between 10 and 25% primarily from anoxia and cardiopulmonary arrest.
- Near-fatal asthma refers to a life-threatening asthma attack that requires ventilatory support; status asthmaticus refers to an asthma attack that does not readily respond to aggressive standard treatment. Failure to halt status asthmaticus precipitates near-fatal asthma and fatal asthma.
- Bronchodilators and anti-inflammatory drugs remain the main pharmacotherapy in status asthmaticus and near-fatal asthma.
- Mortality is highest in African-Americans, Puerto Rican Americans, Cuban Americans, women, and persons aged ≥65 years.
- Controlled modes of ventilation that allow for a prolonged expiratory time are favored in near-fatal asthmatics.
- General anesthesia by either intravenous infusion or gas inhalation are therapeutic options for the most severe patients.
- Coordination of discharge and follow-up care can safely reduce hospital length of stay and prevent future attacks of status asthmaticus.

INTRODUCTION

Status asthmaticus (SA) and near-fatal asthma (NFA) are common medical emergencies faced by critical care physicians. SA is defined as an acute, severe asthma exacerbation that does not respond readily to initial intensive therapy, while NFA refers loosely to a SA attack that progresses to respiratory failure (Fig. 1) Timely evaluation and treatment in the clinic, emergency room, or ultimately the intensive care unit (ICU) can prevent the morbidity and mortality associated with acute hypoxemic respiratory failure. Fatal asthma occurs from cardiopulmonary arrest, cerebral anoxia, or a complication of treatments, e.g., barotraumas, ventilator-associated pneumonia. Critical care physicians or intensivists must be skilled in managing the critically ill asthmatics with respiratory failure and knowledgeable about the few but potentially serious complications associated with mechanical ventilation. Bronchodilator and systemic corticosteroids remain the cornerstone drug therapy for managing SA and NFA patients in the ICU. NFA patients on mechanical ventilation require modes that allow for prolonged expiration and reverse the dynamic hyperinflation associated with the attack. Several adjuncts to mechanical ventilation, including heliox, general anesthesia, and extra-corporeal carbon dioxide removal can be used as life-saving measures in extreme cases (Fig. 1).

TRIAGE OF PATIENTS TO ICU

Most asthmatic patients requiring hospital admission do not need ICU level care. Of the two million emergency department visits attributed annually to severe asthma exacerbations, approximately 25% of patients are hospitalized and of these, 5–10% require the ICU. The majority of hospitalized asthmatics improve while in the emergency department and warrant observation on a ward for a few days (average length of stay 3.2 days) to ensure continued improvement. Number of hospital discharges with asthma as the first diagnosis was 440,000 in 2006 *(1)*. In an analysis of nearly 30,000 hospital

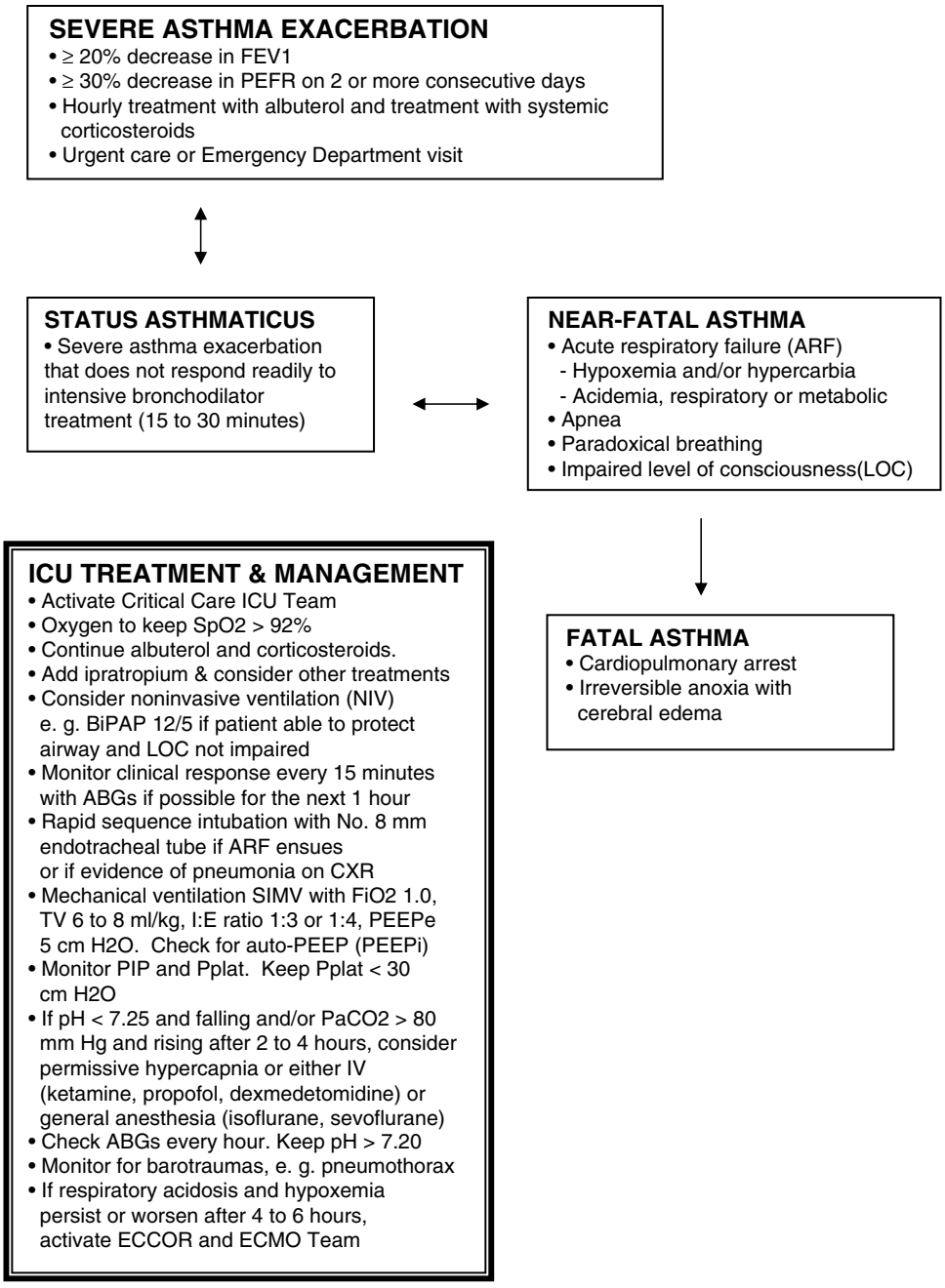

Fig. 1. Deterioration of severe asthma exacerbation: status astmaticus and near-fatal asthma with suggested ICU treatment and management.

admissions for acute asthma, 10.1% required admission to the ICU and 2.1% required intubation and mechanical ventilation *(2)*. Intubated patients averaged 4.5 extra days in the hospital and over $11,000 in additional costs as compared to asthma admissions to non-ICU beds. Absolute criteria for triaging acute, severe asthmatic patients are lacking; existing guidelines recommend that patients with peak expiratory flow rate (PEFR) <200 L/min, a pulsus paradoxus >15 mmHg, use of accessory muscles of respiration, or a <10% improvement in PEFR be monitored in an ICU *(3)* but data supporting these recommendations are scant. Clearly, worrisome patients – with worsening respiratory fatigue or acidemia – should be immediately stabilized and transferred to an ICU for critical care management and monitoring.

EPIDEMIOLOGY OF FATAL ASTHMA

Approximately 11 people die from asthma each day in the United States. Death from asthma in the United States rose from a low of 1,674 in 1977 to 5,667 in 1996 but has steadily declined by at least 30% since 1996 with 3,447 deaths reported in 2007 or 1.1 patients per 100,000 population *(4)*. Although asthma mortality in the United States is among the lowest in the world, approximately 3,000–4,000 asthma-related deaths still occur annually, particularly in African Americans, Puerto Rican Americans, Cuban Americans, women, and persons ≥65 years. The highest at-risk-based death rate was in persons aged >65 years (10.5 per 10,000 with current asthma). Males had higher at-risk-based death rates than females (2.3 and 1.8, respectively). For most age groups, males had higher rates than females; only for persons aged >65 years was the rate for females (11.3 per 10,000 with current asthma) higher than for males (9.1). Blacks had higher at-risk-based death rates (3.4) than whites (1.9). This was true for males and females, adults and children, and for each age group. Asthma is reported as a contributing factor for nearly 7,000 other deaths each year *(5)*. It has been suggested that 1–7% of severe asthmatics will die each year of their disease, and perhaps 17% of those who survive NFA attacks will eventually succumb to asthma *(6)*.

Mortality rates for NFA patients requiring mechanical ventilation can approach 25% *(7, 8)* but the rate is probably less than 5% in most settings. In general, morbidity and mortality of hospitalized patients with SA have decreased significantly and much of the credit is due to rapid assessment and treatment by out-of-hospital providers and better ICU care *(9)*. Hospital care for asthma is not without problems with patients having died because of professional inexperience and errors *(10)*, and therapeutic measures may cause serious complications.

RISK FACTORS FOR FATAL ASTHMA

The single greatest risk factor for fatal asthma is a history of NFA, i.e., acute respiratory failure, need for ventilator support. One study found a 16-fold increased risk of asthma death for patients with a prior history of NFA. Psychiatric illness, for one, is consistently associated with an increased risk of fatal asthma *(11)*. Similarly, persistent smoking carries a twofold increased risk of death in asthmatics. Another oft reported risk factor for fatal asthma is frequent short-acting β_2-agonist use *(12)*. In a case–control study, the use of short-acting β_2-agonists conferred a two to threefold increased risk per bronchodilator canister per month *(12)*.

Table 1
Risk Factors for Fatal Asthma

History of near fatal asthma (NFA)	*Rapid onset of attack ("brittle asthma")*
Female gender	Elderly and poor
African American ethnicity	Psychiatric illness
Puerto Rican American ethnicity	Blunted perception of dyspnea or inability to distinguish danger from discomfort
Cuban American ethnicity	$\beta(\text{beta})_2$-agonist usage (long/short acting)

Patients with SA and NFA may have blunted perceptions of dyspnea or an inability to distinguish danger from discomfort. In one study, 11 severe patients had blunted ventilatory responses and lower Borg dyspnea scores compared to mild asthmatics when exposed to hypoxic conditions, suggesting that these patients were unable to recognize their deterioration and impending respiratory failure (Table 1) *(13)*.

Demographics

The majority of adult patients seen in asthma referral clinics are women *(14)* and this is in contrast to the pediatric population where boys are more prevalent. Furthermore, the age-adjusted mortality rates are significantly higher for females compared to males, as they are for African Americans compared to Caucasian Americans *(5)*. Nearly 65% of asthma deaths are attributed to women and among African Americans, women have the highest mortality rate, more than 2.5 times higher than Caucasian women. Why women make up 60–80% of adult, severe asthma patients is unclear. Genetic predisposition, hormonal effects, patient behaviors, and increased prevalence of vocal cord dysfunction, and gastroesophageal reflux disease leading to very poorly controlled asthma may be contributors in women.

Genetics

Genetic polymorphisms such as single nucleotide polymorphisms are factors in the pathophysiology of severe asthma and possibly fatal asthma. Several studies have outlined the effect of the Gly-16 polymorphism of the β2-adrenoreceptor. Patients homozygous for Gly-16 undergo desensitization and down-regulation of this β-receptor response with chronic albuterol use; this genotype is more prevalent in the acute, severe asthma population *(15, 16)*. Certain polymorphisms for interleukin-4 (IL-4) and its receptor correlate loosely with SA *(17)*. Variation in one gene, corticotropin-releasing hormone receptor 1 (CRHR1), which is involved in the release of ACTH, was consistently associated with enhanced response to corticosteroids. Genetic variants in CRHR1 may adversely influence the clinical response to corticosteroids and lead to SA. Between 25 and 35% of asthma patients do not respond with a >5% improvement FEV_1 or better asthma control after 6–12 weeks of inhaled corticosteroid treatments *(18)*. Whether this genetic predisposition affects the acute treatment and outcomes of SA and NFA are not known. Other factors that may play a role in predisposition to SA are transforming growth factor-β (TGF-β) *(19)* and 5-lipoxygenase activating protein (FLAP) *(20)*.

Psychosocial and Socioeconomic Factors

Poverty and poor access to medical care correlate with increased risk for fatal asthma. For example, 21% of all asthma deaths among young people in the late 1980 occurred in the inner cities of Chicago and New York *(21)*. Several hypotheses have been proposed to explain the correlation between socioeconomic status and fatal asthma. Certainly, one of the most important is that poor patients have inadequate medical care and asthma education. Risk factors for death from asthma include lack of appropriate use of anti-inflammatory controller medication, particularly inhaled corticosteroids, inappropriate use of long-acting β_2-agonists without controller medication(s), limited self-management skills, increased exposures to air pollution and indoor allergens (house, dust, mite, cockroach), dietary factors, and drug abuse with cocaine and heroin in adult asthmatics. Cocaine and heroin users were intubated significantly more often than non-users for NFA (17 vs. 2.3% respectively, $p=0.0036$) *(22)*.

Stress

The effect of psychosocial stress on asthma has been demonstrated in several studies. One recent study demonstrated a strong correlation between worsening airway inflammation following antigen challenge during a week of intensive examinations among a university cohort *(23)*. In the ENFUMOSA *(24)* study, men with severe asthma reported that stress was a common trigger for exacerbations. Psychiatric illness has also consistently been associated with an increased risk of fatal asthma *(11)*.

Pregnancy

The impact of pregnancy on asthma is reviewed comprehensively in Chap. 9 of this book. Uncontrolled asthma in pregnant asthmatics puts them at higher risk for complications that can include early labor, hypertension, gestational diabetes, and NFA for mother and fetus. Teenage mothers with asthma face higher risks than older women. Most asthma drugs are safe to take during pregnancy, and good control of asthma reduces these risks of severe exacerbations to normal levels.

Pregnant asthmatics presenting with severe asthma exacerbations must avoid hypoxia at all costs to prevent fetal anoxia. The threshold to intubate pregnant asthmatics with SA should be very low to prevent and limit hypoxia to mother and fetus *(25)*. No maternal deaths occurred in 80 pregnancies in 73 women with SA. Infants delivered from gravidas who experienced at least one episode of SA during gestation had decreased birth weights ($p=0.03$) compared with infants delivered from gravidas who did not require emergency therapy or develop SA *(26)*.

PATHOPHYSIOLOGY OF NEAR-FATAL AND FATAL ASTHMA

Acute, severe asthma exacerbations can deteriorate into SA with hypoxemia via lung hyperinflation and regional ventilation/perfusion (V/Q) alterations. Studies of patients presenting to the ED with severe asthma attacks using multiple inert gas elimination techniques have shown a bimodal blood flow pattern with a significant portion of the cardiac output perfusing poorly ventilated lungs.

Carbon dioxide retention does not usually develop in SA until the FEV_1 is less than 30% of predicted and one large meta-analysis of severe asthmatics found that only

13% had $PaCO_2$ values >45 mmHg *(27)*. Increased physiologic dead space associated with the V/Q abnormalities, dynamic hyperinflation with severe peripheral air trapping, and alveolar hypoventilation secondary to respiratory fatigue all lead to hypercarbia, a heightened respiratory drive, and intrinsic positive end expiratory pressure ($PEEP_i$).

Asthma is a spectrum of disease and research efforts have attempted to delineate specific biomarkers that might differentiate NFA from milder forms of asthma. Marked airway thickening and a brisk infiltration of neutrophils into the airways are consistent findings in NFA. In cases of fatal asthma, bronchial thickening is 25–30% greater than normal airways, while in NFA patients this is less dramatic *(28)*. The predominance of eosinophils or neutrophils in the airways of NFA defines two distinct phenotypes and clinical presentations. Significantly increased numbers of neutrophils and levels of the neutrophil chemoattractant, IL-8, in bronchoalveolar lavage fluid (BALF) were reported in asthmatics requiring mechanical ventilation compared to milder patients *(29)*. In addition, increased matrix metalloproteinases, presumably triggered by neutrophil-mediated epithelial cell injury, were found in the BALF in severe asthmatics *(27)*. This neutrophilic NFA phenotype has a sudden and rapid onset of SA but respond rapidly to treatment and require shorter hospital stays *(30)*.

In contrast, eosinophils and neutrophils, rather than neutrophils alone, in transbronchial biopsy specimens were found to correlate with the number of NFA events in very poorly controlled severe asthma, i.e., patients requiring at least 10 mg of prednisone daily >75% of the year *(31)*. This is characteristic of the most common NFA phenotype, marked by a more gradual deterioration over days or weeks in patients with poorly responsive severe asthma *(32)*. Both phenotypes often have severe airways obstruction and concomitant static hyperinflation. Prevention of NFA may eventually be predicated on identifying predominantly neutrophilic or eosinophilic inflammation phenotypes using screening biomarkers and treatments specific to modulating small airways inflammation, e.g., with 5-lipoxygenase inhibitors, leukotriene receptor antagonists, theophylline, omalizumab, systemic corticosteroids. This discourse presumes NFA, either predominantly neutrophilic or eosinophilic is not complicated by infection, e.g., acute pneumonia, bacterial or viral, pulmonary embolism or drug-induced lung disease. Asthma attacks with eosinophilia (≥275 cells/mm^3) predict a higher mortality from COPD in a general population sample *(33)*.

Two other pathologic features of interest in NFA and fatal asthma are mucus cell hyperplasia and smooth muscle hyperplasia. The contributions of mucous cell metaplasia are debated but in many cases of fatal asthma and SA, mucus plugging with airway cast formation is extensive *(34)* and appear to be more often associated with the eosinophilic NFA phenotype *(35)*. Airway samples in fatal asthma can reveal a marked infiltration of the mucus glands by mast cells and neutrophils *(36)*. Smooth muscle hyperplasia is prominent in the larger generation airways and this has been documented in cases of fatal asthma *(37)*. Excess growth of these myocytes leads to a web-like binder around the airways that are hypercontractile to stimuli. Several inflammatory mediators have been implicated as potential triggers of the smooth muscle hyperplasia, including histamine and Th2 cytokines.

CLINICAL EVALUATION UPON ADMISSION TO THE ICU

SA is a medical emergency and non-intubated SA patients admitted to the ICU require urgent assessment, timely institution of treatments, and monitoring by critical care nurse and critical care respiratory therapist led by the intensivist. A coordinated critical team response is absolutely vital. Patients with signs of respiratory failure: a decreased level of consciousness, shallow respirations, central cyanosis, or other signs of profound fatigue, should be endotracheally intubated immediately. Most patients, however, examined and reassessed by the intensivist during the first hours in the ICU do not require mechanical ventilation. Clinical evaluation every 15 min for response or lack of response to treatments is routine to determine the patient's clinical course and monitor response to interventions, e.g., vital signs, ABGs, peak inspiratory pressures, plateau pressures, flow volume loop on ventilator display, signs of patient-ventilator dyssynchrony.

Much of the relevant physical examination of a SA patient can be obtained from the vital signs and by observation. The most worrisome patients will often be sitting upright with flared nostrils, diaphoretic, tachypneic, wheezing and have sternocleidomastoid contraction with respiration. Brenner and colleagues showed a good correlation between patient position and accessory muscle use and a reduction in PEFR and partial pressure of oxygen (PaO_2) *(38)*. In general, however, physical findings in SA gauge the work of breathing rather than the degree of airway obstruction. Paradoxical breathing signifies impending respiratory arrest from total exhaustion and should prompt immediate endotracheal intubation and mechanical ventilation, not non-invasive mask ventilation (NIV) or continuous positive airway pressure ventilation (CPAP).

The vital signs of a patient in SA during the first 12–24 h will consistently register respiratory rates >30 per minute and heart rates >120 per minute *(39)*. Blood pressure can fluctuate depending on the degree of hemodynamic embarrassment due to high intrathoracic pressures from dynamic hyperinlation, a consequence of progressive air-trapping from the patient's bronchial obstruction and mechanical ventilation. The most worrisome patients are hypotensive because of dehydration and marked lung hyperinflation, which compromises systemic venous return, cardiac preload, and coronary perfusion. Safe endotracheal intubation in these patients is often a challenge and efforts to avoid causing further hypotension should be made, e.g., avoid over-zealous bag ventilation, choice of sedation in rapid sequence intubation. Perhaps more useful than blood pressure is the pulsus paradoxus. Hypercapnic SA patients had an increased mean pulsus paradoxus (23 mmHg) compared to normocapnic acute asthmatics (14 mmHg) *(40)*. It should be remembered that as respiratory failure progresses, a drop in pulsus paradoxus to near normal readings may be seen.

The remainder of the physical examination should look for possible mechanical complications of SA. Pneumomediastinum and pneumothorax may be suspected by an unexpected change in vital signs, i.e., increased tachypnea, tachycardia, hypoxemia and observing an unexpected jugular venous distension, deviated trachea, palpating subcutaneous emphysema, or auscultating asymmetric breath sounds or a Hamman's mediastinal crunch.

Assessment of Airway Obstruction

The intensivist should order a PEFR or spirometry in the non-intubated SA patient, if not done recently in the emergency room. Severely compromised patients will be

unable to perform the test properly and it should be deferred. SA patients typically have PEFR readings <25% predicted *(41)* and FEV_1 <20% predicted *(42)*. In one study of 86 patients presenting with acute, severe asthma, a FEV_1 reading of <1 L (<25% predicted) or a PEFR <200 L/min (<30% predicted) identified all patients with hypercarbia ($PaCO_2$ >42 mmHg) or severe hypoxemia (PaO_2 <60 mmHg) *(43)*. Reduction in PEFR to <33% of normal is considered life-threatening. One advantage to performing spirometry with a full flow-volume loop is in diagnosing asthma mimics like vocal cord dysfunction or a tracheal tumor that may be admitted to the ICU in extremis.

Arterial Blood Gas Measurement

In SA patients in the ICU, arterial blood gases (ABGs) should be obtained early and frequently during the first 4 h and with every change in condition or ventilator adjustment. ABGs provide important information regarding respiratory reserve, metabolic disturbances, and degree of hypoxemia. Respiratory alkalosis is the most common abnormality found during asthma exacerbations, *(44)* but as PEFR and FEV_1 drop to <30% of predicted, hypercarbia and respiratory acidosis develop *(43)*. It is prudent to remember that acute respiratory alkalosis may signal sepsis, pneumothorax, pulmonary edema, pulmonary embolism, or cerebral edema. Furthermore, concomitant lactic acidosis occurs in up to 28% of SA patients with elevated $PaCO_2$ levels *(44)*. Lactate production presumably stems from overload of the thoracic cage muscles and tissue hypoxia. If ABGs document a pH <7.20 and $PaCO_2$ >80 mmHg and rising after 2–4 h of ICU care and mechanical ventilation, either permissive hypercapnia or general anesthesia should be considered.

Chest Radiography

As with ABGs, chest radiographs (CXRs) are not routinely performed in all SA patients in the emergency room. Abnormal CXR findings other than hyperinflation or subsegmental atelectasis in all asthma exacerbations are <5% *(37)*. Complications from barotrauma in SA patients, however, are sufficiently prevalent to justify routine chest radiographs in this population. A review of 54 admission CXRs on hospitalized asthmatics found that 20 (34%) were felt to have major abnormalities that warranted attention *(45)*. Most of these major abnormalities were focal infiltrates, and only one patient was found to have a pneumothorax. We recommend daily CXR review in the intubated asthmatic to ascertain the placement of the endotracheal tube, central lines, nasogastric tube, and to detect early pneumonia, pneumothorax, and pneumomediastinum. Acute pneumonia, viral, bacterial, or fungal can complicate SA and cause adult respiratory distress syndrome to occur with a very high mortality. Influenza A (H1N1) pneumonias were reported in obese asthmatics taking oral prednisone for severe asthma exacerbations prior to their acute presentation to the hospital (Fig. 2) *(46)*.

Other Tests

Few other studies need be obtained in evaluating patients with SA in the ICU. Electrocardiograms in middle-aged patients or those with suspected ischemic heart disease are standard. Screening laboratory chemistries may reveal hypokalemia related to aggressive β_2-agonist usage or abnormalities in sodium and glucose suggesting concomitant illness. A complete blood count could reveal signs of an acute infectious process, but this will be infrequent unless circumstances dictate otherwise, e.g., viral infections,

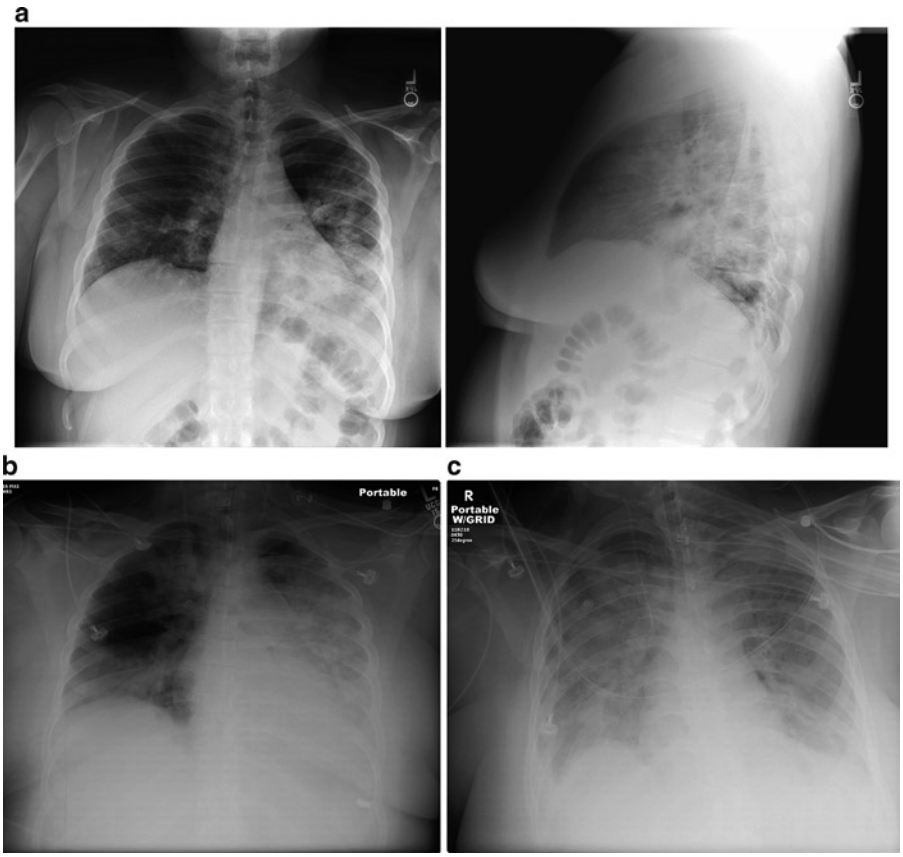

Fig. 2. Progression of near-fatal asthma with H1N1 confirmed pneumonia to frank adult respiratory distress syndrome in a 25-year-old woman with asthma and obesity. (**A**) Chest X-ray (CXR) posterior-anterior and lateral views upon arrival to the ICU from the Emergency Department. (**B**) Progression of left lower alveolar densities to involve left upper lobe and right lower lobe. Endotracheal tube inserted for mechanical ventilation. (**C**) Bilateral diffuse air space densities. The patient expired despite critical care support and ECMO.

such as H1N1 which could concurrently trigger severe asthma exacerbation. In the latter situation, treatment with antiviral antibiotics, e.g., oseltamivir 150 mg twice daily for adults, and for longer duration than standard therapy is important but secondary bacterial pneumonia is virtually assured while intubated on mechanical ventilation. Moderate (absolute eosinophil count 1,500–5,000 cells/mm^3) to severe peripheral eosinophilia (absolute eosinophil count >5,000 eosinophils/mm^3) should raise concern for allergic bronchopulmonary aspergillosis with massive mucous plugging, Loffler's syndrome, and Churg–Strauss syndrome. In general, specific laboratory tests and studies should be ordered only if other diagnoses or contributing factors are under consideration.

INITIAL ICU MANAGEMENT

As with most ICU patients, treatment of patients with SA continues in parallel with their ongoing assessment and diagnostic evaluation. Timely intervention and a team approach with intensivist, critical care respiratory therapist, and critical care nurse are

necessary if intubation and mechanical ventilation are to be avoided. The cornerstones of SA treatment are oxygen, bronchodilators, systemic corticosteroids, and, if necessary, ventilatory support for NFA.

Oxygen

Modest hypoxemia is common in severe asthma exacerbations, but a PaO_2 <55 mmHg is rare *(3)*. Supplemental oxygen should be administered to improve the hypoxia caused by (V/Q) mismatch, airway plugging and atelectasis; oxygen therapy may ameliorate some of the symptoms of air hunger. In the majority of SA patients, FiO_2 levels of 0.30–0.50 will correct the hypoxemia; failure to do so should prompt investigation for pulmonary parenchymal or vascular disease. FiO_2 level of 1.0 may increase $PaCO_2$ levels by 5–6 mmHg and, infrequently, may suppress the respiratory drive in SA patients. Intensivists should refrain from routinely administering unnecessarily high oxygen concentrations without close patient monitoring.

Bronchodilators

The cornerstone of acute asthma management, bronchodilators have several modes of delivery, mechanisms action, and potential complications. Delivery of the short-acting β_2-agonist albuterol or its active isomer levalbuterol by intermittent inhalation is the most common therapy for severe asthma exacerbations and SA. While delivery of short-acting β_2-agonists by dry powder, nebulization or meter dose inhalation are effective in severe acute asthma *(47)* each modality can offer distinct advantages. Delivery by nebulization provides adequate drug delivery in a wide range of clinical settings: the infant by mask delivery, the tachypenic adolescent or even the intubated patient with respiratory failure. Nebulized delivery may decrease some of the adverse effects, e.g., tachycardia, as compared to oral or systemic delivery. Delivery by MDI with the use of a spacer has also been effectively employed in acute settings but is often more cumbersome, particularly in the anxious or uncomfortable patient. In the calm, cooperative patient delivery of β_2-agonists by metered dose inhaler (MDI) may provide more rapid and efficacious delivery to the airways. In the acutely ill patient with SA or NFA aerosol delivery remains the mode of choice.

Delivery by continuous nebulization may offer distinct advantages to intermittent dosing. Even with similar per hour dosing, e.g., 0.5–1.0 mg/h vs. 2.5 mg every 2–4 h continuous nebulization, in some studies, shows a more rapid clinical improvement with a decreased medical personnel workload than intermittent administration *(48)*. The addition of heliox as a carrier gas may also improve drug delivery in SA *(49)*.

Alternatively, systemic delivery, e.g., subcutaneous terbutaline may offer a more reliable dosing in the profoundly ill or pregnant patient. Systemic β_2 receptor stimulation using subcutaneous epinephrine can be effective and may forestall respiratory failure in selected cases but with the potential for significant adverse cardiovascular effects, including coronary ischemia. Epinephrine with its significant α-adrenergic stimulation may initially reduce edema by decreasing blood flow but can also promote delayed airway edema and should be used with extreme caution in patients with coincident cardiac disease.

Anticholingerics or antagonists of relevant muscarinic receptor subtypes in the tracheobronchial tree are emerging as important bronchodilator therapy for persistent asthma.

Whether the addition of an inhaled ipratroprium, 0.5 mg every 6 h to albuterol is superior to albuterol treatment alone in SA or NFA is not known. The benefits for adults are less certain, but in critically ill asthmatics who have COPD physiology with a FEV_1 <50% predicted, the addition of ipratropium to albuterol improved FEV_1 to a greater degree than albuterol alone and, most importantly, decreased the need for hospitalization *(50)*.

Systemic Corticosteroids

Intravenous (IV) methylprednisolone 60 mg every 6 h is administered to the critically ill asthmatic for the first ICU day. This should be instituted the same time albuterol is given. There is typically a 6–24 h delay in clinical response to corticosteroids in SA and NFA but they have been shown to reduce fatal asthma. If the patient improves within 24 h, the dose of methylprednisolone is decreased to 60 mg every 12 h for the next day or two after which prednisone 1 mg/kg is substituted or no greater than 60 mg daily for 2 days, followed by a drop to 40 mg for the next 3 days. If improvement continues, the patient may be discharged from hospital with a prednisone taper, i.e., 30 mg for 3 days, 20 mg for 3 days, and 10 mg for 3 days. Follow-up in clinic is imperative to prevent SA relapse and assess asthma control.

Methylxanthines

The methyxanthines, theophylline, and aminophylline, are less specific bronchodilators, purportedly capable of increasing diaphragmatic contractility in the failing SA patient. In SA, the use of IV aminophylline is not likely to result in any additional bronchodilation compared to standard care with inhaled bronchodilators and oral or intravenous corticosteroids. Side effects such as palpitations, arrhythmias and vomiting can increased if IV aminophylline is used.

Other Therapies

Leukotriene receptor antagonists such as montelukast have demonstrated efficacy in chronic asthma, but their efficacy in acute asthma is emerging. In a randomized, double blind, parallel-group pilot study, adults with moderate to severe acute asthma received standard therapy plus either intravenous montelukast (7 mg) or matching placebo *(51)*. A total of 583 adults with acute asthma were treated with standard care within a 60-min screening period. Patients with FEV_1 ≤50% predicted were randomly allocated to intravenous montelukast 7 mg ($n=291$) or placebo ($n=292$) in addition to standard care. This double-blind treatment period lasted until a decision for discharge, hospital admission, or discontinuation from the study. The primary efficacy endpoint was the time-weighted average change in FEV_1 during 60 min after drug administration. Secondary endpoints included the time-weighted average change in FEV_1 at various intervals (10–120 min) and percentage of patients with treatment failure (defined as hospitalization or lack of decision to discharge by 3 h post-administration).

Montelukast significantly increased FEV_1 at 60 min post-dose. Similar improvements in FEV_1-related variables were seen at all time points (all $p<0.05$). Although treatment failure did not differ between groups (OR 0.92; 95% CI, 0.63, 1.34), a prespecified subgroup analysis suggests likely benefit for intravenous montelukast. This benefit was observed at 10 min and over 2 h following intravenous therapy. Patients treated with montelukast tended to receive less β_2-agonists and have fewer treatment failures than patients receiving placebo. The tolerability profile for montelukast was similar to that

observed for placebo, and no unexpected adverse experiences were observed. Unavailable for use in the United States, intravenous montelukast in addition to standard therapy causes rapid benefit, and is well-tolerated, in adults with acute asthma *(51)*.

Magnesium is a purported bronchodilator by inhibiting calcium channels in bronchial smooth muscle and blocking parasympathetic tone in the tracheobronchial tree. Nebulized inhaled magnesium sulfate (95 mg of magnesium sulfate in 3 mL of saline or a 3.2 % solution nebulized every 20 min for a total of four doses) *(52)* in addition to β_2-agonist in the treatment of an acute asthma exacerbation appears to demonstrate bronchodilator benefits between 10 and 90 min in a meta-analysis of six trials involving 296 patients in the Cochrane Library. A trend towards benefit in fewer hospital admissions was found *(53)*.

IV magnesium sulfate infusion (1–2 gm over 20 min) appeared to provide little overall clinical benefit in a meta-analysis of seven trials (five adult and two pediatric) involving 665 patients. While the routine use of IV magnesium was not recommended, severe acute asthma patients who received magnesium were able to significantly avoid hospitalization compared to placebo (OR 0.10, 95% confidence interval 0.04–0.27) and improved FEV_1 by 9.8% over several hours *(54)*.

Non-invasive Ventilation

NIV or CPAP may be attempted in select patients with severe asthma attacks in the ICU. Critically ill asthmatics are arriving from the emergency department more often than in previous years with NIV. NIV decreases morbidity and mortality in COPD, but it should not be used in SA in severe respiratory distress, with altered level of consciousness, or with hemodynamic instability and impending cardiorespiratory arrest. The advantages of NIV include improved patient comfort and reduced need for sedation, while avoiding the complications of endotracheal intubation, including upper airway trauma, sinusitis, otitis, and nosocomial pneumonia against serious hypoxia and cardiopulmonary arrest. A trial of NIV in acute asthma may be justified in carefully selected and monitored patients who do not respond to bronchodilator therapy in the first hour of treatment. However, as its role has been better defined with the caveat that the condition of an asthmatic patient may deteriorate very abruptly, e.g., upon arrival to the ICU. Stringent monitoring to recognize failure of NIV is needed as well as resources for immediate endotracheal intubation and mechanical ventilation *(55)*.

A prospective randomized controlled trial of NIV in 53 found the addition of NIV (mean iPAP 12 cmH_2O and ePAP 5 cmH_2O) to usual care was not inferior to usual care in improving respiratory rate, FEV1, PaO_2/FiO_2, but reduced the mean dose for albuterol treatment and shortened the ICU and hospital stay. There were four instances of usual care failure, and all those patients improved with NIV. Two patients in the NIV arm required invasive ventilation. There was no mortality in either of the arms *(56)*.

INTUBATION

The decision to endotracheally intubate and mechanically ventilate a SA patient may be made urgently, but preferably, is made electively in patients who are failing to respond to treatment and are fatiguing. Intubation and initiation of mechanical ventilation of NFA patients is challenging and must be performed by skilled intensivists or anesthesiologists in the ICU. Hypotension in 20–40% of cases *(57)*, arrhythmias,

Table 2
Indications for Intubation

Absolute	*Relative*
Cardiorespiratory arrest or apnea	Hypercarbia, e.g., $PaCO_2$ >50 mmHg or rising >5 mmHg per hour
Acute respiratory failure with PaO_2 <60 mmHg or $PaCO_2$ >50 mmHg	Worsening respiratory acidosis
Acute on chronic respiratory failure	Inability to care for patient appropriately
Decreased level of consciousness	Clinical signs of fatigue, e.g., paradoxical breathing
Hypopneas	Failure to improve with therapy

barotrauma, laryngospasm, worsening bronchospasm, aspiration, and seizures will be encountered in the peri-intubation period in NFA patients *(39)*. Excessive bag ventilation should be avoided because of the risk of pneumothorax. While awake, nasotracheal intubations may be preferred in these tenuous patients, orotracheal artificial airways are preferred for prolonged management. Orotracheal tubes of at least 8.0 mm diameter significantly decrease inspiratory airway resistance and allow for suctioning of secretions and bronchoscopy. Rapid-sequence intubation protocols should be used. Ketamine, etomidate, or another sedating agent can be used with a non-depolarizing neuromuscular blocking agent (NMBA) such as rocuronium. There are risks with NMBA during mechanical ventilation and a full understanding of their side effects is required and is discussed later (Table 2).

Goals of Mechanical Ventilation

The goals of mechanical ventilation are to provide adequate supplemental oxygen to prevent anoxia and organ ischemia, reduce the work of breathing by the critically ill asthmatic, to prevent severe acidemia, respiratory or metabolic, i.e., pH <7.20 or to allow permissive hypercapnia to prevent ventilator-induced lung injury, including barotraumas. Central to preventing barotraumas is to control dynamic hyperinflation and persistent bronchospasm. The determinants of dynamic hyperinflation are minute volume (respiratory rate x tidal volume) and minute ventilation, expiratory time and thus inspiratory to expiratory ratio (I:E), and airway resistance. Understanding that pathophysiology of SA and NFA changes significantly after intubation and institution mechanical ventilation is key to survival and recovery from NFA.

PATHOPHYSIOLOGY AND MECHANICAL VENTILATION

Near-fatal asthmatic patients that require intubation and ventilation have very high airway resistance and significant distal airway mucous plugging that lead to obstruction of airflow during expiration. Severe airflow obstruction that has developed over days causes significant dynamic hyperinflation and increased intrathoracic pressures at the end of expiration (intrinsic positive end expiratory pressure, PEEPi, or auto-PEEP). The inspiratory capacity (IC) of the near-fatal asthmatic patient is reduced as the residual volume (RV) of the lung steadily increases and the patient breathes near the limits of their total lung capacity (TLC) (Fig. 3). At these lung volumes, there is a mechanical

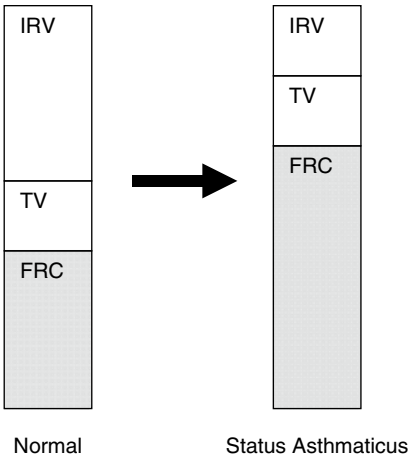

Fig. 3. Effect of dynamic hyperinflation on lung volumes – normal and status asthmaticus (FRC – functional residual capacity, TV – tidal volume, IRV –inspiratory reserve volume).

disadvantage of the respiratory muscles as the diaphragm flattens, the thoracic muscle fibers stretch, and dead space increases. Overall, the severe asthmatic patient has high ventilatory demands and is at a significant mechanical disadvantage to breathe. Fatigue in these patients seems inevitable, but surprisingly, many patients with this physiology improve and do not require intubation (Fig. 3).

NFA patients may worsen in the minutes immediately after intubation. Hypotension often results from a combination of sedative and NMBA, in the setting of high intrathoracic pressures. Intravascular volume supplementation prior to and immediately after intubation can prevent this expected complication. Furthermore, ventilation may be compromised further if sedation is inadequate in the patient awakening from anesthesia or if the initial ventilator settings provide excessive minute ventilation. In either situation, dynamic hyperinflation and gas exchange worsen and barotrauma may result.

Pneumothorax, Pneumomediastinum, Pneumopericardium

The occurrence of life-threatening pneumothorax and tension pneumothorax with NFA before and after institution of mechanical ventilation is rare today. High intrathoracic pressure and hyperinflation are thought to lead to parenchymal or distal airway injury. In the case of pneumomediastinum, “trapped” air tracks along the bronchial tree to the confluence of the pulmonary and mediastinal reflections where small rents or tears allow communication to the mediastinum. This is commonly called the Macklin effect *(58)*. Pneumothoraces may arise through rents in the parenchyma cause by subsegmental alveolar over-distension distal to mucus plugs or severe airway inflammation. Massive auto-PEEP while on mechanical ventilation can go unrecognized immediately after intubation during the early minutes of mechanical ventilation when the patient is either still paralyzed or heavily sedated. Profound hypotension may be the only clue until auto-PEEP is actually measured on the ventilator. Neuromuscular blockade can aggravate dynamic hyperinflation and auto-PEEP after intubation by paralyzing the diaphragm and accessory muscles of respiration.

Pneumothorax warrant urgent tube thoracostomy for decompression and prevention of tension pneumothorax. The authors prefer at least an 18–20 French chest tube to a pleural catheter for drainage in critically ill asthmatics. When mediastinal air is present, cardiac tamponade from pneumopericardium, albeit rare, should be considered and would warrant intervention.

SETTING THE VENTILATOR

The intensivist must pay close attention to the ventilator parameters in newly intubated SA patients. Junior or in-training physicians err frequently in setting the initial ventilator variables in severe asthma patients. Errors occur because physicians attempt to correct the hypercarbia and acidemia too quickly and fail to recognize the extent of the dynamic hyperinflation which carries devastating consequences to the patient. The key goal at this time is to maximize the time for expiration and target a low minute ventilation strategy.

A low minute ventilation strategy (8–10 L/min) aims to permit time for expiration, decrease air trapping, and reduce auto-PEEP. The intensivist should accept a moderate degree of hypercapnia with this strategy and $PaCO_2$ levels <100 mmHg are usually well tolerated in the first day *(59)* so long as pH is maintained >7.20. One important exception to this is in patients who have suffered a cardiorespiratory arrest at the time of presentation. In these patients, $PaCO_2$ levels should be normalized if possible to prevent cerebral vasodilatation and cerebral edema (Table 3).

Controlled modes of ventilation are favored over support modes when initiating mechanical ventilation. Patients have an impressive drive to breathe because of the elevated $PaCO_2$ levels and acidemia and may require deep sedation initially in order to breathe synchronously with the controlled modes. Two common modes of ventilation used in this setting are volume-controlled ventilation, e.g., synchronized intermittent mandatory ventilation (SIMV) and pressure-controlled ventilation (PCV). PCV is favored by some intensivists in this setting because peak airway pressures do not vary as they do in volume control modes but minute ventilation is less tightly controlled. We will discuss the management of the critically ill asthmatic on SIMV but the following guidelines apply to both modes.

Table 3
Suggested initial ventilator settings

	Synchronized, intermittent mandatory ventilation (SIMV)
Modes	*Pressure control ventilation (PCV)*
Rate	8–12 breaths/min
Tidal volume	6–8 cc/kg ideal body weight
Minute ventilation	8–10 L/min
I: E	1:3–1:4
Plateau pressure	<30 cmH_2O
PEEP	<5 cmH_2O
FiO_2	100%

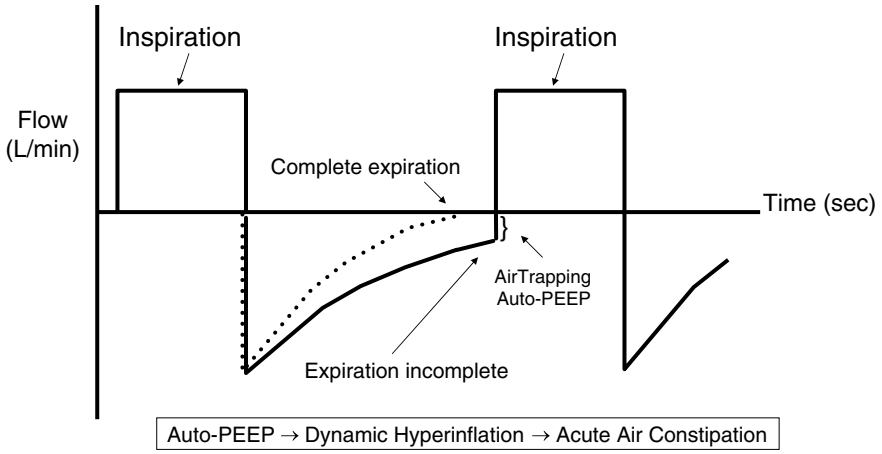

Fig. 4. Ventilator graphic illustrating air-trapping and auto-PEEP (PEEPi) during volume control mechanical ventilation. It is important to increase the expiratory time, reduce the I:E ratio to 1:3 or 1:4 and/or add external PEEP to permit the patient to completely exhale before the next breath.

A minute ventilation of 8–10 L/min can be achieved by targeting tidal volumes of 6–8 mL/kg of ideal body weight and a respiratory rate of 8–12 breaths/min. The set extrinsic PEEP should be 0–5 cmH_2O initially to overcome the endotracheal tube resistance The I:E ratio in the respiratory cycle should be between 1:3 and 1:4. It is imperative to identify and prevent progressive dynamic hyperinflation and acute air constipation in a SA or NFA patient who already may have significant dynamic hyperinflation in addition to baseline static hyperinflation. Failure of the flow (L/min) ventilator graphic to return to baseline should prompt lengthening of the expiratory time or a decrease the I:E ratio and/or add extrinsic PEEP to reduce the patient's work of breathing to exhale trapped air in the lungs (Fig. 4).

In SIMV, inspiratory flow rates of 100 L/min allow for a prolonged expiratory phase by rushing in tidal volume. Peak inspiratory pressure (PIP) alarm may need to be set above 45 cmH_2O, occasionally above 50 cmH_2O to ensure that the patient receives the set tidal volume breath and prevent ventilator cycling. Hypoventilation and worsening gas exchange will occur. High PIPs are generally associated with plateau pressures (Pplat) between 25 and 35 cmH_2O and thus PIP measurements do not to reflect alveolar over-distension and do not predict barotraumas risk. Any patient with persistently high PIP, e.g., >50 cmH_2O, however, should have Pplat checked by programming the ventilator to stop flow at the end of inspiration. Pplat indirectly estimates end-inspiratory alveolar pressure and thus alveolar distension. Pplat should be maintained ≤30 cmH_2O to prevent barotraumas and pneumothorax. The difference between PIP and Pplat pressures reflects the contribution of *inspiratory* (not expiratory) airway resistance to the value of the peak pressure above Pplat. A descending ramp flow waveform is generally recommended to improve distribution of ventilation or a square flow waveform to achieve a shorter inspiratory time. The square waveform may cause higher peak inspiratory pressures.

Auto-PEEP or intrinsic PEEP (PEEPi) should be measured every 6–8 h shift in the ICU, if not more frequently initially, and extrinsic PEEP (PEEPe) increased to match PEEPi to allow exhalation of trapped air in the lungs and to reduce patient-ventilator dyssynchrony. In our experience, the PEEPe applied is typically between 5 and 10 cmH_2O. Transitory use of high PEEPe (>10 cmH_2O) to reduce baseline hyperinflation at the beginning of mechanical ventilation or ventilation with very low respiratory rates, e.g., 2–3 breaths for several minutes can allow auto-PEEP to dissipate.

The inspiratory fraction of oxygen (FiO_2) should be decreased from a level of 1.0–0.50 over the first 2 h. If a FiO_2 >0.55 is required, the intensivist should immediately determine for a concomitant disorder worsening V/Q mismatching or an intrapulmonary shunt from atelectasis, such as pneumonia, pulmonary embolism, or pulmonary edema.

On these initial ventilator settings – with aggressive bronchodilator and systemic corticosteroid therapy – airway resistance and lung compliance will improve during the first 24 h and hypercapnia will correct easily. A beneficial effect with decreased PIP and, most importantly, Pplat and improved gas oxygenation and ventilation should be evident within 2–3 h. The average duration of intubation in most studies of NFA is 3 days *(60)*. Some patients, however, prove refractory to standard medical therapy and ventilator support, e.g., decreasing lung compliance, worsening dynamic hyperinflation as evidenced by higher PIP, and Pplat >30 cmH_2O. If ABGs document a pH <7.20 and $PaCO_2$ >80 mmHg and rising after 2–4 h of ICU care, either permissive hypercapnia or general anesthesia should be considered.

Permissive hypercapnia may be necessary under these circumstances to keep the patient safe from barotrauma so long as proper oxygenation and the pH is maintained, e.g., SpO_2 ≥92% and pH >7.20. $PaCO_2$ levels ≤90–100 are acceptable. The physiological effects of permissive hypercapnia include central nervous system depression, increased intracranial pressure which may be undesirable if there is any evidence of prior cerebral anoxia, a proportional decline in PaO_2 (Haldane effect), a rightward shift in the oxyhemoglobin curve (Bohr effect), pulmonary arterial vasoconstriction, and myocardial depression.

Three adjuncts to standard mechanical ventilation that have been explored in NFA include general anesthesia, inhaled helium–oxygen mixtures or heliox, and extracorporeal CO_2 removal (ECCOR).

ADJUNCTS TO STANDARD MECHANICAL VENTILATION AND PHARMACOTHERAPY

General Anesthesia

The inhaled general anesthetics (halothane, sevoflurane, and isoflurane), and intravenous anesthetics (ketamine and propofol) have been used in SA and NFA cases with continued clinical decline despite mechanical ventilation and aggressive bronchodilator therapy. The rationale for general anesthesia is to further promote bronchodilation, decrease metabolic demand, and eliminate ventilator patient dyssynchrony.

Anesthetic gases are modestly potent, rapidly acting bronchodilators and pulmonary vasodilators *(61)*. A beneficial effect with decreased PIP and, most importantly, Pplat and improved gas oxygenation and ventilation should be evident within 1–2 h. If no

effect is seen in this time period, it is unlikely to work. Finding a ventilator that can handle anesthetic gases is problematic and, overall, this rescue modality has become less popular with the use of other bronchodilating intravenous anesthetic agents, like propofol and ketamine.

Propofol is a complex intravenous anesthetic introduced in the United States in 1989 with an effectively short distribution half-life of 2–3 min. Elimination half-life is between 30 and 60 min by the liver. Induction is rapid within 60–120 s. Hence propofol has a rapid onset and rapid offset of action. As with gas anesthesia, propofol affords bronchodilation in addition to the beneficial anesthetic properties. The dosage of propofol is determined by the need for general anesthesia or sedation. The former can be induced with a target propofol concentration in the range of 4–8 μg/mL in patients under age 55. a lower target should be used in patients over age 55. Respiratory depression ensues and can worsen hypercarbia and hypoxemia on mechanical ventilation. ICU sedation is achieved with lower propofol concentrations between 0.5 and 2.5 μg/mL. Begin propofol at 2–2.5 mg/kg/h and titrate to achieve improvement in lung compliance and gas exchange. Potential adverse effects that occur immediately include hypotension (15%) and bradycardia (5%) as propofol is a negative inotrope and chronotrope in addition to being a vasodilator on initial administration. Propofol infusion syndrome (PRIS) should be suspected with unexplained metabolic acidosis with prolonged use *(53)* and high dosages (>4 mg/kg/h for >48 h) and can be suspected with anion gap metabolic acidosis from elevated serum lactate (early), rhabdomyolysis, hyperkalemia resulting in acute renal failure. The incidence of PRIS is not known but is probably around 1% and higher in critically ill patients requiring high dosages of propofol, which inhibit mitochondria and systemic corticosteroids, which increase proteolysis with myopathy *(62)*.

Finally there was no reported adverse effects in patients with reactive airway disease (smokers or patients with COPD) from propofol containing metabisulfites preservative in contrasts to earlier reports *(63)*. However, the brand propofol containing EDTA as the preservative would avoid reports of bronchoconstriction with generic propofol *(64)*. Underlying allergy to sulfites can worsen life-threatening asthma by causing anaphylactoid reactions or non-immunologic, non-specific histamine release, which is more likely to occur in atopic patients.

Ketamine is a dissociative anesthetic that works as a *N*-methyl d-asparate receptor (NMDAR) antagonist in both children and adults that can cause bronchorrhea and bronchodilation – both of which may be beneficial in NFA *(65)*. Ketamine has a rapid onset of action within 60 s after administration with a half-life of 2–3 h. Catalepsy, amnesia, and analgesia can occur during dissociative anesthesia. The bronchodilatory effects are thought to occur through endogenous norepinephrine release stimulating β_2 receptors or by inhibiting parasympathetic activity of vagus nerve on bronchial smooth muscle. It has been used in low doses to avoid mechanical ventilation 0.75 mg/kg IV bolus followed by a continuous drip of 0.15 mg/kg/h *(66)*. The more commonly used dosages are 1–2 mg/kg IV bolus for induction, followed by a 0.5 mg/kg/h infusion until bronchospasm or clinical improvement is achieved. The potential serious adverse effects of hypertension and tachycardia must be considered prior to dosing and during use. Ketamine's notorious dysphoria and hallucinations are usually managed with coincident benzodiazepine administration. Limited evidence is available in the literature to strongly support the value of ketamine in severe exacerbation of asthma. It should be used

cautiously as adjunctive treatment by experienced intensivists for patients for whom other standard therapies for NFA have clearly failed.

NMBAs, e.g., rocuronium, vecuronium are often used during endotracheal intubation and allow for complete control during mechanical ventilation. However, NMBAs do not promote bronchodilation, nor do they treat the airway inflammation associated with asthma. The use of NMBAs in the critically ill asthmatic should be minimized or avoided altogether if possible. Other more efficacious modes of therapy often obviate the need for NMBAs. When used in combination with corticosteroids, NMBAs are associated with relatively high risk of drug induced prolonged weakness *(67)*. The risk of prolonged weakness is correlated with dose and duration of NMBA and corticosteroids. All NMBAs seem to be implicated and patients with NMBA myopathies may take months to recover normal muscle function *(68)*.

Helium–Oxygen

A helium:oxygen gas (heliox) mixture of 70:30 or 80:20 decreases resistance to airflow in obstructed large airways because helium is not as dense as nitrogen and may provide better drug delivery. It is an excellent option in upper airway obstruction and can be useful in SA. When used in the emergency department in SA, heliox may improve PEFR faster than standard therapy, decrease the pulsus paradoxus, and help prevent the need for intubation in some patients *(69)* and can improve ventilation in intubated NFA patients, in some instances. Oxygen requirements need to be less than 30% FiO_2 for this modality to be tried in NFA. Unfortunately, most ventilators are not calibrated for heliox.

Extra-corporeal Techniques

Perhaps, the last intervention that can prove life-saving in near-fatal asthmatics with worsening gas exchange and acidemia is extra-corporeal CO_2 removal (ECCOR). This technique mirrors that of the more common extra-corporeal membrane oxygenation, or ECMO, in that patients are placed on bypass to provide gas exchange *(70)*. Case reports document the success of this life-saving technique in severe asthmatics on mechanical ventilation and should be considered, if available and appropriate *(71)*.

Sedation

The used of sedatives in asthma patients has a long history of use. William Osler describes his use in the 1892, *The Principles and Practice of Medicine*:

> In a child with very severe attacks, resisting all the usual remedies, the treatment by chloroform gave immediate and permanent relief. … The sedatives antispasmodics … belladonna, henbane, strabonium and lobelia, may be given in solution or used in the form of cigarettes.

Most patients with acute asthma will benefit from anxiolysis and those with NFA require sedation. Reducing the anxiety of air-hunger and illness may allow for better delivery of medical care, decrease ventilation requirements and even obviate the need of mechanical ventilation. Short-acting benzodiazepines, e.g., midazolam or lorazepam allow for careful titration to effect with subsequent continuous or scheduled bolus delivery. While standardized administrations are not established it is reasonable to adopt a

Table 4
Ramsay Sedation Scale

1. Anxious and agitated or restless or both
2. Cooperative, oriented, and calm
3. Responsive to commands only
4. Exhibiting brisk response to light glabellar tap or loud auditory stimulus
5. Exhibiting a sluggish response to a light glabellar tap or loud auditory stimulus
Unresponsive

daily interruption strategy *(72)*. Dosing is initiated incrementally and interrupted on a daily basis by decreasing the dosage until the patient reaches light sedation or 2 on the Ramsey Sedation Scale (RSS). The length of stay and length of time on ventilator are decreased using this method. The duration of mechanical ventilation and length of stay in the ICU can be decreased with proper use of sedatives to promote ventilator-patient synchrony (Table 4).

Dexmedetomidine was introduced in the United States in 1999 and is as effective as propofol and midazolam for sedation of the critically ill. It is a rapid and short-acting α_2-agonist with anxiolytic, anesthetic, and analgesic properties approved by the FDA for use in the ICU for no more than 24 h. A loading dose is not recommended as patients commonly experience hypotension. An infusion of dexmedetomidine 0.2 μg/kg/h can be titrated to 0.8 mg/kg/h to achieve a sedation score 3–5 on the RSS. The distribution half-life is 6 min and elimination half-life 2 h. Dexmedetomidine is metabolized by the liver and metabolites excreted in the kidneys. This drug causes conscious sedation by stimulating the locus caeruleus in the brain stem which controls the sleep–wake cycle. Sedation results from inhibition of the sympathetic vasomotor center of the brain. Unlike propofol and midazolam, which act on γ-aminobutyric acid system and sedates by clouding consciousness, dexmedetomidine produced cooperative conscious sedation by reducing sympathetic activity and arousal. ICU patients given dexmedetomidine remain awake but calm. There is no respiratory depression and it does not interfere with liberating patients from mechanical ventilation in the manner propofol and midazolam do. Hypotension (30%), hypertension (16%), bradycardia (8%), and hypoxemia from hypoventilation (6%) can develop from its use *(73)*.

Dexmedetomidine has not been studied extensively in SA or NFA. Intravenous dexmedetomidine completely blocked histamine-induced bronchoconstriction in dogs. Therefore, dexmedetomidine might be beneficial to decrease airway reactivity in critically ill asthmatics *(74)*. Two cases of NFA were treated with dexmedetomidine to facilitate NIV. One hour after the institution of NPPV, patients tolerated NIV with the mask ventilation and respiratory symptoms markedly improved. RSS score was maintained at two or three during the continuous dexmedetomidine infusion. Patients were successfully weaned from NIV by reducing the inspiratory PAP. Dexmedetomidine helped the agitated patients cooperate with mask ventilation without inducing respiratory depression *(75)*.

LIBERATION FROM NIV, MECHANICAL VENTILATOR, AND TRACHEOTOMY

Liberation from NIV can begin when the patient's respiratory distress has subsided, evidenced by respiratory rate <25 per minute, heart rate <120 per minute, and PaO_2 >60 mmHg. Failure to liberate from NIV should prompt intubation and mechanical ventilation. The majority of intubated NFA patients will be liberated from mechanical ventilation with a mean time to extubation of 3.5 days. Once the patient's airway resistance decreases, airway obstruction improves and hypercarbia resolves, the patient can be switched to a spontaneous support mode of ventilation. Patients unlikely to tolerate extubation can be identified by performing a spontaneous breathing trial of 30–60 min on a CPAP of 5 cmH_2O or a T-piece with supplemental oxygen *(76)*. Patients require close observation immediately post-extubation for worsening bronchospasm and can usually be transferred out of the ICU after 24 h.

Tracheotomy will be required in few NFA patients. NFA patients that have concomitant conditions such as anoxic brain injury from an out-of-hospital cardiopulmonary arrest or lung injury from ventilator-associated pneumonia may require prolonged ventilator support and are more apt to have a tracheotomy performed. The optimal time to perform tracheotomy in NFA patients is not well defined, but the timing should not differ significantly from that of other patients with acute on chronic lung injury.

Hospital outcomes reported prospectively in 89 patients (mean age 42 years) from 1995 to 1998 revealed a morality of 12% for 132 admissions but 21% mortality for patients intubated *(60)*. Women accounted for 79% of hospitalizations and African Americans 67%. Overall median hospital length of stay was 4 days with ICU days 2 but 36% required more than 3 days of intensive care. Twenty-seven were treated initially with NIV but 5 later required intubation. Forty-eight or 36% of all patients required mechanical ventilation and 11 died, all women giving a mortality rate of 8.3%. Ventilator-associated pneumonia and sepsis occurred in 13%, pneumothorax in 3% and ARDS in 2%. Higher APACHE II score (26 vs. 15, $p << 0.0001$) and $PaCO_2$ (63.8 vs. 47.8, $p = 0.01$), lower pH (7.09 vs. 7.27, $p < 0.0001$) found within 24 h of admission predicted increased mortality.

TRANSITION OUT OF THE ICU AND DISCHARGE

Within 12–24 h of reversal of acute respiratory failure or liberation from mechanical ventilation most SA and NFA cases may be cared for outside of the ICU. Medications previously administered parenterally may be changed to oral dosing and outpatient inhaled controller drugs should be restarted or introduced after careful assessment of the reasons for asthma deterioration are fathomed. It is important not to reproach the patient for the hospitalization and to be solicitous of the events preceding SA and NFA to prevent the next exacerbation. Look for evidence of disease heterogeneity causing a variable response to standard asthma controller drugs or pre-existing co-morbidity that was not recognized that could have contributed to SA and NFA, e.g., inability to distinguish danger from discomfort, gastroesophageal reflux, sinopulmonary infections, cigarette smoking, drug abuse. Oral prednisone is typically administered for an additional 10–12 days, e.g., prednisone 40 mg for 3 days, 30 mg for 3 days, 20 mg for 3 days, and 10 mg

for 3 days. Educating the patient about and implementing a "stepped up" asthma control plan similar to those recommended by the current NIH-NAEPP guidelines should be initiated prior to discharge and reinforcement of an updated *written* asthma action plan to better control symptoms and prevent exacerbations as outlined in Chap. 6. The decades old adage of treating SA 3 days before it occurs remains true today to both patient and clinicians *(77)*.

Hospital discharge requires stabilization of asthma symptoms, demonstrated tolerance and understanding of the written asthma action plan, and confirmation of outpatient post-discharge plan, preferably to a chronic disease management program with an asthmatologist and certified asthma educator to reinforce lessons learned in hospital *(78)*. With these elements assured it is not necessary for full resolution of asthma symptoms prior to discharge *(79)*. With asthma education and reliable discharge plans and follow up, asthmatics may have a shorter hospital length of stay without an increased readmission rate *(80)*.

SUMMARY

Once recognized, severe asthma and near-fatal asthma are clearly life endangering diagnoses. Early diagnosis of high-risk individuals, through recognition off the physical signs of progressive respiratory decline and institution of aggressive therapy may forestall respiratory failure the need for mechanical support. Once respiratory failure occurs, successful patient management includes rapid and coordinated critical team response with ICU monitoring, careful use of non-invasive ventilation and, if needed, mechanical ventilation – which may require longer expiratory times and, if constrained, permissive hypercapnia to protect the patient and lungs. Pharmacotherapy, in addition to β_2-agonists and intravenous corticosteroids, with sedatives or even general anesthetics offers further modalities to improve impaired respiratory physiology to achieve survival and recovery. After clinical improvement is established, patients will need to maintain a higher level of asthma care after hospital discharge to help decrease recurrences of SA or NFA.

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III Special Clinical Problems

9 Asthma and Pregnancy

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Contents

KEY POINTS

- Asthma is probably the most common potentially serious medical disorder that may complicate pregnancy.
- A third of pregnant women with asthma will experience worsening of their symptoms, a third will see improvement of their symptoms and a third will see no change.
- The primary goal is to maintain optimal control of asthma for maternal health and well-being as well as fetal maturation.
- Vital patient education should cover the use of controller medication, avoidance of asthma triggers and early treatment of asthma exacerbations.
- Proper asthma management should ideally be started in the preconception period.

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- Since smoking is probably the most modifiable risk factor of asthma, pregnant woman should avoid active and passive smoking.
- Acute asthma exacerbation during the first trimester is associated with an increased risk of congenital malformations.
- Poorly controlled asthma is associated with low birth weight, preeclampsia, and preterm birth.
- Medications used for asthma control in the non-pregnant population are generally the same in pregnancy with a few exceptions.
- Inhaled corticosteroids (ICS) are the preferred controller therapy. Budesonide is the preferred ICS. Long-acting β-agonists (LABA) are the preferred add-on therapy to medium to high dose ICS.
- Major triggers for asthma exacerbations during pregnancy are viral infections and ICS non-adherence.

INTRODUCTION

Asthma can significantly affect pregnancy outcomes if not well-controlled. The National Asthma Education and Prevention Program *(1)* emphasizes that maintaining optimal control of asthma during pregnancy is important for the health and well-being of both the mother and her baby. Since asthma has a variable course during pregnancy, it is important to monitor closely to make adjustments in therapy. Pregnant women may be ambivalent about taking medications during pregnancy due to concerns about adverse effects on the fetus; however, the epidemiologic evidence is extremely strong in favor of using medications for asthma control. In fact, asthma control is especially crucial during first trimester when organogenesis takes place. Congenital malformations were significantly more common in asthmatic women who had an asthma exacerbation during the first trimester *(2)*. Overall, maternal asthma increases the risk of preeclampsia, congenital malformations, low birth weight, perinatal mortality and preterm birth, but the risks are lower if asthma is well-controlled.

PRECONCEPTION COUNSELING AND EVALUATION

By using national health surveys, data on the trend and prevalence of asthma in the preconception period has been reported. Among adult women of child-bearing age, a twofold increase in asthma prevalence from 2.9 to 5.8% occurred between 1976–1980 and 1988–1994. Among women aged 18–24, the increase was threefold, from 1.8 to 6.0% *(3)*. In another study, approximately 4.1% of all pregnant women experienced an asthma attack in the preceding year (the preconception period) *(4)*. Preconception counseling is extremely important for women with asthma to clarify concerns about possible adverse effects on the fetus of the medications used to treat asthma and to ensure excellent asthma control, especially in the first trimester *(5)*.

In 2006, the U.S. Center for Disease Control (CDC) published recommendations to improve health care for women before pregnancy and between pregnancies. The Pregnancy Risk Assessment Monitoring System (PRAMS) provided data on 18 behaviors and conditions that are relevant to preconception health and 10 that are relevant to postpartum health. According to the PRAMS 2004 data, the prevalence during the

preconception period was 23.2% for tobacco use, 6.9% for asthma, 13.1% for being overweight (BMI: 26.0–29.0), 21.9% for being obese (BMI: ≥29.0), and 30.3% for receiving prepregnancy health counseling *(6)*. Based on this report, many more women would benefit from preconception health counseling.

Before becoming pregnant, it is advised that women with asthma undergo a complete assessment of asthma control and be switched to preferred controller medications, as well as receive information on the importance of controlled asthma for fetal health. It may take several months to adjust medications and obtain good control of asthma, which is optimal prior to attempting conception *(7)*. Additional measures, like avoiding triggers for asthma exacerbations, can be instituted during the preconception period to minimize the severity or frequency of asthma symptoms during pregnancy, and thus decrease reliance on, and fetal exposure to, medications. Since a significant percentage of child-bearing age asthmatic women do not have asthma optimally controlled *(4)*, primary care providers play a crucial role in counseling, treating and referring them to specialists in a timely manner. Early pregnancy is a critical time in fetal development because the major part of organogenesis is over by 8 weeks of gestation. A significant number of pregnant women do not visit their obstetrician until several weeks or even months into pregnancy.

A study conducted by Nettleman et al. reported that the recommended appointment times by obstetric clinics ranged from immediately upon discovery of pregnancy (approximately 4 weeks of gestation) to 10.6 weeks, or an average of 6.37 weeks. Twenty-five percent of clinics recommended a first appointment at ≥8 weeks of gestation. Thus, some women, even with full-coverage health insurance, may not have their first prenatal visit until near the end of the first trimester *(8)*. Primary care providers could help women in optimally managing their asthma during the preconception period and first few weeks of pregnancy. This could lead to better outcomes.

THE EPIDEMIOLOGY OF ASTHMA DURING PREGNANCY

Overall, the prevalence and morbidity of asthma are increasing, although mortality has gone down *(9)*. According to a large epidemiologic study by Kwon and colleagues, asthma was estimated to affect approximately 8.4–8.8% of pregnant women in the United States during 2000–2003 *(4)*. The study showed that only half of the women who took controller medication before pregnancy took them during pregnancy. In addition, only about half of women who had daily symptoms during pregnancy took any controller medication during pregnancy, reflecting poorly controlled asthma *(4)*. The need for emergency department care in the year prior to pregnancy was predictive of emergency visits during pregnancy *(4)*. Approximately 10% of women cared for by asthma specialists (a referral population) required emergency care or hospitalization for asthma during pregnancy *(10)*. Younger women and women with normal BMI were less likely to take controller medications regularly during pregnancy. Well-educated women, older women and overweight or obese women were more likely to take them *(4)*.

Carroll et al. conducted a population-based cohort study of asthma-related morbidity in 4,315 black and white pregnant women enrolled in the Tennessee Medicaid Program,

TennCare, from 1995 to 2001 *(11)*. This low income population of pregnant asthmatics had high asthma-related morbidity. During pregnancy, 12.7% of women received rescue corticosteroids, 11.1% of women had asthma-related ER visits and 6.3% of women were hospitalized for asthma. Blacks were more likely than whites to receive a course of rescue corticosteroids, have an emergency department visit, or be hospitalized for asthma.

Chung et al. conducted a historical cohort study in New Jersey between 1989 and 1993 (N=556,597). The study looked at racial/ethnic disparities in the rate of asthma during pregnancy and examined insurance type, maternal education and prenatal care as potential determinants of disparities. The study found that Medicaid and HealthStart enrollees were more often diagnosed with asthma symptoms in pregnancy than women with standard insurance. When such factors that reflected socioeconomic status were included in the analysis, the effect of race was decreased, and insurance type was determined to be the most important socioeconomic factor and accounted for most of the racial disparity *(12)*.

NORMAL PHYSIOLOGY DURING PREGNANCY

Multiple physiologic changes during pregnancy interact with the pathophysiology of asthma. During normal pregnancy there is a 20% increase in oxygen consumption and a 15% increase in the maternal metabolic rate. These demands are met by several physiologic changes during pregnancy *(13)*.

Respiratory Changes During Pregnancy

To compensate for the increased oxygen demand of pregnancy, minute volume is increased by 40–50%. This hyperventilation is due to an increasing tidal volume. These changes are due to the stimulatory effect of progesterone on the respiratory center. The respiratory rate remains relatively unchanged during pregnancy. Therefore, tachypnea during pregnancy (respiratory rate >20) is an abnormal finding and should be further investigated. Hyperventilation leads to respiratory alkalosis that is compensated by metabolic acidosis. Typical blood gases in early pregnancy have a pH of 7.40–7.45, a pCO_2 of 28–32 mmHg, and a pO_2 of 106–110 mmHg (Table 1). The pO_2 in the umbilical vein is lower than that in the placental arteriovenous capillary network due to the decrease in oxygen tension in transfer from the maternal placental channels to the fetal interfacing blood supply; thus maternal hypoxemia (<95 mmHg) quickly results in a decreased oxygen supply to the fetus. Chronic hypoxemia could lead to restricted intrauterine growth and lowered birth weight. When interpreting maternal ABGs, a

Table 1
Normal Arterial Blood Gas Calues in Non-Pregnant and Pregnant Women *(10)*

	pH	*pO_2 mmHg*	*pCO_2 mmHg*
Non-pregnant women	7.4	91–95	36–39.4
Pregnant women	7.4–7.45	106–110	28–32

Table 2
Changes in Lung Function Values During Pregnancy *(10)*

Respiratory rate	Unchanged
FEV1	Unchanged
PEFR	Unchanged
Minute volume/ventilation	Increased by 30–50%
Tidal volume	Increased by 30–50%
FVC	Unchanged
FEV1/FVC	Unchanged
Maximum mid expiratory flow rate (forced expiratory flow 25–75)	Unchanged
Functional residual volume	Decreased by 18%

FEV1 forced expiratory volume in 1 s; *PEFR* peak expiratory flow rate; *FVC* forced vital capacity.

normal looking pCO_2 for a non-pregnant person actually reflects a maternal hypercapnic environment. A low pCO_2 is essential for fetal acid-base balance and increased maternal pCO_2 will cause fetal acidosis.

As the uterus enlarges, it pushes the diaphragm upward approximately 4–5 cm resulting in a reduction in the functional residual capacity (FRC) of about 18%. Because of this change, pregnant women more rapidly desaturate during hypopneic periods due to loss of reserve lung volume. Pregnancy does not change forced expiratory volume in one second (FEV1) or peak expiratory flow rate (PEFR). As in the general population, FEV1 and PEFR during pregnancy correlate well with asthma symptoms and exacerbations making them acceptable measurements to help monitor asthma control *(14)* (Table 2).

Cardiovascular Changes

Many of the significant physiologic changes occur in the cardiovascular system. Most of these changes occur in the first trimester, plateau in the second trimester and peak again in the third trimester. The important changes to mention are a fall in systemic vascular resistance (SVR); a rise in heart rate (HR), an increase in cardiac output (CO), and a decrease in blood pressure (BP).

Falling of the SVR is likely due to peripheral arterial vasodilatation in early pregnancy mediated by progesterone *(15)*. The conversion of the uteroplacental circulation from high to low resistance flow acts to further reduce SVR. HR goes up as a compensatory mechanism to the falling SVR. BP also falls in early pregnancy because of the decrease in SVR. Fall in SVR and SBP reach a nadir at approximately 24 weeks of gestation and return to pre-pregnancy values at term. Fall in SVR also triggers a 40–50% increase in CO and the glomerular filtration rate.

Blood volume starts to rise during the first trimester and reaches a maximum by the third trimester that is 40–50% above the pre-pregnant state. Because plasma volume increases more than red cell mass, the hematocrit generally falls, resulting in the "physiologic anemia of pregnancy."

DYSPNEA DURING PREGNANCY AND DIAGNOSIS OF ASTHMA

Sixty to seventy percent of women experience dyspnea during the course of normal pregnancy. Dyspnea of pregnancy is often described as "air hunger" *(16)*. Dyspnea of pregnancy may be due to increased awareness of the "physiologic hyperventilation of pregnancy" *(17)*. Dyspnea of pregnancy is usually worse in the sitting position and is not exertional. It starts in the first or second trimester and peaks in the second trimester, then becomes relatively stable in third trimester. Normal dyspnea of pregnancy has a gradual onset. Dyspnea during pregnancy could be thus physiologic, but when it is accompanied by wheezing and/or coughing, it is likely to be caused by asthma. A diagnosis of asthma should be based on the history, the physical exam and pulmonary function tests. Symptoms of asthma are wheezing, cough, chest tightness and dyspnea. Typically, asthma symptoms get worse in the presence of environmental stimuli and at night. Patients usually have a known history of asthma. On exam, the clinician may notice some expiratory wheezing. Spirometry may only be abnormal during an acute attack. The demonstration of a reduced FEV1 or FEV1/FVC ratio with a 12% or more improvement in FEV1 with bronchodilator confirms the diagnosis of asthma in pregnancy. Patients with asthma usually show reversibility on spirometry but some patients need oral corticosteroid therapy in order to show the reversibility *(18)*. Clinicians should consider the diagnosis of asthma when pregnant women present with intermittent shortness of breath that is at least partially reversible and when other causes of dyspnea are ruled out.

To estimate the prevalence of asthma as a cause of dyspnea during pregnancy, Bidad et al. conducted a study in Tehran University, Iran, on 165 pregnant women who had been referred to the prenatal clinic for the complaint of dyspnea. Exclusion criteria included: any pulmonary disease other than asthma, gestational hypertension, major congenital anomalies or multiple gestations. This study showed asthma as a cause of dyspnea in 38.8% cases, while dyspnea was determined to be physiologic in 36.4% of cases, and 24.8% cases were diagnosed as having probable asthma (normal spirometry but symptoms and signs suggestive of asthma) *(19)*. Interestingly, this study showed that 25.4% of the women diagnosed as having definite asthma were newly identified and had no previous diagnosis of asthma by a physician.

Differential Diagnosis of Asthma During Pregnancy Should Include

1. Dyspnea of pregnancy due to hyperventilation.
2. Pulmonary embolism: Pregnancy is a procoagulable state, which can increase the risk for thromboembolism *(15)*, particularly in those with additional risk factors like smoking.
3. Amniotic fluid embolism.
4. Bronchitis or pneumonia.
5. Postnasal drip due to allergic rhinitis or sinusitis.
6. Congestive heart failure, cardiomyopathy or pulmonary edema.
7. Gastroesophageal reflux disease.
8. Vocal cord dysfunction.

Diagnostic Work Up of Asthma During Pregnancy

A clinical impression of asthma should be confirmed by reversible airway obstruction on spirometry *(18)*. Women with a clinical presentation consistent with the new onset of asthma but whose pulmonary function tests failed to show the reversibility should be treated for asthma (e.g., normal FEV1 prior to bronchodilator and failure to improve further). Methacholine testing is contraindicated during pregnancy but can be done in the postpartum period if needed *(20)*.

Smith et al. compared formal allergy assessment (structured history and skin test) in making an accurate allergy diagnosis with a structured allergy history alone or the patient's self-report *(21)*. Self-reporting commonly resulted in misclassification of the allergy diagnosis with underestimation of dust mite and pollen sensitivities. A structured history obtained by the health care provider alone resulted in false positive rates for sensistivity to dust mites of 75%, grass pollen of 48%, tree pollen of 54%, cat of 32% and dog of 27% compared with formal allergy evaluation by an allergy specialist that included skin prick testing. Coming up with accurate allergy diagnosis is very important during pregnancy as most asthmatics are atopic and avoidance of allergen triggers is part of management. However, skin tests are not generally recommended during pregnancy because skin testing with potent antigens may rarely cause systemic allergic reactions *(1, 20)*. Instead, blood tests for specific IgE measurement can be utilized. Both positive and negative results would help the patient and clinician in coming up with better trigger avoidance strategies.

THE RISK OF CONGENITAL MALFORMATIONS AND LOW BIRTH WEIGHT

Maternal asthma exacerbations have been found to be associated with a 50% increased risk of congenital malformations *(2)*.

According to a study published by Blais et al. in 2010, the prevalence of any congenital malformation was 9.5 and 7.5% for women with and without asthma, respectively *(22)*. Another study by Blais et al. from 2008 showed the prevalence of malformations was 12.8 and 8.9%, respectively, for women who had and those who did not have an asthma exacerbation during pregnancy. The risk seems even higher for women who did not fill any prescriptions for oral corticosteroids during pregnancy, with a twofold increase for women with an exacerbation during the first trimester who did not have oral corticosteroids on hand. Filling a prescription for an oral corticosteroid does not mean that the individual necessarily used it, but may indicate that the patient has excellent medical care with an asthma action plan that includes an oral corticosteroid if needed.

In a meta-analysis, Murphy et al. found that women with an asthma exacerbation during pregnancy are at increased risk of having low-birth-weight babies when compared to women without asthma *(23)*. Severe and poorly controlled asthma may cause prematurity, increased need for Cesarean section delivery, preeclampsia, growth restriction and increased maternal mortality and morbidity *(24, 25)*. Schatz et al. *(26)* studied a voluntary sample of 486 asthmatic pregnant women and 486 non-asthmatic pregnant controls. The study findings suggest that overall perinatal outcomes for women with well-controlled asthma during pregnancy are comparable to those of non-asthmatic pregnant women.

EFFECT OF PREGNANCY ON ASTHMA

Pregnancy can influence the disease course of asthma. The risk of asthma exacerbations requiring intervention in pregnant women is higher than in non-pregnant female asthmatics *(10)*. About 18% of all pregnant women have at least one ED visit *(10)* and up to 62% of women with asthma exacerbation require hospitalization *(27)*. Kircher et al. noted improvement of asthma control during pregnancy in 33.6%, worsening in 36.3%, unchanged control in 26.4%, and the course was uncertain in 3.7% *(28)*. Worsening of asthma during pregnancy is related to the baseline asthma severity. Schatz et al. *(29)* enrolled 1,739 pregnant asthmatics before 26 weeks of gestation and classified them into mild, moderate and severe disease groups. They noted correlation between severity of asthma and outcome of the pregnancy, with 51.9% of those in the severe group having an asthma exacerbation, 25.7% of the moderate group and 12.6% of the mild group. The variable course of asthma was also reflected in this cohort, with 30% of pregnant women whose asthma was classified as mild at the beginning switched to either the moderate or severe group, 23% of the initially moderate–severe asthma patients reclassified as mild later in pregnancy. These findings emphasize the need for close follow-up of all pregnant asthmatics. The same group previously reported that pregnant women were more likely to get asthma exacerbations between 29 and 36 weeks and likely to have less frequent and less severe attacks during the last 4 weeks of pregnancy *(30)*. With successive pregnancies, asthma was noted to have the same course as experienced in previous pregnancies *(30)*.

According to a study done by Belanger et al., the pre-pregnancy severity of asthma and use of medication according to Global initiative for Asthma guidelines had more effect than other factors like age, race, BMI, parity and smoking on the course of asthma during pregnancy *(31, 32)*. Women with only intermittent asthma who had appropriate treatment got the most benefit: a 62% decreased risk for worsening asthma. Women with mild persistent asthma also showed a 52% decreased risk of worsened asthma; however, if asthma medications were stopped, even mild asthma was at risk to become severe and poorly-controlled *(32)*. This is further support for the American College of Obstetricians and Gynecologists' position that asthma medications be continued during pregnancy for the well-being of mother and fetus *(9)*.

ASTHMA MANAGEMENT DURING PREGNANCY

Successful management of asthma depends on a comprehensive approach. To achieve adequate control of asthma, EPR-3 recommends routine monitoring of asthma control during all prenatal visits, use of albuterol (salbutamol outside of the US) as the preferred SABA when needed; use of ICS, and specifically budesonide, as the preferred long-term controller medication, and use of intranasal corticosteroids to treat concomitant allergic rhinitis, if present *(18)*.

The Expert Panel Report of the Working Group on Asthma and Pregnancy – 2004 Update stressed on four important components of asthma management *(1)*.

1. *Objective monitoring of maternal lung function and fetal well-being as guide to the therapy*: Asthma control should be assessed according to the frequency and severity of symptoms and functional limitation, frequency of rescue inhaler use, history of

Table 3
Assessment of Asthma Control in Pregnant Women

Variable	*Well-controlled asthma*	*Asthma not well-controlled*	*Very poorly controlled asthma*
Frequency of symptoms	≤2 days/week	>2 days/week	Throughout the day
Frequency of nighttime symptoms	≤2 times/months	1–3 times/week	>4 times/week
Use of SABA for symptom control	≤2 days/week	>2 days/week	Several times/day
Interference with normal activity	None	Some limitation	Extremely limited
FEV1 or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/personal best
Exacerbations	0–1 in past 12 months	>2 in past 12 months	>2 in past 12 months
ACT score	20 or more	16–19	15 or less

The frequency and effects of symptoms should be based on patients' recall of the previous 2–4 weeks. The level of control is based on most severe category. Data from National Heart, Lung and Blood institute, National Asthma Education and Prevention Program. Expert panel report 3 Guidelines for the diagnosis and management of asthma 2007 update *(1)*.

SABA short-acting β2 agonist; *FEV1* forced expiratory volume in 1 s; *ACT* asthma control test score.

exacerbations requiring oral corticosteroid therapy, emergency department visits or hospitalizations (Table 3) *(1, 20)*. Patients often underestimate the severity of their asthma symptoms and may have difficulty in recognizing early signs of worsening symptoms of asthma. Asthma symptoms are usually greatest at night and in the morning. Women who are having frequent symptoms should monitor PEFR twice a day: upon awakening and 12 h later. At office visits, spirometry should be the preferred method of assessing asthma control *(20)*. Schatz et al. reported that lower function (FEV1) during pregnancy is associated with an increased incidence of gestational hypertension and prematurity *(33)*. Early ultrasound of the fetus, between 12 and 20 weeks gestation, is recommended to determine the gestational age as accurately as possible and to provide a benchmark against which future fetal growth can be measured. Pregnant asthmatics should have follow-up in the clinic once every 1–2 weeks until asthma is controlled and then monthly throughout pregnancy.

2. *Patient education*: All women should be educated about the interrelationship of asthma and pregnancy and be made aware of complications of poorly controlled asthma. Women should be taught about initial home management of asthma exacerbations according to a treatment plan (Table 4) *(1)*, technique of using an inhaler, adherence to medications and control of environmental triggers. Asthma management during pregnancy is most successful when a woman receives regular care, and follows her treatment plan. A study done by Murphy et al. indicated a significant improvement in asthma self-management skills following the implementation of an educational program *(34)*. Providing information to women on asthma education resources would be very useful. Examples: March of Dimes website www.marchofdimes.com/complications_asthma.html. Providers should inform patients that the outcome is most favorable for the mother and baby when asthma is well-controlled during pregnancy. Also, pregnant

Table 4
Management of Asthma Exacerbation During Pregnancy and Lactation: Home Treatment or Asthma Action Plan[a]

Assess severity

- Measure PEF; value <50% personal best or predicted best suggests severe exacerbation
- Note signs and symptoms: degree of SOB, wheezing, chest tightness, cough correlate imperfectly with severity of exacerbation
- Accessory muscle use and suprasternal retractions suggest severe exacerbation
- Note presence of fetal activity[b]

Initial treatment

- Short-acting β2-agonist: up to three treatments of 2–3 puffs every 20 min by MDI or one nebulizer treatment

Good response	*Incomplete response*	*Poor response*
Mild exacerbation	***Moderate exacerbation***	***Severe exacerbation***
PEF>80% predicted or personal best	PEF 50–80% of predicted or personal best	PEF <50% predicted or personal best
No wheezing or SOB	Persistent wheezing and SOB	Marked wheezing and SOB
Response to short-acting β2-agonist sustained for more than 4 h		
Appropriate fetal activity[a]	Decreased fetal activity[a]	Decreased fetal activity[a]
Treatment	***Treatment***	***Treatment***
May continue inhaled β2-agonist every 3–4 h for 24–48 h	Add oral corticosteroid	Add oral corticosteroid
For patients on ICS, double dose for 7–10 days	Continue short-acting inhaled β2-agonist	Repeat short—acting β2-agonist immediately
Contact clinician for follow-up instructions	Contact clinician urgently (this day) for instruction	If distress is severe and non-responsive, call your clinician immediately and proceed to emergency department; consider calling ambulance or 911

MDI metered dose inhaler; *PEF* peak expiratory flow; *SOB* shortness of breath; *ICS* inhaled corticosteroids.

[a]Data are from the National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report, 2004 update.

[b]Fetal activity is monitored by observing fetal kick counts.

asthmatic women should be informed that it is safer to take asthma medications than it is to have asthma that is not optimally controlled. Women who smoke must be informed of the adverse effects of smoking on the fetus and on asthma control.

3. *Control of environmental triggers and co-morbid conditions of asthma*: Avoiding or controlling asthma triggers can reduce symptoms. Seventy to eighty percent patients with asthma have positive skin tests for common allergens, including animal dander, dust mites, cockroach, pollen and molds for which environmental control measures may be helpful (Table 5) *(1, 20, 25)*. Immunotherapy should not be started during pregnancy *(35)*.

Table 5
Summary of Control Measures for Environmental Factors that can Make Asthma Worse

Allergens

Reduce or eliminate exposure to the allergen(s) patients are sensitive to, including

- **Animal dander**: Remove pets from house; if removal is not acceptable, keep pets out of patient's bedroom and seal or cover with a filter the air duct that leads to the bedroom
- **Dust mites**: Encase pillow and mattress with impermeable coverings; wash sheets and blankets weekly in hot water
- **Cockroaches**: Do not leave food or garbage exposed; use poison baits or traps rather than chemical agents, which can aggravate asthma
- **Pollens and outdoor molds**: Patients should stay indoors especially during the afternoon – with windows closed during the season in which they have problem with outdoor allergens
- **Indoor molds**: Fix all leaks and eliminate water sources associated with mold growth; clean moldy surfaces. Consider reducing indoor humidity to less than 50%

Tobacco smoke

- Advise patients and others in the home who smoke to stop smoking or to smoke outside the home

Indoor/outdoor pollutants and irritants

Discuss the ways to reduce exposure to the following

- Wood burning stoves or fire places
- Unvented stoves or heaters
- Strong odors and sprays such as perfume, talcum powder, hair sprays, paints or new carpet

Vacuum cleaning

- Advise patients to try to get someone else to vacuum once or twice a week. Ask patients to stay out of rooms while they are being vacuumed and for short while afterwards
- If patients do the vacuuming, advise them to use a dust mask, a central cleaner with collecting bag outside the home, or a vacuum cleaner with a HEPA* filter or double layer bag

Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report-2004 update.

**HEPA* high-efficiency particulate air.

If the patient is on maintenance or near-maintenance allergen immunotherapy and not having any adverse reactions to the injections, and having clinical benefit, continuation of immunotherapy is recommended without any further increase in dose. Dose reduction may be considered to further reduce the risk of anaphylaxis. All pregnant asthmatic women should be up to date on influenza and pneumococcal vaccines as respiratory infections are frequent triggers for asthma exacerbation. Live vaccines should be avoided during pregnancy. Non-immunologic triggers that should be avoided include tobacco and marijuana smoke, air pollution, and in some sensitive patients, high levels of sulfites in foods, aspirin or NSAIDs. Beta blockers should be avoided. Patients with exercise-induced asthma should be encouraged to take SABA about 10 min before the exercise. Co-morbid conditions that can potentially cause asthma to flare up such as GERD or allergic rhinitis should be treated appropriately.

4. *Pharmacotherapy*: About half of asthmatic women stop their asthma controller medications during pregnancy; non-adherence is consequently a major cause of worsening asthma symptoms. Medication adherence can be improved by education that highlights

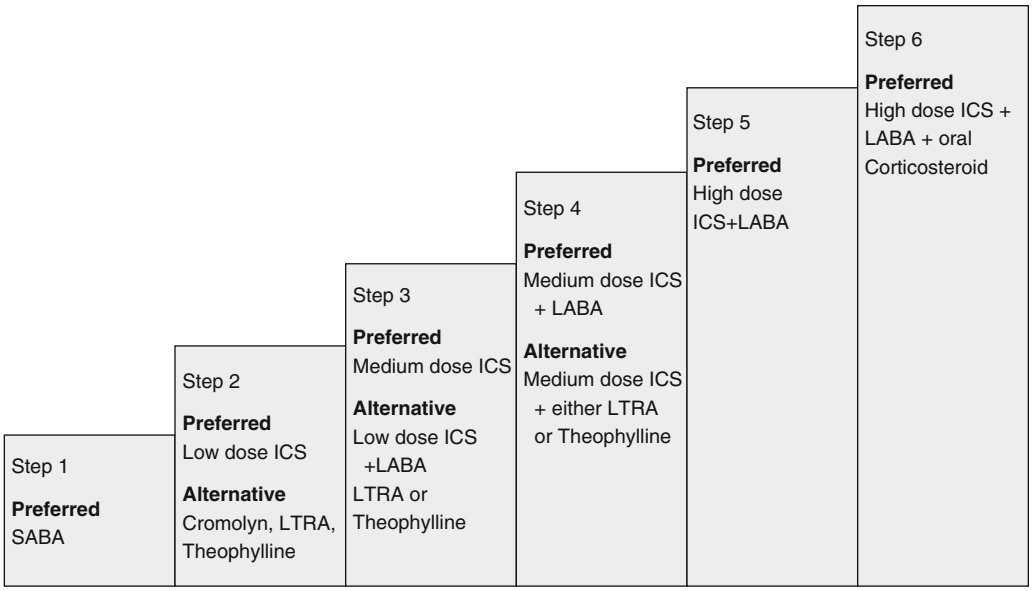

Fig. 1. Stepwise approach for managing asthma in pregnant women *(1)*.

the benefits to fetal and maternal health when asthma control medications are continued. Since the recent data on safety of inhaled corticosteroid during pregnancy is reassuring, health care providers should encourage pregnant women to continue asthma medications throughout pregnancy *(36)*. If asthma is not controlled despite consideration of the non-pharmacological strategies stated above, it is recommended to increase therapy by one step (Fig. 1). A two-step increase and/or a course of oral corticosteroids are recommended for women with very poorly controlled asthma. Most medications used in non-pregnant women can also be used in pregnancy, but there are a few exceptions (Tables 6 and 7). Zileuton should not be used during pregnancy. On step 3 therapy, medium strength ICS (pregnancy category B) are preferred over low-potency ICS + LABA (category C). Studies show that pregnant women with poorly controlled asthma symptoms use more rescue medications and less controller medication. Louik et al. conducted a study on a random sample of 3,609 mothers of non-malformed infants born in Massachusetts between 1998 and 2006. LTRA were used by only 3.4% of asthmatic women; ICS use increased only from 19% during 1997–1999 to 23.3% in 2003–2005 but use of β2-agonists exceeded 50% in both periods. Less than 40% of women with poorly controlled asthma reported the use of controller medications *(37)*, thus there is much room for improvement in pharmacotherapy.

MANAGEMENT OF ASTHMA EXACERBATION DURING PREGNANCY

In addition to preventing maternal and fetal hypoxia, the goals of acute asthma exacerbation treatment in pregnant patients should be the same as in non-pregnant patients *(38)*. Intense fetal and maternal monitoring is recommended. Blood gases should be interpreted with caution. A $pCO_2 > 35$ mmHg and/or a $pO_2 < 70$ mmHg during an acute

Table 6
Pregnancy Categories for Frequently Prescribed and Over the Counter Asthma and Allergy Medications

Agent	*B*	*C*
Bronchodilators	Terbutaline	Albuterol
	Ipratropium bromide	Levalbuterol
		Metaproterenol
		Formoterol
		Epinephrine
		Theophylline
		Tiotropium
Inhaled corticosteroid	Budesonide	Fluticasone
		Flunisolide
		Triamcinolone
		Beclomethasone
		Mometasone
		Ciclesonide
Oral corticosteroids		Methyl prednisolone
		Prednisone
		Prednisolone
		Hydrocortisone
Leukotriene receptor antagonist	Zafirlukast	
	Montelukast	
Leukotriene synthesis inhibitor		Zileuton
Mast cell stabilizer[a]	Cromolyn	
	Nedocromil	
Decongestants		Phenylephrine
		Pseudoephedrine
Antitussives		Dextromethorphan
Nasal steroids	Budesonide	Fluticasone
		Mometasone
		Beclomethasone
		Ciclesonide
		Triamcinolone
Antihistamines	Loratadine	Fexofenadine
	Levocetirizine	Desloratadine
	Cetirizine	
	Chlorpheniramine	
	Diphenhydramine	Hydroxyzine

[a]No longer available in US.

asthma exacerbation represent severe compromise. Maternal oxygen saturation should be kept above 95% if possible for fetal health. Prior to discharge from the ER or hospital, it is advisable to do ambulatory pulse oximetry to make sure pregnant women do not desaturate with their day-to-day activities *(39)*. Blood sugars should be monitored closely in pregnant women receiving systemic corticosteroids because of the significant effects of hyperglycemia on the fetus.

Table 7
US Food and Drug Administration Pregnancy Category for Fetal Risk*

A = No risk based on human studies; remote risk not ruled out.
B = Animal studies indicate no risk to fetus but no human studies available; or, animal studies indicate adverse effect but human studies do not show risk.
C = Animal studies indicate risk and no human studies available, or no animal or human studies available, but benefits justify possible risks.
D = Evidence of risk to human fetus, but may have benefits in certain situations.
X = Evidence of fetal risk in animal or human studies and risk outweighs benefit; use is contraindicated.

*Code of Federal Regulations, Title 21, volume 4. Revised as of April 1, 2010.

OBSTETRICAL CARE

Women with asthma that is not well controlled may benefit from increased fetal surveillance. During labor and delivery, only 10–20% of asthmatic women have symptoms *(40)*.Women who required systemic corticosteroids in the past year may need stress-dose corticosteroid during this period, for example, 100 mg hydrocortisone IV every 8 h during labor and delivery and for 24 h post-partum. Clinicians should try to maintain adequate hydration. If preterm labor occurs, tocolytic therapy may be considered. Magnesium sulfate and terbutaline are preferred because of their bronchodilatory effects, but indomethacin may induce bronchospasm, especially in aspirin sensitive patients, and thus should be avoided. Dinoprost, ergotamine and other ergot derivatives may cause bronchospasm, especially when used in combination with general anesthesia and should be avoided in asthmatic patients during delivery *(39)*. Oxytocin is the drug of choice for induction of labor and control of post-partum hemorrhage *(10)*. If prostaglandin treatment is needed, E1 or E2 can be used. Narcotics (besides fentanyl) release histamine and may worsen bronchospasm. Analgesia should be maintained during labor and delivery as pain is associated with asthma exacerbations; analgesia should not compromise patient's respiratory status *(20)*. Lumbar epidural analgesia is preferred for pain control. If a Cesarean section is needed, preanesthetic atropine and glycopyrrolate may augment bronchodilation and ketamine is a preferred anesthetic agent *(1)*. During pregnancy, reduced FRC and increased O_2 consumption may lower O_2 reserve. This can cause a precipitous drop in the PaO_2 due to apnea at the time of intubation. Preoxygenation of pregnant women with 100% oxygen is helpful before intubation and cricoid pressure must be maintained to prevent gastric content aspiration.

In most of women, asthma reverts back to the pre-pregnancy level of severity within 3 months after delivery *(30)*. The NAEPP reports no contraindication for the use of prednisone, theophylline, antihistamines, ICS or inhaled β2-agonists during breast feeding *(1)*. Patients should be encouraged to continue their asthma medications during the post-partum.

INFLUENZA INFECTION DURING PREGNANCY

Pandemic novel influenza A (H1N1) infection is a substantial threat to pregnant women. Miller et al. *(41)* conducted an observational study on 18 pregnant women who were admitted to the hospital with the diagnosis of H1N1 from 18 May to 24 June 2009. Demographically, 11% were health care workers, 83% were black, 11% were Hispanics and 6% were white. Half of the pregnant women presented with gastrointestinal or abdominal complaints, and 72% met the criteria for sepsis. The most common co-morbid conditions were asthma, diabetes, sickle cell disease, smoking and obesity *(41–43)*. Admitted pregnant women with H1N1 were found to be at increased risk for fetal distress, premature birth, emergency Cesarean section and fetal death. A reverse transcriptase polymerase chain reaction detection assay was reported superior to the antigen-based rapid test for diagnosis *(44)*. Antiviral treatment with oseltamivir within 2 days of symptom onset was associated with an 84% reduction in the odds of admission to an intensive care unit *(41, 45)*. In future pandemics, efforts should be made to ensure vaccinations and antiviral drugs are promptly provided to pregnant women, especially in primary care settings. Special efforts to educate asthmatic women of childbearing age on the importance of annual influenza vaccination are recommended.

TOBACCO SMOKING IN THE PREGNANT ASTHMATIC

Smoking during pregnancy is a significant risk factor for poor perinatal outcome, including low birth weights, premature birth and infant mortality *(46)*. In a large study of pregnant asthmatics, Newman et al. found that active smokers had significantly more days with asthma symptoms as well as small for gestational age infants and lower mean birth weight compared to non-smokers and those with passive smoke exposure *(47)*. During pregnancy, many women will be highly motivated to quit smoking and will be receptive to targeted interventions that will help them achieve success. The U.S. Preventive Services Task Force (USPSTF) recommends asking all pregnant women during prenatal visits about tobacco use and providing augmented, pregnancy-tailored counseling for those who smoke *(48)*. The USPSTF has concluded that the use of nicotine replacement products or other pharmaceuticals for smoking cessation aids during pregnancy and lactation have not been sufficiently evaluated to determine their efficacy or safety *(48)*. Unfortunately, within one year of delivery, over half of women who quit smoking will resume the habit.

MATERNAL FACTORS THAT AFFECT THE INCIDENCE OF ASTHMA IN OFFSPRING

1. *Overweight and obesity in the pre-pregnancy period*: A population-based study of children ($N = 1{,}971$) born in U.S. cities in 1998–2000 showed children had a 52% higher risk of having an asthma diagnosis by age 3 if their mothers were obese in the pre-pregnancy period *(49)*. A separate study that was done in the Netherlands corroborated these results. This was a prospective birth cohort study of 3,963 children and their mothers with follow-up for 8 years; the study showed that the child's risk of asthma increased with increasing maternal BMI in children with a predisposition for asthma (one parent with allergy or asthma), irrespective of the child's BMI. Maternal obesity (BMI ≥ 30) before pregnancy (vs. normal weight) was more strongly associated

with asthma at 8 years than maternal moderate overweight (BMI >25 and <30) (vs. normal weight). The author postulated this increased incidence of asthma could be from increased inflammation in obese/overweight women resulting in an intergenerational linkage of obesity and asthma. These findings stress the importance of counseling patients to reach and maintain an ideal body weight in the preconception period.

2. *Control and severity of asthma during pregnancy*: Martel et al. conducted a cohort study on 8,226 children of asthmatic mothers and found that compared with children of mild, well-controlled asthmatic mothers, children whose mothers had moderate-to-severe, uncontrolled asthma during pregnancy had an increased incidence of asthma *(50)*.
3. *Maternal diet and childhood asthma*: There is interest in more complete characterization of environmental influences on the development of childhood asthma, including maternal diet, however, there is no data yet of sufficient strength to change current practice. Willers et al. conducted a study of 4,146 pregnant women (1,327 atopic and 2,819 non-atopic) and followed their children over 8 years. The study showed no associations between maternal vegetable, fish, egg, milk or milk products consumption during pregnancy and childhood asthma symptoms until age of 8, except tree nuts and peanuts or their products. The study indicated an increased risk of asthma in children with maternal daily consumption of nut products during pregnancy *(51)*. A major limitation of the study was that the questionnaire did not have information on specific foods or portion sizes.
4. *Tobacco smoking*: Karmaus et al. assessed the joint effect of a risk triad involving recurrent lower respiratory tract infections (RLRTI), maternal smoking during pregnancy and breast feeding for less than 3 months. This study showed a stronger association of above triad with asthma at ages 4 and 10 compared to other risk triads (like maternal smoking, breast feeding less than 3 months but no RLRTI) (RR was 3.1). The authors concluded that a proportion of asthma cases in childhood can be prevented by avoiding smoking during pregnancy, promoting breast feeding and avoidance of RLRTI in early childhood *(52)*. Midodzi et al. looked at risk factors for the development of asthma in preschool children (2–5 years).The study reported maternal smoking during pregnancy, male sex, single parent, low birth weight, childhood allergies, parental atopy and low socio economic status as independent risk factors for development of childhood asthma. The hazard ratio for maternal smoking (more than five cigarettes a day) was 1.34. Protective factors including breast feeding more than 3 months, frequent upper respiratory infection, older siblings, early day care attendance and living in rural areas *(53)*.
5. *Maternal anxiety*: Symptoms of maternal anxiety as an indicator of stress during fetal life may increase the risk of asthma in childhood. Cookson et al. conducted a longitudinal study on 5,810 children *(54)*. They found a higher likelihood of asthma at age 7.5 years (odds ratio, 1.64; 95% CI, 1.25–2.17) in children of mothers in the highest compared with lowest quartile of anxiety scores at 32 weeks of gestation *(54)*.

CONCLUSION

Asthma is a common morbidity during pregnancy but can be well-controlled in most cases. The consequences of poorly-controlled asthma are potentially severe and devastating. Increased awareness of the critical importance of asthma control by physicians who care for women of child-bearing age may improve outcomes, primarily through patient education as to the importance of medication adherence, keeping in mind that

about half of women deliberately stop their asthma medications in pregnancy. The management of asthma during pregnancy should be based upon objective assessment, trigger avoidance, patient education and step therapy. Poorly-controlled controlled asthma is a greater risk to the fetus than asthma medications *(1)*. It is recommended that pregnant asthmatics have follow-up every 1–2 weeks until asthma control is achieved and then, at least every month throughout the pregnancy *(20)*. All asthma medications should be continued during pregnancy and lactation.

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10 Exercise-Induced Asthma

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Contents

KEY POINTS

- Exercise-induced asthma (EIA) occurs in 90% of individuals with asthma.
- Exercise-induced bronchospasm (EIB) occurs in up to 29% of non-asthmatics.
- EIA/EIB may occur in up to 76% of athletes depending on the sport and the diagnostic criteria used.
- EIA/EIB may present with classic asthma symptoms, however, children may have atypical symptoms.
- The symptoms of EIA usually peak at 8–15 min after cessation of exercise.
- There is a late asthmatic phase seen in 30–89% of patients approximately 3–8 h after exercise.
- EIB may be an asymptomatic and diagnosed only by exercise/challenge testing with lung function measurements.
- The pathogenesis of EIA/EIB is complex and may involve environmental conditions and exposures and inflammation.

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- Management includes nonpharmacologic measures as well as use of β-agonists, leukotriene inhibitors, inhaled corticosteroids, cromolyn sodium, nedocromil, and ipratropium.
- Athletes wishing to use medications during competition should undergo a medical evaluation, and they may need to apply for therapeutic use exemption if medications are prescribed. Athletes should refer to the World Anti-doping Agency website for specific guidelines.

INTRODUCTION

Exercise is one of the most common triggers of asthma in both children and adults. However, there are two considerations that make it especially important in children. The first is that children and adolescents are frequently involved in competitive sports. Soccer, basketball, track, figure skating, swimming, and cycling are some of the activities that involve a significant aerobic component, leading to attainment of near maximum heart rates, which is associated with a higher probability for exercise-induced asthma (EIA) to occur. Other sports may be less commonly associated with EIA or exercise-induced bronchospasm (EIB) (Table 1). Secondly, in view of the increasing problem of childhood obesity, thought to be secondary to both diet and a lack of physical activity in modern society, the medical profession has embarked on a path to encourage physical fitness in children. This is, of course, a necessary step to curb the progressive increase in the incidence of childhood obesity, but it also means that we must find a way for those children with EIA to engage in physical activity. Interestingly, obesity itself is associated with asthma, which then discourages patients from engaging in physical activity, creating a vicious cycle. The solution to this serious problem is not insurmountable, and with control of EIA, obesity can also be tackled effectively, leading to improvements in both diseases.

Table 1

High-risk sports for EIA/EIB (high-endurance sports)
Basketball
Boxing
Cycling
Running (track)
Soccer
Swimming
Winter sports (due to cold air exposure)
Sports that are probably have low asthmogenic potential[a]
Athletic field events
Baseball
Bowling
Golf
Softball
Tennis

[a]There are no data, but recommendation is based on the low-endurance and/or low-exposure nature of these activities (indoors or non-aerobic).

Although the previous discussion emphasizes the importance of EIA in children, one should not discount its role in adults as well. The benefits of an exercise program that begins in childhood should indeed be carried through to adulthood, and this means that EIA in adults must be controlled to the point that these individuals can exercise as well. This chapter focuses on the definition, diagnosis, and management of patients with EIA and provides an optimistic viewpoint that all children and adults with EIA should, with complete control of their EIA or EIB, be able to live a life free of restriction from any limitation of activity. In short, their quality of life should be equivalent to those individuals without EIA. After all, achieving optimal quality of life is one of the main goals of treatment of asthma.

DEFINITION OF EIA AND EIB

The terms "exercise-induced asthma" and "exercise-induced bronchospasm" are often used interchangeably and for general purposes represent the same clinical entity. EIA represents transient airway obstruction in a known asthmatic when associated with strenuous exercise, which is defined by stringent heart rate or ventilatory parameters, performed over 5–10 min. The degree of observable airway obstruction is usually defined using spirometric measurements, particularly FEV1. EIB is essentially the same condition but also includes non-asthmatics.

These definitions have been validated by the European Respiratory Society (ERS), European Academy of Allergy and Clinical Immunology (EAACI) and the Global Allergy and Asthma European Network (GA²LEN) in their Practical Allergology (PRACTALL) report *(1)*.

EPIDEMIOLOGICAL FEATURES

Exercise-induced bronchoconstriction or bronchospasm is common in asthmatics, but as mentioned above, may also occur in non-asthmatics. It is estimated that 12% of the pediatric population has exercised-induced bronchospasm. Thirty percent of children who demonstrate wheezing during exercise will go on to develop asthma as adults. Among school-age children, the incidence of EIB could be as high as 23%, and a significant portion of these patients do not carry asthma as a diagnosis. EIA and EIB can have its initial presentation in adulthood as well.

EIA occurs in 90% of asthmatics and in 29% of non-asthmatics. In athletes, studies have shown an incidence that ranges from 8% to 79%, depending on the type of activity, environmental venue and the criteria used in making the diagnosis *(2, 3)*. Knopfli and his colleagues prospectively studied triathletes of the Swiss national team and estimated that with high levels of exercise, the relative risk of developing EIB was 195–286 *(4)*.

The epidemiology of EIA and EIB are reviewed in detail in the ERS/EAACI/GA²LEN report, which cites 24 studies outlining the method, condition, study population, disease prevalence, study type, and level of evidence *(5)*. The report notes that the diagnosis of EIA and EIB varies depending on the methodology used. In competitive athletes in various sports, if methacholine alone was used as the diagnostic criteria, the prevalence of EIA/EIB was 49%. If physician diagnosis was used, the prevalence was only 14% and if a combination of methacholine challenge and symptoms were used, the prevalence was 55%.

In figure skaters, the prevelance of EIA/EIB was 55% as determined by rink exercise testing and eucapnic voluntary hyperventilation (EVH). The prevalence in swimmers who were given a questionnaire followed by histamine challenge was 48%.

Another measure of the severity of EIA or EIB is the frequency of use of short-acting β-agonists (SABA). This seemed to depend on the sport and the relative emphasis of the sport on endurance vs. speed/power. The patients who were engaged in endurance sports had a higher β-agonist use. For example, 17.6% of cross-country skiers and 15.3% of cyclers used β-agonists, compared with 4.6% of snowboarders and 4% of track and field participants. Landeau and associates performed methacholine challenge testing on Canadian high-level athletes participating in four different environmental conditions – dry air, cold air, humid air, and mixed air. Humid air environments led to a higher incidence of positive methacholine challenge tests (76%) than cold air (52%), followed by dry air and mixed air (both 32%).

CLINICAL FEATURES

Clinical manifestations of EIA/EIB include cough, wheezing, shortness of breath, chest tightness, fatigue, or abdominal pain *(6)*. Other associated symptoms or signs include side-aches, fatigue, and dizziness. Lack of symptoms does not rule out EIA/EIB, as evidence of airway obstruction can frequently occur in asymptomatic individuals. Symptoms of EIA/EIB may begin 6–8 min after the start of exercise, typically peaking at 5–15 min after stopping *(7)*. Symptoms may spontaneously abate. However, some athletes may require treatment. Death has been reported with EIA, particularly in younger athletes *(8)*. Thus, the prevention of attacks of bronchospasm is critical.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Not all athletes who have symptoms of bronchospasm have asthma. The differential diagnosis includes gastroesophageal reflux, panic attacks, arrhythmia, pulmonary shunts, cardiac shunts, and a group of conditions known as exercise-induced laryngeal dysfunction (EILD), which includes vocal cord dysfunction (VCD), laryngeal prolapse and exercise-induced laryngomalacia (Table 2) *(9)*. The evaluation of athletes thought to have EIA/EIB may include pulmonary function testing with diffusion capacity, radiographic imaging, echocardiogram, and referral to an asthma specialist, depending on the clinical presentation. A diagnostic algorithm for the diagnosis of EIA/EIB is shown in Fig. 1. Other algorithms are available to help the clinician distinguish EIA/EIB from other causes of exercise-related respiratory disease *(10)*.

The “gold-standard” for the diagnosis of EIA/EIB is an exercise challenge test. The laboratory definition of EIA/EIB is a drop in FEV1 at any time after exercise. The extent of the drop required to make the diagnosis of EIA/EIB is still controversial, with 10, 12, and 15% all being used in various protocols. The degree of exercise that should be performed in an exercise challenge test depends on the protocol, but it is generally agreed that about 85% of maximum heart rate must be achieved for a duration of at least 5 min. In practice, there has been considerable variation in the procedure for conducting exercise challenge tests, leading to recommendations that a standardized protocol must be established, which will set guidelines on the use of equipment, e.g., treadmills, and

Table 2
Differential Diagnosis of EIA or EIB

1. Exercise-induced laryngeal dysfunction (EILD)
   a. Vocal cord dysfunction
   b. Exercise-induced laryngeal prolapse
   c. Exercise-induced laryngomalacia
2. Swimming-induced pulmonary edema
3. Gastroesophageal reflux (GERD)
4. Exercise-induced hyperventilation
5. Exercise-induced anaphylaxis (EIAna)
6. Food-dependent exercise-induced anaphylaxis (FDEIAna)
7. Panic attacks
8. Cardiac arrhythmias
9. Cardiac shunts (atrial septal defects (ASD))
10. Idiopathic arterial hypoxemia of exercise
11. Underlying chronic lung diseases
    a. Cystic fibrosis
12. Mitochondrial defects
13. Poor physical fitness

testing algorithms *(11)*. A typical exercise challenge test protocol is outlined in the Chap. 5.

From a practical standpoint, in cases where a treadmill is not available, some physicians have used free running for 1 mile in an outdoor environment as a test for EIA/EIB. Using this method, Kukafka et al. found a substantial number of recognized patients with EIB among varsity athletes *(12)*. They also noted that an association between EIB and a history of wheezing as well as residing in a poverty-stricken area. Thus, they suggested that active screening for EIB may be indicated to identify at risk individuals.

EVH is a method of diagnosing EIA/EIB. The laboratory protocol of EVH involves having athletes inhale dry air containing 5% carbon dioxide at 19°C for 6 min at a target ventilation equivalent to 30 times baseline FEV1. In a study by Rundell et al. comparing this protocol with exercise, 38 athletes engaged in cross-country skiing, ice skating, or running for 6–8 min. AHR was defined as a fall in FEV1 of 10% or more. Of the 38 athletes, 19 were found to have AHR, of whom 58% were identified by exercise and 89% by EVH. The authors concluded that EVH done in a laboratory was a more sensitive test to identify AHR in cold weather elite athletes than field exercise in cold weather *(13)*.

Swimming-induced pulmonary edema (SIPE) presents as a cough or wheezing and develops immediately after swimming *(14)*. Other symptoms and signs include shortness of breath, hemoptysis, sputum production, and poor oxygen saturation. Pulmonary function tests reveal a restrictive pattern, and there is evidence of pulmonary edema. The spirometric changes can persist for up to a week.

Exercise-induced arterial hypoxemia is a result of a diffusion defect leading to a ventilation–perfusion mismatch. It is thought that this occurs when capillary perfusion

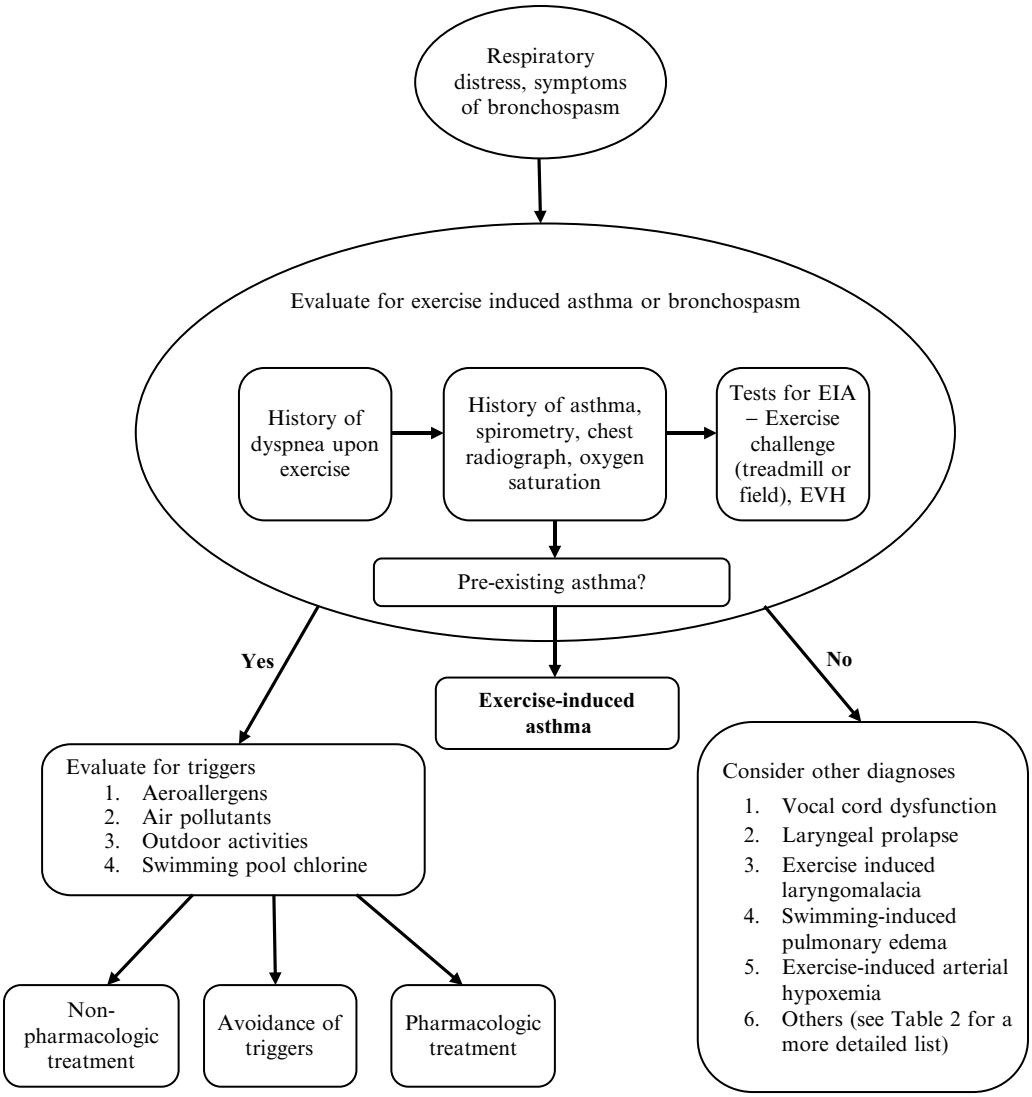

Fig. 1. An algorithm for the diagnosis of exercise-induced asthma or bronchospasm.

rates of red blood cells exceeds the capacity for diffusion of gases as the time spent by the red blood cells in the capillary–alveolar interface decreases. This may occur in up to 50% of highly trained athletes who are able to improve their cardiovascular capacity to levels that exceed ventilatory requirements, hence the mismatch *(15)*.

Poor physical fitness may be a possible differential diagnosis for EIA in those patients with high expectations of themselves, and who may engage in overtraining. There may be a significant psychological component as well, but it is important to be able to distinguish this from EIA, as the approach to treatment are very different, and misdiagnosis can lead to serious adverse effects.

VOCAL CORD DYSFUNCTION

The condition of respiratory distress secondary to VCD deserves a special mention because of its predominance in young teenaged girls and young women who are high achievers. VCD is the most notable member of a group of conditions collectively known as EILD. Other members of this group include laryngeal prolapse and exercise-induced laryngomalacia. The clinical manifestation of EILD is one of inspiratory stridor with tightness in the throat, but young female adults and teenagers frequently have difficulty verbalizing their symptoms. The symptoms resolve more quickly than EIA/EIB, but often times the correct diagnosis is delayed until multiple courses of asthma medications have been tried. Diagnostic techniques include spirometry, the classic finding being a flattening of the inspiratory limb of the flow–volume loop so that the FIF50/FEF50 ratio is less than 1.0, while the patient is symptomatic. Another test for VCD is rhinolaryngoscopy, and if this can be done during an acute episode, the paradoxical movement of the vocal cords can be directly visualized, thus making the diagnosis. It should be noted that because EIA/EIB is so common, both these conditions can exist simultaneously.

PATHOGENESIS

Air Temperature

One of the first studied etiologies of EIA was the cooling and re-warming of the airways that occurred with high minute ventilation during exercise *(16)*. With the high ventilation rates associated with higher oxygen requirements during vigorous exercise, and the increased role of mouth breathing, the warming and humidification function of the upper airways is inadequate or bypassed. Cold and dry air can cause changes in osmolality in the airway epithelium, which leads to an inflammatory state *(5, 6)* that involves the release of proinflammatory cytokines or mediators, including chemokines, histamine, or leukotrienes. The cold air can also stimulate cholinergic receptors, which may lead to an added bronchoconstrictive effect. In addition, the cold air also leads to pulmonary vasoconstriction, which triggers a reactive hyperemia upon re-warming. At the same time the pulmonary vasoconstriction subsides and this results in edema, vascular bronchial congestion, and bronchoconstriction *(17)*.

The Role of Inflammatory Mediators

Recruitment of inflammatory cells to the airway has been shown to occur in EIA/EIB. Interestingly, in asthmatics with EIA, there is primarily an eosinophilic response, but EIB patients appear to have more of a neutrophilic response. In EIA, eosinophils, eosinophilic cationic protein, neutrophils, myeloperoxidase, cystinyl leukotrienes/phospholipase A2 have all been shown to play a role in the pathogenesis. In addition, lipoxin A4 *(18)*, endothelin-1 *(19)*, adenosine *(20)*, T cells *(21)*, and nitric oxide *(22)* are also felt to play a role.

It is believed that leukotrienes may play a significant role in the pathogenesis of EIA/EIB. In guinea pigs, hyperpnea-induced bronchoconstriction was reduced by 50–90% by inhibition of the leukotriene pathway *(23)*. A guinea pig model for hyperpnea-induced bronchoconstriction was used to demonstrate that calcitonin gene-related

peptide (CGRP) can modulate leukotriene D4-induced airway hyperresponsiveness. CGRP inhibits release of leukotrienes LTC4 and LTD4 from platelet activating factor stimulated rat lungs and ionophore-stimulated guinea pig lungs *(24)*. Cellular changes occur in the blood early in EIB, including the appearance of CR1, the C3b receptor on neutrophils. The involvement of neutrophils in EIA/EIB suggests a role of neutrophilic chemotactic factors. LTB4 is one neutrophilic chemotactic factor released during mast cell activation which can help explain the neutrophilic inflammation seen in EIA/EIB *(25, 26)*.

There may also be a role for T cells. An increase in the number of CD25+ T cells (Th2) and CD23+ B cells *(27)* in the peripheral blood was observed to occur during EIB. Th2 cells lead to the activation of cytokines IL-3, IL-4, and IL-5, as well as granulocyte-macrophage stimulating factor (GM-CSF). With increases in IL-4, an important cytokine in the class switching of B cells to produce IgE, mast cell activation occurs and is accompanied by the release of mediators of allergic inflammation. IL-5 can at the same time stimulate eosinophil differentiation and recruitment, also resulting in allergic inflammation in the airway. The prominent role of leukotriene activity on the inflammatory state of the airway during EIA/EIB may explain why leukotriene pathway modifiers have been found to be efficacious in the treatment of EIA/EIB.

More recently, there has been evidence for a role in airway vascular remodeling mediated by vascular endothelial growth factor (VEGF) in the pathogenesis of asthma, and also EIA/EIB. It is postulated that VEGF causes increased microvascular permeability and edema in the airway of patients with asthma *(28)*. Cysteinyl leukotrienes have been demonstrated to induce VEGF production in human bronchial smooth muscle cells and monocytes *(29)*. The same appears to be true in exercise-induced asthma. Another potential pathophysiologic mechanism involves the gel-forming mucin MUC5AC. Expression of MUC5AC is increased following exercise challenge and is associated with EIA/EIB *(30)*. The cysteinyl leukotrienes have been found to be potent mucin secretogogues in animal models systems, providing a further link between the leukotriene pathway and the pathogenesis of EIA/EIB.

Multifactorial Approach to the Pathogenesis of EIA

It has been proposed that environmental conditions including temperature and airway osmolality may play a role, along with environmental exposures and physiologic changes, reflecting the multi-factorial nature of the pathogenesis of the disease *(31)*. There may also be a genetic predisposition for some individuals to develop EIA or EIB. The degree to which various pathogenic pathways contribute may be dependent on the type of exercise, the extent of exposure to confounding triggers, and host characteristics. Figure 2 shows the various pathophysiologic pathways in EIA/EIB and their interaction, illustrating the complex matrix of pathologic mechanisms that contribute to the development of the disease.

MANAGEMENT OF THE PATIENT WITH EIA/EIB

Nonpharmacologic Management

Nonpharmacologic management of EIA/EIB is important as it avoids possible pharmacologic adverse reactions. Proper conditioning and modified training techniques may be employed to circumvent EIA/EIB. Measures such as careful warm-up and cool-down

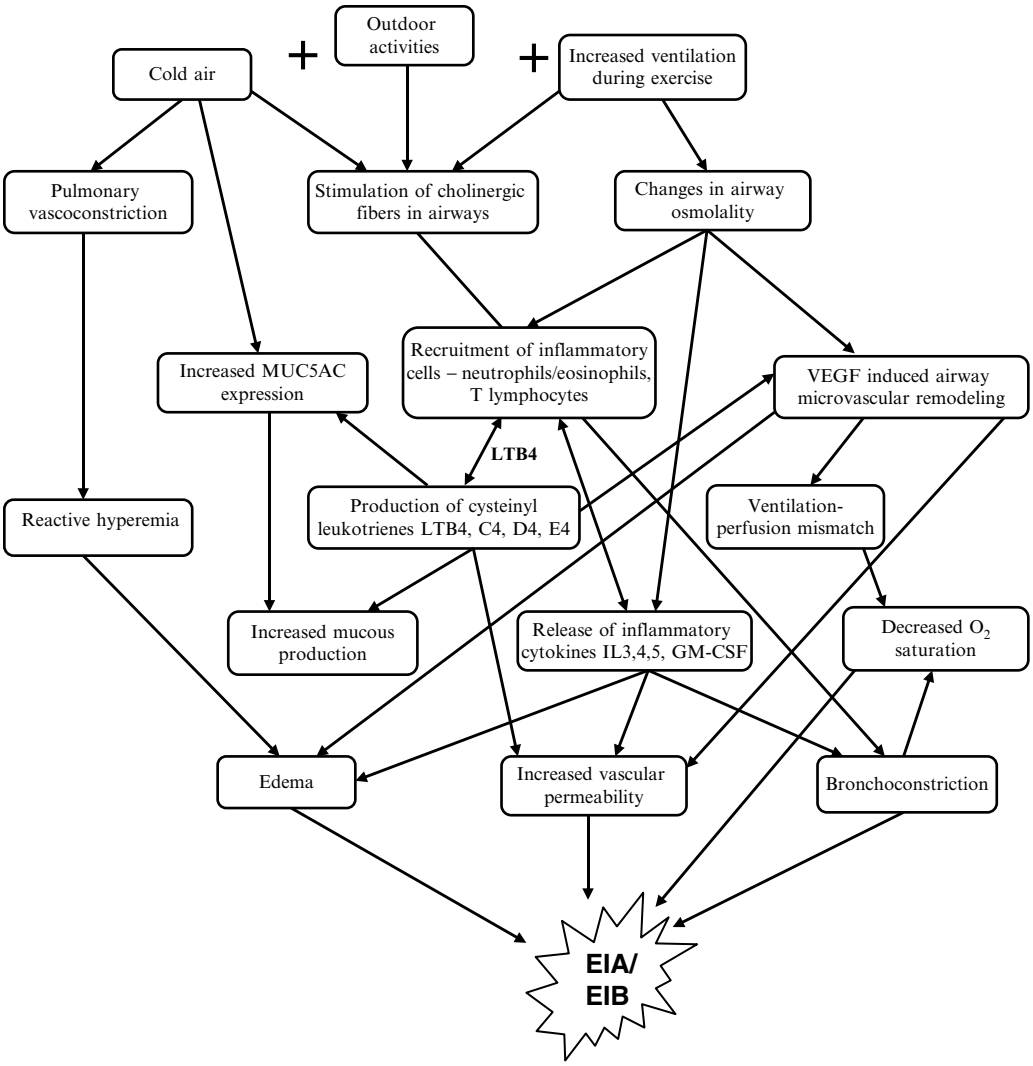

Fig. 2. Pathogenesis of EIA and EIB.

regimens, including stretching exercises and calisthenics, along with nose breathing to allow for proper "air-conditioning," use of a face mask, avoidance of triggering conditions and avoidance of high-risk activities should be utilized, especially in children. A warm-up period of 15 min, in which the heart rate reaches 50–60% of maximum heart rate, has been suggested as a method to reduce manifestations of EIA/EIB. For non-competitive athletes, environmental conditions should be considered and avoidance of triggers such as cold dry air, pollen in those patients who are allergic, avoidance of swimming pools with high chlorine content, and avoidance of days with high pollution indices. It is also important to realize that in addition to a warm-up period, there should be a pre-defined cool-down period of about 10–15 min to prevent rapid re-warming of the airway epithelium, thereby preventing EIA/EIB. A warm-up and cool-down protocol for the athlete with EIA/EIB is illustrated in Fig. 3.

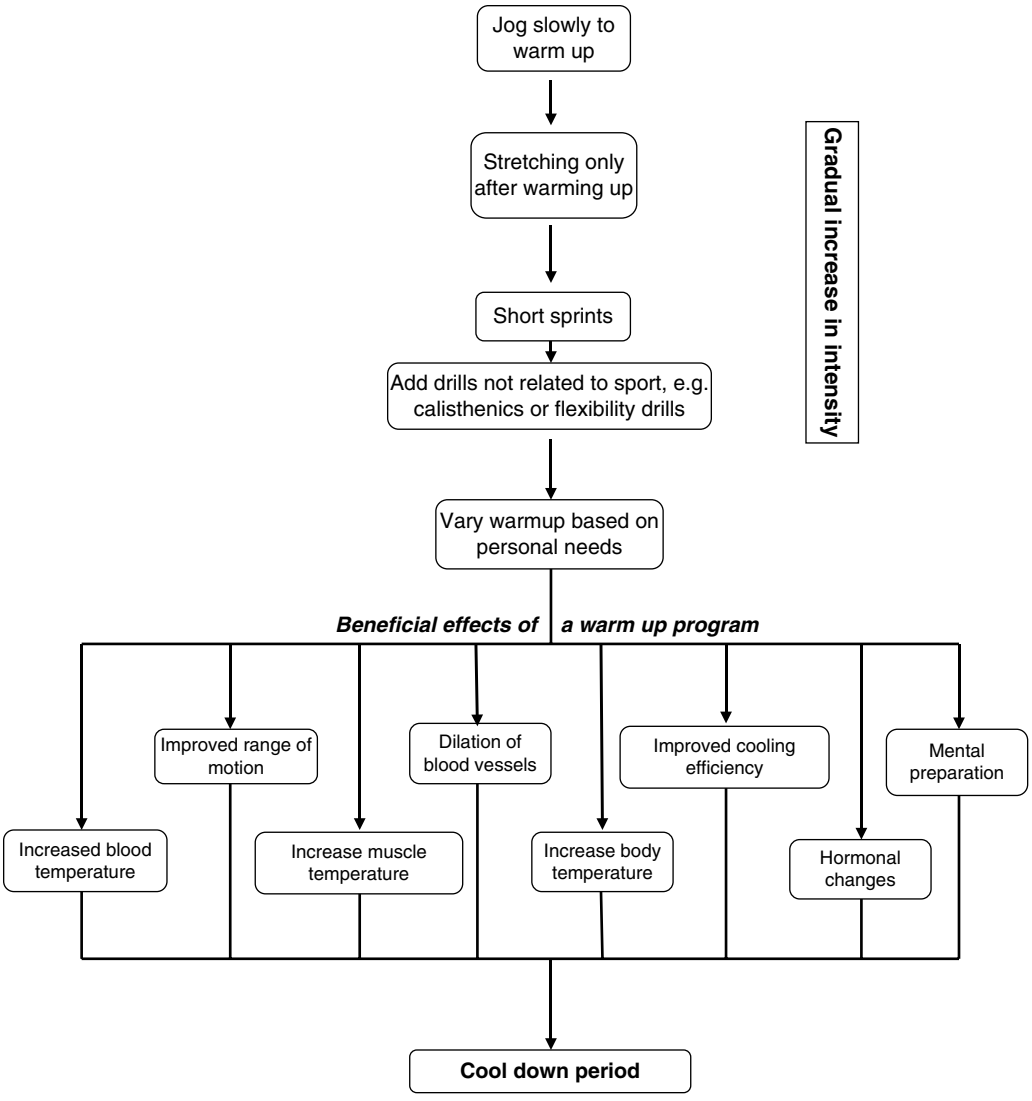

Fig. 3. A sample warm-up and cool-down routine to minimize occurrences of EIA/EIB.

It is also essential in patients with EIA to ensure that underlying asthma is optimally treated and completely controlled. Those patients with poorly controlled asthma may be symptomatic all the time, and vigorous exercise demands drawing from a respiratory reserve that these patients do not have. In patients with allergies, it is important to determine the allergens that the patient is sensitized to, either by skin testing or by an in vitro specific IgE test, in order that the patient can practice appropriate avoidance measures. Immunotherapy may also be an adjunct treatment in patients with an underlying allergy, and may perhaps allow the patient to decrease their controller medication requirement.

Pharmacologic Management

Drugs that may be effective in the treatment or prevention of EIA/EIB include antihistamines, inhaled short-acting β-agonists, inhaled long-acting β-agonist, leukotriene

pathway inhibitors, inhaled ipratropium, and inhaled corticosteroids. In children, inhaled disodium cromoglycate or nedocromil, with their low adverse side effect profile, may be useful. Formoterol, with its rapid onset of action and long duration of effect may be especially useful in endurance exercises; however, tachyphylaxis has been reported with chronic (twice daily) use. Pharmacologic treatment of EIA/EIB is generally more effective if the medicine is taken prior to a planned exercise, allowing for the time for the medication to take effect.

β-Agonists

Albuterol is the most common SABA used, though levalbuterol is just as effective. Both have a rapid onset of action and a duration of action between 4 and 6 h. The usual dosage is two puffs taken 15 min before the initiation of exercising. Long-acting β-agonists can also be effective. Salmeterol has been used as a single dose to prevent occurrences of EIA/EIB. In a placebo-controlled crossover study, a 50-μg dose in children prevented EIA at 1, 5, and 9 h after dosing. The mean maximal fall in FEV1 in the salmeterol-treated group was 2.7% when exercise challenge was done 1 h after dosing of salmeterol (compared with 24.6% in the placebo group). At 9 h after dosing, the mean maximal fall in FEV1 was 3.4% in the salmeterol-treated group and 26.6% in the placebo group *(32)*. Athletes should note that a tachyphylaxis may develop if SABAs or LABAs are used daily for treatment. It may present in the form of a shortened duration of action or a less effective bronchodilator response. Some individuals may also be poor responders to bronchodilators as a result of a genetic polymorphism. It should also be noted that the FDA has recently issued a recommendation that LABAs not be used as a single agent for asthma due to the unexplained higher mortality in asthmatics taking LABAs. For this reason, it may be argued that LABAs should only be used in combination with inhaled glucocorticoids in the treatment of EIA/EIB.

Cromolyn and Nedocromil

Sodium cromoglycate and nedocromil are relatively safe medications that were frequently used in the treatment of asthma, but have recently fallen out of favor. However, there remains a role in the treatment of EIA/EIB. Both these drugs are mast cell stabilizers. Premedication with either of these drugs 15 min before exercise has a protective effect over EIA/EIB. The protective effect usually lasts less than 2 h in most patients *(33)*. With nebulized cromolyn, the protective effect was found to be dose-dependent within the range of dosing of 2–40 mg *(34)*. This was not observed with nedocromil when administered within its therapeutic range of 0.5–20 mg.

Inhaled Corticosteroids

Inhaled corticosteroids are the first-line therapy for the treatment of persistent asthma. Since EIA/EIB have been associated with inflammatory changes, it would be logical to assume that corticosteroids may play a role in the treatment of EIA/EIB as well. Obviously, those patients with underlying asthma would probably already be on inhaled corticosteroids, but in some cases of non-asthma related EIB, inhaled corticosteroids may still be prescribed for its protective effect. Inhaled glucocorticoids have been shown to significantly improve EIA/EIB after 1 week of use, but the maximal effect occurs after 3–4 weeks or longer of continued use. The effects of inhaled glucocorticoids in the elite athlete group have been less convincing, although no large-scale studies are available.

Inhaled Ipratropium

Studies on the effects of ipratropium in EIA/EIB have been inconsistent. Ipratropium appears to provide an additive effect when added to an inhaled short-acting β-agonist.

Montelukast

Because of the probable involvement of the leukotriene pathway in the pathogenesis of EIA/EIB, leukotriene receptor antagonists and inhibitors of leukotriene synthesis have been extensively studied as therapeutic agents. Zafirlukast, a selective LTD4-receptor antagonist administered in a single dose ranging from 5 to 40 mg prior to exercise, reduced the maximum mean fall of FEV1 after exercise to 8.7–11%, when compared with placebo at 16.3–17.1% *(35)*. The duration of action was observed to persist up to 4 h. In a 12-week placebo-controlled study using 10 mg of montelukast, there was significant improvement in EIA/EIB compared with placebo, and no tachyphylaxis was observed *(36)*. The same results were observed in studies utilizing 2 days *(37)* and 1 week *(38)* of montelukast. The results of montelukast on asthma symptoms in elite athletes has been variable, with some studies showing a protective effect against EIB and lung function reduction when EVH was performed. As in the case with most other drugs, host factors and genetics may play a role in the efficacy of the drug.

Other Medications

Theophylline is much less widely used in the treatment of asthma than it was 20 years ago due to the introduction of newer and safer medications. However, oral theophylline granules administered at least 2 h before exercise has a variable and dose-related bronchodilator effect. A therapeutic serum level of greater than 5 ng/mL is required for efficacy *(39)*. The routine use of theophylline to treat EIA/EIB is not recommended.

Furosemide has been shown to significantly inhibit bornchoconstriction in EIA/EIB patients. At a dose of 20 mg/m^2 body surface area, inhaled furosemide prevents EIA without increasing diuresis *(40)*. Furosemide may generate its effect through its action on post-ganglionic cholinergic fibers or by acting as a mast cell stabilizer as in the case of sodium cromoglycate. It may also increase production of prostaglandin E2 in the airways, which has a protective effect in patients with asthma *(40)*.

Vitamins (C and D) and Supplements

Other medications have also been studied in the treatment of EIA/EIB. Vitamin D has been postulated to inhibit the influx of proinflammatory cytokines into the lung and also to stimulate production of IL-10 *(41)*. Low vitamin D levels have been associated with increased airway reactivity with exercise *(42)*. However, the effect of supplementation with Vitamin D is not yet known. A small double-blind crossover study of eight patients with confirmed EIA/EIB was conducted to study the effects of Vitamin C (ascorbic acid) on pulmonary function. The patients received either ascorbic acid or placebo for 2 weeks, entered a washout period of 1 week, and then crossed over to the other arm. Pulmonary function before and after exercise challenge, symptom scores, fractional exhaled nitric oxide (FeNO), the urinary leukotrienes LTC4-LTE4, and 9a,11b-prostaglandin (PGF2) were evaluated at the beginning of the study and then at the end of each treatment arm. When the patients had received ascorbic acid, they were found to have improved asthma symptom scores, and reduced post-exercise FeNO, LTC4-LTE4, and

Table 3
Pharmacologic Agents to Treat EIA/EIB

Drug class	*Drug name*	*Dosage*	*Tachyphylaxis*	*Use in competition (http://www.wada-ama.org/)*	*Comments*
Inhaled corticosteroids	Fluticasone dipropionate Budesonide Mometasone furoate Beclomethasone	Variable (refer to package insert from corresponding manufacturers)	No	Not prohibited	Glucocorticoids are prohibited during competition when administered via oral, intramuscular, rectal, and intravenous routes A declaration of use must be made for inhalation route
Leukotriene pathway modifier	Montelukast Zafirlukast	10 mg po qhs 20 mg po bid	No	Not prohibited	
Cromolyn	Intal	2 puffs qid	No	Not prohibited	
Nedocromil	Tilade	2 puffs bid	No	Not prohibited	
SABA	Albuterol, Levalbuterol	2 puffs before exercise	Yes	All prohibited except albuterol (salbutamol) less than 1,600 μg/day	Blood levels of greater than 1,000 ng/mL are presumed not to be according to intended therapeutic use
LABA	Salmeterol and Formoterol	2 puffs twice a day	Yes	Only salmeterol according to manufacturer's instructions is permitted	

A complete list of prohibited substances by the World Anti-doping Agency (WADA) is available at their website (http://www.wada-ama.org/) and is also available as an iphone app.

9a,11b-prostaglandin levels. More importantly, their maximum fall in post-exercise FEV1 was reduced in the ascorbic acid group compared with the placebo group (6.4 ± 2 vs. 14.3 ± 1.6%, respectively) *(43)*. This was a very small study, but suggests that further larger-scale trials should be conducted.

The treatment of EIA/EIB depends on the circumstance. If the patient has underlying asthma, his/her asthma should be controlled in the normal way according to the most recent asthma guidelines (currently EPR-3), and then medications can be added or adjusted for the exercise-induced component. A summary of medications used to treat EIA/EIB and their restrictions for use in the elite athlete is provided in Table 3.

SPECIAL CONSIDERATIONS FOR MANAGEMENT OF THE COMPETITIVE ATHLETE

An evaluation of a competitive athlete is likely to be more detailed than that of a casual athlete, particularly if therapeutic use exemption (TUE) is anticipated. In the competitive athlete, given the concern of "doping," a more formal evaluation would need to be undertaken. Field exercise challenge, non-field exercise challenge, methacholine/histamine/cyclic AMP challenge, hyperosmolar provocation testing and most recently, EVH testing are recognized by the International Olympic Committee (IOC) and World Anti-Doping Association (WADA). Carlsen et al. have conveniently tabulated pharmacologic management of EIA/EIB, including medication restriction or approval by the IOC or WADA *(44)*. Medication agents prohibited during competition include oral β-agonists and oral corticosteroids. Immunotherapy is permitted in competition. An application for a TUE may be necessary for inhaled β-agonists.

SUMMARY

Exercise-induced asthma or bronchospasm is a common occurrence in both children and adults. It is especially relevant in young athletes who are involved in competitive sports. Proper pharmacologic management will allow athletes with EIA/EIB to compete at any level of exercise. Besides medications, aerobic fitness and good control of preexisting bronchial reactivity can help diminish the effect and intensity of EIA/EIB. The pathogenesis of EIA/EIB is still not completely understood, but probably involves multiple immunologic pathways. As in asthma, the hallmark of EIA/EIB is inflammation of the airways. Leukotrienes seem to play a significant role in the pathogenesis of EIA/EIB and this may explain the apparent success of leukotriene pathway inhibitors to treat this condition. In the elite athlete, medications become an issue because of the potential for banned substances in competition. However, with proper control of their EIA/EIB, it is possible for these patients to compete at any level, whether recreational or world class.

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11 Viral Disease, Air Pollutants, Nanoparticles, and Asthma

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Contents

KEY POINTS

- Viral respiratory tract infections are the most common triggers of significant asthma exacerbations.
- "Upper respiratory tract infections" (URIs) do not just involve the upper respiratory tract.
- Human rhinovirus (HRV), which causes the common cold, is the virus most likely to trigger an asthma exacerbation.
- In contrast to the usual spring and summer temperate zone pollen season, viral infections begin to peak in the fall.
- The number, species, and typical course of viral respiratory tract infections that trigger asthma vary with a person's age.
- Both acute sinusitis and asthma exacerbations are associated with viral respiratory tract infection and therefore antibiotics are rarely needed in uncomplicated cases.
- Sulfur dioxide, nitrogen dioxide, ozone, and particulate matter in air pollution may exacerbate asthma, and patients should be cautioned to stay indoors when levels of these irritants are high.
- Indoor air pollution, especially from tobacco smoke, can be reduced with benefit to the asthma patient.

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INTRODUCTION

Health care providers who treat patients with respiratory disease are often asked by their patients, "What caused my asthma? And what causes my asthma suddenly to become worse?" These questions have always been difficult to answer, and moving directly to a discussion of the management of asthma is a much easier road to take. In recent years, though, enough information has accumulated about the causes of asthma that one can weave a story containing useful advice that may help patients participate in the management of their disease. And there are also recent studies that can provide answers to the questions posed by physicians who have watched in puzzlement as their previously well-controlled asthma patients have spiraled rapidly out of control. This story has been growing increasingly complex, with an ever-expanding cast of players that sometimes creates a tangled web of interactions.

This chapter will look at how viral infections, air pollution, and possibly nanoparticles may act as causal agents of asthma. The concept of causal agent, though, has a variety of different interpretations. In general, agents may act on the respiratory tract to initiate asthma or to exacerbate it. Initiation (or inception or development) of asthma refers to the start of asthma in a patient who was previously entirely free of this problem. An exacerbation (or trigger or precipitating event) means the significant and often sudden worsening of an established chronic asthmatic condition. Avoidance of a proven initiating factor, if possible, could permit the primary prevention of asthma. In contrast, avoidance of triggering events will not halt the disease but only decrease the number of exacerbations in someone who already has chronic illness. In studying and treating asthma, identification of a specific trigger is usually much easier than trying to prove an initiating cause.

VIRAL DISEASE AND ASTHMA

Conceptual Framework for Viewing the Virus–Asthma Interaction

Viruses that affect asthma are acting on a complex and varied phenotype, and therefore the outcome of each infection can be quite varied. A simple linear cause-and-effect relationship between a viral infection and an asthmatic episode usually does not exist. Koch's modified postulates for infection-caused disease are:

- The microorganism must be present in every case of the disease.
- The microorganism must be isolated from a diseased organism and grown in pure culture.
- The cultured microorganism should cause disease when introduced into a healthy organism.
- The microorganism must be recovered from an inoculated, diseased experimental host.

This linear way of looking at viral-induced disease is not comprehensive enough to allow sufficient insight into the relationship between viral illness and asthma. No one viral infection consistently causes asthma in all or even most individuals. Systems biology, though, can provide a conceptual framework for better understanding of the virus–asthma interaction. Systems biology looks at the web of factors in the initial state of the individual patient and then examines how one or more external or internal influences perturb this state *(1)*.

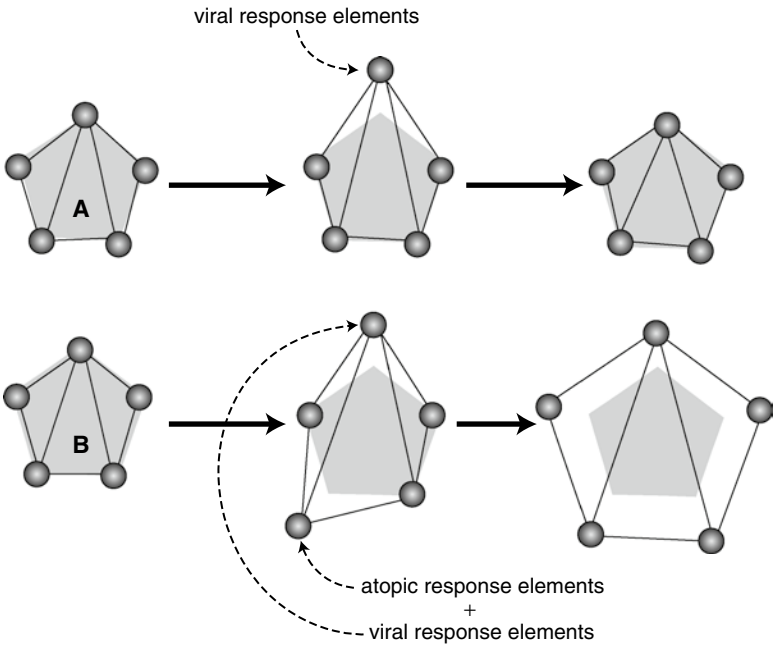

Fig. 1. The system regulating mucosal immune inflammation has many connecting elements. Perturbation of these elements may boost inflammation to a persistently high level.

In Fig. 1, the path taken by system A illustrates how one factor, for example a simple rhinovirus infection, may have very little long-term effect on mucosal inflammation in an individual with no atopic stressors and no genetic propensity toward asthma. This individual will return quickly to equilibrium and a low inflammatory state. The path of system B illustrates how multiple stressors, including genetic factors and atopic immune development, may interact with a viral infection to cause a long lasting or perhaps permanent change in the level of mucosal inflammation. Some details of risk factors will be outlined and discussed in this chapter, but systems biology or systems medicine cannot yet specify each feature of the set of interactions in a way that leads to firm predictions about asthma. Out of the complexity of the systems approach, though, some simple and compact principles do emerge, so that every precondition does not have to be known to predict the outcome of intervention or treatment.

Some general factors that appear to be important in the asthmatic response to viral infection include:

- Age
- Sex
- Genetic inheritance
- Immune status
- Asthma phenotype
- Viral genotype
- Local environmental effect on atopic development

Table 1
Types of Respiratory Viral Infections

Respiratory virus	*Relative frequency of infection*
Human rhinovirus (HRV)	+++
Influenza virus	++
Coronavirus	++
Parainfluenza virus	+
Respiratory syncytial virus (RSV)	+
Adenovirus	+
Metapneumovirus	+
Other viruses	+

Though two-dimensional paper does not allow multidimensional maps, we can walk down a branching path in a narrative fashion to show the interaction of factors important in viral-caused asthma.

Advances in Viral Respiratory Disease

In most of the twentieth century, the office or hospital diagnosis of viral respiratory infection was most often a good guess, a probability statement. Common and more affordable viral molecular diagnostics, especially reverse transcriptase PCR (RT-PCR), and viral culture can now improve the accuracy of the guess when precision is needed. Viruses may be detected in symptomatic or in asymptomatic patients.

Two thirds or more of acute respiratory tract infections (RTIs) occurring in the community can be identified as viral. Traditionally, these have been divided into upper and lower RTI, but the difference between upper and lower infection seems to be more indistinct than previously believed. Human rhinovirus (HRV), for example, replicates initially in the upper respiratory tract yet may cause extensive lower respiratory tract illness. The frequently used term viral upper RTI (URTI) is somewhat of a misnomer.

The most commonly occurring respiratory virus is HRV, which accounts for nearly half of cases of viral respiratory illness, followed by influenza virus and coronavirus, with lesser contributions from parainfluenza virus, respiratory syncytial virus (RSV), adenovirus, metapneumovirus, and other miscellaneous viral species *(2)* (*see* Table 1).

The three main types of viruses that are known to affect asthma are HRV, RSV, and influenza. The peak periods of viral infection tend to vary from year to year, but generally in North America rhinovirus peaks in the fall and early spring, influenza in the early winter, and RSV in midwinter (Fig. 2). Many communities can monitor the progress of these annual epidemics with viral culture and molecular diagnostics, thereby giving physicians a higher probability of knowing in advance what virus a patient may have. A molecular diagnostic panel is commercially available for identifying acute viral respiratory infection, though the cost-effectiveness of this type of testing for routine clinical use is yet to be determined.

More details of the immunobiology of the major asthmogenic viral infection, HRV, have been revealed in the past several years *(3)*. The intercellular adhesion molecule ICAM-1 found on nasal epithelial cells is the attachment point for the majority of serotypes of HRV*(4)*. HRV is divided into clades or strains HRV-A, HRV-B, and HRV-C. HRV-C has proven extremely difficult to culture. There are over 100 different serotypes *(5)*.

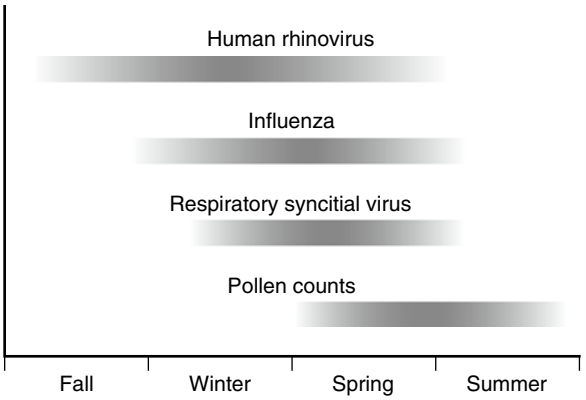

Fig. 2. Respiratory virus peaks compared with pollen counts for a typical year in a Northern California inland valley area. These may vary from year-to-year in this location. Data is compiled from community monitoring.

Age and Virus–Asthma Interactions

Viral species influence asthma in the various age groups in different ways. Age is a marker for the development and maturation of the immune system, which diversifies greatly over time. As the human body ages, the immune system molds itself to the environment to become a mirror image of specific, usually protein, molecules in the external local surroundings. Age also has an important effect on the physics of scaling in the respiratory system. Airway resistance is inversely proportional to the fourth power of diameter, which enlarges with age until young adulthood and then slowly declines. Small increases in airway diameter therefore lead to huge reductions in airway resistance and give more "breathing room."

School-Age Children

Viral Triggers of Asthma

About 80% of significant, prolonged wheezing episodes in children are triggered by respiratory viruses and HRV is most often involved *(3)*. The common rhinovirus cold accounts in large part for the fall seasonal peak of asthma in school-age children. Epidemiologic evidence combined with viral molecular diagnosis has suggested that this peak is a consequence of children returning to the classroom with the subsequent spread of respiratory viruses, mainly rhinoviruses *(6)*.

Viral exacerbations of asthma tend to be prolonged and severe. Triggers such as a gust of pollen-laden breeze may be ameliorated by moving the young patient indoors, and exercise triggers can be removed by stopping the exercise, but a viral trigger is usually steady and persistent and replicates within the body. A study of children aged 6–8 years with asthma concluded that an asthma exacerbation was of a greater severity if a viral infection was present as opposed to a nonviral illness *(7)*. Airway hyperreactivity and a corresponding cough and wheeze may be noted for well over 4 weeks after a rhinovirus infection in the asthmatic child.

Atopy confers additional risk on asthmatic children who become ill with respiratory virus infection *(10)*. School-aged children with atopic asthma, as opposed to those with

nonatopic asthma, have been noted in a number of studies to experience more frequent symptomatic colds, more episodes of viral-triggered asthma, and more prolonged airway hyperreactivity after the colds *(7–9)*. The tendency to have higher numbers of symptomatic RTIs and a longer duration of illness was also noted for allergic children in general, with and without asthma *(9)*. Parents of children with atopy and asthma tend to be frustrated by the prolonged recovery time compared with their nonatopic siblings, and school absences are more problematic.

Treatment and Prevention of Viral-Triggered Wheezing in School-Age Children

Inhaled corticosteroids and leukotriene receptor antagonists (LTRAs) are well known to control the number of wheezing exacerbations in school-age children with chronic persistent asthma, an effect that appears to encompass those episodes caused by viral illness. A survey of school children in Ontario found that children presenting in September to the emergency department for asthma exacerbations, presumably mostly viral triggered, were less likely to have used preventive anti-inflammatory medications than their counterparts who did not have such severe exacerbations *(12)*. A retrospective study suggested that inhaled fluticasone and salmeterol administered prior to and during the fall could reduce the morbidity of the fall viral season in patients with asthma *(13)*. A trial of a montelukast added to usual asthma therapy was able to attenuate the fall asthma peak in one study *(14)* though this effect did not reach statistical significance in a later trial *(15)*. Inhaled corticosteroids might be expected to prevent viral-induced wheezing in children with minimal chronic disease as well. A preventive effect, though, has not been consistently shown in clinical trials. A study conducted in school-aged children without persistent disease but with a history of viral-triggered wheezing demonstrated that inhaled beclomethasone diproponate was not superior to placebo in reducing future episodes. The inhaled steroid failed to reduce days with symptoms, or the frequency, severity, or duration of episodes of upper or lower respiratory illness *(11)*. Preventive medication should therefore be targeted especially to those patients with persistent chronic asthma.

For acute treatment of a viral-provoked asthma exacerbation, oral systemic corticosteroids continue to be the most effective choice *(16)* and are part of the current therapy protocols *(17)*. Use of high-dose acute corticosteroid inhalers continues to be studied with varying success.

Whether vaccination can prevent asthma exacerbations is unclear. The Expert Panel Report concluded that influenza vaccine does not reduce the frequency or severity of asthma exacerbations during the influenza season *(17)*. Many patients in the community with asthma experience severe complications from an influenza infection, so all reasonable means of prevention should still be taken, including vaccination. The influenza virus appears to be a less potent trigger of asthma than HRV, and influenza peaks are not as well correlated with childhood asthma peaks as in the case of HRV.

An oral influenza antiviral (oseltamivir) improved pulmonary function and reduced exacerbation frequency in one randomized, placebo-controlled trial in school-age asthmatic children who had influenza *(18)*. Unfortunately, increasing resistance of the influenza virus to antiviral agents limits their use as a long-term strategy to reduce illness in asthmatic children. The concept of using antivirals to reduce asthma morbidity in children seems theoretically promising.

Infants and Preschool Children 0–4

The preschool years can lay the groundwork for the later asthma issues of the type that have been discussed. Diagnosing viral-triggered asthma in infants and preschool children, though, must be done with caution. Asthma is defined as a chronic disease, and several, or even many, self-limited acute wheezing illnesses do not necessarily add up to a chronic illness. Often children in this age group will experience wheezing in association with a variety of viral infections. Parents are naturally anxious about treatment and prognosis in these children.

Preschool children who experience RSV- and HRV-induced wheezing are more likely to develop asthma in later years. The Childhood Origins of Asthma study (COAST) showed that viral wheezing illnesses in infancy and early childhood caused by HRV were the most significant predictors of the subsequent development of asthma at age 6 *(19)*. A bidirectional causation has been proposed with RSV: severe RSV was associated with a short-term increase in bronchial hyperresponsiveness, and, in turn, the presence of asthma was associated with long-term increased susceptibility for severe RSV disease *(20)*.

Inception of Asthma

Whether early childhood viral infection initiates a series of events that lead to asthma has been an area of much interest and study. One analysis showed that infants reaching 4 months of age at the winter virus peak had a 29% increased risk of developing later asthma compared with those reaching age 1 year at the winter peak *(21)*. If viruses do initiate asthma in some patients, then prevention of RSV or HRV or a similar illness in a critical time period might prevent or reduce the frequency of asthma in later years. Nonatopic infants who had received palivizumab (a humanized MAb against RSV) for prevention of RSV infection showed an 80% reduction in risk of recurrent wheezing from ages 2 to 5 *(22)*, though no effect was noted in atopic children.

The hypothesis that early viral infections lead to asthma is made less convincing by epidemiologic studies showing that frequent exposure to viral RTIs throughout early childhood may actually decrease the risk of later asthma. Studies in the United States and in the United Kingdom have shown that day care attendance and other factors that increase the frequency of viral RTIs reduce the risk of later (after 5–6 years) frequent wheezing *(23, 24)*. One interesting medical editorial on this topic was subtitled with tongue-in-cheek, "Please sneeze on my child" *(25)*. That strategy may not be practical, but clinicians should be able to reassure worried parents that day care exposure does not seem to result in a long-term risk of asthma.

Viral Triggers of Asthma in Preschool Children

While the factors that contribute to the development of asthma are still unclear, there is little doubt that viral infections act as potent triggers of asthma in preschool children. As noted, HRV is the most potent of triggers, though all HRVs do not seem to be alike. Pathogenicity of HRV appears to vary among groups A, B, and C. HRV-C was found in a study of hospitalized preschool children to be associated with asthma more often than HRV-A *(26)*, and HRV-C was noted to be the most frequent type found in patients presenting to the emergency department *(27)*. In contrast, experimental infection with a type of HRV-A resulted in no worse illness in allergic than in nonallergic subjects *(28)*.

Table 2
Classification Systems for Wheezing Preschool Children

Wheezing type (retrospective)	*Trigger type*	*Asthma risk type (Asthma Predictive Index)*
Transient early wheezers • Wheezing in the interval from 0–3 years old, not at 6 years Late-onset wheezers • Wheezing at 6 years but not in the interval from 0 to 3 years old Persistent wheezers • Wheezing in the interval 0–3 years old and at 6 years old Ref. Martinez et al. *(60)*	Episodic, viral-triggered wheeze Multitrigger wheeze Ref. European Respiratory Society *(61)*	High risk • Has recurrent wheezing during 0–3 years old and – Parent with asthma[a] or – Eczema in child[a] Or – 2 of 3: allergic rhinitis,[a] wheezing without colds, eosinophilia Low risk • Wheezing present but – Criteria above not met Ref. Castro-Rodriguez *(30)*

[a] Physician diagnosis.

Knowledge of a circulating virulent HRV strain in the community could put clinicians on the alert for more serious symptoms in their asthmatic patients with colds.

Treatment of Viral-Triggered Wheezing in Infants and Preschool Children

There are several competing classification systems for the wheezing preschool child that aim to help with prognosis and treatment (Table 2). As a conceptual model, one can create two opposing poles. At one pole is the small child who experiences rare mild wheezing with acute viral illness, has no wheezing or cough between episodes, and has no atopy or parental asthma. These children appear to benefit very little or not at all from acute or chronic corticosteroid therapy for viral-triggered wheezing illness *(29)*. At the other pole are children who wheeze daily or weekly, have an atopic history, have a parental history of asthma, and may be on chronic controller therapy. A viral infection in these children appears to be a trigger that requires a step up in asthma therapy, perhaps to a burst of oral corticosteroids. Between these poles of severity are many children whose therapy must be individualized. The criteria from the National Asthma Education and Prevention Program help select preschool children who may benefit from acute and/or chronic corticosteroids. These guidelines use the Asthma Predictive Index *(30)* to specify which wheezy small children have or likely will have chronic asthma and could benefit from various forms of inhaled and oral corticosteroid therapy.

Owing to concerns about oral corticosteroids, other forms of treatment for viral wheezing have been examined in preschool children. A study in 1- to 6-year-old children showed a benefit of episodic high-dose inhaled steroids with viral RTI and wheezing *(31)*, though some adverse effects on growth were noted. The effectiveness

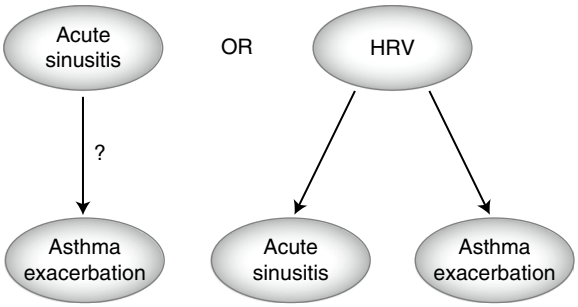

Fig. 3. Diagram illustrating the links between sinusitis, HRV, and asthma.

of a LTRA, montelukast, was examined in a study of 2–5 year olds with a history of intermittent asthma. This study showed a reduction of typically viral-induced asthma exacerbations in children given the LTRA as a daily controller *(32)*. Both inhaled corticosteroids and LTRAs are options to control chronic asthmatic wheezing in this age group *(17)*.

Prolonged or chronic cough after viral RTI may be a problem. Preschool children, whether asthmatic or not, spend a considerable percentage of the year with viral RTI symptoms that are distressing to patient and parent.

Teens and Young Adults

The years from teen through young adulthood tend to be the healthiest years of an individual's life. An expanded antiviral immunologic repertoire helps in reducing the number of annual viral RTIs. While childhood is the time of most frequent viral RTIs, young adults who are exposed to their own small children may have a secondary peak near their 30s.

Acute sinusitis is a common problem in this age group. Sinusitis has been known to precede a worsening of asthma, and episodes of acute sinusitis have often been the occasion for a course of antibiotics. The entity of viral rhinosinusitis, though, is far more common than previously believed. A viral RTI can produce a week or more of purulent discharge and radiographic abnormalities of the sinus cavities on CT scans *(33)*. Most acute sinusitis is not predominantly initiated by bacteria nor, at least in the first week or so, antibiotic-responsive *(34, 35)*. The mechanism by which acute viral sinusitis becomes linked with worsening asthma is generally through the association of both diseases with viral infection (Fig. 3).

The adult group of patients with asthma diverges into several different phenotypes, likely representing various diseases. Asthma is often said to be a syndrome rather than one disease. Different phenotypes may have varying responses to viral infection. A cluster analysis divided asthma patients into five different groups. One group, "benign asthma" seemed to have well-controlled symptoms regardless of triggers, viral or otherwise. Another group that was female preponderant, "obese nonesosinophilic," had minimal atopy or eosinophilic inflammation yet a high level of symptoms in response to typical triggers *(36)*.

Chronic adult diseases of previously unknown cause have occasionally been found, in whole or in part, to have an infectious etiology. These include peptic ulcer disease (*Helicobacter pylori*), polyarteritis nodosa (hepatitis B and C), reactive arthritis (*Shigella* and *Chlamydia*), and Lyme arthritis (*Borrelia burgdorferi*). A survey of asthma patients, of mean age 38, suggested that 45% of initial attacks started after an illness suggestive of a respiratory infection *(37)*. This subset tended to be nonatopic and may represent a distinct phenotype. Viral and nonviral initiating infectious agents have been proposed for adult "infectious asthma," including mycoplasma, chlamydia, adenovirus, and adult RSV, but reasonable proof of an infectious mechanism is still pending.

Regardless of initiating cause, asthma is exacerbated in adults, as in children, by viral respiratory infections. Respiratory virus is found at least 50% of the time in adults with asthma exacerbations, but not as frequently as in childhood acute significant wheezing episodes *(3)*.

Older Adults and the Elderly

Older and elderly adults experience some degree of immune senescence but also have expanded specific antiviral immunity. The types of viral illness that exacerbate asthma are slightly different than in younger years. The peak of ED visits and asthma admissions for adults over 50 tends not to be in the fall but rather from December to January, suggesting a broader range of viral triggers than in the fall rhinovirus peak *(38)*.

The contribution of influenza to excess morbidity in older adults is well known, but less generally appreciated is the contribution of rhinovirus to serious illness. Concomitant heart disease, chronic obstruction pulmonary disease, and hypertension can make viral-exacerbated asthma a more complicated and serious illness in older adults. A rhinovirus outbreak in a nursing home for elderly patients resulted in two thirds of the affected patients having lower respiratory tract symptoms, nearly one-third requiring corticosteroid or bronchodilator therapy, and three individuals having serious morbidity including one death *(39)*. A peak of rhinovirus RTI may be seen in grandparents who care for small children.

Consistently effective treatments for viral-caused respiratory disease have been frustratingly slow to arrive in the modern pharmacopoeia. Despite these obstacles, however, a proactive approach, including vaccination and respiratory hygiene, can improve the care of the patient at risk for viral illness and bronchospasm and avert complications.

AIR POLLUTANTS AND NANOPARTICLES

Air Gases and Particles

Since the time of Albert Einstein, scientists have known to be wary of "spooky action at distance." Particles that affect the respiratory tract must first be dispersed into the air and enter and contact the respiratory tissue to have an effect. These particles vary in size from molecules in the angstrom range (1×10^{-10} m), to so-called nanoparticles ($1–100 \times 10^{-9}$ m), to large pollen grains (50×10^{-6} m), on up to the largest dust particles that can remain suspended in air (about 100×10^{-6} m).

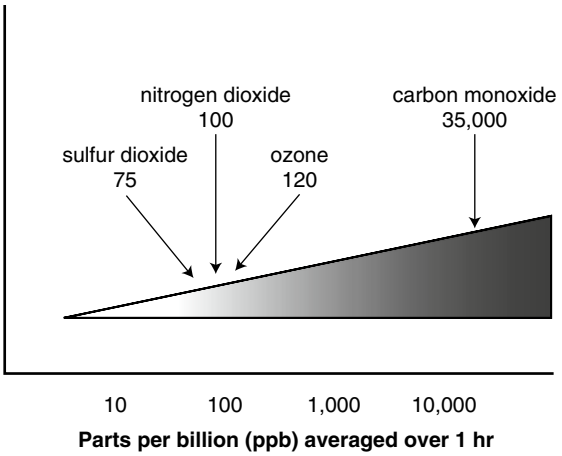

Fig. 4. Exposure limits for gases from the US National Ambient Air Quality Standards for 2010.

Air particles are divided into several common ranges for study purposes:

- *PM10* – particulates of an aerodynamic diameter of less than 10 μm or 10,000 nm
- *Fine particles* of diameters below 2.5 μm or 2,500 nm
- *Ultrafine particles or nanoparticles* of diameters below 0.1 μm or 100 nm

Study of the real-world, clinical effects of the individual components of air pollution is challenging since most or all components tend to be released into the air at about the same time.

Air Pollution Outdoors

Unwanted and/or unhealthy gases and particles make up the components of air pollution. Outdoor air quality issues vary to great extent by specific location and depend on weather and climate, the level of vehicle traffic, and the type of fuel used for energy and manufacture. In the United States, the Office of Air Quality Planning and Standards (OAQPS) has established the National Ambient Air Quality Standard (NAAQS) for each of the several pollutants. Carbon monoxide, lead, nitrogen dioxide (NO_2), ozone, sulfur dioxide (SO_2), and particulate matter in the air have maximum exposure standards (Fig. 4).

Studies of the effect of air pollution on health attempt to use statistical analysis to separate the individual contribution of each component of pollution. Additionally, provocation/exposure testing can be performed in the laboratory.

Many of the same questions that can be asked about viral disease can be asked about air pollution – does it initiate asthma and does it trigger asthma? Clearly not everyone breathing air pollution gets asthma or wheezing, but exposure does seem to increase the risk.

Clinical Effects of Pollution in Outdoor Air

Inception of Asthma by Air Pollutants

A population study in the Netherlands found that children with higher exposure to traffic-related pollutants (NO_2, particulate matter) were more likely to develop asthma *(40)*. Data from the Taiwan Children Health Study showed an increased prevalence

of bronchitic symptoms among children with long-term exposure to outdoor air pollutants *(41)*.

In addition to irritant properties, air pollution may contain immunologically active particles. Nanoparticles, including particles of diesel exhaust, which are suspended in air are especially interesting to immunologists studying the development of asthma. They have been proposed to act as adjuvants and immunomodulators *(42)*. Most diesel particulates have sizes of less than 1 μm and represent a mixture of fine particles and nanoparticles.

Triggering of Asthma by Air Pollutants

Acute wheezing may be triggered by exposure to high levels of pollutant gases including nitrogen dioxide, sulfur dioxide, and carbon monoxide. Burning of fossil fuels is the main source of these pollutants in most locations. Nitrogen dioxide and sulfur dioxide gases diffuse rapidly and impact upon the wet respiratory tract to produce highly irritating acids. Sulfur dioxide can cause respiratory constriction in asthmatic patients at concentrations of 0.1 ppm when exercising *(44)*. Healthy adults begin experiencing increased airway resistance at 5 ppm, and even nonasthmatic adults will develop bronchospasm at 20 ppm, though these levels would be highly unusual in outdoor air pollution. Nitrogen oxides, and especially NO_2, are also irritating to the upper and lower respiratory tracts at low levels, and patients with asthma are more susceptible to these adverse effects. Higher concentrations of outdoor NO_2 were associated with more asthma symptoms in a study of inner city children *(45)*. Though the mechanism of action is uncertain, exposure to carbon monoxide in city air was found in one European study to worsen lung function in adult patients with asthma *(43)*.

Ozone, while of critical importance to global health in the upper atmosphere, is an especially noxious chemical when generated at or near ground level. Ozone (O_3) is not produced directly by traffic or by hydrocarbon burning. Instead, the combination of NO_2 and hydrocarbons with air and sunlight form the secondary pollutant ozone. High average ozone and airborne particulate matter were associated with more frequent asthma symptoms and ED visits and hospital stays in a study of asthma sufferers in the San Joaquin Valley in California *(46)*. Ozone from air pollution has been shown to exacerbate asthma in children and adults, though this effect may be greater in children *(47)*. A study of over 90,000 emergency department visits in Atlanta for pediatric asthma showed a relationship to ozone and primary pollutant concentrations from traffic sources. These pollutants increased ED visits even at relatively low concentrations *(48)*.

The study of particulate matter in the air is quite complex, since the exact composition varies geographically. In general, high levels of particulate matter have long been associated in epidemiological studies with increased levels of respiratory disease. Ongoing research is examining the importance of particle size, fine versus more coarse, in asthma and chronic respiratory illness. One study in Turkey showed an 18% rise in asthma admissions when air contained high levels of coarse particles *(49)*. In contrast, a US study did not find increased hospitalizations for respiratory disease during those periods with high coarse particle levels *(50)*. The evidence for a negative effect on health from suspended fine particles is stronger *(51)*.

Genetic and phenotype differences may be important in the sensitivity of the asthma patient to air pollution. The risk of childhood asthma in Mexico City was modulated in some children by genes controlling the response to oxidative stress, such as might occur while breathing ozone *(52)*.

Avoidance and Treatment Issues

Advice on how to avoid high concentrations of air pollutants is important for asthma patients. Air pollution, like pollens and viruses, follows a seasonal pattern, and knowledge of the local pattern can help the primary physician with diagnosis and treatment. In the United States, a daily Air Quality Index (AQI) is computed and distributed for most large population areas. The AQI, which is determined on the basis of the highest pollutant of the day, may be considered safe for patients with chronic respiratory disease if less than 50 (green zone). On days with poor air quality, asthma sufferers should come inside where pollutant levels are typically much lower. Indoor ozone levels vary from 10 to 80% of outdoor concentrations, depending on the size of outdoor air flows into a building *(53)*.

Although asthma patients should continue their controller therapy during periods of high air pollution, pretreatment with controller medications may not always be successful. Budesonide treatment in one study was not successful in preventing ozone-triggered functional airways impairment in test subjects with mild persistent asthma *(54)*.

Indoor Air Pollution

While outdoor air pollution rightly receives a great deal of media and government attention, indoor air pollution can make living inside hazardous as well. Fortunately, indoor air problems are usually amenable to personal control and behavioral advice. Air quality issues may occur in both home and work environments. The field of occupational medicine examines workplace concerns and is reviewed in another chapter. Home air quality is typically not regulated, though pollution may result from several indoor sources.

Hydrocarbon fuels are, of course, burned inside as well as outdoors. Indoor gas cooking and heating stoves may produce NO_2, high levels of which have been associated with increased asthma symptoms in children *(55)*. Good ventilation is essential if natural gas is to be burned indoors. Indoor nitrogen oxides are also produced by wood-burning stoves, especially if not well vented.

The most serious and prevalent type of home air pollution is secondhand or environmental tobacco smoke (ETS). The risk from this indoor pollutant begins in utero. Maternal smoking during pregnancy is associated with increased infant wheezing *(56)*. This risk of respiratory morbidity continues to increase with postnatal parental smoking *(57)*. Laws regulating indoor tobacco smoking in one European country were followed by improved quality-of-life scores in a group of asthmatic indoor workers *(58)* and also by a reduction in the overall rate of hospitalizations for childhood asthma *(59)*.

As noted previously, indoor ozone is usually much less than outdoor levels. In recent years, though, indoor ozone generators have been marketed to the public for odor control and purported heath benefits. A US EPA review has warned the public about the potential hazards of adding an additional amount of a measured air pollutant to the indoor air.

CONCLUSION

This chapter has examined some of the most significant initiating and exacerbating causes of asthma. Viral respiratory infections, and to a lesser extent air pollution, are common triggers of exacerbations and may interact with individuals to affect the development of some forms of asthma. These causal factors do not exist in isolation but rather interact with the personal attributes of each patient, including his or her genetic and environmental background. The role of viruses and pollutants in asthma is important knowledge that has consequences for prevention, treatment, and avoidance of illness. Helpful education may be given to patients and appropriate treatments selected, and health care providers can avoid the considerable human effort and resources wasted on interventions that are useless or harmful.

Viral and pollutant triggers demonstrate that the highly complex inflammatory asthmatic response is called forth on many more occasions than simply by the contact of pollen grains and other allergens with the respiratory tract. Since so much of immune inflammation seems to have arisen from the need to combat infection, the interaction between asthmatic inflammation and viral infection is a natural topic for further investigation. Some of the most significant advances in medical care have come through the treatment and prevention of viral illnesses, and furthering the understanding of respiratory viruses is a worthy priority for the future study of asthma prevention and treatment. In addition to natural harmful infectious particles, humans in recent decades have added many substances of their own creation, including the molecules and particles that constitute indoor and outdoor air pollution. Control of this problem is very important for overall respiratory health.

Important action and advice is available for each asthma patient. By understanding and anticipating respiratory viral infections and air pollution as important causes of asthma, the health care provider can provide superior care for those who suffer from this chronic disease.

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12 Occupational Asthma

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Contents

KEY POINTS

- Occupational asthma is the most common occupational lung disease.
- Occupational asthma and work aggravated asthma are the two forms of asthma causally related to the workplace.

From: *Bronchial Asthma: A Guide for Practical Understanding and Treatment, 6th ed.*
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- Reactive airways dysfunction syndrome is a separate entity and a subtype of occupational asthma.
- The diagnosis of occupational asthma is most often made on clinical grounds; the gold standard test, specific inhalation challenge, is rarely used.
- Low molecular weight isocyanates are the most common compounds that cause occupational asthma.
- Workers with occupational asthma secondary to low molecular weight agents may not have elevated specific IgE levels. The mechanisms of occupational asthma associated with these compounds are partially described.
- Not all patients with occupational asthma will improve after removal from the workplace.

EPIDEMIOLOGY OF OCCUPATIONAL ASTHMA

There are 25 million asthmatics in the USA, but estimates of the fraction that have occupational asthma (OA) vary widely. The reported prevalence of OA among all adult asthmatics ranges between 2 and 36% *(1, 2)*. It is estimated that up to 25% of all "adult-onset" asthmatics have a workplace trigger for their disease. One explanation for the varied prevalence rates is that the OA diagnosis may not be as stringent in some retrospective studies as it is in documented worker compensation cases. In one of the largest retrospective series covering three decades of studies, Blanc and Toren concluded that one in ten adult asthmatics had an occupational trigger for their disease *(3)*. The more conservative estimate, therefore, is that the prevalence of OA is 5–10% of all adult asthma cases.

Despite more streamlined improved reporting systems, the true incidence of OA remains unknown. Twenty-five new cases of OA per million population were reported annually in the United Kingdom (UK) in the 1990s, while 3–18 cases per million were reported in the USA *(4–6)*. Several large organizations track incident cases, including the Surveillance of Work-related and Occupational Respiratory Diseases (SWORD) *(7)* in the UK, and Sentinel Event Notification System for Occupational Risks (SENSOR) *(5)* in the USA. The SENSOR program documents occupational diseases in four states (California, Michigan, Massachusetts, and New Jersey) and is a rich source of epidemiologic data.

The economic impact and morbidity of OA is substantial when costs from lost work productivity, disease treatment, employer and employee health insurance costs, and legal fees are considered. Five to twenty percent of all asthmatics suffer partial disability that affects their ability to work *(8)* and 40–80% lose considerable income as a consequence of their disease (*9, 10*). Using a proportional attributable risk of 15% for both asthma and COPD, Leigh et al. estimated the 1996 U.S. costs of OA at $1.6 billion and the COPD costs at $5 billion *(11)*. Clearly, both OA and COPD are diseases that place considerable financial burdens on patients, employers, and public health systems. Prevention strategies likely will be the only cost-effective intervention to tackle this problem.

UPDATED DEFINITIONS FOR WORK-RELATED ASTHMA

In 2008, the ACCP published their updated state-of-the-art consensus statement on the "Diagnosis and Management of Work-Related Asthma" *(12)*. This is one of several major government or professional society guidelines that have been rewritten and published in the past 3 years. The National Institute of Occupational Science and Health

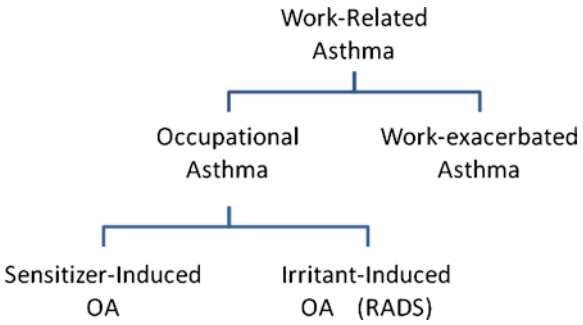

Fig. 1. Classification scheme for the major types of asthma in the workplace. This scheme is based on the American College of Chest Physicians 2008 guidelines and is adapted from Tarlo et al. *(12)*, Chest.

(NIOSH) rewrote their "State-Based Surveillance" consensus definitions for OA, which are available online through their www.cdc.gov/niosh website. Similarly, the British Thoracic Society (BTS) and the Agency of Healthcare Research and Quality (AHRQ) consensus statements are publicly available (*13, 14*). These collective efforts, particularly those of the ACCP, have significantly improved the standardization of the terminology and definitions for asthma in the workplace, which previously varied considerably (*5, 7, 15*).

The term occupational asthma does not correctly refer to all patients suffering from asthma in the workplace (Fig. 1). The term occupational asthma encompasses all workers who develop new respiratory symptoms and obstructive airways physiology consistent with the diagnosis of asthma, and the cause can be directly attributed to an exposure in the workplace. The key element is that OA is asthma caused by an organic protein, chemical, or other compound unique to the workplace. OA is further split into two subtypes: sensitizer-induced OA (>90% of the cases) and irritant-induced asthma including reactive airway dysfunction syndrome. Work-exacerbated, or work-aggravated, asthma (WEA) refers to previously diagnosed asthma that is worsened, but not caused, by agents found in the workplace. The distinction between these two entities is not superfluous as it impacts treatment strategies and medicolegal decisions. Millions of people with established asthma work and exacerbations of disease can occur in the workplace. Clearly, these patients should not have their work eligibility affected by their disease and, in general, their symptoms should be controllable. Patients with preexisting asthma whose disease becomes uncontrolled in a new work environment should be evaluated as a new case of OA. OA, therefore, represents the majority of asthma cases caused by an agent in the workplace and the evaluation and diagnosis of this entity must follow established protocols and guidelines.

REACTIVE AIRWAYS DYSFUNCTION SYNDROME: "CLASSIC" IRRITANT-INDUCED ASTHMA

Reactive airway dysfunction syndrome (RADS) refers to an asthma-like respiratory syndrome due to irritating vapors, fumes, or smoke in individuals with no prior respiratory disease. The incidence of RADS as a portion of new-onset OA ranges as high as

Table 1
Selected Reports of RADS and Causative Agents

Agent	*Setting*
Glacial acetic acid	Hospital chemical spill
Phthalic anhydride	**Truck tanker spill**
Hydrogen sulfide	Swine confinement facility
Various	World Trade Center site
Methyl isocyanate	Bhopal chemical plant
Denitrogen tetroxide	Railroad tanker spill
Hydrofluoric acid	Household exposure

25% *(16)* with 9.3–10% *(17)* as a more typically reported range. Scenarios that lead to RADS often involve inadvertent exposure to multiple workers. It is likely that any mucosal irritant may lead to RADS if administered at a high enough exposure level. Some of the identified agents are listed in Table 1.

The initial respiratory symptoms of RADS may manifest within minutes to hours of exposure to the implicated irritant. Previous exposure or previous sensitization is neither required nor characteristic of this syndrome. Rather, a rapid time course to symptoms, no prior exposure history, and good prior respiratory health are characteristic of the syndrome. The nonimmunologic, lymphocyte-predominant response that is characteristic of this syndrome is attributed to direct airway injury caused by the inhaled irritant. While most individuals with RADS will have a single identifiable exposure some may have multiple exposures to the irritant. Most criteria for RADS also require the symptoms to be present 1 month after exposure to distinguish RADS from the direct toxin-mediated pathology. Persistent respiratory symptoms are typically managed with bronchodilators and assiduous irritant avoidance. The course of disease may resolve over weeks to years or in some case persist indefinitely.

Noteworthy exposures include the Bhopal chemical plant toxic gas release in India and the World Trade Center (WTC) collapse in New York (*18, 19*). In Bhopal, India, 30 tons of methyl isocyanate were accidentally released overnight on December 3, 1984. Some 2,500 people died acutely and many more incurred less than lethal injuries. Retrospective evaluations found persistent respiratory complaints and RADS-like pattern in exposed individuals *(20)*. In New York, rescue personnel were exposed to various inhaled irritants during the rescue efforts after the destruction of the WTC. Quite early, Prezant et al. *(19)* recognized WTC Cough and RADS among the exposed individuals. Dust samples collected within the first 48 h included high levels of glass fibers, cement, silicates, asbestos, and polycyclic aromatic hydrocarbons *(21)*. High percentages of $PM_{2.5}$ (particulate matter ≤2.5 μm) were found in suspended dust 1 month (16–86% of total dust) and 6 months (7–85%) after the WTC attack *(22)*. The incidence of irritant-induced OA among first-responder personnel was reported to be quite high initially. Longer term studies in well-characterized subjects suggest that the incidence of irritant-induced OA in WTC rescue personnel is 22.6% *(23)*.

MAKING A DIAGNOSIS OF OCCUPATIONAL ASTHMA

Making an accurate diagnosis of OA requires that several key relationships between asthma and work be established. In essence, the following three criteria need to be met:

- A worker receives a diagnosis of de novo asthma or recrudescence of previously quiescent asthma.
- A worker is exposed to a sensitizing agent or an irritant in the workplace that is known to cause OA.
- A sufficient causal relationship is established between the causative agent and the worker's symptoms.

In addition to the clinical history and physical examination, several other tools should be employed to investigate the potential causal relationship between asthma and the workplace. These include symptom diaries, employment questionnaires, lung function testing with consideration of methacholine challenge testing (MCT), peak flow rate monitoring performed at and away from work, immunologic testing, and occasional workplace site visits.

THE ADULT ASTHMATIC WITH OCCUPATIONAL ASTHMA: CLINICAL PRESENTATION

Episodic wheezing, dyspnea, cough, and nocturnal awakenings are the typical presenting complaints of an adult patient with OA. These symptoms do not differ from that of other asthmatics, but the care provider should consider the diagnosis of OA in the newly asthmatic adult patient. Shortness of breath with or without wheezing was the chief complaint of 36% of workers exposed to wood products containing methylene diphenyl diisocyanate for up to eight 8 months, with a slightly increased figure of 45% at 20 months. The second most common symptom in this cohort, chest tightness, occurred in 38% of these workers at 20 months. These symptoms plus cough, phlegm production, and sudden attacks of shortness of breath occurred in at least 25% of all workers by 20 months. While the chief complaints in OA may not differ from those with other forms of asthma, the temporal nature may vary. Patients with OA may report that their symptoms are better on the weekends and worse at the end of the workday or at night. Asking directed questions regarding the timing of the symptoms is the key to eliciting an OA clinical history. Several questions include:

- Were there changes at the workplace in the period preceding symptoms?
- Was there a notable exposure at work in the day prior to the onset of symptoms?
- Are there other associated symptoms such as runny nose or itchy eyes?
- Is there a noticeable difference in symptoms at home during the weekend or on vacation?

This last question has a very high sensitivity (88–90%) for the diagnosis of sensitizer-induced OA, but it is not specific. At best, clinical history and examination can provide a correct diagnosis of OA in 75% of cases, but these estimates come from studies of patients with high pretest probabilities of OA referred for specific inhalation challenge *(24)*. Realistically, the likelihood of making a correct diagnosis of OA based on history and physical alone is probably about 50%. Further testing and more thorough evaluation is frequently warranted.

WORKSITE EVALUATION

Questionnaires can help determine the extent of a worker's exposure to specific compounds, but a workplace visit and an on-site investigation may be necessary in some instances. The focus of these assessments is twofold. First, is the asthmatic exposed to a single agent in the workplace that is known to cause asthma? Second, is there a clear temporal association between the patient's symptoms and the workplace exposure to this agent? Questions should address the time of day that symptoms develop and whether these symptoms resolve during extended breaks from work (e.g., weekends or vacations). One study reported that only 50% of pulmonologists and allergists asked about the association between asthma symptoms and work habits *(25)*. A failure to ask such questions may lead to the wrong diagnosis.

More than 250 specific agents have been causally linked to OA, but most cases of OA are caused by only a handful of compounds. Table 2 lists some major classes of compounds that are known to cause OA and the industries that often employ them. Clinicians must elicit a detailed work history in adult onset asthmatics. Specific job duties, date of hire, and job environment should be asked directly and documented in an evaluation. Often workers are unaware of all the products used in their industrial plant and clinicians should ask that the worker or the worker's employers provide copies of the material safety data sheets (MSDS) from their employers and any reports from worksite visits. OSHA requires that potential sensitizing agents that are >1% of the chemicals in compound or product be listed in the MSDS. Although all physicians have the right to request and review the MSDS from employers, this is a time-consuming process and is unfortunately often forgotten.

Inhalation is the primary portal of entry for chemicals and other compounds and repeated exposure leads to systemic sensitization. An evaluation of the exposure risk for a worker often cannot be done efficiently without help from outside experts. Occupational hygienists or occupational medicine professionals specialize in sampling techniques and sensitive assays, such as liquid chromatography, gas chromatography, and mass spectrometry, to measure concentrations of particulate airborne compounds. Unless trained in this highly specialized area, clinicians should focus their efforts on the patient's complaints as they pertain to the worksite.

Table 2
Common Low and High Molecular Weight Compounds that Cause Sensitizer-Induced OA

Low molecular weight compounds	*Occupations*
Isocyanates	Plastics workers, painters, insulators
Anhydrides	Plastics and resins workers
Amines	Lacquer and shellac workers
Metals (e.g., platinum, vanadium salts)	Platers, welders, chemical workers
Chloramine-T	Cleaners

LUNG FUNCTION TESTING

Once clinicians suspect a temporal relationship between a patient's asthma symptoms and the workplace, they should order complete lung function testing, including spirometry with and without bronchodilator, lung volumes and diffusion capacity testing. Measurements of peak expiratory flow rates (PEFR), usually with an inexpensive handheld device, must be performed at the worksite and away from it. Newer patient-activated, portable devices store full spirometry data including FEV_1 readings, but they remain expensive. These devices record and log spirometry readings and reduce the problem of falsified records. Training in the forced vital capacity maneuver and adherence to PEFR and spirometry measurement diaries is essential.

One formal study of serial PEFR during and after work is named the "stop-resume work test" *(26)*. Essentially, this test asks that the worker monitor and record at least four serial peak expiratory flow readings a day while at work and at home. This test is repeated for several continuous weeks, including weekends and rest days. The OASYS scoring system (Fig. 2) has sensitivity of 78% and specificity of 92% for the diagnosis of OA when serial PEFRs are recorded at least 4 times daily for greater than 3 weeks, and a sensitivity of 64% and specificity of 83% when PEFRs are recorded less than 4 times/day for less than 3 weeks *(27)*. Workers with asthma caused by an occupational agent will demonstrate significant peak flow variability (20–30%) with higher readings on weekends and lower readings during and after work. Such a variation should not be seen with asthmatics who do not have a workplace trigger. It is important that clinicians ask that measurements be recorded over days to weeks, but adherence to this regimen can be difficult.

In addition to spirometry, repeated airway hyperresponsiveness measurements with MCT provide strong evidence for OA. MCT will change depending on whether the OA patient has been recently exposed to the agent that caused their OA or whether they have been away from work for an extended period (>2 weeks). A threefold difference in the methacholine concentration required to trigger a positive response (a 20% decrease in the forced expiratory volume in 1 s FEV_1) is strongly indicative of OA. There are a few studies supporting repeated MCT to diagnose OA, but it remains a valuable tool for occupational medicine specialists and its use is supported in consensus guidelines.

An OA diagnosis can be wrong even when it is based upon accurate symptom data, spirometry readings, and MCT results. Several studies published in the mid-1980s to early 1990s showed a discrepancy between the clinical diagnosis of OA and the diagnosis confirmed by specific inhalation challenge, the gold standard test (*28, 29*). In one study, 63 workers diagnosed with OA by specialist physicians secondary to isocyanate exposure underwent inhalation challenge testing to isocyanate *(29)*. Only 48% of the workers demonstrated airway hyperresponsiveness to isocyanates, although most workers reported respiratory symptoms during the test. Forty-three percent of the workers had no response to isocyanate, but showed airway hyperresponsiveness to methacholine. Proving a causal relationship between a specific compound and a worker's asthma is not straightforward.

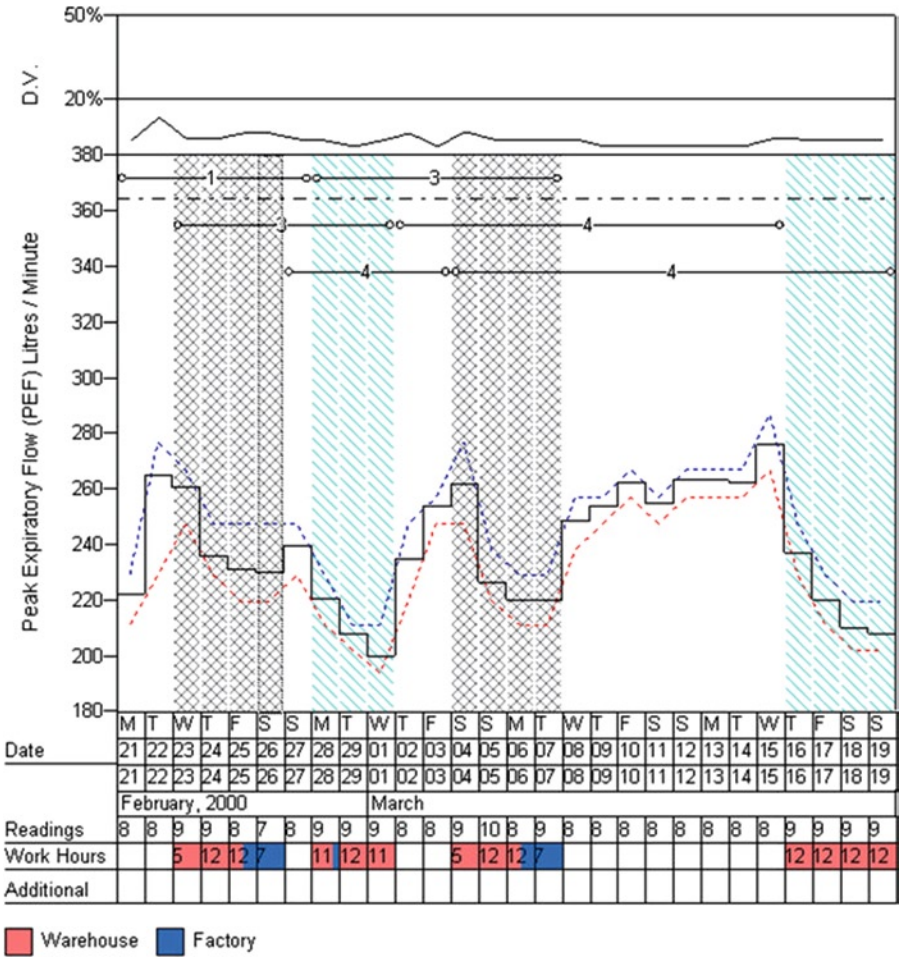

Fig. 2. Occupation Asthma System (OASYS) plot of serial peak flow rates (PEFR) at work and at home. This is a well-validated computer-aided tool to assist in the diagnosis of occupational asthma based on patterns of PEFR change.

THE OLD GOLD STANDARD: SPECIFIC INHALATION CHALLENGE

Specific inhalation challenge (SIC) mirrors other inhalation challenge testing except that patients are exposed to aerosols of occupational antigens. While considered the "gold standard" test to document OA, SIC is not performed commonly in the USA and cannot be considered part of the standard evaluation. In many countries, clinicians order SIC routinely. A recent survey of 123 U.S. and Canadian pulmonary and allergy medicine training programs found that only 15 centers performed SIC tests *(30)*. Of 2,065 patients diagnosed in the USA with OA in the preceding years, only 130 (6%) had been diagnosed with the help of SIC testing. In contrast, 130 of 308 of OA cases (42%) in Canada underwent SIC testing. Sixty percent (74 of 123) of the training programs believed SIC was useful, but only 55% of the respondents could order the test if they

wanted it. A list of the 15 centers performing SIC in the USA and Canada can be found in the 2002 manuscript of Ortega et al. *(30)*.

As with most "gold standards," problems exist with SIC. False negative tests with SIC occur if the wrong compound (e.g., wrong isocyanate) is chosen or if SIC is performed long after the worker has left the workplace. Sastre et al. demonstrated that 5 of 22 workers with apparent isocyanate-induced OA had a negative SIC, but 3 of these 5 workers were subsequently positive when tested a second time *(31)*. Despite these deficiencies, SIC remains the gold standard test for making the diagnosis of OA in as many as 50% of patients in Canada and throughout much of the world. The same cannot be said for the USA where SIC is rarely ordered and performed.

IMMUNOLOGIC TESTING

Skin prick testing and in vitro IgE specific assays can determine if a worker has developed an antibody response to a high molecular weight protein or glycoprotein in the workplace. They are not particularly useful in investigating low molecular weight sensitizers since IgE responses to these compounds are inconsistent. A positive skin prick testing test to an agent known to cause OA is helpful in identifying the nature of the exposure, whereas a negative test has a high negative predictive value for ruling-out a specific exposure. Testing for an IgE-mediated response to a panel of common high molecular weight proteins is relatively straightforward, while testing for low molecular weight antigens, such as diisocyanate, is not. Diisocyanate, for example, may lead to elevated IgE levels in only 20–30% of exposures where it appears to act as a hapten *(32)*. Nonspecific RAST panels and hypersensitivity panels may prove helpful in some patients specifically exposed to Aspergillus or other fungi at work. Newer commercially available in vitro assays are becoming available to detect isocyanate and other low molecular weight agent induced OA. For example, the production of monocyte chemotactic protein-1 by peripheral blood mononuclear cells in patients with diisocyanate-induced OA can distinguish them from nonasthmatic workers *(32)*. Overall, however, experience is limited with these kits and larger scale reports need to be published. In our experience, skin prick tests provide important supporting data demonstrating sensitization to occupational antigens.

OTHER DIAGNOSTIC STUDIES

Surrogates of airway inflammation, such as sputum eosinophilia and exhaled nitric oxide, contribute to the management of patients with asthma and these markers are now being evaluated in OA. In a cohort of asthmatic patients without OA, Green and colleagues showed that the number of exacerbations decreased significantly when patients were managed by maintaining sputum eosinophil counts less than 3% or exhaled nitric oxide concentrations less than 5.0 ppb. This approach has been applied to OA, as well. For one, peripheral blood and airway eosinophilia is evident in all forms of OA, including RADS, and induced sputum eosinophils and neutrophils increase after exposure to specific work-related compounds, like isocyanates *(33)*. In one study, serial spirometry measurements plus induced sputum eosinophil counts improved the accuracy of the OA diagnosis compared to spirometry testing alone *(34)*. Compared to sputum eosinophil

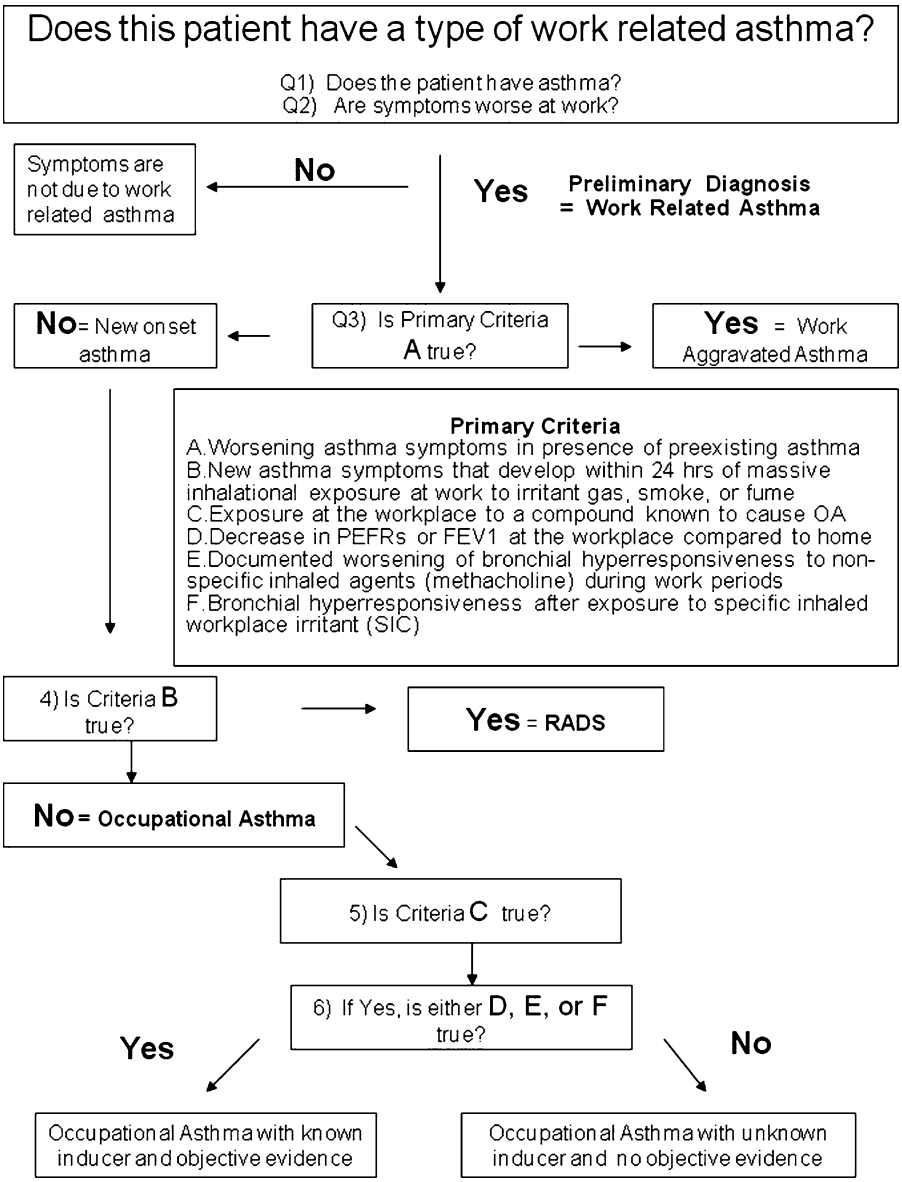

Fig. 3. Flowchart depicting stepwise approach to work-related asthma. It is adapted from the National Institute of Occupational Safety and Health (NIOSH) "Decision Logic" worksheet that is part of their NIOSH Work Related Asthma Surveillance program.

counts, however, data with exhaled nitric oxide in OA is scant. One study documented that exhaled nitric oxide levels increased in workers with a positive inhalation challenge and not in those with negative tests in a small cohort of 40 workers *(35)*. The potential strength of the exhaled nitric oxide test lies in its use for disease management. At this juncture, induced sputum eosinophil counts and exhaled nitric oxide measurements cannot be recommended in supporting the diagnosis of OA or in managing OA patients, and in general, diagnosis is based on clinical logic (Fig. 3).

GENE POLYMORPHISMS AND OCCUPATIONAL ASTHMA

Genetic polymorphisms are a research focus in asthma and this has spilled over to OA as well. Obviously, a genetic profile that potentially predisposes workers to an increased incidence of OA would be on interest to certain industries with high incidences of OA (e.g., animal care and food industries). While no such gene has been identified to date, researchers continue to focus on two candidate families: the glutathione S-transferase (GST) and HLA family. The GST family of genes involves a host of enzymes that protect the host lung epithelium from oxidative stress. The GSTP1 Val/Val genotype has been associated with both allergic asthma and toluene diisocyanate-induced OA (*36, 37*). In one study, the presence of GSTP1 Val/Val genotype appeared to have a protective effect against OA in workers exposed to TDI over 10 years *(38)*. Broberg et al. investigated the association between genotype and toluene metabolites (i.e., toluene diamine, TDA) in workers exposed to TDI *(39)*. They found that workers with the GSTP1 105 Val/Val genotype had about one-half of the levels of TDA in the serum and urine compared to workers with other GSTP1 105 variants, thereby suggesting that genotype affected retention and exposure to TDI. Other genes in the GST family appear to confer an increased risk of OA also.

The second class of genes of interest in OA is the HLA class II molecules – part of the major histocompatibility complex – that are involved in antigen presentation. Young et al. demonstrated a strong correlation between increased expression of HLADR3 and the development of OA after exposure to trimellitic anhydride *(40)*. However, this correlation is not apparent with exposures to other compounds.

PATHOGENESIS OF OCCUPATIONAL ASTHMA

As with all asthma, the mechanisms leading to the development of OA are not fully known. Two major classes of agents – high molecular weight (HMW) and low molecular weight (LMW) agents – cause OA and the mechanisms appear to differ significantly. Common HMW organic proteins that cause OA include grains, latex, animal-derived proteins, and seafood. More than 140 LMW chemicals and compounds trigger sensitization in humans, and this list includes isocyanates (e.g., toluene diisocyanate, TDI), anhydrides, dyes, and smaller organic compounds.

High molecular weight antigens (>5,000 k daltons in size) act like other environmental antigens that lead to sensitization and IgG and IgE antibody production. In general, months to years of exposure are necessary to develop this allergic response and latency helps distinguish OA from RADS. HMW organic proteins can trigger a vigorous immune response and the period of latency may be less than 1 year. A recent, prospective study following 118 apprentice bakers and new animal workers found that 64% of the new hires developed positive skin prick test responses to grains and animal proteins yet only 12% developed asthma symptoms *(41)*. The incidence of occupational rhinitis in this study was higher than OA, which is consistent with most studies.

The pathways leading to systemic sensitization to HMW proteins and polysaccharides do not differ significantly from the pathways involved in the development of environmental asthma. Briefly, a HMW antigen, such as an animal dander protein, will associate with an MHC II molecule on a dendritic cell and be transported to a lymph node. An allergenic

peptide sequence will interact with naïve T-cells and some undergo transformation to Th2 or Th1 cells. Cytokines (IL-4, IL-5, and IL-13) from these cells then stimulate IgE production from B cells and eosinophil recruitment from the bone marrow. The pathologic sequence in IgE-mediated OA resembles that of more common forms of asthma, except the sequence of events can occur more rapidly.

The development of OA from LMW compounds can result in a type I, IgE-mediated immune response by acting as haptens, but in most cases, it does not. Admittedly, evidence supporting the concept that LMW agents act as haptens is slim. It has been suggested that the degree of hydrophilicity of the LMW compound may impact its function and determine whether it stimulates a type I immune response. Hydrophilic LMW compounds, for example, may cross the respiratory epithelial membrane more readily, bind lung proteins, and trigger IgE production, while more hydrophobic compounds may not.

Most LMW agents, like TDI, cause a delayed type III, cell-mediated immune response by binding to organic macromolecules at the airway–epithelium interface. This inflammatory response appears to occur more rapidly than with HMW compounds *(42)* and is characterized, in part, by increased numbers of airway CD8+ lymphocytes. Affinity of certain LMW compounds for various organic proteins and other adducts has been shown. Trimellitic anhydride, for example, can bind with amino groups, alcohols, and epithelial cell proteins *(43)*. Intracellular glutathione may also act as a transfer molecule for LMW agents and serve as an intermediary in the development of the allergic response *(44)*.

Another factor that may enhance sensitization to LMW compounds is tobacco smoke. Workers exposed to second-hand environmental tobacco smoke at work have a higher incidence of work-related asthmatic symptoms *(45)*. As an example, the risk of sensitization to platinum salts in refinery workers is higher in workers who smoked *(46)*. Overall, the diverse mechanisms involved in the development of LMW antigen-associated OA are interesting and further investigation will provide information to determine the relevance to all asthma.

SPECIFIC CASES OF INTEREST

Based on surveys from NIOSH, the prevalence of OA in hospital and biomedical workers is as high as 15% *(47)*. We will discuss three types of exposures in workers in the biomedical field that commonly present to clinicians for evaluation of respiratory symptoms: (1) cleaning staff, (2) all hospital staff exposed to latex, and (3) laboratory workers who handle animals.

Cleaning Solutions and Asthma

Compounds in cleaning solutions can be both respiratory irritant and sensitizers. The incidence of OA in cleaning staff has either increased significantly, or more likely, is much better recognized. Fifteen percent of new OA cases in Catalonia, Spain in 2002 were caused by cleaning agents, while cleaners made up 12% of new WRA cases in the USA in the SENSOR surveillance program (*48, 49*). One hospital studied the exposure problem among its cleaning workers and identified mirror cleaning, sink cleaning, and toilet cleaning with disinfectants (ammonia, isopropyl alcohol, 2-butoxyethanol,

mono-ethanolamine) as the highest exposure activities *(50)*. The recognition of the dangers of volatile organic compound exposures in cleaners is still quite new. It is likely that new exposure standards and preventive measure will be addressed.

Latex Allergy and Asthma

Allergy and OA related to latex and natural rubber compounds represent a significant and illustrative example of occupational illness. Latex-related allergy and asthma was recognized first in the 1970s in latex-exposed patients, such as those with spina bifida. It gained prominence during the late 1980s and 1990s with the implementation of NIOSH/CDC universal precautions for blood-borne infections. The CDC precautions increased the use of latex gloves and heightened worker exposure to natural rubber products. As with other examples of HMW agent related OA, the incidence and severity of disease correlates with exposure level. Currently, latex-related OA represents some 4% of all work-related asthma cases (10.3% in Michigan). Diagnosis is similar to other OA cases with the exception of immunologic testing. RAST testing is less sensitive in the case of latex allergy and OA with nearly a 30% false negative rate as compared to patch or skin prick testing.

While latex allergy and OA are present in other industries (e.g., food handling, manufacturing) the incidence is twice as high in health care workers (5–18%) as in the general populace *(51)*, and it is more prevalent in work areas with high level exposures to latex gloves and glove dust. With the recognition of latex allergy as a problem, NIOSH implemented recommendations to decrease the incidence of latex related allergy and OA by decreasing workplace latex antigen exposures. In hospitals where these recommendations are implemented (the use of powderless gloves, nonlatex gloves, and gloves of higher quality manufacture techniques) the incidence of latex-related OA and allergy has decreased *(7)*.

Occupational Asthma in Animal Workers

The incidence of atopic sensitization to small laboratory animals and pets is reported between 15 and 40% *(52)* and preexisting atopy to environmental allergens is the primary risk factor for developing animal allergy. Two million people work in jobs that expose them constantly to animals. Inhalation of animal proteins in dander, fur, feces, urine, and saliva can lead to sensitization. Proteins isolated in the urine of rodents, called lipocalins, for example, trigger an IgE-mediated response. Lipocalin sequences are now added to skin prick and RAST panel tests. While low exposure to these proteins can lead to sensitization and OA, high exposure time increases these risks significantly. Implementation of prevention strategies that decrease total exposure to inhaled animal proteins remains a key goal for NIOSH and should be for all medical centers and industries.

PREVENTION OF ASTHMA IN THE WORKPLACE

Screening for preexisting atopic conditions in new workers is not legal; therefore, employer interventions must be aimed at limiting exposures to certain airborne antigens. The Occupational Safety and Health Administration (OSHA) and NIOSH regulations regarding worker contact with specific compounds often appear burdensome to

Table 3
Key Activities to Prevent Asthma in the Workplace (Adapted from Tarlo et al. 2005)

1. Identify and move susceptible workers to work areas without exposure to known sensitizers
2. Known asthmatic patients should have limited exposure to potential respiratory irritants
3. Elimination of sensitizer agents and substitution with safer substances, improved facility ventilation, increased dust reduction techniques, and better housekeeping practices are all appropriate interventions to decrease the incidences of work-related asthma
4. Job rotation, rest periods, shift or location changes may reduce the number of workers exposed or duration of exposure
5. Workers should wear personal protective equipment, which includes respirators, gloves, goggles, and coveralls, when appropriate

industry, but these regulations will remain the primary strategy to combat OA (Table 3). These recommendations encourage employers to formulate their own policies and procedures regarding this issue. Ventilation and individual protection strategies are near the top of many NIOSH recommendations for specific worker groups. A proactive employer will institute these guidelines and a workplace screening program *(53)*. Small studies have shown that such measures can decrease the incidence of OA. In one recent example, Grammer et al. offered personal protective masks to 66 workers newly hired in a plant producing an acid anhydride *(54)*. Over 7 years, the workers who used the protective masks decreased their absolute risk of developing rhinitis or OA from 10 to 2%. Preventing exposure to airborne agents should decrease the incidence of OA, but installation of new ventilation systems is costly for employers and personal protective industrial masks and helmet respirators do not seem practical to many workers.

TREATMENT

Minimizing allergen exposure is an essential component of every asthma treatment plan. Similarly, quitting work or avoiding the worksite exposure is the primary treatment in OA. Inhaled corticosteroids, long-acting β2-agonists, and rescue drug medications should be prescribed according to the guidelines of the NAEPP *(55)*, but the efficaciousness of these therapies in OA is less well established.

Studies have shown that patients that remain in the workplace after the diagnosis of OA suffer worsening lung function despite appropriate steroid therapy *(9)*. In one crossover study, Malo et al. found that the addition of inhaled corticosteroids to worksite removal did improve asthma symptoms, airway hyperresponsiveness, and quality of life measures more than work removal alone *(56)*. In another recent study, Marabini et al. treated 20 OA patients who remained at their job with beclamethasone dipropionate (500 μg BID) and salmeterol (50 μg BID) for 3 years *(57)*. At the time of enrollment, their FEV_1% predicted was mildly reduced at 80.2%. After 3 years, lung function remained the same, as did airway hyperreactivity, symptoms and rescue β2-agonist drug usage. While lung function and symptoms did not improve with inhaled corticosteroid treatment, neither did they worsen. The authors surmised that the outcome in these 20 workers might be the same with adequate controller therapy, whether they quit or

continued to work. At this time, this approach cannot be recommended. Larger, prospective studies needed to evaluate this question may never be performed.

Management of work-aggravated asthma, where asthma is a preexisting condition and the disease flares with work exposures, differs from that of OA. Avoidance of work-site exposures is important, but pharmacotherapy can control symptoms. In general, fewer workers with work-aggravated asthma lose their jobs than workers with OA. This practice may be influenced both by the medicolegal complexities associated with OA and the belief that work-aggravated asthma represents a milder form of the disease *(58)*. Like work-aggravated asthma, irritant-induced asthma or RADS is amenable to drug therapy and workers often return to their jobs.

OUTCOMES FOR WORKERS WITH ASTHMA

Unfortunately, asthma symptoms and airway hyperresponsiveness persist in many patients after removal from the worksite and, in this sense, OA mirrors environmental asthma. More than 50% of workers with OA have persistent asthma symptoms and airway hyperresponsiveness in the years succeeding their quit date. As should be expected, specific IgE to the offending compound that caused the OA decreases significantly once the worker leaves. Immune cell memory does not fade completely, however, and re-challenge with the same compound 2 years later will trigger an asthmatic attack in the vast majority of those affected.

Biologically, it makes sense that once an insult – be it an environmental, infectious, or an occupational one – triggers structural airway changes, such as airway wall thickening and smooth muscle hypertrophy, the disease will not abate completely in all patients. Simple avoidance alleviates, but does not necessarily cure, the disease. Nonetheless, early removal from the workplace portends a better prognosis.

COMPENSATION AND DISABILITY

The economic realities of OA for a worker can be overwhelming and life-changing. Several groups have studied the economic impact of OA on workers and an interesting review on this topic has recently been published. In one study 55 U.S. workers with OA, 69% remained unemployed an average of 2.5 years after the diagnosis *(59)*. In Vandenplas et al.'s meta-analysis of six studies from three European countries and Canada, about one-third of workers with OA reported prolonged unemployment or work disruption and one-half to two-thirds reported significant lost income *(58)*.

Diagnoses of OA inherently lead to decisions regarding the impairment, disability, and compensation of workers. Physicians should advocate for workers diagnosed with OA and adopt a proactive approach by reporting the diagnosis to compensation boards, surveillance organizations (e.g., SENTINEL), government agencies (e.g., OSHA), and possibly employers. Impairment and disability programs are exceedingly complex and differ significantly among states and countries. In general, impairment is based on the degree of lung function compromise. Workers with objectively recorded and diagnosed OA should receive temporary disability immediately and decisions regarding permanent disability should be made after some period of observation and review. Most workers receive complete, permanent disability for the job that caused their OA and for any job

where they might be exposed to the same product or compound. The role played by physicians should focus on making an objective and accurate diagnosis. If the diagnosis of OA is established, physicians should initiate appropriate controller drug therapy, remove patients from the work environment, request temporary disability from that job, and report the case to the appropriate monitoring and surveillance boards.

CONCLUSIONS

OA is the primary lung disease in the workplace and is of increasing importance to OSHA, state regulatory boards, and employers. Every measure must be taken to prevent sensitization to occupational antigens that commonly cause OA and occupational rhinitis. Studies in the past decade have helped to elucidate some of the mechanisms leading to asthma secondary to HMW and some LMW compounds, but other pathways need exploring. Many workers remain symptomatic and suffer continued loss of lung function after being removed from the work environment. Disability and compensation issues will become increasingly common and the specialist will need to remain updated on this important disease.

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13 Allergic Bronchopulmonary Aspergillosis

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Contents

KEY POINTS

- Bronchial reactivity is present in patients with Allergic bronchopulmonary aspergillosis (ABPA).
- ABPA represents an IgE mediated hypersensitivity to fungal antigens.
- Control of the inflammatory response is central to the therapy of ABPA.
- Uncontrolled ABPA leads to progressive airway destruction and respiratory decline.
- Consider the diagnosis of ABPA in difficult to control cases of asthma.
- Antifungal therapy represents a possible steroid-sparing therapy.

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- ABPA is not an invasive fungal infection but may mimic invasive diseases.
- Consider fungi beyond aspergillus as the cause of symptoms, i.e., ABPM.
- Severe asthma with fungal sensitization (SAFS) mimics ABPA.
- Chest imaging helps determine diagnosis and prognosis of disease.

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) describes a syndrome in which patients with asthma harbor the saprophytic growth of *Aspergillus* species within their airways. An intense allergic inflammation results in response to fungal antigens leading to clinical disease. Recurring clinical exacerbations can lead to bronchiectasis, pulmonary fibrosis and even death. ABPA is present in 1–2% of all asthmatics and up to 15% of patients with cystic fibrosis (CF) *(1)*. While the initial manifestations of disease may be subtle, more severe disease may be dramatic and, at times, life-threatening. ABPA may go unrecognized, since the early clinical course may be as indolent as a moderate to severe persistent asthma. As with rhinosinusitis, gastroesophageal reflux disease (GERD) and COPD, ABPA should be included whenever considering an asthma diagnosis. Assiduous therapy in ABPA can decrease the frequency of exacerbations and may slow the progressive lung damage, leading to pulmonary fibrosis and death.

ABPA DEFINED

ABPA represents a specific hypersensitivity to *Aspergillus* species within the lung manifest immunologically by elevated immunoglobulins specific to this fungus' antigens. An initial inoculum of fungal spores is thought to enter and seed the respiratory airways. Subsequently the fungus grows septated hyphe in a saprophytic manner within the susceptible airways. Susceptibility may arise from a genetic predisposition or abnormal mucociliary clearance (e.g., areas of scarring, bronchiectasis) *(2, 3)*. Since the fungi are fully contained within the airways – without invasion or penetration to the submucosa – they are not considered invasive *(4)*. However, even without invasive growth, an intense and perhaps overly exuberant, allergic exudate and TH-2 dominant inflammatory response are stimulated. The characteristic ABPA inflammation contains large numbers of eosinophils, as well as neutrophils, Curschmann's spirals, desquamated epithelial cells and mucus *(4)*. The often associated parenchymal infiltrates are similar in character to those of eosinophilic pneumonia and are thought to arise in areas distal to mucus obstructed airways. It is the unchecked acute and chronic inflammation which leads to progressive airway damage, airway hyper-responsiveness and bronchiectasis. As bronchiectasis becomes more severe, the density and number of inflammatory cells increases *(5)*. The inflammation persists and fibrotic changes can result.

The inflammatory and interleukin profile of inflammation in ABPA appears to have an asthma-like TH-2 dominant pattern *(6)* with relatively low levels of interleukin-10 (IL-10) *(7)*. *Aspergillus* as a Type II allergen it thought to produce proteases which impair tolerance – T-cell activity *(8)*. An increased sensitivity of the peripheral blood monocytes cells to IL-4 is also observed in ABPA *(9)*.

Since other non*aspergillus* species may cause similar clinical manifestations, an alternative more encompassing name, allergic bronchopulmonary mycosis (ABPM),

Table 1
Implicated Fungi of Allergic Bronchopulmonary Mycosis (APBM)

Fungi	*Reference*
Aspergillus sp	
Candida sp	*(62)*
Fusarium	*(63, 64)*
Pseudoaalescheria boydii	*(65)*
Scedosporium apiospermum	*(66)*
Curvularia sp	*(67–69)*
Blastomyces dermatitidis	*(70)*

may better describe the syndrome. ABPA is a more widely recognized term than ABPM. Nonetheless, other fungi should be considered as potentially causative. Clinicians should look for other fungi in the appropriate clinical scenarios, particularly when there is no evidence for *Aspergillus* (*see* Table 1).

Beyond this allergic lung disease, *Aspergillus* and other fungi may cause other pulmonary diseases including: pulmonary aspergilloma, chronic necrotizing aspergillosis, invasive pulmonary aspergillosis and severe asthma with fungal sensitization (SAFS). The invasive fungal infections (IFI) due to *Aspergillus* should not be confused with ABPA since the clinical significance and therapies are different *(10)*. Selected cases of true infection may be difficult to differentiate from ABPA. Uncommonly cases of ABPA may progress to include features of, or progress into invasive disease *(11, 12)*. When asthmatic patients do not meet criteria for ABPM but demonstrate "fungal sensitization" to fungal antigens, treatment ought to be considered *(13, 14)*. Nonetheless, the clinical setting and radiographic findings are often adequate to distinguish these invasive infections from ABPA and SAFS.

OTHER FUNGAL LUNG DISEASES

Pulmonary aspergilloma, or more generically, pulmonary mycetoma, is an anatomically opportunistic fungal infection. A mycetoma typically forms within a cavity previously created by granulomatous lung disease (e.g., sarcoidosis, tuberculosis) or other cavitary lung diseases (e.g., pulmonary abcess). Within the remaining cavity, inflammatory cells, fungi and cellular debris combine to form a sphere or fungus ball, i.e., mycetoma. A posterior–anterior chest radiograph or CT of the chest may incidentally reveal such a mass as the first indication of disease. A suggestive and nearly pathognomonic crescent shaped radiolucency or even a mobile sphere within the cavity may be detected *(15)*. Most patients do not develop overt clinical disease, but should significant hemoptysis (>50–200 ml per episode) or growth occur, surgical therapy may be beneficial.

Chronic necrotizing aspergillosis or so-called "semi-invasive" aspergillosis describes a progressive lung infection with parenchymal destruction and in most cases locally limited. Radiographically, necrotizing aspergillosis may have similar characteristics as ABPA and when they are not clinically distinct may require bronchoscopy and biopsy

and/or search for serum markers of IFI *(10, 16–18)*. Treatment with systemic antifungal therapy has greatly reduced the need for surgical resection *(19)*.

Invasive fungal disease with *Aspergillus* is difficult to recognize early. Fortunately, this severe disease is usually only found in patients with serious immune compromise (e.g., persistent neutropenia, leukemia, or organ-transplant related immune suppression). This distinct clinical setting is most often adequate to distinguish this often disseminating disease from ABPA. Given the high mortality among at-risk individuals, any evidence of fungus should prompt a presumptive diagnosis of invasive disease and initiation of empiric therapy – more definitive diagnosis requires biopsy. The radiographic changes of invasive disease can be focal or diffuse, but typically do not have the prominent airway findings of ABPA *(15)*.

MAKING THE DIAGNOSIS

At its essence a diagnosis of active ABPA requires three elements be present: (1) bronchial reactivity (asthma), (2) noninvasive fungi and (3) an active allergic response to the fungus. While some authors also call for bronchiectasis to be present, we prefer not to require this for diagnosis.

Since the first case series descriptions of the syndrome, various diagnostic criteria have been proposed. The variations in diagnostic criteria seem to reflect clinician preferences and the serologic testing available to them. In his initial description of ABPA in 1952, Hinson identified patients who had fungus in their airways, recurrent fevers, chest radiograph changes and blood eosinophilia *(4)*. In the 1970s Safirstein (1973) and Rosenberg (1977) proposed similar criteria, which called for major (required) and minor (supportive) diagnostic information (Table 2). They added serologic testing data beyond

Table 2
Selected Antifungal Therapy Reports in ABPA

Drug (dosing)	*Description*	*Outcome (reference)*
Ketaconazole (400 mg/day)	12 months	Decreased IgE and symptoms *(71)*
Itraconazole (400 mg/day)	RDBPC, $n=29$, 16 weeks	Decreased IgE, fewer exacerbations *(42)*
Itraconazole (400 mg/day)	RDBPC, $n=55$, 16 weeks	Decrease of corticosteroid dose, improved X-rays and PFTs *(41)*
Itraconazole	Open, $n=14$, 2 years	Decrease of corticosteroid dose, total IgE *(49)*
Itraconazole (≥200 mg/day)	Observational, $n=14$	Decreased steroid use, decreased eosinophilia, decreased exacerbations *(49)*
Itraconzaole (300 mg/day)	Retro cohort $n=33 > 6$ months	Decreased steroid use, decreased IgE, improved ((FEV??) *(32)*
Voriconazole (wt based dosing)	Retro case review $n=13$ (less than?????)	Decreased of total IgE, increased FEV1/FVC *(51)*

Table 3
Diagnostic Schema for ABPA

Safirstein et al. *(20)*
Major and minor criteria in 50 patients with ABPA
Major
- Recurrent pulmonary densities in CXR
- Eosinophilia in sputum and blood
- Asthma
- Allergy to aspergillus fumigatus (Type 1 or Type 3)

Minor
- Recovery of Asp Fumigatus from sputum
- Asp fumigatus serum precipitins
- History of recurrent pneumonia
- History of plugs in expectorated sputum

All patients fulfilled major criteria and 66–88% of patients fulfilled one or more minor criteria

Rosenberg et al. *(72)*
Major and minor criteria
Major
- History of pulmonary infiltrates
- Peripheral blood eosinophilia
- Asthma
- Immediate skin reactivity to *Asp*. Precipitins to *Asp*. Antigens
- Central bronchiectasis
- Elevated serum IgE

Minor
- Recovery of *Asp*. from sputum
- History of expectoration of brown plugs or flecks
- Arthus reaction to *Asp*. antigen (Type 3)

peripheral blood eosinophilia (high serum IgE, immediate skin reaction to *Aspergillus* antigen, precipitating antibodies) and called for central bronchiectasis to be present. They differ subtly on the inclusion of serum precipitins to *Aspergillus* antigens and use of IgE levels (>1,000 ng/mm^3) *(20, 21)* (Table 3).

The diagnosis of ABPA requires bronchoreactvity, intense inflammation and associated fungus. Standard criteria are used to demonstrate asthma as outlined by regional societies. To establish the presence of fungus, we obtain a culture of a high quality expectorated sputum. Rarely, a bronchoscopy will be necessary to obtain culture material or to perform airway assessments. We use total serum IgE levels – in a similar manner as recommended for CF patients – as a screening test in at-risk patients *(22)*. When this general marker of allergic inflammation exceeds 1,000 ng/mm^3 we perform further specific testing.

Enzyme-linked immunosorbent assay (ELISA) or immunoblot is used to identify specific IgE and IgG to Aspergillus or other fungal species. When present this humoral sensitization to fungal antigens fosters the immunologic mechanisms responsible for the chronic airway inflammation of ABPA. These assays are useful as alternatives to or in conjunction with skin prick testing to *Aspergillus* specific antigens or serum precipitans

levels *(23, 24)*. No single testing method of specific immunity has shown ideal statistical sensitivity or specificity *(25)*.

A diagnosis of ABPA or flare of existing disease is made when there is evidence of a specific allergic response to fungus and total IgE levels are greater than 1,000 ng/ml or twice a patient's baseline. A recent study suggests that thymus activation-regulated chemokine (TARC) had a superior diagnostic accuracy to other serologic markers for the diagnosis of ABPA in CF patients *(26)*.

Bronchiectasis, found in the preponderance (>80%) of cases of ABPA, is best detected by noncontrast high-resolution computed tomography (CT) and may not be apparent on posterio-anterior chest radiographs. Bronchiectasis should be considered a late finding in ABPA. Waiting for bronchiectasis to become apparent may significantly delay the recognition of early ABPA and thwart efforts at preventing the permanent airway damage.

CLINICAL MANIFESTATIONS

Individuals with asthma or CF are at risk for ABPA. Nearly 2% of patients with asthma have ABPA. In asthma patients who require oral steroids the incidence triples to some 6% *(27)*. Initially, these patients may have few distinguishing findings other than difficult-to-control or persistent asthma. With progression of disease, patients may report intense bouts of coughing, production of sputum with grit or small bits of hard matter. These represent mucus plugs or small casts of the airways and often contain fungal elements when examined by microscopy. ABPA may be present in 2–15% of patients with CF *(1)*.

Unusual presentations and manifestations of ABPA include eosinophilic pleural effusions, hemoptysis and the development of super infections *(28)*. Hemoptysis in ABPA from bronchiectasis is often minimal and rarely massive.

RADIOLOGY

Chest radiographs of ABPA patients may be normal or show signs of bronchiectasis, mucus plugging or focal infiltrates in an alveolar filling pattern *(20, 21)* (*see* Fig. 1). Central airway bronchiectasis – third to fifth generation bronchi (thickened, dilated or distorted airways) – is characteristic of ABPA. Chest radiographic patterns include circular shadows, parallel nontapering lines (ectatic airways), dense cylindrical shadows (mucus plugs), finger-in-glove (mucus plugs) or signet ring patterns (increased bronchus:artery ratio) *(15, 29)*. The findings of bronchiectasis are most clearly identified by high resolution/thin cut CT scan. Distal to an obstructed airway, an alveolar pattern or infiltrate may develop. These diffuse or "fleeting infiltrates" of ABPA may be wedge-shaped in a pattern representing the affected segment or subsegment obstructed by mucus plugging or intense eosinophilic inflammation. While chest CT is more sensitive and specific then chest radiographs for revealing the findings that support a diagnosis of APBA it is not routinely required. Serial imaging by chest radiographs or CT is important in assessing response to therapy and monitoring for progression of disease or complications *(30)*. This is of particular importance because radiographs may reveal focal infiltrates, mucus plugs or bronchiectasis even in the asymptomatic patient *(20)*.

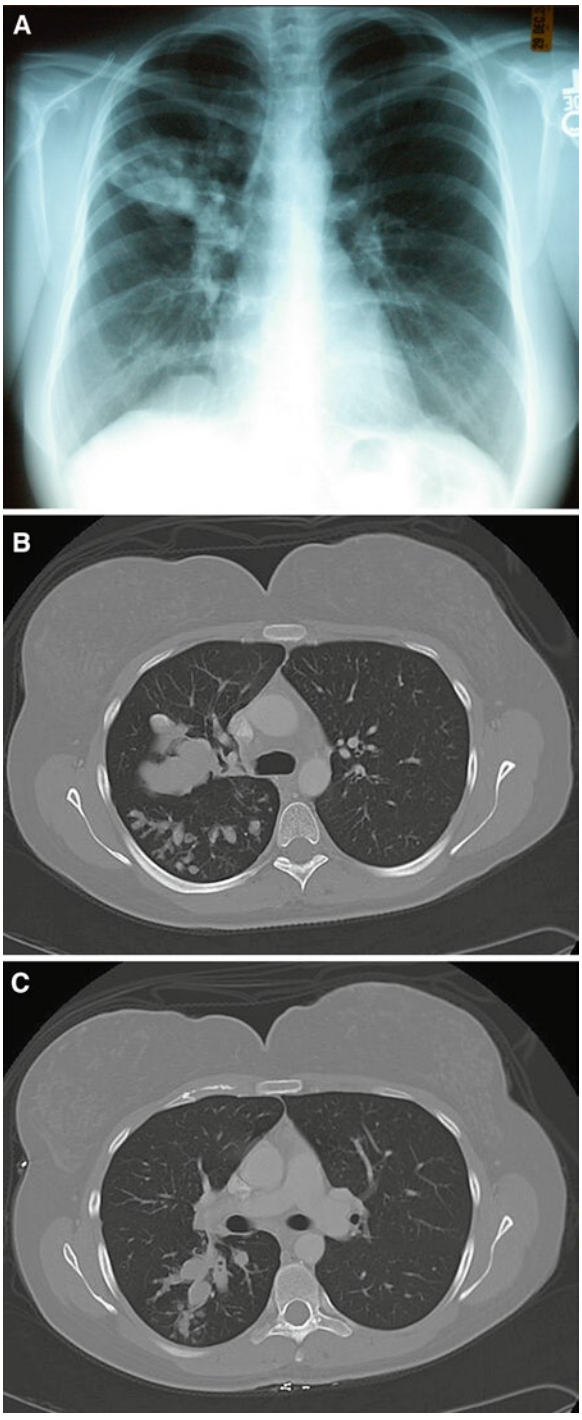

Fig. 1. PA and lateral chest radiographs of a woman with ABPA: dense airway filling and parenchymal infiltrate are present. The companion CT images show finger-in glove finding of mucus filled and grossly dilated airways, and findings of bronchiectasis (dilated, thickened and irregular bronchi).

SEROLOGY

Serologic measures such as total immunoglobulin type E (IgE), and specific IgE/IgG (ELISA, immunoblot and/or immunoprecipitins) are helpful in the diagnosis and management of ABPA. Such immunologic testing in conjunction with antigen specific skin prick testing can detect if a patient has a significant allergic response to specific fungal antigens. Total serum IgE levels are used by most clinicians both for screening and to monitor response to therapy *(13, 22, 23)*. Levels greater than >1,000 ng/ml in patients with CF or others are considered consistent with a diagnosis of ABPA or poorly controlled disease. IgE levels often correlate well with clinical status and identify response to therapy *(31)*. Serial measurements of IgE thus may guide therapeutic efforts *(32)*. However, elevated serum IgE levels are not specific to ABPA and may also be elevated in other fungal infections, asthma without ABPA, SAFS, parasitic infections, and allergic rhinosinusitis. Total and specific IgE levels can be elevated in the absence of ABPA when bronchiectasis is present – some 11% of patients with CF and 17% of those with idiopathic bronchiectasis may have elevated levels with or without the other diagnostic criteria for ABPA *(33, 34)*. Notably, measurements of fungal specific or total IgG or IgA levels do not correlate with disease activity.

CLASSIFICATIONS OF ABPA

At least two different classification schemes have been proposed for assessing the severity of ABPA. The first, a staging system, reflects the various manifestations of ABPA but may not necessarily reflect the progression of disease. This places patients into five stages: I–V. The stages reflect a combination of disease response to steroids, severity of disease, time course and radiographic changes *(35)* (*see* Table 4).

The second classification system orders patients into groups based on radiographic abnormalities. This method, classifying patients based on varying degrees of structural lung damage (no changes, central bronchiectasis, central bronchiectasis and more), appears to order patients by severity of disease (mild, moderate severe) *(36)* (*see* Table 4).

A third classification system, using solely a radiographic scoring system has also been devised which roughly correlates with clinical disease *(37)*. This is supported by other observers who found patients with a greater mucus plugging on CT were less responsive to therapy.

APBA LOOK-ALIKES

A diagnosis of SAFS may represent a continuum along the spectrum of ABPA but is usually reserved for asthma patients with demonstrated reactivity to fungal antigens (20–30% of asthmatics) but do not meet all serologic diagnostic criteria for ABPA *(13, 14)*.

Allergic fungal sinusitis may be confused with ABPA, particularly since many asthma patients have concurrent sinus disease. Allergic fungal sinusitis is similar to ABPA but with the sinus cavities as the site of saprophytic infection and may be coincident with ABPA. (In one study some 13% of patients with ABPA had findings of sinusitis on CT *(29)*). Serologic measures (specific IgE/IgG ELISA, total IgE, specific

Table 4
Classifications of ABPA

Stage *(35)*	
I	Acute – meets diagnostic criteria and is responsive to steroid therapy
II	Remission – free of significant symptoms or asthma after steroid therapy
III	Exacerbation – characterized by periods of worsened symptoms, radiographs or increased serum IgE
IV	Corticosteroid-dependent asthma – patients unable to discontinue steroid therapy
V	Fibrotic disease – significant structural changes (radiographic) and irreversible airflow obstruction with steroid dependent asthma
Severity	
Mild – ABPA-serologic	
	Aspergillus skin test (+), elevated serum IgE and eosinophilia
Moderate – ABPA Central Bronchiectasis (CB)	
	Serologic diagnosis
	Central bronchiectasis on chest CT
Severe – ABPA-CB-Other radiologic features (ORF)	
	Serologic diagnosis
	Central bronchiectasis
	Other radiologic features, including: pulmonary fibrosis, blebs, bullae, pneumothorax, pleural effusion or collapse *(36)*

immunoprecipitins) will not distinguish ABPA from allergic sinusitis. Radiographic imaging (sinus CT) and suggestive findings on history and physical examination may identify this ABPA look alike.

Individuals with CF, an autosomal recessive genetic disease, have a relatively high incidence of ABPA (2–15%) as compared to the general population *(1, 3, 38)*. Whether this reflects a genetic predisposition or an increased risk due to the associated bronchiectasis remains uncertain. Rarely, the onset of ABPA may actually represent the first sign of CF. Based on retrospective analyses of patients with ABPA, some investigators suggest that CF genes are more common in individuals with ABPA *(39)*. They suggest that individuals who are heterozygotic for a gene which causes CF are predisposed to develop ABPA. However, there are no prospective population studies to confirm this interpretation.

Other eosinophilic pneumonias should be kept in mind when considering ABPA. These loosely describe a collection of pulmonary pathologies associated with elevated serum eosinophil levels such as the pulmonary infiltrates with eosinophilia (PIE) syndromes. Of these diseases, Churg–Strauss and infectious eosinophilic pneumonias bear some resemblances to ABPA. Both may be associated with wheezing, eosinophilic pulmonary infiltrates and blood eosinophilia.

The allergic granulomatous, angiitis and periarteritis nodosa of Churg and Strauss often has systemic findings due to vasculitis. The eosinophilia is much greater than typically seen in ABPA. Definitive diagnosis relies on pathologic examination of a biopsy *(40)*. Infectious eosinophilic pneumonias, which may result from infection with an endemic parasite (e.g., Paragonamiasis, Strongyloides) or fungi (i.e., *coccidioides immitis*),

characteristically present with very high levels of eosinophilia, exposure to the infecting agent and prominent systemic infectious manifestations *(40)*.

THERAPY

The related goals of therapy, preservation of respiratory function and control of symptoms guide therapeutic decisions. Total serum (i.e., not *Aspergillus*-specific) immunoglobulin, type E (IgE), levels provide measures of allergic disease and response to therapy *(13, 22, 23, 32)*. Additionally, pulmonary function testing, patient symptoms, other markers of inflammation and radiographs are used singly and in combination to adjust therapy.

The unchecked inflammation and the implication that this inflammation is ultimately destructive to the airways supports the primary therapy with corticosteroids aimed at control of inflammation. There is also an emerging body of literature illustrating the importance of antifungal therapy for ABPA *(14, 16, 32, 34, 41–44)*. Since asymptomatic patients may have progressive disease *(20)*, we also follow total IgE levels, chest radiographs and respiratory function to monitor disease activity. In stable patients, quarterly or semi-annual assessments with improvement prompt a decrease in steroid dosing. Patients with worsened findings trigger increased or resumption of steroid therapy and consideration of antifungal medication. In nonresponsive or recalcitrant cases, we pursue a reevaluation for IFI (using imaging, biopsy, serum or BAL galactomannin *(16)*, and/or serum 1→3-Beta-D-Glucan *(17, 18)*), super infection or a secondary diagnosis.

Despite control of pulmonary function, symptoms and radiographic abnormalities, some patients will have persistently elevated IgE levels. Thus, a 50% decrease in total IgE has been proposed as an alternate measure of significant response to therapy.

CORTICOSTEROIDS

Oral corticosteroids are the mainstay of therapy for ABPA. The use of corticosteroids in ABPA has moderate case-based data and empiric clinical evidence as support. In a 1973 review of 50 patients with ABPA, Safirstein found steroid therapy (average daily dose: 10.5 mg) decreased the frequency of exacerbations *(20)*. Common practice initiates therapy with a daily dose of 0.5 mg/kg. In acute cases, steroids are administered for 2–8 weeks followed by a gradual reduction. The reduction of steroids is guided by symptoms, serology, pulmonary function testing and radiographs. The sequential tapering down of steroids may be to lower daily doses or more commonly to every other day dosing.

In an effort to decrease the adverse effects of systemic steroids, inhaled steroids are often proposed as possible adjuncts to disease control. While many clinicians may prescribe inhaled steroids, they are routinely employed primarily as therapy for the coincident asthma. A few case series suggest some efficacy in control of symptoms using inhaled corticosteroids *(45)*. More formal prospective trials have only shown better asthma control without significant benefit in other ABPA disease manifestations *(46)*.

Allergen avoidance is a long-standing therapeutic recommendation for allergic diseases. Unfortunately this is not easily accomplished in the case of ABPA and has yet to prove clinical benefit. *Aspergillus* is a nearly ubiquitous organism, as such, environmental control is unlikely. Additionally, the patient themselves harbors the antigen source

within their own airways. Since the offending organism/allergen has taken up residence in the patient, antifungal medications have been used in an attempt to decrease the allergen load and saprophytic organisms.

ANTIFUNGAL MEDICATIONS

For several decades antifungal medications have been considered and used in patients with ABPA in attempts to decrease the antigen burden and need for steroid therapy. Initial trials of inhaled antifungals such as natamycin and more recent efforts failed to show clinical efficacy *(47, 48)*. Inhaled, instilled and systemic delivery of amphotericin has been used without formal assessments. However, the azoles, a newer group of antifungal medications, may have some utility in ABPA and have been the subject of a number of studies in ABPA (*see* Table 2).

Ketaconazole, the first studied, showed some clinical improvements but the associated risk of liver toxicity and adrenal suppression has prevented it from gaining much use in ABPA. Itraconazole with moderately good oral preparations, better safety profile and excellent activity against aspergillus species has shown an ability to decrease the average steroid dose (14 mg per day) needed for ABPA *(41, 49)*. Most reports are of case–controlled studies, but recent blinded, prospective trials have shown modest benefits with the use of itraconazole *(42)*. The mechanism of these ascribed benefits may be through inhibition of fungal growth, interference with steroid metabolism, anti-inflammatory effects or some other yet to be recognized process. Voriconazole, another azole with a good oral preparation and excellent efficacy against aspergillus, may also prove useful but lacks rigorous clinical testing *(43, 50, 51)*. One set of two cases reports clinical response in patients treated with posaconazole after azole resistant isolates were identified *(73)*.

For patients who respond rapidly and remain stable after moderate courses of steroids, the added expense, monitoring and additional risks of oral azole therapy may not be justifiable. On the other hand, for patients in whom the adverse effects of corticosteroids are severe and have disease severe enough to need prolonged daily therapy, the corticosteroid sparing effects of adjunctive azole therapy appear worthwhile.

OMALIZUMAB

Omalizumab, a humanized monoclonal antibody of IgE, inhibits IgE binding to receptors on effector cells. Periodic injections of omalizumab improve clinical control in patients with allergic asthma (and moderately elevated serum IgE levels) *(52)*. Off-label use in patients with ABPA has shown clinical improvement and decreases corticosteroid requirements for disease control in small studies *(53–57)*. There is currently a randomized, double-blind placebo controlled study of the use of Omalizumab in CF patients with ABPA. (http://www.clinicaltrials.gov/)

OTHER THERAPEUTIC CONSIDERATIONS

Other considerations in the management of ABPA relate primarily to the complications of bronchiectasis and medical therapies.

The associated bronchiectatic airways of ABPA thwart the normal mucociliary clearance of the lung. Devices and maneuvers to improve airway clearance have become a standard in the management of bronchiectasis *(58)*. As an adjunct to chemotherapy, sputum clearance may be of benefit to patients with ABPA particularly if they have already developed significant bronchiectasis.

The progression from a noninvasive hypersensitive state to a disseminated infection, albeit rare in the immunocompetent host, remains of concern in patients with ABPA. Consideration of a disseminated infection presenting with characteristics of ABPA should be considered even in an immune competent patient. Chronic corticosteroid therapy should be considered as a risk for development of subsequent invasive disease *(59)*. Since corticosteroids are the primary therapy of ABPA, any progression to invasive or disseminated disease must always be kept in mind. Radiographic imaging can usually distinguish an invasive pattern from aspergilloma type or allergic related disease patterns in addition to the BAL and serum markers listed above *(16–18)*.

The damaged bronchiectatic airways of the ABPA patient bring increased risk for other airway infections as well. Bacterial super infection should be considered in the ABPA patient who worsens or has increased symptoms despite appropriate therapy. Probable pathogens are numerous, but are likely to be those most commonly implicated in nonspecific bronchiectasis: *H. influenza*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and mycobacterial species *(1, 60, 61)*. Intermittent surveillance with sputum cultures may identify the probable pathogens and the chronically infected, at risk patient.

An increased risk of hemoptysis accompanies most diseases with chronic lung infections or bronchiectasis. ABPA is no exception. Small amounts of bloody sputum may be present with cases of more severe ABPA disease. Should severe hemopytsis develop, an aspergilloma or bronchial artery source should be considered. Chest imaging can usually identify an aspergilloma which may require definitive treatment of bleeding with surgical resection *(12)*.

SUMMARY

Allergic bronchopulmonary aspergillosis is a potentially severe and destructive lung disease which may accompany asthma and CF. A diagnosis of ABPA should be suspected in patients with asthma who have difficult to control symptoms, require systemic steroids for control, have sputum production or have abnormal chest radiographs. The diagnosis of ABPA is made when a specific and intense allergic response to *Aspergillus* species is present in a patient with asthma without evidence of invasive fungal disease. Serum IgE levels (>1,000 ng/mm^3) are sensitive for diagnosis and assist in management. Therapy aims to preserve lung function, maintain quality of life, and reduce exacerbation rate through the control of the inflammatory response with prednisone and decreasing antigen exposure. Antifungal therapy with azoles may decrease the need for systemic steroid therapy and improve lung function. Omalizumab has demonstrated some potential to be a steroid-sparing therapy.

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14 Rhinitis, Sinusitis, and Asthma

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Contents

KEY POINTS

- Rhinitis, sinusitis, and chronic rhinosinusitis (CRS) are common co-morbid findings in asthmatic subjects.
- Rhinitis, sinusitis, and CRS arise along a continuum of shared etiologies: allergy, anatomic obstruction, and environmental factors can cause a breakdown of normal immune response and mucosal clearance.
- Upper and lower airway mucosal tissues are similar and share physiologic attributes and responses to certain signals.
- The upper airway is the air "conditioner," the filter, and the immune guardian of the lower airway.
- There are potential neurologic reflex links, cytokine communication, direct physical communication, and shared inflammatory pathways in common between the upper and lower airways.

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- Common pathways may act to generate similar responses in lower airways in the presence of upper airway inflammation.
- There are well documented epidemiologic links between upper airway inflammation and enhanced inflammatory response in the lower airway.
- Addressing upper airway inflammation has been shown to elicit a beneficial lower airway response in asthmatics.
- Aspirin sensitivity demonstrates a unique etiology of upper and lower airway inflammation.
- Aspirin desensitization has been shown to improve clinical wellness and reduce medication requirements aspirin sensitive in appropriately chosen subjects.
- Incorporating upper airway clinical management tools for asthmatic patients improves outcomes and reduces morbidity and cost of care.

INTRODUCTION

Asthma and sinusitis are both described in ancient medical literature. The word asthma is a derivation from the ancient Greek, *aazein*, meaning "gasping" or "panting." (Homer, Iliad, book 15. The term "asthma" was used to describe Hector's state: "He saw Hector lying on the ground with his comrades gathered round him, gasping for breath.") Similar descriptions exist in medicinal remedies recorded from ancient Egypt, and it is from ancient Egypt that some of the first references to the potential shared pathophysiology of asthma and rhinitis/sinus disease originate. Interestingly, peppermint vapor and other herbs (and paraphernalia for its delivery) were used to treat both rhinitis/sinusitis and asthma. Perhaps the first documented connection between asthma and the sinuses dates to approximately 1000 bc with medicinal "Peppermint buckets" being found in Egyptian tombs. It is thought that this remedy was prescribed for treating upper and lower airway maladies. (Ebers, George, 1873–1874, "Ebers Papyrus" describing treatment for asthma using heated herbal preparations found on Egyptian papyrus describing the treatment of various maladies.)

It was not for another 2,200 or so years until there were follow-up data supporting this connection.

In the modern world, physiologic unity between the upper and lower airway has been proposed for over a 100 years. In the late 1800s, Kratchmer demonstrated that chemical irritation of the nasal mucosa of cats and rabbits with ether, tobacco smoke, or sulfur dioxide resulted in bronchospasm *(1)*. In succeeding years, several authors postulated that a relationship existed between rhinosinusitis and asthma in humans based on clinical/anecdotal observations *(2)*. Keller noted, in 1920, that 86% of patients with lower respiratory disease complained of concurrent nasal symptoms *(3)*. In 1925, Gottlieb expanded the reflex hypothesis to include four possible mechanisms to support the association between sinusitis and asthma; mucopurulent postnasal drainage leading to infection of the trachea and bronchi, absorption of "toxic products" from retained purulent sinus material, nasal obstruction leading to mouth breathing of cold, dry air and the related induction of bronchospasm, and nerve reflex bronchospasm through irritation of the "nasal ganglion" *(4)*. After reviewing 1,074 cases, Rackemann and Tobey wrote in 1929 that "lesions in the nose and sinuses….may develop from the same fundamental cause as the asthma itself" *(5)*. By the 1930s, a clearer epidemiologic relationship between upper airway disease and asthma was established, but the potential for benefit

of identifying or treating sinus disease in asthmatics was largely ignored *(6)*. Ironically, at the same time, the connection between asthma and sinus disease found its way into popular culture before it became established in the medical community *(7)* with many references to the overlap between the upper and lower airways appearing in the general media of the time. One enterprising physician advertised and marketed a combined asthma and sinus disease cure, "Glyoxilide," a sham product promoted as a cure for asthma and sinusitis with the anecdotal reported benefit of: "Hay fever, asthma, severe sinusitis, generalized, pigmented, itching hives constantly……One dose of glyoxylide was given in May, 1934. Recovery complete in all respects within 6 months." The product was ineffective, but the connection between the upper and lower airway was prescient *(8)*. In the following decades, the embers of this concept were kept smoldering by otolaryngologists. In the 1940s and 1950s, a considerable number of sinus surgeries were performed with the sole intent of trying to improve the clinical status of asthmatics that were refractory to other interventions. The goal of these surgeries was to identify and remove purulent or diseased tissue and improve the patency of the nasal airway, thereby improving lower airway function. Anecdotal reports of significant benefit were noted for many patients *(9)*. However, until the 1960s, improvements after sinus surgery were mistakenly thought to be related more to a placebo response rather than an actual physiologic response generated by the surgery, minimizing the potential physiologic connection between the sinuses and the lungs. In the late 1960s, at the dawn of the "imaging age," descriptions of cases began appearing wherein asthma control was achieved following sinus surgery for chronic sinus disease. This connection was more widely considered with the dawning of the age of CT when sinus abnormalities became more easily definable. However, critics continued to point to a lack of physiologic proof to support a specific mechanism to explain the relationship between sinusitis and asthma *(10, 11)*.

A link between the upper and lower airway still seemed logical and intuitive. The nasal and bronchial airway have many common features: both are lined by pseudostratified epithelium, and share an array of similar excretory cells, immune cells, immune mediator responses, and have shared/communicating neurologic pathways. Furthermore, studies previously cited from the early 1900s demonstrated a shared direct and indirect nasobronchial reflex. Later, researchers furthered these concepts by demonstrating a neurologic reflex between nose and lung – with cold, dry air nasal challenges producing direct bronchial constriction *(12)*.

Advancements in molecular immunology have given birth to studies showing a correlation between chronic lower airway neurotransmitter release and recruitment and potentiation of lower airway inflammatory infiltrates. The upper and lower airway appear to share similar responses to inflammatory mediator release, with many cytokines having similar physiologic effects on both upper and lower airway mucosa. Systemic circulating levels of these mediators have been shown to be elevated as a result of upper or lower airway inflammation *(13, 14)*. Beyond the direct neurologic connection, further studies suggested that there is likely a significant amount of indirect neurogenic communication facilitated by these mediators. The lungs can be seen as "innocent bystanders," being prompted to respond to mediators produced "at a distance." Examples of this sort of connection can be seen with both allergic and nonallergic (viral, irritant) stimulation that is limited to the upper airway, and also manifests itself with a lower airway response (Table 1) *(15, 16)*.

Table 1
Inflammation of the Upper Airways can Influence the Lower Airway

- Common viral illnesses, allergic rhinits and sinusitis can aggravating and/or cause lower airways disease
- Treatment of the nose and sinuses prevents or improves asthma symptoms and lower airway hyperresponsiveness

PATHOPHYSIOLOGY OF RHINOSINUSITIS

Rhinitis and Sinusitis

Rhinitis and sinusitis are manifestations of inflammatory processes involving the nasal and/or sinus mucosa. Sinusitis is regarded as a combined inflammatory and potentially infectious milieu. Rhinitis and sinusitis commonly coexist (at least transiently) in affected individuals; hence, the terminology *rhinosinusitis.*

Not all forms of rhinosinusitis share a common pathology.

1. *Acute* (<2 weeks of symptoms) and *subacute* (2–6 weeks of symptoms) *rhinosinusitis* (ARS) are usually infectious in nature and most commonly follow a viral upper respiratory tract infection. Local inflammation results, which alters the character of the underlying mucosa, changes the character of mucus produced (making mucociliary clearance less effective) and alters the patency of mucosal ostia – facilitating subsequent bacterial infection. *Recurrent acute or subacute* rhinosinusitis assumes there is complete clearing in-between events. Subacute and recurrent rhinosinusitis commonly have another underlying pathology beyond a simple infectious trigger that promotes a recurring pattern or persistence, such as underlying allergy or structural abnormalities of the nose and/or sinuses.
2. *Chronic sinus disease* (>6 weeks of symptoms) results from a wide range of processes, not all of which are clearly infectious in origin. Still, all forms of rhinosinusitis are commonly treated with antibiotics, sometimes exclusively and often for prolonged periods of time with variable levels of success *(17)*.
3. *Rhinosinusitis with polyposis* represents a subgroup of chronic rhinosinusitis (CRS), whose infectious component is typically a secondary event, promoted by obstruction of mucosal drainage and aeration pathways by the polyps' mass *(18)*.

As noted above, inflammatory events in the nose frequently lead to some element of sinus ostia occlusion. Occlusion of the ostia prevents normal mucus drainage and reduces oxygen tension in the sinuses. This increases the acidity of sinus secretions, impairs function of the cilia, diminishes the integrity of the sinus mucosa, and inhibits the normal bactericidal function of granulocytes. Such a sequence of events leads to changes in the sinus flora which favor overgrowth of bacterial species that thrive in lower oxygen environments. Ostial obstruction also causes (relative) negative atmospheric pressure to develop within the sinuses. Both the negative pressure and the mucosal dysfunction within the sinuses allow the altered nasal flora to overcome the usual mucosal ciliary beat patterns and enter the sinus cavities resulting in infection *(19, 20)*.

Nearly all cases of acute and subacute rhinosinusitis have been shown to have a bacterial component; with *Streptococcus pneumonae*, *Haemophilus influenzae*, or *Moraxella catarrhalis* (found particularly in children) being found with the greatest frequency. The relative incidence of each may vary by community according to prevalence of pneumococcal vaccine use, relative ages, antibiotic use, and other factors. Bacterial pathogens can be grown from tissue obtained during sinus surgery in nearly all cases of CRS. In patients with chronic sinus disease, Staphylococcal incidence rises. Even fungi and anaerobic bacteria can be cultured from a minority of tissue samples in CRS *(21)*.

Histologically, acute, subacute, and CRS without nasal polyps are characterized by a predominantly neutrophilic inflammation; CRS with nasal polyps is characterized by predominantly eosinophilic inflammation except in conditions such as cystic fibrosis and bronchiectasis *(22–24)*. An additional role has been proposed for resident staphylococcal-derived superantigens in the pathogenesis of CRS associated with nasal polyps, as well *(25)*. There is no doubt that the inflammatory cells seen in CRS are activated as if there were ongoing exposure to an antigen but why some patients evolve into a chronic eosinophilic inflammatory state and others a primarily neutrophilic state remains elusive and beyond the scope of this chapter.

In general, the greater the chronicity of rhinitis, the greater the apparent contribution of eosinophils to the inflammatory milieu. Eosinophils can secrete more than 30 different kinds of cytokines and chemokines, which can exert effects on other immune cells: up-regulating or down-regulating various lymphocyte subtype activity. In CRS, the secretion profile favors pro-inflammatory cytokines (e.g., IL-4, IL-5, IL-13) and chemokines (e.g., eotaxin) which appear to play a direct role in ongoing active rhinitis and sinus disease and an indirect role by recruiting cells that favor the establishment of chronic inflammation *(26)*.

What are most consistently seen in asthmatic CRS are immunologic and cellular changes suggestive of a Th2-like eosinophilic inflammation. Eosinophils contribute to direct epithelial damage, promoting ostial closure and proliferation of polypoid disease. Resident epithelial and mast cells and other tissue-infiltrating cell types such as dendritic and T helper cells also contribute to perpetuating eosinophilic inflammation inherent to both the upper and lower airway.

Genetic advancements have further supported the importance of the eosinophil in understanding upper and lower airway interactions. Changes in gene expression preceding chronic eosinophilic inflammation are not fully understood. However, the identification of overlapping genes and gene networks common to allergic rhinitis, chronic eosinophilic rhinosinusitis with or without nasal polyposis, and asthma support a common origin of eosinophilic inflammation uniting the upper and lower airway *(27)*.

Allergy plays a significant role in the development of rhinitis, asthma, and CRS *(28, 29)*. Nevertheless, there is some discordance between markers of the atopic phenotype and the nasal–sinus inflammatory mechanisms that are associated with eosinophilic inflammation. For example, in patients with nasal polyps, neither total IgE concentrations, eosinophilic cationic protein (ECP), IL-4, or IL-5 concentrations appear differently in allergic (atopic) vs. nonallergic subjects *(30)*.

Furthermore, there can be other important factors that may promote CRS independent of eosinophilic-based disease or classic atopy. These include unfortunate anatomy (anatomic variation that does not readily facilitate mucociliary clearance and easy drainage of mucus, such as septal deviation, hypertrophic turbinates, concha bullosa), exposure to air pollutants (ozone, diesel emission particles, smoke) medications that may alter fluid status (diuretics, anticholinergics) and coexisting diseases that alter the character of nasal/sinus mucus production (e.g., cystic fibrosis) and mobility (ciliar dyskinesia).

The link between CRS and asthma will be explored further, but even something as apparently disconnected from airway reactivity as postnasal drip and resultant cough can impact the lower airways. What remains clear is the fact that the immunologic and pathologic changes seen in nose during allergic activation and in the sinuses during acute, subacute and chronic sinusitis share many (most) features of the inflammatory physiology of asthma. These common features form the foundation for considering the causal link between CRS and asthma. The frequency with which asthma emerges in this clinical setting, particularly in the presence of polypoid sinus disease, suggests a close relationship.

POSTULATED MECHANISMS TO EXPLAIN THE RHINOSINUSITIS–ASTHMA RELATIONSHIP

There is an old adage, "The nose is the preferred organ of respiration." The nasal cavity serves several important purposes in preparing inspired air for the lower airways. The main function of the nose is to act as a conditioner of inhaled air so that it reaches the lower airways in a state that maintains optimal lower airway mucosal function (Table 2).

The anatomic characteristics of the nasal passages provide the capacity to warm, filter, and humidify inspired air. The nasal mucosa and turbinates are generously vascularized, and serve a significant role in humidifying air as it is transported to the lower airways. The nasal mucosa is also able to alter the temperature of inspired air as it passes to the lower airways.

A dense, subepithelial capillary network provides warming and the potential to increase the nasal surface area. Pooling of large volumes of blood in the venous sinusoids that lie below the subepithelial capillary network allows the submucosal tissue to engorge, and this increases (edit for syntax) contact surface area with the inspired air stream. Activation of the approximately 45,000 seromucous submucosal glands in each nasal cavity and of the abundant goblet cells provide significant air humidification – up to 80% for the more delicate lower airway surface.

Table 2
The Nose as a Protective Organ

Warm inspired air for the lower airway
Humidify inspired air to 80%
Filter particulates and noxious chemicals
Antibacterial/antiviral mucous barrier
Nitric oxide infectious protection

In addition to preparing air for delivery to the lower airways, the nose is also an important filtration device for removing particulate matter and gaseous materials from inspired air and preventing delivery of these particles to the lower airway. A network of coordinated microcilia clean the mucosal surface of the sinuses and nose in an escalator-like fashion, moving the secretory layer of nasal mucous to the nasopharynx where any trapped particles or absorbed gases are swallowed and eliminated through the gastrointestinal tract.

This filtration function is also important for antimicrobial protection of the lower airways. The nasal mucosa is a major site of IgA secretion/expression (and some IgG secretion). IgA and IgG are produced by plasma cells adjacent to submucosal glands, and these immunoglobulins function to inhibit the attachment and proliferation of pathogenic organisms.

There is much more to the nasal immune defense repertoire than immunoglobulin activity. Other components of nasal secretions are important factors of the body's innate immune defenses. The antimicrobial action of nasal secretions was specifically commented upon by Alexander Fleming in his search for antimicrobial compounds in 1922. Since that time, a multitude of defensive compounds have been described. Nasal secretions contain several known antimicrobial proteins and peptides, including lysozyme and lactoferrin, secretory phospholipase A_2, defensins, statherin, mucus glycoproteins, secretory leukoprotease inhibitor (SLPI), uric acid, peroxidase, aminopeptidase, immunoglobulins, and neutral endopeptidases. The nasal mucosa is the first outpost of the immune response of the airways *(31, 32)*. Mediators of innate mucosal host defense found in nasal secretions can act to selectively disrupt bacterial cell walls and membranes, sequester microbial nutrients, or act as decoys for microbial attachment.

Additional antimicrobial protection is achieved through a vigorous cleansing mechanism and the production of nitric oxide (NO) primarily produced from the sinuses. NO produced by the upper airways plays a protective role for the entire respiratory tree. NO has strong antiviral and bacteriostatic activity, improves oxygenation, can affect vascular tone, exerts bronchodilatory effects, and modulates lower airways responsiveness. It is important to note in the context of this chapter that NO production is reduced or absent in several chronic inflammatory conditions of the upper airway including CRS with or without nasal polyposis *(33)*.

All these functions rely on a reactive network (including nervous tissue) capable of responding to the character of the inspired air reflexively with the goal being to provide the healthiest air possible for the lower airway. When any of them go awry, upper *and* lower airway calamity may ensue.

For example, in studies of exercise-induced asthma, the bypassing of nasal breathing with exaggerated mouth breathing can act as a physiologic trigger for bronchospasm by inhibiting the upper airway's ability to adequately adjust humidity and temperature of air as it is rapidly passed on to the lungs. In patients who have undergone laryngectomy and have chronic tracheostomies, chronic bronchitis associated with grossly impaired tracheal mucociliary function and bacterial colonization frequently develops.

Whatever the mechanism, it appears that inhibiting the functional capacity of the sinuses and nose deprives the lower airways of various protective mechanisms, with detrimental consequences.

Nasobronchial Reflex

It has been nearly a century since Sluder first proposed that nasal irritation could cause bronchial hyperreactivity (BHR) and lead to the development of bronchial asthma. In this paradigm, nasal stimulation, through an afferent arm of the trigeminal nerve in the pharyngolaryngeal area induces bronchospasm through vagal efferents. The most cited study in the last 50 years supporting this theory is by Kaufman et al. *(34)*. In this study, six patients without known lung disease underwent unilateral trigeminal nerve resection for neuralgia. Using silica as a nasal irritant, each nostril was sequentially challenged. The un-resected side, when challenged, demonstrated a decrease in lung function with concomitant bronchoconstriction. This response was inhibited by pretreatment with topical atropine. The same response was not seen when the same challenge was given to the resected side, suggesting a cholinergic reflex arc mediated by the trigeminal nerve afferents.

Since this report, additional evidence supporting the nasobronchial reflex theory has been conflicting. Further animal studies conducted with thermal, chemical, and mechanical stimuli failed to demonstrate reflex changes in the lung. However, nasal provocations with high flow bursts of cold, dry air in both patients with asthma and healthy controls produced an increase in lower airway resistance; A similiar response was not seen when warm air was used nor when cold air was delivered into the mouth. Furthermore, the nasal application of lidocaine and the inhalation of atropine reduced the effect of nasal cold air provocation on the lower airways. Togias demonstrated that 30% of patients with active rhinitis and asthma will experience a brief sudden reduction in FEV1 and FVC with the topical nasal application of capsaicin *(35)*. Corren reviewed all studies up to 2007 and concluded investigations of a neural connection between the nose and sinuses and the lung are inconsistent *(36)*.

These findings suggest that the role of a direct nasobronchial reflex arc in asthma is unclear and not likely to be clinically relevant beyond brief episodes of asthma worsening. Furthermore, tachyphylaxis of the sensory nerves to repeated stimulation makes this mechanism less important in the overall scheme of asthma care. Still, in active allergic disease, the neurosensory apparatus of the upper and lower airway are up-regulated to a state of hyperresponsiveness which could then be more susceptible to such reflex stimuli, at least transiently *(37)*.

Systemic Response to Cellular and Soluble Inflammatory Materials Originating in the Nose and Sinuses

There is considerable evidence to support a systemic link between the upper and lower airway in asthma. Activated eosinophil counts are found in asthmatic patients with and without AR but not in healthy control subjects. Asthmatic patients with or without rhinitis have elevated numbers of eosinophils in the nasal mucosa compared with controls. Provocation studies with histamine, allergen, and rhinovirus are also supportive of a link. Stimulation of the nose by histamine or a sensitized allergen can result in a fall in FEV1 in patients with pure allergic rhinitis and no prior evidence of asthma either clinically and/or by pulmonary function testing. Nasal challenge with allergen results in an influx of eosinophils in both the nasal and bronchial mucosa, correlating

with an up-regulation in the bronchial mucosa of adhesion molecules ICAM-1, VCAM-1, and E-selectin *(38)*. The reverse also occurs following segmental bronchial allergen provocation/challenge with allergen, resulting in an increase in nasal mucosal eosinophils, mast cells, basophils, eotaxin-positive cells, and levels of interleukin-5. In grass-sensitive allergic rhinitis patients without asthma, segmental bronchial stimulation with grass antigen can produce nasal and bronchial symptoms as well as a diminution in pulmonary and nasal function *(39)*.

In these examples, there is a sort of "innocent bystander" effect demonstrated by the section of airway that was not directly challenged by allergen, but responds in kind by virtue of the tissues sharing responsiveness to chemical signals released locally and then exerting an effect at distant sites *(40)*.

This effect has an "endocrine" effect with regard to airway communication and shared responses to environmental challenges.

Further, cytokine release (IL-5) can also exert an effect on bone marrow and produce increases in eosinopoiesis, priming an "inflammatory directionality" to immune responsiveness. Other cytokines are released that also contribute to driving cellular profiles that favor an ongoing allergic/inflammatory response, as well, and can act to favor the production of pro-inflammatory T-cell profiles (TH2) that perpetuate the preferential expression of allergy/inflammatory phenotypes in patients with upper, lower, or both upper and lower airway allergic sensitization.

Another example of the shared upper and lower airway inflammatory relationship is shown by the effect of rhinoviral upper respiratory infections (URI) on asthma. Respiratory viruses evoke the production of a broad array of pro-inflammatory signaling compounds – IL-6, IL-8, IL-16, etc. that promote the influx and activation of lymphocytes, neutrophils, monocytes, and eosinophils resulting in a rather broad inflammatory milieu and accentuating airway reactivity. Studies have shown that the lower airway is more responsive to both histamine and allergen inhalation during a rhinoviral infection. Challenge studies inoculating allergic asthmatics with rhinovirus result in an increase in circulating neutrophils 48 h later and an increase in bronchial neutrophils 96 h later *(41)*.

Rhinoviruses are proven triggers of asthma exacerbations, with direct correlation between infections and increases in emergency room visits and hospitalizations *(42)*.

In allergic patients, a propensity toward TH2 (pro-allergic inflammation profile) vs. TH1 (not so much) profiles may also create differential immune responses to airway viral infections that predispose an allergic patient toward a flare of lower airway symptoms that would not be seen in a nonallergic patient. Allergic sensitization may prime a patient for exaggerated airway mucosal responses.

This upper/lower airway relationship is a very complicated dance. In one study, priming the nasal airway of individuals with allergic rhinitis with allergen was shown to reduce the severity and duration of an experimentally induced rhinovirus infection. This data suggests that part of the pathophysiology of upper airway induced lower airway inflammation/hyper-responsiveness may be an example of the upper airway acting in its own best interest at the expense of the lower airway.

Overall, there are good data supporting a systemic link between the upper and lower airway, with the greatest clinical correlation existing in atopic individuals.

Purulent Postnasal/Sinus Drainage with or Without Aspiration

Another theoretical link between rhinosinusitis and lower airway reactivity postulates that inflammatory materials from the upper airway are capable of reaching the lower airways through postnasal drainage and/or aspiration, especially at night, leading to deterioration of lung function, increased airways responsiveness, and the generation of lower airway symptoms. The rabbit model of acute sinusitis has provided strong evidence that such a mechanism might exist in humans *(43)*. The prominent occurrence of the "Chronic Upper Airway Cough Syndrome" such as following the common cold, suggests a possible mechanistic link. Furthermore, the beneficial response sometimes observed from the administration of drying agents such as decongestants and/or first-generation antihistamines suggests that such a postnasal drainage mechanism might exist, at least selectively in some patients. Supporting the concept of aspiration as a mechanism of asthma exacerbations in humans has proven more problematic. Many interventions directed at the upper airway may affect the lower airway, and vice versa. Chronic Upper Airway Cough Syndrome can be antibiotic responsive, but proving the location of a low grade infection as a primary etiology is difficult.

Regarding direct aspiration, some aspiration of nasal secretions has been shown to exist in normal individuals without clinical consequences. Furthermore, the only human study that has attempted to address the theory of aspiration in a direct fashion was Bardin et al. who injected 99mTc in the maxillary sinuses of patients with chronic sinusitis and moderate-to-severe asthma. This study did not support the aspiration model as a mechanism to explain changes in asthma activity *(44)*.

An animal model demonstrating the ability of laboratory- induced sinusitis to trigger asthma-like activity has been elucidated. Irvin, in 1992, induced sterile sinusitis in rabbits by injecting C5a des arg into the sinuses of New Zealand white rabbits and measured their pulmonary function and lower airway hyperresponsiveness *(45)*. This model demonstrated that lower airway hyperreactivity developed as a result of the complement-induced maxillary sinusitis. The authors reviewed each of the mechanistic models originally described by Gottlieb in 1925 and suggested that the most likely mechanism in this animal model was direct passage (postnasal drip) of inflammatory mediators from the upper to the lower airway that then induced an asthma-like condition.

In humans, it is not yet known if the Chronic Upper Airway Cough Syndrome is due to direct irritation or inflammation of lower airway structures that stimulates cough receptors and bronchial mucosal reactivity via postnasal drip *(46)*. The crucial unanswered question in the aspiration model is whether or not chronic low-grade purulent postnasal drip is sufficient to produce cough through direct drainage down the nasopharynx, or if it manifests primarily as overlapping responses to cell signaling pathways independent of potential aspiration, as mentioned in the first two hypotheses.

In creating a model of the upper airway's effect on the lower airway, more information is required before an exact mechanism can be definitively proven. Historically, it was thought that direct aspiration of digestive compounds was responsible for the correlation between GERD and asthma. A similar question must be asked for the notion of aspiration of upper airway contents. The lower airway is a highly protected area from aspiration syndromes. There are studies linking aspiration and GERD in children that manifests with lower airway reactivity, yet epidemiologic studies of adult stroke patients have not been able to correlate any neurologic loss of airway privilege with asthma other than the obvious mechanical risks of aspiration – chemical and bacterial pneumonia, etc.

Table 3
Proposed Mechanisms Explaining the Sinusitis/Asthma Association

Nasobronchial reflex via a trigeminal-afferent-vagal-efferent neural arc
Systemic response to cellular and soluble inflammatory materials generated from the nose/sinuses triggering lower airway hyperreactivity
Postnasal/sinus drainage with or without aspiration of mucopurulent material inducing lower airway hyperreactivity

Summary of Mechanisms

The clinical link between dysfunctional activity of the upper airway and pulmonary symptoms such as wheeze and/or cough appears secure; the exact mechanism(s) defining such a link remains elusive (Table 3).

The most compelling clinical evidence comes from exhaustive studies linking cough to rhinosinus diseases. Formerly broadly called the *Postnasal Drip Syndrome* (and now termed *Chronic Upper Airway Cough Syndrome*), pathology of the upper airway, particularly from the viral infections, is a major source of cough in the general population; and in asthmatics, flares of cough and wheezing associated with decline in objective measures of airway caliber. Although lacking specific pathognomonic features, this syndrome appears prominently in any algorithm describing the clinical evaluation of a patient presenting with chronic cough or wheezing.

Evidence-based guidelines extend the etiology of Chronic Upper Airway Cough Syndrome to include a wide array of various forms of upper airway pathology including (1) allergic rhinitis, (2) perennial nonallergic rhinitis, (3) NARES (nonallergic rhinitis with eosinophilia), (4) postinfectious upper airway cough, (5) bacterial sinusitis, (6) chronic sinusitis, (7) allergic fungal sinusitis, (8) miscellaneous forms of rhinitis due to physical or chemical irritants/aggravants, and (9) rhinitis of pregnancy. Although there is agreement regarding the clinical correlation, the pathophysiologic triggers have not been clearly defined and/or accepted. ACCP evidence-based clinical practice guidelines postulate that the nasobronchial reflex and/or postnasal drainage of inflammatory secretions may be more likely than systemic absorption of cellular and soluble materials.

This wide array of medical conditions with differing etiologies underscores the conclusion that while there is ready agreement about the existence of an upper and lower airway connection, researchers cannot define a single link common to support the epidemiologic findings. Whatever the specific the mechanisms, there is no doubt that a subset of patients with wheezing and or cough can experience significant clinical benefit from directing treatment to any coexisting upper airway pathology.

EPIDEMIOLOGY SUPPORTING THE RHINOSINUSITIS–ASTHMA RELATIONSHIP

Epidemiologic data supports an association between asthma and upper airway disorders such as rhinosinusitis and allergic rhinitis. The vast majority of studies suggest that the respiratory tract as a whole functions in a unified manner *(47)*. In general, rhinitis is

present in 28–94% of patients with asthma compared to 20% of the general population. Conversely, 19–38% of patients with rhinitis present with coexisting asthma. Rhinitis occurs simultaneously or precedes asthma in up to 64% of patients with asthma *(48)*. Even in rhinitis patients who do not carry a diagnosis of asthma, bronchial hyperresponsiveness can be demonstrated to varying degrees in up to 70% when compared to controls. There is the strongest association between allergic rhinitis and asthma with approximately 90% of asthmatics having some format of allergic rhinitis. Furthermore, there is an apparent relationship between the severity of allergic rhinitis and the severity of asthma. Those patients who have severe or poorly controlled allergic rhinitis tend to have more persistent asthma than those with mild or well-controlled rhinitis. Importantly, good allergic rhinitis symptom control is associated with better asthma control *(38)*.

The association between rhinosinusitis and asthma is equally strong. Nearly 100% of steroid asthmatics will have abnormal sinus CT scans. Nearly 90% of mild to moderate asthmatics will also have abnormal sinus CT scans. Using a combination of sinus CT scores and symptoms scores, three-fourth of all asthmatics with either steroid dependent or mild to moderate disease will have clinical evidence of rhinosinusitis *(49)*. Furthermore, there is a significant correlation between clinical and sinus CT scan severity scores in both groups with the more severe asthmatics having more severe sinus disease. Nearly all patients with CRS will have either a history of asthma, ongoing asthma, or demonstrable increased BHR as demonstrated by abnormal methacholine or histamine challenges *(50)* (Table 4) .

It can be argued that in nearly all patients with asthma, there is some evidence of upper airway dysfunction such as rhinosinusitis (Fig. 1). Still, these studies suffer from a lack of a clear definitive cause-and-effect pathway and the association may represent merely an epiphenomenon. The strongest epidemiologic evidence linking the upper and lower airways is studies demonstrating that atopy and particularly allergic rhinitis are risk factors of asthma as sinus disease. There is abundant evidence that patients with allergic rhinitis experience three to eight times the risk of asthma compared with those without AR. BHR, the hallmark of asthma, is present in a high proportion of patients with rhinitis, especially allergic rhinitis. Spirometric abnormalities and BHR can be frquently demonstrated in patients with only AR symptoms who deny asthma. At the cellular level, there is a significant relationship between nasal eosinophil counts and spirometric findings including FEF 25–75, FEV1, and BHR *(51)*. These observations underscore the concept that the intensity of nasal and sinus eosinophilic inflammation can significantly affect bronchial stability. This relationship has been acknowledged in several official position papers and international guidelines *(52)* (Table 5).

Table 4
Is Sinusitis Associated with Asthma?

- From 40 to 60% of patients with asthma have radiographic imaging evidence of sinusitis
- In children with asthma, the incidence of sinusitis may be as high as 75%
- Management of sinusitis in children and adults results in objective and subjective improvement of asthma

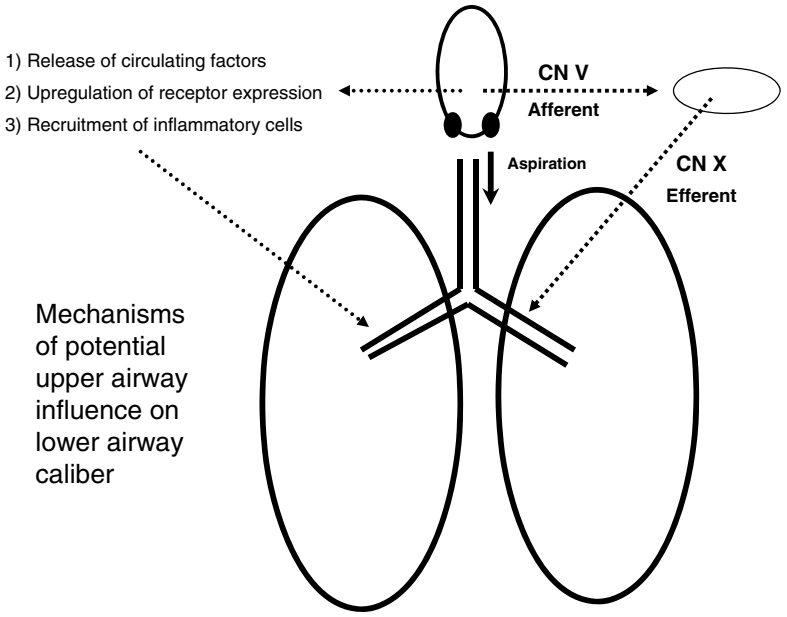

Fig. 1. Mechanisms of potential upper airway influence on lower airway caliber.

Table 5
Epidemiologic Evidence Supporting the Association of Rhinosinusitis and Asthma

- Rhinitis and asthma frequently occur together and are temporally related
- Rhinitis, particularly allergic rhinitis, often precedes asthma development
- Sinus mucosal changes by CT scan are found in nearly all patients with asthma
- The abnormal sinus changes as measured by CT scanning increase directly with asthma severity scores and steroid dependency
- Improvement in rhinosinusitis symptoms correlates directly with improvement in asthma severity scores and steroid dependency

Another way to view epidemiologically the relationship between rhinitis, rhinosinusitis, and asthma is to study the effect of rhinosinusitis treatment has on asthma stability. There are numerous studies that have demonstrated that both nasal corticosteroids and antihistamines improve lower respiratory symptoms and spirometric values and reduce bronchodilator use and admissions to the emergency room for asthma flares in atopic asthmatics. When there is a classic allergic asthma trigger such as seasonal AR and asthma, antihistamines and montelukast have been shown to be equally effective in reducing asthma symptoms and bronchodilator use. Allergists have long noted the "atopic march" when children and young adults develop allergic rhinitis and later develop intermittent or more chronic forms of asthma. Furthermore, interrupting the allergic evolution through immunotherapy can reduce the eventual appearance of asthma in these circumstances, at least in children.

Adult and pediatric patients who undergo successful surgical and/or medical treatment of their CRS often experience a decrease in requirement for asthma medications, improvement in pulmonary function, and fewer asthma exacerbations. Studies using a 2- or 3-week course of antibiotics such as a macrolide or a beta lactam accompanied by prolonged therapy with nasal douches and intranasal corticosteroids over several months result in both subjective and objective improvement in asthma symptoms severity. Ragab et al. published the first prospective study comparing surgical and medical therapy for patients with CRS with or without nasal polyps and asthma in 2006 *(53)*. They compared a 12-week course of antibiotics (erythromycin), nasal rinsing, and intranasal steroids compared to a surgical group who underwent first sinus surgery and then a 2-week course of the same medications. All patients stayed on nasal corticosteroids and rinsing. Both groups demonstrated improvement both objectively and subjectively in their asthma with a direct correlation between the improvement in upper airway symptoms, and asthma control (Table 5).

If the medical approach is unsuccessful, functional endoscopic sinus surgery (FESS) can follow. Improvement, in these circumstances, has been demonstrated in multiple studies in up to 90% of patients provided the presence of concurrent allergy or immune deficiency has been ruled out. Even patients with nasal polyps, CRS, and asthma report significant clinical benefit in both upper and lower airway stability scores following FESS intervention. The one subgroup of CRS with polyps and asthma that typically does poorly following FESS as measured by asthma severity and need for repeat sinus surgery is the acetylsalicylic acid (ASA)-sensitive asthmatic. We suspect that the source of treatment failure within this subgroup is the aggressiveness of the mucosal inflammation that exists as evidenced by the high rate of polyp regrowth, sometimes within days following surgery. These patients should be approached with caution and always managed in conjunction with allergy/immunology consultation.

THE EVALUATION AND TREATMENT OF THE UPPER AIRWAY IN ASTHMA

Diagnosis and Medical Management

The first step in making a diagnosis is considering a diagnosis. As seen in other chapters in this text, asthma can present in myriad ways, as can rhinosinusitis.

All patients presenting with asthma deserve a careful evaluation of the upper airway to optimize the management of their asthma.

The National Asthma Education and Prevention Program of the National Heart, Lung and Blood Institute stated in 2007 in their *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* that "recommends that clinicians evaluate patients who have asthma regarding the presence of rhinitis/sinusitis diagnosis or symptoms…..it is important for clinicians to appreciate the connection between upper and lower airway conditions and the part the connection plays in asthma management." Whether there is accompanying rhinitis or rhinosinusitis, the ultimate goal in any asthma patient is to achieve a clear upper airway. This can only be accomplished by defining the presence and source of any upper airway disease.

There is general agreement that no one causative factor fully explains or adequately accounts for the clinical and pathologic manifestations or the heterogeneity of rhinosinusitis.

There are numerous causes of the condition, including viral, bacterial, fungal, allergic and structural. In addition, many patients have seemingly idiopathic disease. CRS is particularly complicated and is further subdivided into CRS without polyps, CRS with polyps, and classic allergic fungal rhinosinusitis. Any sinusitis classification system must include information about the type of infection (viral, bacterial, and fungal), complications, inflammatory markers, and radiographic findings to categorize patients. Considering a more complex system of categorization allows the subdivision of patients into more detailed subgroups to help determine the precise target and therefore direct the most definitive intervention (Table 6) (Fig. 2).

The first step is to determine by patient history if he/she notes accompanying nasal symptoms with his/her asthma and whether symptoms are chronic or triggered by a season or other environmental precipitin. In children, a history of chronic mouth breathing and/or nocturnal snoring suggests the possibility of adenoidal or tonsillar-adenoidal

Table 6
CRS: 12 Weeks or Longer of Two or More of the Signs/Symptoms + Objective Measure

Signs/symptoms	*Objective measure*
Mucopurulent drainage (anterior, posterior, or both)	CT imaging demonstrating inflammation
Nasal obstruction	Polyps in the nasal cavity or middle meatus
Facial pain-pressure-fullness	Purulent mucous in the middle meatus or nasal floor
Decreased/absent sense of smell	Purulent stream in posterior oropharynx

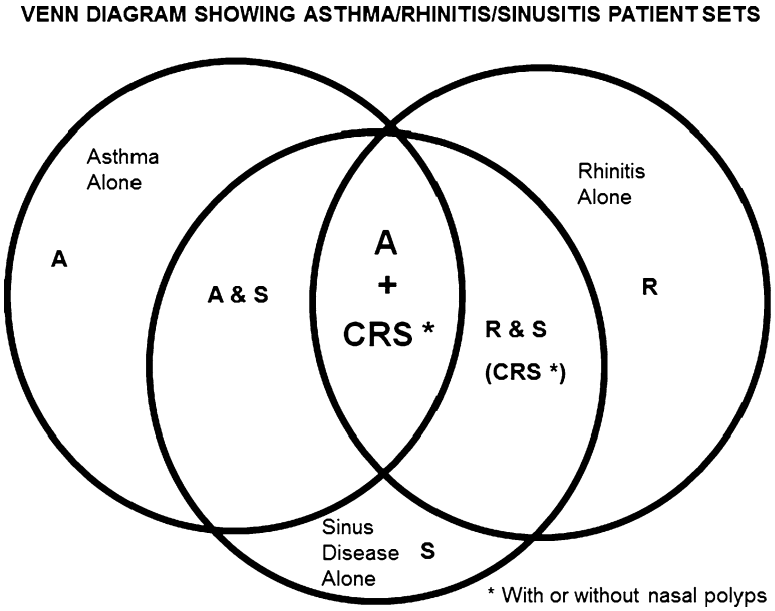

Fig. 2. Venn diagram showing asthma/rhinitis/sinusitis patient sets.

hypertrophy which is a common trigger of sinus disease, particularly between the ages of 4 and 12 years *(54)*. Also, one should determine whether sinus infection precedes or follows an asthma attack as well as the frequency of sinusitis and the results of antibiotic therapy. Fetid breath is also an excellent indicator of bacterial infection in both children and adults. Chronic sore throat is also a potential accompanying symptom. A key historical point common to most cases (~80%) of patients with nasal polyposis is a reduction or loss of sense of smell and taste.

An examination of the nasal passages should be undertaken for evidence of enlarged and/or obstructive turbinates, mucosal paleness indicative of allergic disease, and evidence of infection such as mucosal erythema, mucous bridging between the turbinates and septum and/or mucopurulent pooling of secretions on the floor of the nose. Oropharyngeal examination may reveal mucopurulent streaming down the posterior nasopharynx or "cobblestoning," a granular appearing posterior mucosa which is indicative of local lymphocytic hyperplasia. In children, this examination also provides a look at the tonsillar tissue for obstructive enlargement which may, but not always, accompanying adenoidal hypertrophy.

All patients with asthma which is chronic or episodic and accompanied by upper airway symptoms should have an imaging study of the sinuses. CT scanning has replaced regular radiography as the preferred imaging test to visualize the sinuses *(55)*. In most communities, the radiologist performs limited or "screening" CT scanning for about the same price as regular sinus radiography. In patients with sinusitis, localizing the condition by means of CT scanning and correcting anatomic factors is important. For episodic asthma, imaging is preferably done in between acute events mostly because we are interested in evidence of chronic disease and conditions that may impair drainage, especially from the maxillary ostia. Possible ancillary findings include nasal polyps, thickened mucosa, enlarged turbinates, concha bullosa, or even a deviated septum which compresses the sinus drainage areas (middle meatus). The magnitude and extent of any diseased sinuses can be clearly identified by this procedure. If the ostia are patent, the patient's condition should respond to systemic medical management. If the sinus openings are fully closed, systemic medical therapy may be insufficient, and surgical correction may be required. In any case, the presence of significant local (sinus opacification or an air-fluid level accompanied by diffusely thickened sinus mucosa) or diffuse sinus disease (multiple sinuses involved with mucosal thickening, opacification, and/or air-fluid levels) demands aggressive medical management with systemic and topical corticosteroids and 2–3 weeks of broad-spectrum antibiotics directed at those organisms commonly found in bacterial sinus disease.

Nasal irrigations or sprays with hypertonic and isotonic saline with or without concurrent nasal corticosteroids have been advocated as a long-term component in the management of CRS. The positive effects of washing the nasal cavities with hypertonic or isotonic saline include the elimination of allergens/pollutants and thinning and removal of secretions through reflex flushing of the sinuses and nasal cavity. A systematic review of eight studies demonstrated nasal hypertonic and isotonic saline (irrigation or spray) is a beneficial adjunct in the treatment of CRS. There is evidence in the literature that hypertonic and isotonic saline irrigation with Sinus Rinse (Rx) or the Netti Pot (Rx) is a more effective method of delivery than the spray format and should be encouraged.

Once medical treatment has been completed, reversibility and chronicity are then determined by the patient's clinical pattern following medical management and the results of a repeat imaging study which is typically done 2–4 weeks following the completion of antibiotics. It should be emphasized that one or two opacified ethmoid air cells or focal thickening of the floor of one or both maxillary sinuses is not typically indicative of clinically significant sinus disease but will still be reported by radiologists as "sinusitis." Additionally, the use of MRI imaging for making determinations about the severity of CRS is fraught with a high frequency of false-positive assessments and, as a consequence, disappointing therapeutic outcomes. Many radiologic reviews deem making a diagnosis of sinusitis with MRI scanning too undependable and should be approached with caution *(55)*.

Surgical Management

Surgery is reserved for patients who are refractory to medical treatment, have no major allergy trigger, or for patients with a clear anatomic obstruction as causes of CRS. Patients with CRS with nasal polyposis usually require surgery to remove the inspissated mucus and sinus ostia obstruction from polypoid tissue, thereby reestablishing sinus ventilation and drainage. Over the past two decades, the surgical management of CRS has evolved because of advancing technology an appreciation of the importance of maintaining as much normal anatomy as possible. FESS is the preferred invasive technique in which involved sinus air cells are opened under direct visualization and maximum nasal and sinus tissue is preserved. The goal of this generally well-tolerated procedure is to restore sinus ventilation and normal function of the mucociliary clearance system. As surgery strives to restore functional integrity of inflamed mucosal lining, a conservative mucosa-sparing approach is strongly advocated.

Despite the widespread use of FESS in the management of CRS, a Cochrane review by Khalil and Nunez concluded that there is a lack of good evidence in the literature for its superiority over medical treatment in CRS *(56)*. This is likely a reflection of the lack of randomized trials designed directly to compare medical with surgical management of CRS and to a lack of carefully defining the cause of CRS in the individual patient. The definitions and characterization of the causes of CRS have been inconsistent in early studies because of a lack of consensus among sub-specialties in the past. For example, if allergic disease is a major cause of sinusitis and asthma, surgical intervention will typically reduce infection frequency yet inflammation of the upper and lower airway will remain, minimizing the long term clinical benefit. Immune deficiencies such as IgA deficiency or Common Variable Immunodeficiency will continue to promote infection despite additional exteriorization of the sinus cavities surgically. Genetically based mucosal/mucous abnormalities such as ciliary dyskinesia or cystic fibrosis will continue to promote sinus disease following surgical intervention. ASA-sensitive patients with nasal polyposis, CRS, and asthma are particularly recalcitrant to the benefits of FESS and commonly demonstrate prompt polyp re-growth and return of sinus disease – sometimes within a month of surgical intervention. Despite these caveats, the effectiveness of modern surgical therapy for both subjective improvement of symptoms and reduction in sinus infections in patients with medically refractory, carefully differentiated CRS is well established.

ASA HYPERSENSITIVITY TETRAD OF NSAID INTOLERANCE, CRS, NASAL/SINUS POLYPOSIS AND ASTHMA

ASA hypersensitivity tetrad (aspirin-induced respiratory disease – AERD) is a unique clinical syndrome that underscores a systemic connection between the upper and lower airway. In this syndrome, there is intense eosinophilic airway disease without concomitant IgE-mediated allergic sources.

In 1902, shortly after aspirin (ASA) was invented, cases of severe anaphylactoid reactions after aspirin ingestion emerged. In 1922, Widal et al. were the first to portray the association of aspirin sensitivity, aspirin-induced asthma (AIA), chronic hyperplastic sinusitis, and nasal polyposis *(57)*. The full clinical picture was subsequently pointed out in studies by Samter and Beers and eventually termed "Samter's Tetrad" *(58)*. There is a wide variation in clinical presentation. In many cases, nasal polyps appear as the first symptom of ASA sensitivity. In other patients, there is little to no asthma difficulties. Still, in most patients with ASA sensitivity, there will eventually develop some element of rhinosinusitis, nasal polyps, and asthma of varying severity.

In the last two decades, evidence suggests that the pathogenesis of aspirin intolerance is not an IgE-mediated reaction, but an abnormal metabolism of arachidonic acid affecting both the lipoxygenase (LO) and the cyclooxygenase (COX) pathways. This deviation results in an imbalance of the synthesis of eicosanoids, leukotrienes, and prostaglandins resulting in a reduction of anti-inflammatory prostaglandins, especially E2, and an increase in the synthesis of cysteinyl-leukotrienes, such as leukotriene-A4, -B4, -C4 and -D4. The shunt favoring cysteinyl-leukotrienes results in an intense eosinophilic inflammatory process involving generally the entire respiratory tract producing the clinical features of this syndrome *(59)*. There is a wide variation in clinical presentation with one end of the ASA intolerant clinical spectrum free of CRS, polyps and asthma and the other end with complex, unstable, severe upper and lower airway disease. The reason for such a variation in clinical presentation remains a mystery but likely resides in the genetically controlled complexity and overlapping nature of our regulatory immune system.

Rhinosinusitis is the predominating symptom in ASA-intolerant patients. Nasal symptoms first develop typically around the age of 30–40 years and are very unusual under the age of 10 years. Nasal stuffiness and evolving hyposmia/anosmia with reduction in the sense of taste is the hallmark of chronic sinus involvement with nasal polyposis. A persistent loss of the sense of smell and alteration of the sense of taste in the presence of nasal stuffiness is generally pathognomonic of nasal polyposis, with or without historical evidence of ASA intolerance. ASA intolerance among adult asthmatics varies between 3–11% based on history and 8–30% based on oral ASA challenge. In 70% of ASA-intolerant patients, nasal polyps can be found contrasted with the general population where the overall prevalence of nasal polyps is about 4%. Furthermore, among asthmatics with nasal polyps, 30–40% will prove to be ASA intolerant despite a negative clinical history *(60)*. These data underscore the importance of understanding how to diagnose nasal polyps in an asthmatic patient and the need to caution those patients concerning the risks of future nonsteroidal anti-inflammatory drug (NSAID) administration. Typical for the polyps in ASA-intolerant patients is their aggressive growth and poor response to surgical intervention.

Most AERD patients experienced an average of five bouts of sinusitis per year *(61)*. During the bouts of sinusitis, asthma tends to increase in severity, usually requiring systemic corticosteroids, emergency department visits, and hospitalization for asthma care. Any treatment that decreases nasal congestion and sinus infections in these patients significantly alters a chain of negative events in patients with AERD. In some patients with AERD, topical nasal and bronchial inhaled corticosteroids (ICS) are an effective treatment *(62)*. The addition of zileuton or montelukast has also been shown to be an effective treatment for AERD. The predominant effects of these drugs are directed at the asthma, although zileuton has been reported to be beneficial to the upper airways in patients with nasal polyps and asthma *(63)*. Systemic corticosteroids are a particularly effective treatment for eosinophilic inflammatory polypoid disease typical of AERD as well as for asthma and are commonly used. Unfortunately, their profound efficacy has led to many patients with AERD experiencing a higher incidence of corticosteroid-induced side effects, such as osteoporosis, easy bruising, cataracts, and adrenal suppression. Sinus and nasal polyp operations are effective in de-bulking polypoid tissue and in opening sinus ostia to improve comfort and drainage. Unfortunately nasal polyps and sinus disease nearly always recur and any coexisting asthma is ultimately unchanged or even aggravated.

We recommend that patients with AERD who do not respond to nasal and ICS and leukotriene modifiers such as zileuton and montelukast undergo aspirin desensitization followed by daily aspirin as add-on therapy. Patients with aggressive upper airway polypoid disease are prime candidates, with a near 100% decrease in the need for further polyp-sinus surgery provided the treatment is tolerated and compliance is good. Over time, slowly reducing disease-controlling drugs, including the dose of aspirin, can be accomplished in many patients. Those AERD patients who successfully undergo ASA desensitization can consider decreasing the dose of ASA after 6 months of therapy but generally efficacy is not maintained below two 325 grain ASA tablets daily.

In the appendix are policy statements we use for justification of ASA desensitization and an example of typical physician orders for the procedure. More abbreviated approaches with less cost and risk of adversity are currently under investigation. We have found that pretreating our ASA-sensitive patients with montelukast and zileuton prior to ASA desensitization reduces the need for hospitalization to generally 1 day in approximately 80% of cases. This success rate is in direct contrast with the 20% who are able to achieve this goal without pretreatment medications. More recently, intranasal ketorolac challenge and desensitization followed by rapid oral aspirin desensitization has been equally successful in a clinical trial *(64)*. Combining these approaches may prove to be the most cost-effective methodology for managing AERD but further studies are needed.

SUMMARY

Rhinitis/sinusitis/CRS is a common co-morbid finding in asthmatic subjects, with a ballpark figure of approximately half of asthmatics manifesting some component of accompanying upper airway pathology. The normal function of the upper airway is protective of the lower airway; acting as a particulate filter, an immunologic gauntlet for preventing lower airway infection, and as a “conditioner” of incoming air for

maximizing the lower airway's ability to perform the critical tasks of respiration. The upper and lower airway are likely in constant "contact" via possible neurologic connections and circulating cell signaling substances, forming what has been termed the "united airways," with the mucosa in each region having very similar physiology, cellular mechanics, and responses. When things in the upper go awry, havoc may ensue below; and these communicating pathways can serve as facilitators for exacerbating lower airway inflammation and hyperreactivity.

Upper airway pathology, such as allergy based inflammation and potential sinusitis; and anatomic pathology, such as polyposis or upper airway structure or function that does not allow for normal mucociliary clearance is well correlated with exacerbation of lower airway inflammation and clinical data also demonstrate the salutary nature of addressing upper airway problems and achieving improvement in lower airway pathology, as well.

Keeping this upper/lower airway dynamic in mind is an important medical management consideration, and proceeding with proper identification of upper airway diatheses can be beneficial in gaining improved symptom control of both airways. Proper identification of those problems which can be best managed medically, or those that may require surgical intervention, make specific evaluation critically important. Identification of allergic triggers, infections, or other processes which can be alleviated with medical remediation can mitigate lower airway symptoms and minimize other medication requirements in our pursuit of ameliorating asthma symptoms and findings. Proper identification of surgical dilemmas renders our care more efficient and minimizes long-term morbidity and complications.

While there are still many avenues of investigation that need to be explored to better explain the pathophysiology of CRS and asthma, the clinical correlation is well established and worthy of consideration. The most important aspect of the connection between CRS and asthma is that a proper diagnosis must first be considered before it can be made.

APPENDIX

Inpatient Aspirin (ASA) (NSAID) Desensitization Policy
Indications

1. Aspirin (ASA) desensitization is indicated for patients who have aspirin-exacerbated respiratory disease (AERD)
   (a) Demonstrate suboptimal control of their asthma and/or rhinosinusitis with ICS and leukotriene-modifying drugs (LTMDs).
   (b) Have required multiple polypectomies for nasal polyp control.
   (c) Require ASA for another medical indication, such as those who require antiplatelet therapy with aspirin or anti-inflammatory therapy with other Cox-1 inhibitors.
2. This procedure is limited to patients who have been identified as having AERD after experiencing a respiratory reaction to aspirin or any of the nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase-1. Aspirin desensitization may be possible for individuals without AERD, but with histories of cutaneous reactions to aspirin or other NSAIDs. However, cutaneous ASA/NSAID reactors are a heterogeneous group of patients and may require different desensitization protocols not addressed in this paper.

Policy

1. Physicians specifically trained in desensitization protocols, such as board certified allergists/immunologists, can safely direct aspirin desensitization in the appropriate medical setting with the appropriate support staff.
2. General requirements for aspirin desensitization
   (a) Aspirin desensitization should be performed in a facility able to provide advanced cardiac care, ventilator support, and frequent or constant observation by qualified personnel. The level of monitoring will be dependent upon the degree of ASA sensitivity and general medical health of the patient and ultimately determined by the supervising physician at the time of the admission request.
   (b) The supervising physician must be immediately available and should be present at the bedside at the time of the first challenge and through any reaction.
      – The first reaction is almost always the most severe and is unpredictable.
      – If the first reaction has been managed without physician intervention, then subsequent challenges may proceed without the supervising physician being physically present.
3. Inpatient aspirin desensitization may be considered when the following conditions exist:
   (a) A physician experienced in assessing and treating patients with acute severe asthma exacerbations is immediately available for patient evaluation and treatment.
   (b) There is sufficient staff so that at least one experienced staff member as outlined above is readily available to care and assess the individual patient being desensitized for the full course of the desensitization. At times, the supervising physician may require that a staff member be constantly assigned to monitor a patient undergoing ASA desensitization. Again, this is at the discretion of the supervising physician.
   (c) Medically qualified personnel experienced in assessing and treating patients with acute severe asthma exacerbations are available to monitor the patient. Depending on the specific licensing criteria and the scope of practice, limitations in particular state this could include Registered Nurses, Nurse Practitioners, Physicians' Assistants, Respiratory Therapists, and/or other personnel.
   (d) Equipment is immediately available for continuous respiratory and cardiovascular monitoring, pulse oximetry, spirometry, and cardiopulmonary resuscitation.
4. Inpatient desensitization should always be used in patients with the following risk factors.
   (a) Beta-blocker use.
   (b) Recent myocardial infarction.
   (c) Any other underlying medical condition or drug treatment regimen that would make the management of severe asthma or anaphylactoid reaction difficult.
   (d) Severe asthma.
   (e) History of severe or life-threatening ASA/NSAID reaction.
5. Oral aspirin challenge:
   (a) Discuss the risks and benefits of the procedure with the patient and document the discussion in the medical record. Advise the patient that the procedure generally takes 2 days to complete. Obtain written informed consent.
   (b) Begin early in the morning. Establish intravenous access.

(c) Prior to dosing, measure FEV1 and perform clinical assessment to determine baseline.
(d) Start with aspirin 20.25 mg by mouth, followed by 40.5, 81, 162.5, and 325 mg at 90-min intervals. (Since many practitioners have no access to anything but commercially available forms of ASA, the dosing is based on using 81 mg ASA tablets and using pill cutter to obtain the lower doses. While almost no one reacts to 20.25 mg, an occasional reaction occurs to 40.5 mg.)
(e) Measure FEV1 and perform clinical assessment at least every 90 min and/or with any symptoms. Based on individual patient characteristics, the dosing interval may be extended to 3 h. A lower respiratory tract reaction is defined as a 15% decrease in the FEV1 from baseline FEV1. Record any change in baseline naso-ocular symptoms.
(f) Reactions will likely occur with one of the early doses, usually 81 mg. If it does, treat the reaction with the appropriate medication(s) described below.
(g) When the patient is completely stabilized after a reaction, but not less than 3 h after the last dose, the provoking dose can be repeated.
(h) When the provoking dose is tolerated, dose escalation may continue.
(i) Persistent greater than 15% decrease in FEV1, with or without other associated symptoms lasting greater than 3 h despite therapy, is an indication to discontinue the desensitization process for the day.
(j) If a second day of desensitization is needed, start the day by repeating the last tolerated dose.
(k) Continue the desensitization procedure, as indicated above, until the goal of 325 mg of ASA is tolerated. Most individuals will take 2 days to complete the desensitization procedure.

6. Adverse reaction treatment policy:
(a) For isolated pulmonary symptoms, have an albuterol meter dose inhaler with a spacer tube (inhale up to five breaths) or a hand-held nebulizer with albuterol already prepared ready to deliver. Aspirin reactions can persist for several hours. Repeat the treatment, as necessary.
(b) For laryngeal symptoms, use racemic epinephrine in a hand-held nebulizer.
(c) For laryngeal edema with hypotension, use intramuscular epinephrine.
(d) For isolated hypotension, use intramuscular epinephrine.
(e) For ocular and/or nasal reactions, use oral antihistamines.
(f) Refer to Anaphylaxis Practice Parameter for specific medication guidance and additional anaphylaxis management recommendations.

Physician Orders for Aspirin Desensitization

❑ Oral Aspirin Challenge Protocol

- Establish intravenous access.
  - ○ May use intradermal lidocaine 1% solution 0.1 mL or EMLA (lidocaine 2.5%, prilocaine 2.5%) cream 5 g PRN for IV starts.
- Measure FEV1 and perform clinical assessment to determine baseline.
- Start with aspirin 20.25 mg by mouth, followed by 40.5, 81, 162.5, and 325 mg at 90-min intervals.
- Measure FEV1 and perform clinical assessment at least every 90 min and/or with any symptoms. Based on individual patient characteristics, the dosing interval may be extended to 3 h. A lower respiratory tract reaction is defined as a 15% decrease in the FEV1 from baseline FEV1.
  - ○ Record any change in baseline naso-ocular symptoms.
- Reactions will likely occur with one of the early doses, usually 81 mg. If it does, treat the reaction with the appropriate medication(s) described below.
- When the patient is completely stabilized after a reaction, but not less than 3 h after the last dose, the provoking dose can be repeated.
- When the provoking dose is tolerated, dose escalation may continue.
- Persistent greater than 15% decrease in FEV1, with or without other associated symptoms lasting greater than 3 h despite therapy, is an indication to discontinue the desensitization process for the day.
- If a second day of desensitization is needed, start the day by repeating the last tolerated dose.
- Continue the desensitization procedure, as indicated above, until the goal of 325 mg of ASA is tolerated. Most individuals will not take 2 days to complete the desensitization procedure.
- Other: _____

Adverse Reaction Treatment Protocols

- For isolated pulmonary symptoms, have an albuterol meter dose inhaler with a spacer tube (inhale up to five breaths) or a hand held nebulizer with albuterol _____already prepared ready to deliver q _____ PRN.
- For laryngeal symptoms, use racemic epinephrine _____ in a hand held nebulizer q _____ × _____ doses.
- For laryngeal edema with hypotension, use intramuscular epinephrine _____ q _____ × _____ doses.
- For isolated hypotension, use intramuscular epinephrine _____ q _____ × _____ doses.
- For ocular and/or nasal reactions, use oral pseudoephedrine 60 mg and/or diphenhydramine 50 mg q 6 h as directed _____
- Other: _____

Physician's Signature Date Time

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15 Anesthesia for Patients with Asthma

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Contents

KEY POINTS

- Perioperative bronchospasm in the asthmatic is a rare but potentially catastrophic event.
- The preoperative evaluation of the asthmatic patient should identify risk factors for bronchospasm or acute asthma exacerbation.
- Optimization of preoperative asthma management can reduce the incidence of perioperative bronchospasm.
- Asthmatic patients may experience sudden and severe bronchospasm during anesthesia.
- Regional anesthesia is preferred when possible because it avoids tracheal instrumentation and other potential triggers of bronchospasm.
- Histamine releasing drugs should be avoided.
- Exacerbation of asthma during general anesthesia and positive pressure ventilation may cause air trapping from dynamic hyperinflation that will impair venous return, decrease cardiac output and, in severe cases, lead to pulseless electrical activity.
- Light levels of anesthesia may precipitate bronchospasm and this complicates the management at the end of the operation.
- Deep extubation at the end of surgery should be considered if appropriate.
- Optimization of postoperative pain relief to facilitate early mobilization should decrease the incidence of postoperative respiratory complications.

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INTRODUCTION

Patients with asthma have a small but definite increase in the risk for major complications during anesthesia *(1, 2)*. The information presented here is intended to help nonanesthesiologists provide perioperative care and consultation that will minimize these risks. The essentials of preoperative assessment are reviewed along with the goals and possible approaches to preoperative optimization. The possible choices for anesthesia (general or regional) are reviewed along with the options for airway management and intraoperative techniques with an emphasis on avoiding bronchospasm or air trapping and dynamic hyperinflation. The management of acute intraoperative bronchospasm is reviewed as well as the critical components of the immediate postoperative care that should be emphasized to minimize the incidence of perioperative complications.

PREOPERATIVE ASSESSMENT

The goal of the preoperative assessment in patients with asthma is to risk-stratify the severity of asthma and assure optimal medical management to minimize the potential for perioperative complications *(3)*. The NIH Guidelines for Asthma Education and Prevention classify the severity of a patient's asthma as intermittent or persistent and subdivide the latter as mild, moderate, or severe depending upon the frequency of the symptoms *(4)*. This classification can be correlated with the American Society of Anesthesiologists physical status classification to provide a general assessment of the perioperative risks for a patient (Table 1). The patient's own subjective assessment of the control of their asthma symptoms can be simply assessed by the Asthma Control Test *(5)* but their responses are often not reliable if there is a strong desire for a surgical procedure. In addition, pulmonary function studies may normalize or stabilize between exacerbations of their symptoms. The preoperative assessment should therefore attempt to objectively quantify the baseline severity of the patient's disease. The peak expiratory flow (PEF) is a useful monitor of preoperative asthma control. The normal range for the PEF is quite variable (200–600 L/min) and dependent upon the patient's age, gender, height, and weight. It is more useful to make comparisons with the patient's previous personal best performances. A decline in PEF may herald worsening airway obstruction. In general, values ≥80% of usual predicted peak flow are considered normal variation,

Table 1
Asthma Severity Classification

ASA physical status	*NHLBI asthma guidelines severity classification*	*Frequency of symptoms*
1. Normal, healthy	–	–
2. Mild systemic disease	Intermittent/persistent (mild)	<2× per week/>2× per week, but not daily
3. Severe systemic disease	Persistent (moderate)	Daily
4. Constant, life-threatening disease	Persistent (severe)	Daily with frequent nighttime awakenings
5. Moribund		

while values <80 to <50% of predicted should alert the examiner to potentially significant changes and values that are <50% of previous or predicted usually signifies that medical attention is needed.

The severity of the asthma is not necessarily correlated with the risk of intraoperative complications; rather it is the quality and stability of the medical management and control of symptoms that are more critical. Complications are reported to be more frequent in older patients and in patients with more poorly controlled symptoms *(1, 3, 6)*. The preoperative assessment should consequently detail the patient's exercise capacity and ability to perform activities of daily living. Poor exercise tolerance has been correlated with an increased risk of postoperative complications. The preoperative evaluation should also characterize any markers of changes in the severity of the patient's symptoms or any incubating infections that could exacerbate symptoms. An increase in rescue inhaler use, a history of emergency room visits or hospitalizations for the treatment of asthma, or past history of difficulties during anesthesia should alert the practitioner to the potential of poorly controlled asthma. Other symptoms such as fever, cough, or increased sputum production that suggest a developing infection and consequent worsening of asthma symptoms may warrant the postponement of an elective operation.

Known triggers of asthmatic symptoms for each patient should be detailed including specific allergies, response to cigarette smoke, cold air, or dust as airway reactivity to these antigens may correlate with intraoperative bronchoreactivity. Avoidance of any precipitants and treatment of allergies in the preoperative period may prevent later attacks. Medications and previous reactions to medications must be reviewed in detail. In particular, bronchoreactivity to aspirin or other nonsteroidal anti-inflammatory drugs may be seen in the triad of aspirin-induced asthma and would preclude the use of these drugs for perioperative analgesia. Commonly associated comorbidities including congestive heart failure, chronic obstructive pulmonary disease, and obstructive sleep apnea should also be carefully evaluated.

Comprehensive assessment and preoperative preparation that optimizes control of asthmatic symptoms minimizes the risk of perioperative complications *(7)*. The patient's compliance to their treatment regimen and avoidance of potential triggers such as known allergens or smoking are central to this effort. All therapies should be continued up to and including the day of surgery. Key components of the preoperative evaluation of patients with asthma are summarized in Table 2 *(8)*.

PREOPERATIVE PREPARATION

The physical examination of the asthmatic patient on the day of surgery is critical, but may be misleading and provide a false sense of security. An absence of wheezing does not predict the likelihood or severity of an acute exacerbation. In the setting of severe air trapping, wheezing may not be auscultated at all due to the complete lack of airflow. Elderly patients and patients with long-term chronic asthma may not experience the sensation of dyspnea until symptoms are severe. The respiratory rate and rhythm should be observed. Signs and symptoms of right heart failure should be assessed. If there are concerns, a preoperative chest X-ray may demonstrate signs of air trapping and may be invaluable for comparison should complications occur in the perioperative period, but also may be normal even in the setting of severe bronchoconstriction.

Table 2
Preoperative Anesthetic Evaluation of Patients With Asthma

Presentation	*Concern*	*Risks*
Asymptomatic asthma	Minimal	Possible bronchospasm secondary to common triggers
Chronic asthma	Possibility of irreversible airway disease and chronically decreased reserve	Possible perioperative pulmonary complications, especially with thoracic or upper abdominal surgical site
	Possibility of suboptimal medical control	As above
Asthma history with acute symptoms	Possibility of poor compliance with chronic therapy or onset of new respiratory tract infection	As above – risk may be reduced by delay for preoperative treatment or initiating treatment immediately for emergency surgical procedures
Unexpected preoperative wheezing (no previous asthma diagnosis)	Undiagnosed medical problem	Possible mistaken diagnosis of asthma and incorrect treatment
	No prior treatment	Possible perioperative pulmonary complications, especially with thoracic or upper abdominal surgical site
		Risk may be reduced by delay for preoperative treatment or initiating treatment immediately for emergency surgical procedures

Comprehensive pulmonary function tests including spirometry, lung volume, and diffusion capacity measurements in addition to bronchodilator testing may aid in the prediction of operative outcomes *(9)* and may reveal other respiratory limitations such as chronic obstructive disease or restrictive ventilatory disorders, but these tests are logistically difficult to obtain and of less help in the immediate preoperative setting. The measurement of the PEF rate and comparison to the patient's previous performance may be helpful and if a peak flow meter is not available a forced expiratory time can be measured by instructing the patient to exhale forcefully from maximal inspiration while listening for gas flow over the trachea. The time to the end of expiration should be shorter than 6 s.

If poor asthma control is identified prior to an elective surgical procedure, the case should be canceled and medical optimization should be coordinated in consultation with the patient's primary care physician or pulmonologist. If the surgical procedure is more urgent, a short course of oral steroids may be indicated to stabilize the acute asthmatic symptoms. Oral methylprednisolone 40 mg daily for 5 days prior to surgery has been shown to decrease postintubation wheezing in newly diagnosed or poorly compliant patients with reversible airway obstruction *(10)*. If the surgical procedure is emergent, an intravenous steroid regimen would be similarly indicated though controlled trials

validating this approach are lacking. Concerns over wound healing and increased risk of infection as a side effect of administration of corticosteroids in the preoperative period have not been supported by clinical reviews *(7, 11)*. In this setting, the 2009 Global Strategy for Asthma Management and Prevention (GINA) guidelines recommend systemic glucocorticosteroid use during the operative period with rapid reduction within 24 h of surgery. However, this recommendation is based on observational studies and nonrandomized trials *(12)*. Preoperative assessment of the patient with asthma should also include a review of the plasma electrolytes. High doses of β-agonist drugs are associated with the development of hypokalemia, hyperglycemia, and hypomagnesemia. These should be normalized prior to any surgical procedure.

Premedication becomes an important component of the preoperative preparation for the patient with asthma because anxiety may exacerbate asthmatic symptoms. Benzodiazepines such as midazolam are commonly used for this indication, but the α_2-agonist dexmedetomidine is increasingly recommended as an alternative with distinct advantages in this setting. It is an anxiolytic but also sympatholytic and an antisialagogue, both desirable actions in these patients, and it does not have the respiratory depressant effects of a benzodiazepine *(13)*. There are multiple case reports demonstrating the ability of dexmedetomidine to suppress upper airway responses to stimulation during awake intubations, but there are no trials to date of its use for premedication in patients with asthma. Takasaki et al. *(14)* report the successful use of dexmedetomidine as a sedative in patients requiring noninvasive positive pressure ventilation for treatment of asthma.

INTRAOPERATIVE MANAGEMENT

Some of the intra- and postoperative risks associated with anesthesia in the patient with asthma are summarized in Table 3. Severe intraoperative complications in patients with asthma include hypoxia and cardiac arrest. Bronchospasm and mucus secretions may compromise oxygen delivery with consequent tissue hypoxia. Cardiac arrest may occur as a result of hypoxemia, as a side effect of the drugs used to treat severe bronchospasm, secondary to underlying electrolyte abnormalities, or as a result of dynamic hyperinflation. Intraoperative management is therefore designed to minimize the risk of bronchospasm by avoiding known triggers (Table 4). Closed claims analysis demonstrates that bronchospasm leading to severe complications is a rare occurrence *(15)*. In addition, bronchospasm occurs in nonasthmatic patients as well so the guidelines for perioperative management presented here have applications beyond this specific patient group.

Foremost among the recommendations for anesthetic management of the patient with asthma is to avoid instrumentation of the airway by using a regional anesthetic when possible. This does not, however, guarantee the absence of bronchospasm. Referring back to the close claims analysis, 20% of the claims in which bronchospasm led to severe complications occurred during a regional anesthetic *(15)*. In addition to avoiding instrumentation of the airway, regional techniques minimize the use of cold, dry medical gases that can provoke bronchospasm. Although supplementary oxygen via nasal prongs or a simple mask is still frequently used, since the patient's upper airway is not bypassed the inspired gases are warmed and humidified before they arrive in the patient's lungs. Inadequate suppression of visceral reflexes and patient anxiety are two

Table 3
Risks of Anesthesia for Patients With Asthma

Risk	*Optimize*	*Avoid*
Intraoperative	Preoperative disease management	Emergency surgery
Respiratory	Bronchodilator therapy	Potential triggers
Bronchospasm	Mechanical ventilation pattern to avoid dynamic hyperinflation	Pulmonary edema
Hypoxemia		
Cardiac		
Right heart failure	Preoperative disease management	Increased pulmonary vascular resistance
Left heart failure	Preoperative disease management	Hypoxemia Decreased preload
Dysrythmias	Plasma electrolytes Adrenergic therapy	Electrolyte abnormalities Aminophylline
Postoperative	Postoperative analgesia	Postoperative mechanical ventilation
Hypoxemia	Consider dexmedetomidine	Residual respiratory depression
Atelectasis	Postoperative respiratory function	Inadequate analgesia
Pneumonia	Prophylactic antibiotics Ambulation	Prolonged bed rest

Table 4
Intraoperative Bronchospasm

Potential triggers	*Suggested alternative or mitigation*
Airway manipulation	Regional anesthesia
Laryngoscopy, intubation	LMA
Suction	Limit, only under deep anesthesia
Cold, dry medical gases	Low flows, airway humidification
Histamine releasing drugs	Limit drug selections
Latex exposure	Avoid exposure
Inadequate anesthesia	Volatile anesthetics, α_2 agonist adjuncts

common triggers of bronchospasm during regional anesthesia. Our own clinical experience has confirmed that the α_2-agonist dexmedetomidine is an excellent choice for an anxiolysis and sedation in these patients because it produces bronchodilator and analgesic effects without causing significant respiratory depression *(16)*.

Many surgical procedures will, however, require general anesthesia for optimal patient management. In these cases, a graded approach can be taken with respect to airway management with an eye towards minimizing the risks if at all possible. In a small number of

cases, general anesthesia can be administered by placement of a mask alone over the patient's nose and mouth. After correct jaw positioning or placement of an oropharyngeal device, the soft tissue obstruction of the airway that may occur in the obtunded state can be avoided. This method avoids stimulation of the subglottic area which can provoke bronchospasm. Although the ideal surgical patient has been fasting and is at low risk for aspiration, mask anesthesia has the disadvantage of not providing any airway protection against possible aspiration of gastric contents. The next step up in airway instrumentation would be placement of a laryngeal mask airway (LMA). This device has an inflatable rim that forms a partial seal around the glottic opening. The LMA also avoids subglottic stimulation as compared to an endotracheal tube. It can be used for longer surgical cases, provides better control of an airway than mask ventilation, and may provide some degree of protection against aspiration. The LMA is not appropriate in cases that require muscle relaxing agents and prolonged positive pressure ventilation or for patients who are at high risk for aspiration. If endotracheal intubation is required for the safe completion of the general anesthetic, it should be stressed that induction and intubation are the most common triggers of bronchospasm. Care should be taken to assure an adequate depth of anesthesia has been reached before beginning laryngoscopy. Many adjuncts have been shown to decrease the sympathetic response to laryngoscopy and intubation including larger doses of narcotics, intravenous lidocaine, and dexmedetomidine. If possible, one or more of these should be included as part of the induction regime *(17)*.

Following induction, maintenance of anesthesia requires the use of medical gases (oxygen, air, nitrous oxide) which are both dry and cold. Exposure of an asthmatic patient's lungs to these gases may precipitate bronchospasm and a drying out of lung secretions, further impairing ventilation and gas exchange. Employing low fresh gas flows and placing an in-line heat and moisture exchange filter (artificial nose) will minimize this risk.

The administration of even a simple general anesthetic may include the use of nearly two dozen drugs. Many of the drugs used during anesthesia may trigger the release of histamine and consequent bronchospasm. Avoiding rapid administration and carefully selecting the drugs used for specific indications can minimize this risk. Among the intravenous induction agents, sodium thiopental should be administered with caution in asthmatics because of its potential for precipitating bronchospasm from histamine release. Propofol is now the most commonly used intravenous induction agent for anesthesia and for all practical purposes has completely replaced thiopental. Current formulations of propofol do not appear to trigger the release of histamine. Etomidate may be preferred in some circumstances when hemodynamic stability is critical, but small clinical trials have shown a greater airway resistance after intubation with etomidate as compared to propofol *(18)*. Ketamine has been advocated as the induction agent of choice for intubation for the patient with status asthmaticus or hemodynamic instability because of its bronchodilator and sympathomimetic side effects. Unfortunately, it is also associated with intraoperative tachycardia and postoperative hallucinations that have limited its widespread adoption. If it is used, midazolam should be administered concurrently to reduce the incidence and severity of postoperative hallucinations.

Neuromuscular blocking drugs are also classic triggers of histamine release, but this side effect was most commonly associated with curare and other drugs in the benzylisoquinolinium class (atracurium, mivacurium) that are no longer available for clinical use.

The steroid-based neuromuscular blocking drugs (pancuronium, vecuronium, rocuronium) do not trigger histamine release and therefore are preferred. Similarly, cis-atracurium, the lone remaining curariform drug, does not induce histamine release. It is the drug of choice in renal failure, and can be safely administered in asthmatics without a risk of bronchospasm *(19)*. In a small number of cases in which there is a high risk of aspiration or potentially difficult intubation such that a rapid onset time and short duration of action are critical. Succinylcholine may still be the relaxant of choice despite the fact that it may trigger bronchospasm in these patients; the benefits may outweigh the risks. The need for succinylcholine for emergency intubation in asthmatic patients may be eliminated by the introduction of sugammadex, the selective binder for rocuronium. However, the approval of sugammadex by the FDA was recently deferred pending further evaluation of the incidence of bronchospasm associated with this drug. European clinical experience suggests this is a rare occurrence, but the use of this drug in asthmatic patients requires further evaluation *(20)*.

Analgesics are frequently administered intraoperatively. Opioids remain the most commonly used drugs for this indication. Rapid administration of large doses of morphine is associated with significant histamine release and can provoke bronchoconstriction. The synthetic opioids (fentanyl, sufentanil, remifentanil) or the longer acting hydromorphone may be a better choice for asthmatics because they do not trigger histamine release. Nonsteroidal anti-inflammatory drugs (ketorolac) are generally safe and commonly used as adjuncts for perioperative analgesia, but given the subset of asthmatics with aspirin-induced asthma, this class of drugs should be avoided in these patients. Acetaminophen is preferable because it does not interfere with cyclo-oxygenase and leukotriene pathways and the recent FDA approval of intravenous acetaminophen for use in the United States should increase the experience with the utility of this drug in this patient population.

Antibiotics are frequently used in the perioperative period both therapeutically and prophylactically and among them vancomycin is one of the more commonly administered infusions during surgery for prevention of staphylococcal infections. It is a potent histamine releaser and may provoke bronchospasm. Slow administration of the antibiotic infusion may prevent significant histamine release but asthmatic patients should be under constant monitoring with attention to airway pressures and the capnograph trace during its administration.

Despite all precautions, intraoperative bronchospasm may still occur. The general axiom that "not all that wheezes is asthma" holds true just as much inside the operating room as outside it. An open mind needs to be maintained whenever evaluating new onset of wheezing in a patient even when there is a previous history of asthma attacks. A differential diagnosis for intraoperative wheezing is presented in Table 5. Each of the potential etiologies should be considered.

Exacerbation of asthma is a common cause of wheezing especially following intubation and during emergence from anesthesia. Typically there are high peak-airway pressures and there is no plateau phase on the capnograph tracing. Instead of a horizontal line during the plateau phase there is a slope that is directed upwards. The steepness of this slope is an indicator of the severity of the bronchospasm and the degree of the ventilation perfusion mismatch. Significant arterial desaturation is usually not associated with an acute asthma attack until severe V/Q mismatching and shunting occurs.

Table 5
Differential Diagnosis of Intraoperative Wheezing

Asthma exacerbation
Anaphylaxis
Aspiration
Partial airway obstruction
Endotracheal tube compression
Obstructive mucus secretions
Endobronchial intubation
Foreign body in airway
Subglottic mass
Pulmonary edema
Pneumothorax
Pulmonary embolus
Pneumonia

If hypoxemia is present then other causes for the wheezing should be considered. Bronchospasm increases the resistance to airflow during the expiratory phase of ventilation leading to a prolonged expiratory phase time. If another breath is initiated either by the patient or the ventilator before the full tidal volume has been exhaled, air remains "trapped." This is known as breath stacking or dynamic hyperinflation. This will generate a buildup of pressure inside the lungs and thoracic cavity that increases with each subsequent breath. The increased pressure will compromise venous return and decrease cardiac output, leading to hypotension and organ hypoperfusion *(21)*. It should be noted that with severe resistance to airflow the expiratory phase may be so long and slow as to not generate enough turbulence to create audible wheezing. Adjustments to the ventilator can help reduce or eliminate breath stacking. Reduction of the respiratory rate, if possible, may be the simplest strategy. This will create more time for the tidal volume to be exhaled before the next inspiration occurs. However, reducing the number of breaths per minute may not always allow for adequate minute ventilation so this strategy can be quickly exhausted and permissive hypercapnea may be required. Increasing the inspiratory flow rate or reducing the inspiratory time also effectively changes inspiratory-to-expiratory ratio in favor of prolonging expiration. A brief disconnection of the ET tube from the ventilator may sometimes be necessary to let the trapped residual air equalize and restore normal cardiac output.

Anaphylaxis usually presents with vasodilatation and profound hypotension and bronchospasm may also be a prominent feature. Other signs include diffuse erythema, angioedema, and urticaria. A high index of suspicion should be maintained when evaluating for anaphylaxis as bronchospasm or hypotension alone may be the only presenting sign. If anaphylaxis is suspected epinephrine is lifesaving and should be given immediately. Treatment should be continued as anaphylaxis often has a bimodal phase increase hours later *(22)*. A serum tryptase level should be collected as well. Tryptase is a mast-cell specific protease which peaks within the first hour and remains elevated for about 4–6 h. The test has a high sensitivity and specificity for mast-cell activated anaphylaxis but the results are not immediately available so clinical recognition and

immediate management are still critical. The tryptase level will be useful in the investigation of an episode of isolated severe bronchospasm, especially when it occurs in a patient without a prior history of asthma, because identifying the allergen could potentially avoid a fatal reaction during their next anesthetic.

Aspiration of gastric fluids during induction may be the cause of postintubation wheezing in itself or may provoke bronchospasm in an asthmatic. The pneumonitis that occurs may cause significant ventilation-perfusion mismatching and hypoxemia. Bronchodilator therapy and postoperative ventilation may be indicated if the symptoms are immediate and severe.

A *partially obstructed airway* can produce intraoperative wheezing. Mechanical kinking of the endotracheal tube by external compression or positioning the patient in unusual positions may produce this effect. Similarly excess mucus secretions, an endobronchial intubation, foreign body (tooth, food particles), or a subglottic mass can have a similar effect. Fiberoptic bronchoscopy can be used to evaluate these possibilities. Foreign body obstruction should be strongly suspected when the wheezing is unilateral. A chest X-ray may demonstrate asymmetric air trapping or a radiopaque object in an airway.

Pulmonary edema is not infrequent in operations which have significant fluid shifts. It may be associated with high peak airway pressures and wheezes similar to asthma. Crackles or ronchi heard on auscultation and fluid coming out of the endotracheal tube, together with a large alveolar to arterial oxygen gradient may help distinguish pulmonary edema from bronchospasm. Pulmonary edema is often diagnosed following extubation when the patient has lost the protective effect of positive pressure ventilation and positive end expiratory pressure (PEEP). In situations such as these, extubation to BiPAP to maintain positive pressure may be helpful. Diuresis or other fluid management strategies can then be initiated to reduce the edema.

Pneumothorax may result from trauma, subclavian or internal jugular vein line insertion, or ventilation with high airway pressures. Signs and symptoms generally include diminished breath sounds and paradoxical movement of the chest wall on the affected side. Tension pneumothorax may cause hypotension and tracheal deviation toward the unaffected side. An abrupt or progressive increase in peak and plateau airway pressures while in volume-control ventilation or decreased tidal volumes and need for increased driving pressures while in pressure-control ventilation mode may signal development of a pneumothorax. When a patient with severe asthma develops decreased oxygen saturation, a pneumothorax should be suspected.

Pulmonary embolism should not be forgotten in the differential of intraoperative wheezing. Although the vascular obstruction itself is not responsible for the wheezing, the subsequent vascular congestion, edema, and atelectasis that can occur may result in partial narrowing of airways which may be heard as a wheeze. Anesthesia and surgical procedures place patients at higher risk for thrombosis by creating conditions of blood stasis, endothelial injury, and hypercoagulability, known as Virchow's triad. Air embolus should also be considered with surgical procedures with an operative field higher than the right atrium and following central line placement.

Pneumonia may also present as wheezing in the anesthetized patient. An intraoperative X-ray may be useful in distinguishing this from other causes.

Treatment of intraoperative bronchospasm should be initiated as soon as other etiologies of wheezing are ruled out to prevent the progression to hypoxemia and more severe complications. The depth of anesthesia should be increased to eliminate inadequate anesthesia as a possible trigger. The inspired oxygen concentration should be increased to compensate for the ventilation perfusion mismatches and increased oxygen demands. Oxygen delivery is seldom the rate limiting step. The use of helium/oxygen mixtures has been suggested when severe airway constriction limits flow but this approach has met limited clinical success, most likely because the addition of helium limits the maximum inspired oxygen concentration to about 30%. Nebulized β_2 agonists remain the mainstay for the treatment of intraoperative bronchospasm. Their delivery is suboptimal when administered through an endotracheal tube. Ten puffs or more of a metered-dose inhaler are required to produce a therapeutic concentration *(7)*. For refractory bronchospasm, intravenous steroids should be administered. Their onset is not immediate, but they will improve the perioperative course if the spasm persists. Nebulized anticholinergics may be of some benefit as well though their onset time is slightly slower than the beta agonists. Nebulized magnesium sulfate has been suggested for refractory bronchospasm and shown to be effective in a few small trials, but further evaluation is necessary. In the patient who is not responsive to nebulized treatments, intravenous therapy should be added. Intravenous aminophylline provides no additional benefit and is associated with an increase incidence of side effects. Low dose intravenous epinephrine (0.007–0.03 μg/kg/min) may be of some help. Intravenous magnesium sulfate and leukotriene receptor antagonists have been suggested to provide therapeutic benefits in a few small trials, but further evaluation of these therapies is needed before they can be confidently recommended *(23)*.

In truly refractory cases of status asthmaticus the volatile anesthetics have been used as a therapy of last resort. All of the volatile anesthetics cause smooth muscle relaxation in isolated tissue preparations. In a clinical setting, the responses are a bit more varied as some are more pungent and irritate the lungs and upper airway when administered in higher concentrations. Classically halothane was used in this setting, but it is no longer available for clinical use in many countries so sevoflurane is the volatile anesthetic of choice among those agents currently available because it is the least irritant among them and has a favorable pharmacokinetic profile *(24, 25)*. Even when rapidly administered in high concentrations the incidence of laryngospasm is negligible.

EMERGENCE FROM ANESTHESIA AND EXTUBATION

Emergence from anesthesia is the second most common time to encounter significant bronchospasm because the patient loses the bronchodilator effect of the volatile anesthetic and the lower anesthetic concentrations do not ablate the response to the noxious stimulus of the endotracheal tube. Prior to decreasing the anesthetic agent concentrations a number of interventions should be considered to decrease the incidence of bronchospasm upon emergence. Any residual neuromuscular blockade should be antagonized with an anticholinesterase such as neostigmine. Although the muscarinic side effects can potentially exacerbate asthmatic symptoms and precipitate bronchospasm, these reversal agents are co-administered with an antimuscarinc drug (atropine, glycopyrrolate) and

clinical experience has demonstrated this to be a safe practice in asthmatic patients and it avoids the potential residual neuromuscular paralysis in the postanesthesia care unit. If bronchospasm has been a recurrent problem during the anesthetic, an additional dose of an inhaled β_2-agonist should be administered via the endotracheal tube prior to discontinuing the anesthetic. It may also be useful to extubate a patient directly to a nebulized bronchodilator. A bolus dose of intravenous dexmedetomidine *(26)* or lidocaine *(27)* may help to suppress airway reflexes during extubation and may be a useful adjunctive therapy. Lastly, suctioning of the airway to remove secretions may trigger bronchospasm so this should be done prior to decreasing the anesthetic gas concentrations. Extubation may also be done during a deeper level of anesthesia, essentially converting an endotracheal general anesthetic to a mask anesthetic to prevent bronchospasm on emergence. This strategy of deep extubation makes sense when there have been periods of significant bronchospasm during the operation and there are no contraindications to mask ventilation. Risks of deep extubation include airway obstruction, laryngospasm, and aspiration, all of which can lead to reintubation. A full stomach in an emergency case or a history of sleep apnea usually contraindicates deep extubation.

In the asthmatic with severe bronchospasm during or persisting after a case, or with other confounding issues such as a difficult airway or a full stomach, foresight may dictate continued intubation and mechanical ventilation. Tenacious airway secretions can be present in some asthmatics. When combined with a blunted cough reflex, hypoventilation, and suboptimal pain control impairing ventilation, the inadequate clearance and depressed respiratory drive may make postoperative respiratory failure inevitable. Reintubation of an active asthmatic can be difficult and manipulation of the airway can further exacerbate an ongoing attack. Continuing intubation and mechanical ventilation while the neuromuscular blockade wears off and the bronchospasm diminishes with further treatment can avoid these complications.

Additional recommendations for some asthmatic patient groups with special considerations are provided in Table 6 *(8)*.

POSTOPERATIVE MANAGEMENT

In the immediate postoperative period, attention should be focused on minimizing the potentially increased risks of respiratory complications such as atelectasis and pneumonia that can be exacerbated by mucus hypersecretion. Avoiding postoperative ventilation is probably the first step. Attention should then be paid to providing adequate pain relief. Inadequate analgesia may result in shallow inspiration, a delayed phase of expiration, and an expiratory grunt. In small children and patients with a depressed level of consciousness, these clinical features could be misdiagnosed as an episode of bronchospasm because the patient cannot verbalize their pain. Once acute pain control has been achieved analgesia can be maintained with longer acting opioids, but postoperative regional analgesia in the form of epidural or peripheral nerve catheter infusions may be quite effective as well *(28)*. This approach avoids the respiratory depressant and sedative effects of the opioids and the infusion of dilute concentrations of local anesthetics combined with narcotics can often provide excellent pain relief and facilitate early physical therapy, early ambulation, and decreased length of hospital stay, all of which will decrease the incidence of perioperative complications. Postoperative options for analgesia are summarized in Table 7 *(8)*.

Table 6
Asthmatic Patient Groups With Special Considerations

Group	*Problems*	*Management considerations for general anesthesia*
Pregnancy for cesarean section	Emergency procedure requiring rapid sequence induction	Ketamine or propofol for induction
	Aspiration risk	Pretreatment with antacid, anticholinergic and pro-kinetic
Pediatric patients	Frequent/recurrent respiratory tract infections	Immediate preoperative evaluation for possible new symptoms
	Inhalation induction frequently used	Sevoflurane is agent of choice
Morbidly obese patients	Technical difficulties with airway management	Balance control of airway with minimizing bronchospasm triggers
	Increased risk of gastric aspiration	Pretreatment with antacid, anticholinergic and pro-kinetic
	Co-existing obstructive sleep apnea	Possible extubation to CPAP
Geriatric patients	Co-existing diseases, e.g., coronary artery disease	Cautious use of β-adrenergic drugs
	Diminished reserve, altered pharmacokinetics, dynamics and consequent sensitivity to depressant drugs	Titrate drugs to effect, avoid long acting depressant drugs
Trauma patients	Unknown medical problems, possible asthma	Maintain level of suspicion for the presence of asthma but consider full differential list
	Undiagnosed pulmonary injury that can mimic asthma	Titrate drugs to effect, avoid long acting drugs
	Unknown drug history with increased risk of adverse drug interactions	

Table 7
Postoperative Analgesia Considerations in Patients With Asthma

Analgesia technique	*Advantages*	*Disadvantages/risks*
Oral medication	Patient-controlled (within limits)	Intermittent dosing schedule
	Limited potential for respiratory depression	Possible bronchospasm if NSAID combinations are given to ASA sensitive patients
Patient controlled analgesia	Patient-controlled (within limits)	No disadvantages specific for patients with asthma
	Decreases treatment delays	
Continuous epidural infusion	Continuous analgesia with decreased risk of impairment of respiration or ability to cough	No disadvantages specific for patients with asthma
Continuous peripheral nerve block infusion	Continuous analgesia with negligible risk of impairment of respiration or ability to cough	No disadvantages specific for patients with asthma

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16 How Drugs Including Recreational Drugs Affect Asthma

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Contents

KEY POINTS

- Drugs and chemicals can interact with asthma making the symptoms worse
- Direct effects of these agents can lead to bronchospasm
- Indirect effects such as drug-induced anaphylaxis or anaphylactoid reactions can cause bronchospasm
- It is likely that the use of some recreational drug, particularly those smoked or inhaled interact with asthma

INTRODUCTION: DRUG-INDUCED ASTHMA

Various drug and chemical exposures are associated with adverse effects on airways. These effects may induce or worsen the symptoms of asthma. The mechanisms of these airway changes vary from direct effects on receptors to immunologically mediated alterations.

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The extent of drug-induced bronchospasm is suggested by the analysis performed by the Swiss Drug Monitoring Center. They evaluated 10 years of spontaneously reported suspected adverse drug reactions (ADRs) and found that 2% of the reports involved drug-induced bronchospasm with 55% of the reactions considered as serious *(1)*. Analgesics and NSAIDS were reported in 24% of the bronchospasm cases with 64.4% classified as serious events. Antibiotic agents (18%), cardiovascular drugs (11%), drug formulation agents (9%), vaccines and immunoglobulins (5.5%), and plasma expanders (15.5%) made up the other major drug classes associated with bronchospasm *(1)*.

An example of an agent that has direct airway receptor effects is methacholine. When this cholinergic drug is inhaled, it causes bronchospasm in a dose-dependent manner. In fact, the threshold dose or concentration of methacholine inhaled that reduces forced expiratory volume in 1 s (FEV1) by 20% of baseline measurement is recognized as a test for airway reactivity. Asthmatic patients demonstrate lower thresholds for reducing FEV1. Other drugs and chemicals that work by increasing synaptic acetylcholine have similar effects on airways. This is demonstrated by organophosphate and carbamate pesticides induced bronchospasm by blocking the enzyme acetylcholinesterase. Therapeutic drugs such as physostigmine and neostigmine, which are also carbamates, are reversible inhibitors of acetylcholinesterase resulting in increased post-synaptic acetylcholine with the ability to cause bronchospasm and bronchorrhea in a dose-dependent manner. Because of a lower exposure threshold for inducing bronchospasm, caution must be exercised when these drugs are used in asthmatics.

Drug-induced anaphylaxis or anaphylactoid reactions can present with isolated bronchospasm or more systemic symptoms. Often the bronchospasm is part of a complex systemic syndrome that includes angioedemia, skin, upper airway, airway and blood pressure manifestations. The classic anaphylaxis reaction is a rapid antigen-induced and usually Ig E-mediated process. It results in histamine, tryptase, and other pharmacologically active mediators being released from the degranulation of mast cells and basophils. Drugs such as morphine, paclitaxil and iodine-containing contrast material can lead to direct degranulation of mast cells generating an anaphylactoid reaction that appears clinically similar to anaphylaxis.

Non-specific bronchial irritation can come from a variety of inhaled irritant chemicals and drugs. This irritation leads to bronchospasm, which can be amplified in the asthmatic patient. A wide variety of exposure to noxious gases such as chlorine, or to nebulized or inhaled therapeutic agents can trigger bronchospasm. In the case of inhaled agents such as bronchodilators, steroids, or sodium cromoglycate, bronchospasm can be triggered by the excipient, pH, osmolality or temperature of the solution *(2)*. Inhalation of antibiotics such as pentamidine or mucolytic agents such as *N*-acetylcysteine can induce cough and bronchospasm. Pretreatment with a bronchodilator may modify or prevent these airway effects.

Large numbers of drugs have been associated with bronchospasm. Table 1 offers a summary of some of these agents. The data that support this effect is often based on case reports or small case series. This chapter will specifically explore the effects of angiotensin converting enzyme inhibitors (ACE inhibitors), non-steroidal anti-inflammatory agents (NSAIDs) and beta-adrenoceptor antagonists (β-blockers), on airway bronchospasm. In addition, the effect of recreational drugs of abuse on bronchospasm will be reviewed.

Table 1
Drugs that Cause Bronchospasm *(2)*

Drug	*Frequency*
ACE inhibitors[a]	++
Acetylcysteine[a]	+
Adenosine	+
Aminoglycoside antibiotics	+
Amiodarone[a]	++
Antidepressants	++
Phenelzine	
Tranylcypromine	
Isocarboxacid	
Aspirin	++
β-blockers	++
Propranalol	
Labetalol	
Atenolol	
Timolol	
Carbamazepine	++
Cephalosporins[a]	+
Cyclophosphamide	++
Cytokines	+
D-tubocurarine[a]	++
D-Pencillamine	++
Desensitization extracts	+
Ergots	++
Erythromycin[a]	++
Gemcitabine[a]	++
Heroin	++
Hydrocortisone	+
Interferon-α	+
Interferon-β	+
Iodine radiocontrasts[a]	++
Isoflurane	++
Isotretinoin	+
L-asparaginase	+
Melphan	++
Mesalamine	++
Methotrexate[a]	++
Methimazide	+
Methylprednisolone	+
Neotigmine	++
Nitrofurantoin[a]	++
NSAID	++
Paclitaxil	+
Penicillins[a]	+
Physostigmine	++
Propofol	+

(*Continued*)

Table 1 (*Continued*)

Drug	*Frequency*
Propylthiouracil	+
Prostaglandin-F2α	+
Polyethylene glycol	+
Rifampicin	+
Risperidone[a]	+
Suxamethonium	++
Sulphonamides[a]	++
Verapamil	+
Vinblastine	++
Vindesin	+
Zanamivir	+

+ = occasional.
++ = frequent.
[a]Also causes bronchospasm with/without laryngeal edema and shock-anaphylactic or anaphylactoid reactions.

SPECIFIC EXAMPLES: DRUG-INDUCED ASTHMA

Angiotensin Converting Enzyme Inhibitors

Associated with cough, ACE inhibitors also cause bronchospasm. In reviewing Swedish ADRs, 424 adverse respiratory reactions with ACE inhibitors were reported between 1981 and 1991. The majority of these cases ($n = 374$, 88.2%) were for cough, but 36 patients (8.5%) had asthma, bronchospasm or dyspnea reported as their ADR. About half of the respiratory symptoms started within 2 weeks of starting the ACE inhibitor and about one-third resulted in hospitalization. The same authors also evaluated data from the World Health Organization international drug information system for the same period of time. They found 318 reports of asthma or bronchospasm, 516 cases of dyspnea and 7,260 reports of cough associated with the use of ACE inhibitors *(3)*.

In a controlled retrospective cohort study of respiratory ADRs associated with the use of ACE inhibitors in New Zealand, Wood *(4)* reported that both bronchospasm and cough occurred at a higher rate in patients treated with ACE inhibitors. No association with sex, past history of bronchospasm, specific ACE inhibitor drug or drug dose was found. The prevalence of bronchospasm was 5.5% for the 1,013 patients on ACE inhibitors compared to 2.3% for the 7,017 control patients on lipid lowering agents ($P < 0.001$). The relative risk of bronchospasm was 2.39 (95% CI, 1.47–3.90) for patients on ACE inhibitors compared to control patients. This compared to the 12.3% prevalence of cough in the ACE inhibitor treated group compared to 2.7% prevalence of cough in the control group ($P < 0.0001$) *(4)*.

In addition to cough, dyspnea and bronchospasm, the incidence of angioedema associated with patients treated with ACE inhibitors has been estimated between 0.1 and 0.7% *(5)*. The proposed mechanism of ACE inhibitor-mediated cough, bronchospasm

and angioedema is through inhibition of the zinc metallo-enzyme, dipeptidyl carboxy peptidase (ACE). With the suppression of ACE, substances normally metabolized accumulate. These substances include bradykinins, tachykinins, substance P, enkephalins, neurotensin and angiotensin I. Many of these substances are involved in the pathologic process of bronchoconstriction, inflammation and airway irritation leading to angioedema, cough and bronchospasm. Additionally, indirect effects of bradykinins and tachykinins can stimulate unmyelinated nerve fibers through J receptors and the vagal afferent nerve fibers leading to cough *(2, 4, 5)*.

NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

Drug-induced bronchospasm can be caused by aspirin (acetylsalicylic acid-ASA) and traditional NSAIDs in 10–20% of adults with asthma *(6, 7)* .The inflammatory airway process that generates this clinical syndrome is called ASA-induced asthma (AIA) and is most often seen in nonatopic, middle-aged females, and develops within 3 h after the exposure to ASA or NSAIDs. The syndrome often includes moderate to severe asthma, eosinophilic inflammation of both nasal and bronchial tissue with increased risk of nasal polyps and chronic rhinosinusitis *(6)*.

Although the exact mechanism of AIA is not known, the over-production of cysteinyl leukotrienes and increased expression of cysteinyl leukotriene receptor 1 are seen *(6)*. Both ASA and NSAIDs block the cyclooxygenase (COX) pathway causing arachidonate substrates to be metabolized by the 5-lipoxygenase (5-LO) pathway. As a result, a number of products are generated in higher than normal concentrations including the cysteinyl 1 leukotrienes, which can induce chemotaxis of inflammatory cells.

In addition to blocking the formation of proinflammatory prostaglandins (PGD2 and PGF2α), ASA and NSAIDs block the formation of the anti-inflammatory prostaglanin, PGE2. Synthesis of cysteinyl leukotrienes is regulated by the rate-limiting enzyme leukotriene C4 (LTC4) synthase. The loss of the anti-inflammatory PGE2 brake on LTC4 synthase overexpression results in more formation of cysteinal leukotrienes and brochospasm *(2)*.

The COX enzymes exist in at least two isoforms including Cox-1 and Cox-2 with Cox-1 being the basic form and Cox-2 being the form induced during inflammation *(7)*. Interestingly, even the topical application of the traditional COX-1 NSAID ketoprofen using ketoprofen adhesive patches or skin lotions has been associated with AIA *(8)*. Highly selective COX-2 inhibitors are clinically used as anti-inflammatory agents and appear to be well tolerated in AIA patients suggesting the importance of the COX-1 isoform in the development of AIA *(7, 9)*.

Overall, there is considerable interest in the interaction between COX-1, ALOX-5 and other enzymes, such as soluble epoxide hydrolase, which produces the pro-inflammatory “DHETs” (dihydroxyeicosatretranoic acids). These and other enzymes metabolize arachidonic acid to a cascade of overlapping pro- and anti-inflammatory mediators that are important in airway inflammation and hyer-responsiveness in asthma (*see* Fig. 1). The right combination of drugs that partially inhibit these pathways, such as omega-3 fatty acids, is an area of intense research and pharmaceutical development.

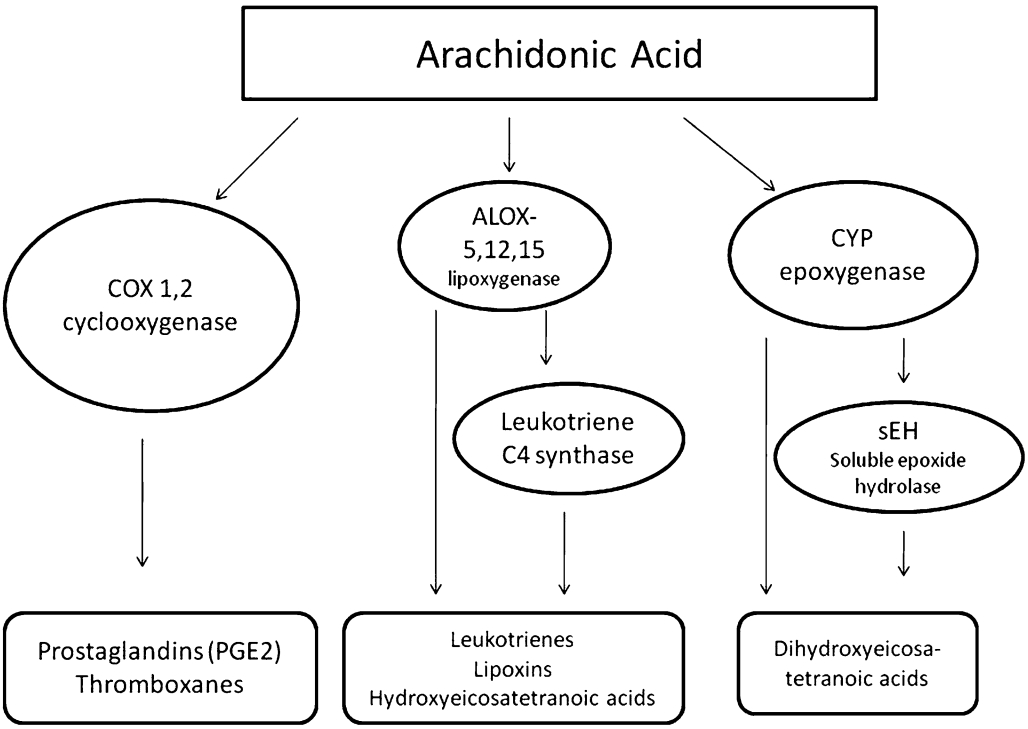

Fig. 1. Metabolic pathways of arachidonic acid relevant to asthma. Ten to 20% of asthmatics are sensitive to cyclooxygenase inhibitors (e.g., NSAIDS, non-steroidal anti-inflammatory drugs). Such patients are commonly treated with leukotriene receptor antagonists or lipoxygenase-5 (ALOX-5) inhibitors.

BETA-ADRENOCEPTOR ANTAGONISTS

The understanding of the interaction of the beta-adrenoceptor (BAR) with asthma has changed over the last several years. Classically, beta2-adrenoceptor (β2AR) agonists have been used to treat acute bronchospasm in asthma. Many BAR antagonists designed to block cardiac beta1-adrenoceptors (β1AR) cross-react and also partially block the β2AR. For over 40 years, BAR antagonists have been known to exacerbate asthma and either induce bronchospasm or block β2AR agonist effects in asthmatics (*2, 10*). More than 25 years ago, Ruffin et al. demonstrated that in asthmatic subjects, acute exposure to the non-selective BAR antagonist propranolol decreased baseline FEV1, inhibited β2AR agonist bronchodilator effect and increased the airway responsiveness to inhaled histamine *(10)*. They also reported that acute exposure to the β1AR cardioselective antagonist atenolol had little effect on baseline FEV1, no inhibition on the inhaled bronchodilator effect of β2AR agonists, but still was associated with increased histamine airway responsiveness compared to placebo particularly at the higher dose. In a recent dose escalation study of the non-cardioselective BAR antagonist nadolol in mild asthma subjects, Hanania et al. *(11)* actually found a significant dose-dependent decrease in

methacholine sensitivity for reaching 20% reduction in FEV1. This finding was balanced by the observation of a small (5%) dose-dependent reduction in baseline FEV1. A meta-analysis of randomized, blinded, placebo-controlled trials on single dose treatment (19 trials) or continued treatment (ten trials) of cardioselective β1AR antagonists on the respiratory function of patients with a reversible airway disease (defined as patients with asthma or a reversible component to chronic obstructive pulmonary disease (COPD)) was performed *(12)*. The single-dose studies of cardioselective β1AR antagonists demonstrated a 7.46% (CI, 5.59–9.32%) reduction in baseline FEV1, compared to placebo, but a 4.63% (CI, 2.47–6.78%) increase was seen in FEV 1 compared to placebo after inhaled β2AR agonist exposure. The continued treatment with a cardioselective β1AR antagonist did not lead to a significant reduction in baseline FEV1 or an increase in rescue inhaler use compared to placebo. Interestingly, those exposed to the cardioselective β1AR antagonists continuously produced an 8.74% (CI, 196–15.52%) increase in FEV1 after inhalation of a β2AR agonist compared to placebo. No clinically significant differences were seen in asthma patients compared to those with a reversible component to their COPD *(12)*.

In a series of provocative articles, Hanania and Bond *(13–15)* have suggested that asthma is like chronic congestive heart failure (CHF). The use of BAR antagonists during the acute phase of the CHF exacerbation is detrimental, while chronically they are beneficial in CHF. Further, in acute decompensation of CHF, the use of BAR agonists plays an important and beneficial role, but their use is thought to be detrimental when used chronically in CHF. They argue that many lines of evidence have also suggested that the chronic use of high-dose BAR agonists is associated with increased morbidity and mortality in asthma, while acutely in asthma exacerbations their use is clearly beneficial *(14)*. Up regulation of the β2AR with chronic low-grade blockade (even the most "cardioselective" β1AR antagonist has some β2AR antagonism) is one theory as to why paradoxically the chronic use β1AR of antagonists may benefit asthma patients. Another theory invokes the concept that many of the β1AR blockers actually have β2AR inverse agonist properties that turn off the "basal" signaling of empty receptors perhaps via modulation of the complicated β2AR G protein-dependent airway smooth muscle pathway *(13)*. In a recent editorial, Lipworth and Williamson noted that β1AR antagonists are "double-edged swords" for the asthmatic. In the acute setting, they can be detrimental but the chronic use of the cardioselective β1AR antagonists should not be prohibited in patients with cardiac diseases and asthma or COPD *(16)*.

OTHER DRUGS

As noted in the introduction, many drugs have been associated with bronchospasm (Table 1). Several case reports have suggested that antithyroid drugs such as methimazole and propylthiouracil have induced asthma *(17, 18)*. Although the symptoms of asthma could be the result of the hyperthyroidism, other data suggest that the use of antithyroid medication is more likely the causative etiology *(19, 20)*. One theory suggests that because these drugs accumulate in neutrophils and bind myeloperoxidase, alteration in myeloperoxidase activity may stimulate neutrophil degranulation leading to bronchospasm and other diseases such as crescentic glomerulonephritis seen in their use *(18)*.

Acetaminophen is not a NSAID drug. It is one of the most common analgesics used in the United States and is sold alone or is combined with cold/cough formulations and prescription opioids *(21)*. Since the late 1960s, it has been suggested that a link exists between the exposure to acetaminophen and bronchoconstriction *(21)*. A survey of nearly 20,000 Danish subjects found a higher prevalence of new-onset asthma in those who reported frequent acetaminophen doses compared to those that did not (12.0 vs. 4.3%, OR = 3.03 (CI, 1.51–6:11; *P*:0.005)). These findings remained statistically significant after adjusting for sex, age, smoking, body mass index, presence of hay fever or eczema, and the use of other medications *(22)*. Epidemiological evidence exists suggesting that the risk of asthma increases in a dose-dependent manner with the exposure to acetaminophen in utero, during infancy and childhood, and during adult life *(21, 23)*. Biologically plausible mechanisms have been proposed including acetaminophen-induced reduction in respiratory tract glutathione resulting in increased airway oxidant-induced inflammation. In addition, acetaminophen-induced cytokine "imbalance or dysregulation" may induce or enhance life-long T-helper type 2 (allergic) responses and cause a dominance over T-helper type 1 (non-allergic) responses. This may explain the increase in atopic diseases including rhinoconjunctivitis, eczema and asthma seen with acetaminophen usage *(21, 23)*.

N-Acetylcysteine (NAC) is a glutathione replacement agent used by the intravenous or oral route to treat acetaminophen poisonings. Inhaled NAC is also used as a mucolytic agent with variable efficiency *(24–26)*. Cough and bronchospasm have been seen with inhaled NAC particularly in asthmatics and this can be prevented with simultaneous inhalation of β2AR agonists *(27)*. Oral NAC (200 mg three times/day) for 9 weeks in 25 "stable symptomatic" asthmatic subjects resulted in no effect on spirometric, lung mechanic or gas exchange variables, nor on the frequency of pulmonary symptoms *(28)*.

While the use of intravenous NAC in the treatment of acetaminophen overdose is relatively new in the United States, it has been the preferred route of administration in Europe, Asia, Canada and Australia since the late 1970s. Both isolated bronchospasm and bronchospasm associated with anaphylactoid reactions have been reported with intravenous NAC *(29, 30)*. Bronchospasm has been reported with intravenous NAC between 0.9 and 26.3% of the time *(31, 32)*. In a recent study of patients in Malaysia admitted with the diagnosis of acetaminophen overdose, those treated with intravenous NAC were found to have a 6.4% incidence of both bronchospasm and cough compared to 1.5% for bronchospasm ($P = 0.03$) and 0.8% ($P = 0.01$) for cough in those not treated with intravenous NAC *(31)*. These episodes were thought to be anaphlactoid in origin with most occurring during the loading phase of NAC dosing. They were treated by reducing the infusion rate and acute treatment with bronchodilators, antihistamines and hydrocortisone *(31)*.

In an attempt to identify risk factors for NAC-induced side effects, Schmidt and Dalhoff retrospectively evaluated 529 consecutive patients with acetaminophen overdose *(33)*. Asthmatics were found to develop bronchospasm and other adverse effects to intravenous NAC 2.9 times more likely (CI 2.1–4.7) than non-asthmatics. The severity of the side effects were the same in the two groups while serum acetaminophen levels were lower ($P = 0.00006$) in patients with side effects compared to those without side effects *(33)*.

RECREATIONAL DRUGS OF ABUSE AND ASTHMA

With the widespread use of illicit drugs, pulmonary complications of their use have been widely recognized and reviewed *(34)*. The 2005–2007 National Surveys on Drug Use and Health (NSDUH) from 29,195 respondents, aged 35–49 estimated the prevalence of morbid conditions *(35)*. Inhalant use was the only illicit drug that was associated with an adjusted duration-dependent greater prevalence of asthma. Several reports have even suggested an association of asthma deaths and the use of illicit drugs *(36–38)*. In one series, 29 of 92 (31.5%) of fatal asthma cases were confounded by significant substance abuse or alcohol ingestion with cocaine. Fourteen of the 29 substance abuse associated asthma deaths were related primarily with cocaine *(37)*. Table 2 summarizes several associations of drugs of abuse and asthma.

Cocaine

Cocaine, an alkaloid from the plant *Erythroxylon coca*, has continued to be a significant drug of abuse with wide negative health effects. Cocaine, like amphetamines and other similar stimulants, has a multitude of complex pharmacological effects. Peripherally, cocaine prevents the neuronal reuptake of epinephrine and norepinephrine, resulting in higher synaptic catecholamine levels. In the central nervous system (CNS), cocaine increases norepinephrine release from presynaptic nerve terminals and prevents dopamine and serotonin reuptake. Unlike amphetamines, cocaine also blocks fast sodium channels at the cell membrane level, giving a profound local anesthetic effect.

During the nineteenth century, patent medicines such as "Dr. Tucker's Asthma Specific" (420 mg of cocaine/oz) were hailed as asthma treatments. The Harrison Narcotics Act of 1914 later prohibited the sale of cocaine-containing elixirs, and the use of cocaine decreased until about 1970, when the illicit use of cocaine developed. Because of the relatively recent popularity of smoking free-base and crack cocaine, increased interest exists in the pulmonary complications of cocaine use. When street cocaine is smoked, not only is the alkaloid cocaine (benzoylecgonine) involved, but also

Table 2
Association Between Recreational Drugs of Abuse and Asthma

Drugs of abuse	*Strength of association*
Cocaine	+++
Amphetamines	+
Opioids	++
Marijuana	++
Tobacco	
Nicotine	?
Tobacco smoke	+++
Volatile substances abuse	+
Hallucinogens	?

+++ many case reports/frequently reported; ++ several case reports/commonly reported; + rare case reports; *?* no case reports/no known association.

the pyrolysis of its metabolites, contaminants, and the fuel used to burn the cocaine. Each of these components of burned or vaporized street cocaine may affect the patient with asthma.

Asthma has been linked with cocaine for several decades, although its causality in this disease process remains unproven. The first known report *(39)* discussing cocaine's potential association with asthma was published in 1932. This case report described the apparent precipitation of an asthma exacerbation in a patient using cocaine as a local anesthetic. The advent of smoked cocaine abuse has drawn significantly more attention to asthma, particularly in the inner cities. In 1990, 21% of all asthma deaths in the 5- to 34-year-old age group in the United States were in New York City and Cook County, IL *(40)*. This astounding fact sparked investigations of the asthma deaths, including the potential association with cocaine abuse. A preliminary study in Chicago *(41)* found drug abuse to be a significant variable in asthma deaths. When 102 cases of fatal asthma and respiratory arrest of indeterminate cause in patients under 45-year-old were investigated *(37)*, mucous plugging or lung hyperinflammation consistent with fatal asthma was identified at autopsy in 70% of the patients. Of these patients, 92 had significant toxicology for illicit drugs or alcohol. Cocaine and its metabolites were the most common illicit drug identified, occurring in 44% of these cases *(37)*. A similar conclusion was drawn in a smaller New York City case–control study of 59 consecutive patients presenting to the hospital emergency department with new-onset wheezing or a recrudescence of asthma after five symptom-free years *(42)*. When compared to 53 age- and gender-matched controls, 36% of the new-onset asthma group and 15% of the controls had positive urine screens for cocaine metabolites. A multi-variate analysis, adjusting for age and sex, suggested that cocaine abuse was associated with a threefold higher prevalence of asthma *(42)*. Another small inner city emergency department study *(43)* noted that 36% of the 22 patients with new-onset wheezing had positive urine levels for cocaine, whereas only 13% of the 22 controls had positive urine for cocaine. A more recent emergency department study of 103 patients with severe asthma symptoms who consented to toxicology testing found that 13% had positive urine screens for cocaine metabolite (baseline for population estimated to be 2%), and twice as many (38%) with positive screens required hospitalization than those with negative screens *(44)*.

A host of case reports and series tie cocaine use, particularly smoked free-base cocaine, with asthma attacks. Six patients were described who presented to a New York City hospital with severe, life-threatening asthma after smoking cocaine *(45)*. Although many had concomitant use of tobacco and/or marijuana or upper respiratory tract infections, the authors believed that cocaine was the precipitating factor in each case. Rebhun *(46)* described three patients with asthma symptoms that only presented after smoking cocaine, despite a habit of previous cocaine snorting. One fatal case of asthma associated with cocaine has been reported again from New York *(47)*. Ironically, the patient's family reported that the patient's brother used crack cocaine and also died from a severe asthma exacerbation. A retrospective study of adult patients admitted to an inner city hospital for asthma exacerbation found 27.6% had used cocaine with significantly more receiving intubation, ICU admission and having longer length of hospital stay than non-users *(48)*.

A case report describes a 32-year-old woman with preexisting asthma, who presented with severe bronchospasm and respiratory failure requiring intubation several hours after snorting cocaine. This was believed to be the first case of near-fatal asthma associated with nasal insufflation of cocaine and has been followed by several others *(45, 49, 50)*.

Pulmonary function testing (PFT) and methacholine challenge testing (MCT) provide some objective evidence of variable expiratory flow limitation, its severity and response to treatment. It is understandable that a series of studies have focused on the use of PFT to further define the relationship between crack or snorted cocaine use and asthma. In general, the results of these studies are inconclusive and somewhat inconsistent. Several spirometry studies *(51–55)* have documented near-normal forced expiratory volume in 1 s (FEV1) and FEV1 divided by forced vital capacity (FVC) ratios in free-base cocaine smokers. Tashkin *(56, 57)* studied 14 former intravenous cocaine users without asthma who were given smoked and intravenous cocaine. Similar increases in heart rate and self-reported levels of intoxications were seen, but only the smoked cocaine alkaloid caused a decrease in airway specific conductance (SGaw) at 5 min *(57)*. Similarly, airway resistance (Raw) was significantly increased in the group that smoked cocaine compared with the intravenous group, an effect that persisted for 30 min. The study demonstrated a bronchoconstrictive effect related solely to inhaled crack cocaine. Because there were no observable differences noted in SGaw and Raw in the intravenous group compared with control groups, it appears that a local irritant effect of the drug, its metabolites or contaminants after pyrolysis, may be responsible for many of the asthmatic exacerbations reported *(57)*. A gas diffusion abnormality, reduced diffusion capacity (DLCO), is reported more commonly in habitual cocaine smokers. Adrenergically mediated pulmonary vasoconstriction and a reduction in circulating pulmonary blood volume have been postulated as possible mechanisms to explain these reductions, which have not been universally reported *(56)*.

Although several potential mechanisms of cocaine-induced asthma have been postulated, no definitive single cause has been defined. One case may shed light on the potential multiple mechanisms involved *(58)*. A 47-year-old woman developed a syndrome of wheezing, shortness of breath and cough, requiring hospitalization three times in a 6-month period, after smoking crack cocaine. Each time, she had fleeting pulmonary infiltrates, fever, a peripheral eosinophilia and a markedly elevated immunoglobulin (Ig)E level. Transbronchial biopsy specimens revealed nondiagnostic interstitial collections of lymphocytes, plasma cells and eosinophils. These findings were called "crack lung," and were temporally related to her inhaled cocaine use, and indicate a probable immunological mechanism for her respiratory syndrome. Whether cocaine-related allergens can prompt an IgE-mediated response, and if so, whether it occurs commonly are unclear. The syndrome this patient experienced may well be idiosyncratic, but clearly, a spectrum of potential mechanisms for reactive airways after smoking cocaine exists.

In Levenson's previously noted autopsy study linking unexplained asthma deaths with illicit drug use (mostly cocaine), the majority of the patients (69%) had the usual asthmatic findings of mucous plugging and hyperinflation, suggesting the chronic inflammatory nature of the disease *(37)*. The observation that eosinophils, key inflammatory promoter cells in asthma, have been found in the sputum of free-base smokers with

asthma supports the claim that cocaine smoking potentiates the airway inflammation of asthma, but does not eliminate the possibility that the smokers had underlying quiescent asthma *(45)*.

Another theory proposed to explain cocaine-associated severe asthma attacks focuses on the observation that patients with near-fatal asthma had a blunted response to hypoxia and an impaired sensation of dyspnea *(59)*. This blunted response may be further augmented by the local anesthetic effect of inhaled cocaine. Finally, an uncommon mimic of an acute asthma exacerbation was reported when an adult patient presented with "wheezing" and respiratory failure requiring mechanical ventilation. On chest computed tomography (CT) scan, it was found that he had aspirated several bags of cocaine during a confrontation with police *(60)*.

Amphetamines

Amphetamines are CNS stimulants with pharmacological properties that result in the increased release of catecholamines similar to cocaine, but without the local anesthetic effects. They were first synthesized in 1927. By the 1930s, inhaled nasal products, such as Benzedrine Nasal Inhaler, were commonly used and abused stimulants. The Controlled Substance Act of 1970 greatly curtailed the legal distribution of most amphetamines outside of prescription use. The illegal production of methamphetamine and designer amphetamine derivatives has created the current demographics of stimulant abuse, causing amphetamine to be more popular than cocaine in many parts of the United States. A more pure and potent form of methamphetamine known as "ice" is volatile and allows a strong rapid high when inhaled or smoked.

Despite the similar pharmacological properties and frequent pyrolysis of methamphetamine, no significant link has yet been made to exacerbations of asthma. To date, two cases have been reported in the medical literature *(61, 62)*. One report *(61)* describes a young man found dead with a bronchodilator inhaler in his hand, autopsy finding of severe acute asthma and significant levels of the designer amphetamine methylenedioxymethamphetmine (MDMA). Another case reported a 30-year-old male truck driver found dead at the side of the road with a nebulizer in this hand *(62)*. His autopsy suggested asthma as the cause of death, with hair and blood levels suggesting chronic methamphetamine use. A causal link was suggested in both case reports, but could not be proven. Two small series *(63, 64)* described 13 patients who abused IV methylphenidate and had panlobular emphysema with significant airflow obstruction. Oral methylphenidate has not been associated with emphysema, and it was postulated that the pathological changes were likely secondary to talc and other embolic materials. Formal PFTs in amphetamine abusers have not been systematically reported.

Opioids

Naturally occurring opioids called opintesane derived from the poppy, *Papaver somniferum*, include morphine and codeine, with heroin remaining the most widely abused semisynthetic form. As with other recreational drugs of abuse, users have devised several means of heroin self-administration, including injection, inhalation, smoking, nasal insufflation and ingestion.

Although the association between opioids and asthma was first suggested in the 1960s, a host of case reports from England in the mid-1980s highlighted a potential interaction between severe and even fatal asthma and recent heroin use *(65–71)*. For example, one report of three chronic heroin inhalers ("chasing the dragon") noted the sudden onset of bronchospasm, respiratory failure and anoxic encephalopathy in two of three patients after using heroin *(68)*. Survey studies *(42, 69, 70)* have provided further indirect evidence linking heroin use with asthma. Of 29 young asthma deaths in an urban setting, 7 had a toxicological screen positive for opioids *(37)*. In a study of 2,276 mostly intravenous heroin abusers, 5% were identified as asthmatic from reviewing medical records and 31 of these addicts with asthma had reported temporal relationship between their heroin use and the onset of an asthma attack *(70)*. The authors concluded that this 1.4% of opioid users who demonstrated reactive airways to heroin represented a significant percentage of the burden on health care services from this addiction *(70)*. Heroin-induced bronchospasm may be more severe in those with previously recognized asthma. In a series of 152 cases of severe exacerbation of asthma, 30.9% were found to have used heroin and these patients were more likely to be intubated (17.0 vs. 2.3%, respectively, $P=0.0036$) than non-users *(48)*. A case of asthma associated with diffuse pulmonary infiltrates and alveolar eosinophils has been reported that resolved rapidly with steroids and abstinence from heroin *(72)*. A series of five cases of sudden onset status asthmaticus were reported temporally after either snorting or smoking heroin *(73)*. All five patients had a history of asthma and this sudden and severe asthma exacerbation required intubation in four out of the five patients. The authors argue that the cases illustrate the importance of considering illicit drug use in sudden onset status asthmaticus.

The results of PFTs evaluating the potential link between asthma and opioid abuse have been contradictory. One study reported four out of six young men who presented with new-onset wheezing and dyspnea after inhaling heroin vapor had either a positive carbachol challenge test or spirometry, suggesting airway obstruction *(65)*. However, they had peripheral or sputum eosinophilia that also strongly suggested an atopic association to their asthma, drawing into question the association with heroin. Other PFT studies refute these results *(72, 74–76)*. In a study of 512 consecutive hospitalized intravenous drug users with positive opioid screens at admission *(76)*, 6% had evidence of airway obstruction on PFT, 7% had restriction and 42% had an abnormally low DLCO.

Krantz *(77)* has reported a series of inner city intensive care unit admissions for asthma in which 41.3% had a positive history of use and urine toxicological screen positive for opioids on admission, compared with a 12.5% positive rate ($P=0.006$) for patients with diabetic ketoacidosis admitted to the same unit. However, other studies *(78–80)* have demonstrated that the administration of morphine or modulation of the opioid receptors can ameliorate bronchoconstriction caused by noxious stimuli in patients with asthma.

Several proposed mechanisms exist for opioid interaction with asthma. Morphine and codeine caused wheezing as a result of the release of histamine from mast cells in animal and some human studies. Decrease in airway SGaw has been shown when μ-opioid receptor agonists, such as codeine, are inhaled in patients with asthma who are histamine

sensitive, but not when taken orally. Whether this is a direct effect on the μ receptor agonist on mast cells or an indirect effect perhaps through stimulation of cholinergic J-receptors is unknown. The development of an allergic response to opioids is suggested by the demonstration of IgG and IgM antibodies to morphine in some pharmaceutical industry workers, many of whom have atopic dermatitis and asthma *(81, 82)*. None of these specific proposed mechanisms have yet to be proven causative, and one or more could contribute to a patient's opioid-associated asthma.

Marijuana

Marijuana comes from the *Cannabis sativan* plant. The word "marijuana" is derived from the Mexican word meaning "inebriant plant." Marijuana is the most commonly used illicit recreational drug in this country. The cannabinoid, Δ9-tetrahydrocannabinol (THC), is primarily responsible for the intoxicating properties of the marijuana cigarettes, commonly known as "joints" or "reefers." Marijuana cigarettes contain about 5% THC, which stimulates CNS cannabinoid-1 (CB-1) receptors or peripheral immune CB-2 receptors *(56, 83)*.

The interaction between marijuana abuse and asthma is a complex one. The acute effects of marijuana or THC inhalation have been reviewed extensively by Tashkin *(56)*. A decrease in Raw and an increase in SGaw have been reported after smoking marijuana or inhaling THC in healthy patients and patients with asthma, with the peak bronchodilator effects seen at 15–20 min and persisting for 60 min. Paradoxically high-dose exposure to THC has a bronchoconstrictor effect, and tolerance to the bronchodilator effect also occurs within several weeks of exposure *(84)*.

Population studies of regular users of marijuana have shown significant increases in cough, sputum production, wheeze, exertional dyspnea and acute bronchitis episodes compared to nonsmokers *(56, 85–87)*. Some investigators *(84)* suggest that the inhaled irritants in the marijuana smoke account for these observed symptoms. The complex interaction between asthma and marijuana appears at this time to be only indirect.

Studies investigating the effects of marijuana smoke on PFTs are conflicting. As mentioned, initial bronchodilator effect with improved FEV1 is seen after marijuana or THC inhalation. Tashkin has shown significant increase at 2–4 h in SGaw in 10 subjects after they smoked marijuana or ingested THC pills *(84)*. Tachyphylaxis develops to this bronchodilation in habitual users, with air flow obstruction being reported in heavy users *(56)*. Airway hyperresponsiveness by the MCT, a key feature of asthma, is not more common in marijuana smokers. Currently, there is no evidence that the long-term changes seen in airflow with chronic marijuana are related to THC, but more likely related to the off-gas from the pyrolysis products.

If marijuana smoke or inhaled THC interacts with asthma, there are several potential mechanisms. As noted, the immediate bronchodilation seen with marijuana smoke or inhaled THC is probably from stimulation of the G protein-coupled CB-1 receptors either causing CNS modulation of bronchial tone or through direct effects. The CB-1 receptors have been found to be in proximity to airway smooth muscle cells *(56, 83)*.

Although tachyphylaxis eventually can negate the bronchodilation, actual bronchoconstriction may be triggered by irritants in the marijuana smoke. It has also been postulated that THC has immunosuppressive properties by interacting with the CB-2

receptor on natural-killer lymphocytes *(88, 89)*. This may allow an exaggerated inflammatory response to the irritant gases, which then contributes to airway injury.

Tobacco and Nicotine

Cigarette smoking is endemic in the United States, and nicotine use remains the most common legal and overall recreational drug of abuse. There are at least 48 million smokers in this country alone, with prevalence use among high school students ranging as high as 35% in 1995 *(90)*. A recent report found large racial variations with prevalence among youth aged 12–17 years, from 27.9% in Native Americans to 5.2% in Japanese American Youth *(91)*. Tobacco is one of the most deadly and expensive drugs of abuse. Annual estimates in the United States alone are more than 430,000 direct deaths and direct health care costs that exceed an astronomical $50 billion as a result of cigarette smoking *(92)*.

It is clear that tobacco contains, in addition to nicotine, numerous toxins and carcinogens that contribute to the development of chronic bronchitis, emphysema and malignancy. Nicotine is a powerful central- and peripheral-acting agent that contributes to cigarette smoking addiction *(93)*, but its direct link to these other pathophysiological processes is less clear. Despite the many studies on nicotine, the drug's direct effects on the lungs are not well defined.

In numerous studies *(94–98)*, either direct (active) or indirect (passive) exposure to environmental tobacco smoke has been proven to be a risk factor for the development and worsening of childhood asthma. This association has been shown even with fetal exposure by maternal smoking *(95, 99)*. Risk-factor analysis for children with acute respiratory failure showed that exposure to second hand tobacco smoke had the highest odds ratio of 22.4±7.4 (95% CI) for requiring intubation *(100)*. The association of tobacco smoke with worsening asthma has also been shown repeatedly in adults *(101)*. Although the evidence does not prove causality, the association is robust and has been consistently shown in many studies. Repeated exposure to tobacco smoke triggers inflammatory responses in certain children and adults that may initiate the development or worsening of asthma symptoms. No such association has been shown for nicotine alone.

Although long-term active and passive exposure to tobacco smoke is associated with PFT changes showing worsening airways obstruction in numerous long-term smokers *(99)*, the data for patients with asthma and passive tobacco smoke exposure are not as convincing (*97, 102, 103*). At least one study in children with asthma reported that passive smoke exposure was associated with a decline in peak flows and an increase in respiratory symptoms *(104)*. In children, an increase in airway hyperresponsiveness as determined by the MCT was not associated with passive tobacco exposure, whereas an increase in asthma symptoms was *(98)*.

Tobacco smoke contains many respiratory irritants, including ammonia, sulfur dioxide and formaldehyde, as well as numerous carcinogens. Different compounds found in cigarette smoke may be injurious to given predisposed individuals, leading to a triggering or lowering of the threshold for asthma. Smoking is also associated with increased airway inflammation. The interaction of tobacco smoke and asthma is likely to be multifactorial even for individuals. Smoking may also modulate immunological responses. Active smoking is associated with an increase in total IgE. An increase in IgE is also seen in first-degree relatives exposed to passive smoking *(98)*.

Volatile Substance Abuse

Volatile substance abuse is the practice of inhaling fumes of heterogeneous volatile compounds to achieve a desired intoxicating effect. Acute and long-term neurological and short-term cardiac toxicity have been reported as a consequence of this relatively new practice *(105)*. First tracked to California in the 1950s, by the mid-1960s, glue sniffing was popular among young people because of its accessibility, cost and rapid effect. Since then, common household solvents and commercially bought solvents, gases and fuels have been inhaled, including acetone, butane, propane, toluene and nitrous oxides. The most common methods of use include "sniffing" fumes directly from a container, "huffing" from a drenched cloth placed over the face and "bagging" from an enclosed bag placed over the head.

A survey in Great Britain found that use in some secondary school students was as high as 6% *(106)*. A study in the United States found 0.4% of students aged 12–17 years abused inhalant substances *(107)*. A major risk factor for volatile substance abuse is low socioeconomic status. Given the low cost of these common substances, use for recreational means is likely to continue.

There is no direct reported association between asthma and inhalation of volatile substances. In a single study, Schickler *(108)* investigated possible PFT abnormalities in a cohort of 42 young solvent inhalers and 20 controls. There were no significant differences in FEV1 or FVC values to suggest a variable obstructive defect, although increased residual volumes were seen in the substance abusers. Five of the volatile substance abusers did report acute wheezing after inhaling toluene, but no abnormalities suggestive of asthma could be demonstrated. Other reported pulmonary symptoms after volatile substance abuse include coughing, chronic rhinitis and increased sputum production, as well as a case report of respiratory decompensation with pulmonary infiltrates after "fire-breathing" *(109, 110)*. Currently, no consistent pattern can be identified linking volatile substance abuse to asthma. If volatile substance abuse becomes a more burdensome problem, then the establishment of an interaction with asthma may become possible.

Hallucinogens

Hallucinogens are a general class of drugs that produce either alterations in perception of the environment or a dissociative state. Several drugs can cause this sensation, including certain designer amphetamines, volatile substances, anticholinergic drugs and steroids. Each has unique neurohormonal actions and effects, but all are potentially hallucinogenic. Three recreationally abused drugs that produce this state in much lower concentrations are lysergic acid diethylamide (LSD), phencyclidine (PCP) and ketamine. PCP, or "angel dust," was marketed in the 1960s as a veterinary dissociative anesthetic with amnestic and analgesic properties, but its hallucinatory effects soon led to its ban. It has been ingested, smoked and snorted illicitly since then and is abused primarily in inner cities and among young polysubstance abusers. Ketamine is still used in both human and veterinary medicine as a dissociative anesthetic, but diversion to illicit use has become an increasingly common problem. Compared to ketamine and PCP, LSD is more potent, easily synthesized and readily available. LSD's actions are unclear, but speculation suggests that it may act on postsynaptic serotonin receptors, producing psychic sensations often described as depersonalization, with sensory hallucinations.

All three can cause adverse psychological reactions, or "bad trips," but serious physiological side effects are uncommon.

There are no reports describing the onset of asthma after illicit PCP, ketamine or LSD use or establishing a causal relationship between them. Ketamine has been used in status asthmaticus because of its favorable effects on airway SGaw. A previously described study on asthma deaths in Cook County, IL *(37)* noted that 2% of the young people with unexplained fatal asthma had positive toxicological screens for PCP. It is unclear, however, what role these intoxications may have played in the asthma-related death. No evidence to date has been found to support the notion that LSD, ketamine or PCP causes or exacerbates asthma.

CONCLUSION

Case reports and small series describing the development of asthma after recreational drug abuse, particularly with cocaine, heroin, tobacco and marijuana use, are increasingly prevalent. The evidence directly linking the association between asthma and drug use for the most part remains tenuous, but a real interaction probably exists in a subset of asthmatics (*see* Tables 1 and 2). Airway irritants in the inhaled substances are able to trigger bronchospasm in many cases, but other mechanisms probably contribute for individual substances, as well. Prescription, recreational and illicit drug use may be an important confounder in certain patients with asthma, and providers must be diligent in reviewing and questioning patients with new-onset and difficult-to-control symptoms about potential drug use.

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IV Living with Asthma

17 The Challenge of Asthma in Minority Populations

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Contents

KEY POINTS

- While asthma affects all races and ethnic groups, there is significant disparity in asthma morbidity and mortality. Minority populations suffer disproportionately higher rates of fatalities, hospitalizations, and emergency department and urgent care visits due to asthma.
- Few studies have addressed ethnic differences in asthma in countries outside of the U.S. International survey data have shown considerable variation in asthma prevalence in both children and adults among countries, with higher prevalence in English-speaking countries, including the United Kingdom, Australia, New Zealand, and Ireland, and some Latin American countries.

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- Puerto Ricans, African-Americans, American Indians/Alaskan Natives, and persons of multiple races have the highest current and lifetime asthma prevalence and attack rates.
- Low socioeconomic status (SES) is an independent and significant factor for increased asthma morbidity and mortality for many minority groups.
- Barriers to care exist because of lower SES, with decreased access, inadequate care or lack of chronic care, including under-prescription of inhaled corticosteroids, increased environmental exposures in urban settings, substandard living conditions, increased psychosocial dysfunction and cultural differences.
- Environmental intervention strategies, which are comprehensive and individualized, can be effective in reducing allergen environmental burden in urban settings and reduce asthma morbidities.
- Genetic variation alone or interacting with environmental exposures contributes to ethnic disparities in asthma.
- Culturally competent strategies can be effective in helping to reduce the disparity in asthma health care and outcomes in racial/ethnic minorities.
- Reduction of asthma disparity in racial and ethnic minority groups is an important challenge and goal.

INTRODUCTION

In the United States, minority groups are increasing in relative proportion of the population, especially Hispanics, Asians, and Pacific Islanders. In 2005, according to Pew Research Center estimates, the U.S. race/ethnic proportions were 67% white, 14% Hispanic, 13% black, and 5% Asian. According to a William H Frey of the Brookings Institute analysis of the 2009 U.S. Census estimates, whites are now a minority in California, Hawaii, New Mexico, Texas, and the District of Columbia *(1)*. By 2050, "minorities" are projected to become the majority, as whites are projected to comprise 47%, Hispanics 29%, blacks 13%, and Asians 9% of the U.S. population *(2)*.

While asthma affects all races and ethnic groups, minority and economically disadvantaged populations suffer significantly and disproportionately higher rates of fatalities, hospitalizations, and emergency department (ED) visits due to asthma. For example, blacks had about threefold more deaths for adults and eightfold more for children than whites according to the latest average annual data for 2005–2007 *(3)*. Asthma in minorities is important from multiple perspectives, including social, economic as well as medical. The elimination of the disparity in asthma burden in minorities and those living in poverty has become a national priority.

In 2005, a national workshop with over 1,000 national experts was conducted to address the problem of disparities in asthma including issues of genetics, indoor and outdoor environment, family/social function, behavioral health, health-care delivery, health-care communications, roles of the community, private insurance, and safety net providers, and state and local policy *(4)*.

The burden and disparity of asthma in race/ethnic minorities presents a significant challenge. In this chapter we will review asthma epidemiology in minorities, examine potential causes for asthma disparities, and discuss strategies of intervention and culturally sensitive care. Different definitions of "minority" exist, including distinctions based on religion. For the purposes of this chapter, minority, in terms of race and ethnicity will

refer to non-white U.S. Office of Management and Budget classification of race. In addition to whites, these racial designations include Black or African-Americans, Asian, Native Hawaiian or other Pacific Islander and American Indian or Alaska native. Ethnicity refers to Hispanic or Latino and Not Hispanic or Latino. The term "race/ethnicity" will be utilized throughout this chapter to refer to minority populations.

ASTHMA DIFFERENCES AMONG COUNTRIES

Worldwide asthma prevalence among children varies considerably. In Phases I and III of the International Study of Asthma and Allergies in Childhood (ISAAC), there were up to 15-fold differences in the prevalence of childhood asthma among participating countries. Among children 13–14 years old who participated in Phase III of ISAAC, the prevalence of current wheeze (defined as "wheezing or whistling in the chest in the last 12 months") ranged from 0.8% in Tibet (China) to 32.6% in Wellington (New Zealand). Amongst those aged 6–7 years, the prevalence of current wheeze ranged from 2.4% in Jodhpur (India) to 37.6% in Costa Rica *(5)*.

In general, asthma prevalence was higher in English-speaking countries and in Latin America, and lower in the Indian subcontinent, Asia-Pacific, Eastern Mediterranean, Northern Africa and Eastern Europe. However, there were significant differences in asthma prevalence among countries within a given geographic region. For example, within Latin America, asthma prevalence was low in Argentina, Chile and Mexico, whereas the prevalence was much higher in Costa Rica. More variation was noted between countries than within countries, though this may be due to selection bias. Interestingly, the proportion of current wheezers who had severe asthma symptoms was higher in Africa, the Indian subcontinent and the Eastern Mediterranean than in English-speaking countries for both age groups *(5)*.

In contrast to much of Asia, several affluent Asian regions such as Hong Kong, Singapore, and Japan were found to have relatively high asthma prevalence. A notable dissimilarity was seen between Hong Kong and Guangzhou (10.1 vs. 2.0%, 12-month prevalence of wheezing), two areas of China that are geographically and ethnically similar but differ in affluence.

In ISAAC, children living in lower income countries tended to have a lower prevalence of current wheeze based on written questionnaire than those living in higher income countries (OR 0.49 [95% CI (confidence interval) 0.37–0.66] in those aged 6–7 years old and OR 0.55 [95% CI 0.42–0.72] in those aged 13–14 years). Similar results were seen for "asthma ever" *(6)*.

Limitations of ISAAC include lack of objective data (e.g., lung function) to validate the questionnaires used across cultures and languages, and variation in the number of areas surveyed within and between countries (e.g., urban areas are over-represented), potential reporting differences, and lack of ethnic-specific data within participating countries. Nonetheless, ISAAC has provided valuable information about childhood asthma for public health practitioners and researchers alike.

Recent worldwide findings for asthma in adults are similar but not identical to those in children. The European Community Respiratory Health Survey (ECRHS) reported a higher prevalence of asthma in adults (ages 20–44 years) living in English-speaking countries (including the United Kingdom, Australia, New Zealand, and Ireland) than in

those living in Eastern and Southern Europe. Overall, there was agreement between the ISAAC and ECRHS findings *(7)*. More recently, the World Health Organization implemented the World Health Study, which provided global patterns of self-reported wheeze and doctor-diagnosed asthma among adults. The prevalence of current wheezing ranged from 2.4% in Vietnam to 24% in Brazil, and that for asthma ranged from 1.8% in Vietnam to 32.8% in Australia. There was a U-shaped pattern for the relationship between national income and either asthma symptoms or asthma diagnosis *(8)*.

There are limited data evaluating racial/ethnic differences in asthma outside the United States. Some examples of studies outside the United States will be summarized. In Sweden, Hjern et al. showed an inverse association between hospitalizations for childhood asthma and birth outside of Western Europe, the United States and Australia. These results were significant after accounting for indicators of socioeconomic status (SES) and other variables, suggesting a role for ethnicity on asthma morbidity among children in Sweden *(9)*. An editorial regarding ethnic differences in asthma in the United Kingdom (UK) concluded that asthma and asthma admissions may be more common in South Asians (Indian subcontinent), but also that asthma may be underdiagnosed and under-treated in this population. Cultural barriers might exist, as dissimilar results were noted in asthma outcomes for South Asians vs. white Europeans despite similar access to treatment and educational resources. Other potential explanations for the ethnic-specific differences include environmental exposures, communication problems, and host factors (e.g., genetics) *(10)*. Similar confounding variables for racial/ethnic minorities that have been studied or postulated in the United States are discussed in Sect. 5.

A more recent study of children in the UK, the MRC Determinants of Adolescent Social well-being and Health (DASH), included 80% minorities and examined parent-reported asthma prevalence among 11- to 13-year-old children by self-reported ethnicity. Compared to whites, Black Africans, Indians and Bangladeshis had a lower and White/Black Caribbeans a higher prevalence of asthma. Residence in the UK for <5 years was protective against asthma in Black/Caribbean and Black Africans compared to those born in the UK. These findings are somewhat contrary to those noted primarily in the United States, which show a higher prevalence of asthma amongst Blacks. This discrepant finding may be due to a diagnostic bias, as there were no differences in report of wheeze among ethnic groups in the study *(11)*.

Similar to U.S. data on American Indians and Alaska natives, Canadian aboriginals have an increased incidence of emergency (2.1 times higher) and office visits (1.6 times higher) for asthma compared to nonaboriginals. Specialty care and spirometry were underutilized in aboriginals, suggesting access barriers to quality care *(12)*.

In New Zealand, mortality and asthma admission rates differed between whites and Maoris or Pacific Islander children likely because of variation in medical management, especially prescribing patterns by medical practitioners. Similar discrepancies in prescribing practices for minorities in the United States have been noted and are discussed elsewhere.

Recent reports from various countries involving different age and racial/ethnic groups have shown conflicting results regarding trends in asthma prevalence. Whereas some areas have reported decrements (e.g., Rome [Italy], Saskatchewan [Canada],

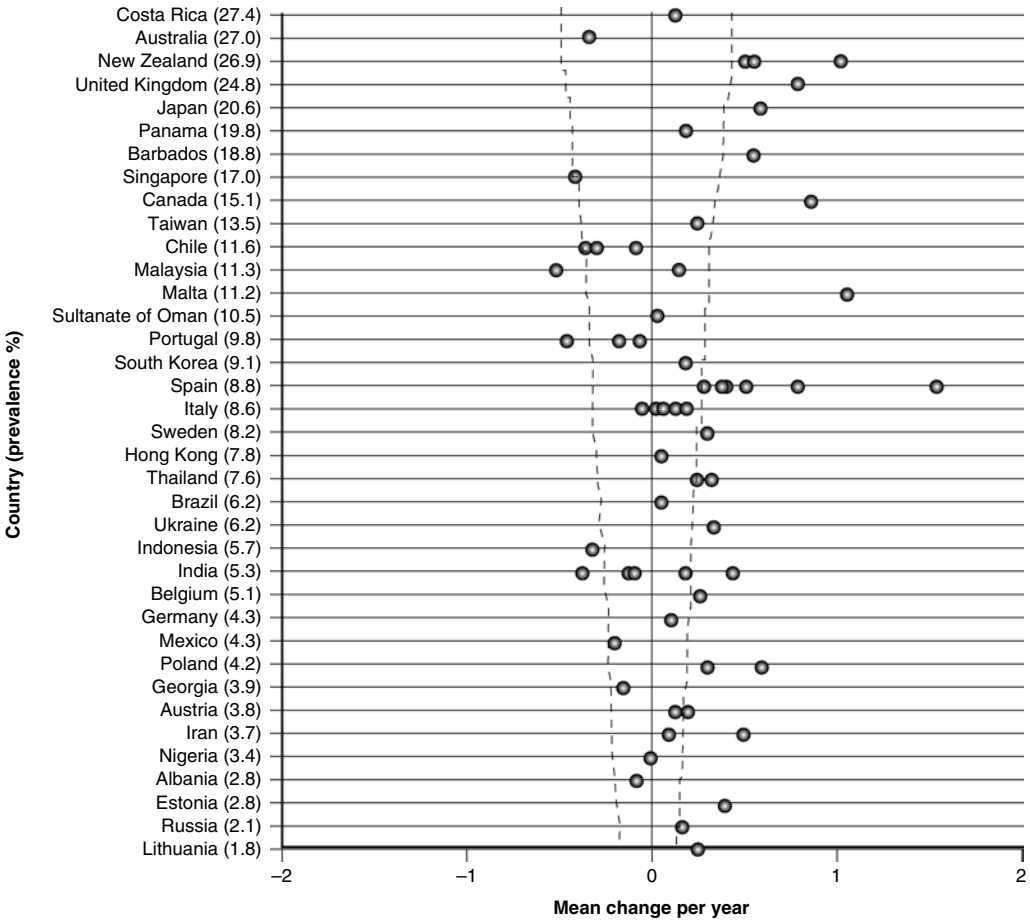

Fig. 1. International Study of Asthma and Allergies in Children (ISAAC): Change per year in lifetime prevalence of asthma between phase 1 and 2, in children age 6–7 years, with countries ordered by mean prevalence current asthma prevalence (reprinted from *(5)* with permission from BMJ Publishing Group Ltd.).

Melbourne [Australia], and Mexico), others have reported increments in asthma prevalence (e.g., Saudi Arabia, South Australia, and Greece). Studies are difficult to compare because of differences in asthma definition, survey techniques, time periods, and population characteristics *(13)*. However, a recent publication based on ISAAC data describes global trends in asthma prevalence within countries between phase 1 (early–mid 1990s) and phase 3 (early 2000s) (*see* Figs. 1 and 2). As the same validated questionnaire was used at both points and Bland–Altman plots were used to avoid the issue of regression toward the mean, these are the best data available on global asthma prevalence trends. Overall, there was a trend for lifetime asthma prevalence to increase amongst both 6- to 7-year olds and 13- to 14-year olds, although the increase was smaller in 13- to 14-year olds *(5)*.

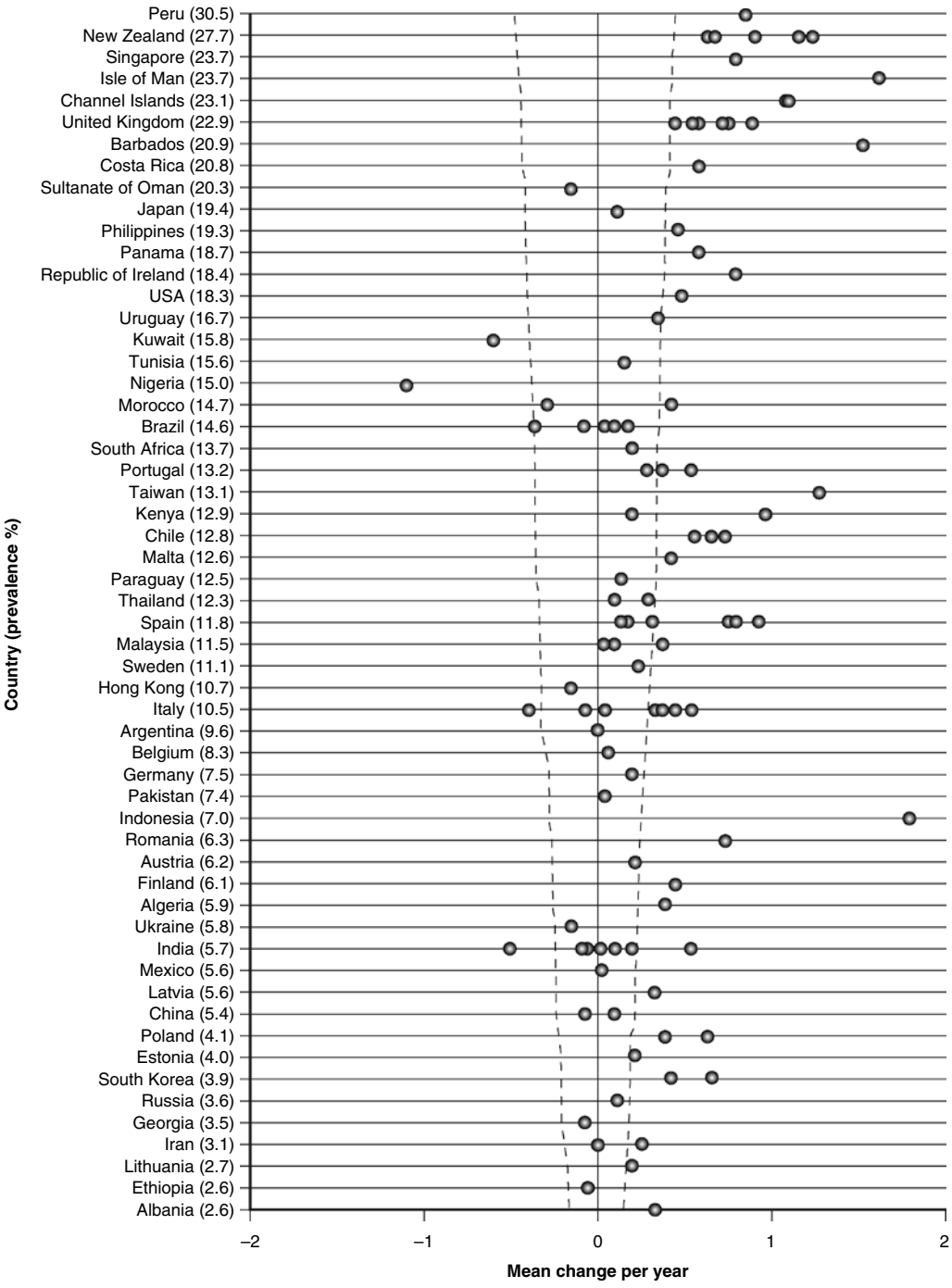

Fig. 2. International Study of Asthma and Allergies in Children (ISAAC): Change per year in lifetime prevalence of asthma between phase 1 and 2, in children age 13–14 years, with countries ordered by mean prevalence current asthma prevalence (reprinted from *(5)* with permission from BMJ Publishing Group Ltd.).

ASTHMA PREVALENCE, HEALTH CARE USE, AND MORTALITY, 1997–2008

Race/Ethnic Differences Within the United States

Nationwide surveys in the United States have shown significant race/ethnic disparities in asthma morbidity and mortality. There has been increasing data available on race/ethnicity differences in asthma, compared with earlier reports that mostly compared non-Hispanic whites, non-Hispanic blacks, and Hispanics.

The most recent (2006–2008) data from the National Health Interview Survey (NHIS) in the United States show substantial racial/ethnic differences in prevalence, morbidity, and mortality from asthma. In that survey, the difference in current asthma prevalence between blacks and whites was substantially greater in children (0–17 years of age) (2006–2008 annual average) than in adults (age ≥ 18 years of age). Among children, the current prevalence of asthma was 14.6% (95% CI = 13.5–15.9%) for blacks in contrast to 8.2% (95% CI = 7.7–8.7%) for whites. In comparison, there was only a modest difference in current asthma prevalence between black (7.8%, 95% CI = 7.3–8.4%) and white (7.2%, 95% CI = 7.0–7.5%) adults.

Although the age-adjusted prevalence of current asthma was lower in Hispanic children and adults (6.3%, 95% CI = 5.8–6.8%) than that in non-Hispanic (8.1%, 95% CI = 7.8–8.4%), there are differences in asthma prevalence among Hispanic subgroups. For example, Hispanics of Puerto Rican ancestry had distinctively higher asthma prevalence (14.2%, 95% CI = 12.5–16.2%) than Hispanics of Mexican ancestry (4.9%, 95% CI = 4.5–5.5%).

Compared with the age-adjusted prevalence of current asthma in whites of all ages (7.5%, 95% CI = 7.2–7.7%), the prevalence in Asians was lower (4.8%, 95% CI = 4.2–5.6%), but slightly higher in American Indian/Alaskan Natives (8.5%, 95% CI = 6.4–11.2%). Persons of multiple races had a significantly higher current prevalence rate (14.8%, 95% CI = 12.7–17.0%).

Similar differences among race/ethnicity groups were also noted in reported asthma attacks and lifetime asthma diagnosis. Whereas the current and asthma attack prevalence as well as the lifetime diagnosis of asthma was greater for males in the pediatric age group (0–17 years), females had greater current and asthma attack prevalence and lifetime diagnosis of asthma in the adult (18+ years) age group for all race/ethnic groups (Tables 1–3).

The NHIS and the National Vital Statistics System data reveal significant race/ethnic disparities for asthma in morbidity and mortality between blacks and whites. Compared to the differences in asthma prevalence, there were disproportionably higher rates of asthma ED visits noted for blacks compared to whites for all age groups. For the annual average for the period of 2005–2007, both blacks (167.9/10,000, 95% CI = 148.3–187.5/10,000) and Hispanics (64.8/10,000, 95% CI = 52.8–76.9/10,000) had significantly higher rates of emergency room department visits than whites (42.5/10,000, 95% CI = 38.1–47.0/10,000) (Table 4).

Moreover, the rates of hospitalizations (Table 5) *(14)* and deaths due to asthma (Tables 6 and 7) are still alarmingly higher for blacks than whites. While the age-adjusted death rate from asthma in adults (age group ≥ 18 years) has generally decreased, a nearly threefold difference in average annual death rate between blacks and whites has

Table 1
Estimated Current Prevalence of Self-Reported Asthma, Self-Reported Asthma Attack Prevalence, and Self-Reported Lifetime Asthma Diagnosis by Sex, Age-Adjusted and Race/Ethnicity (Annual Average 2006–2008; National Health Interview Survey – United States)[a–c]

Prevalence		*Current asthma prevalence*			*Asthma attack prevalence*			*Lifetime asthma diagnosis*		
Sex		*All*	*Male*	*Female*	*All*	*Male*	*Female*	*All*	*Male*	*Female*
Age	*Race/ethnicity*									
All ages	All	7.8	6.9	8.6	4.2	3.5	4.9	12.0	11.4	12.5
(age-adjusted)	White	7.5	6.6	8.4	4.1	3.3	4.8	11.7	11.1	12.2
	Black	9.6	8.5	10.3	5.0	4.2	5.6	13.8	12.9	14.3
	American Indian/Alaska Native	8.5	6.7	10.4	5.4	4.3	6.7	13.4	11.3	15.5
	Asian	4.8	4.9	4.8	2.7	2.9	2.5	9.0	8.9	9.1
	Native Hawaiian/other Pacific Islander	*	*	*	*	*	*	17.5	17.6	*
	Multiple race	14.8	12.1	17.4	8.7	5.9	11.2	20.5	18.1	22.8
	Hispanic	6.3	5.5	7.2	3.6	3.0	4.3	9.9	8.9	10.9
	Puerto Rican	14.2	11.3	16.9	8.4	6.1	10.4	21.8	19.8	23.4
	Mexican	4.9	3.9	6.1	2.8	2.1	3.5	8.0	6.7	9.3
	Non-Hispanic	8.1	7.2	8.9	4.3	3.6	5.0	12.5	12.0	12.9
	Non-Hispanic White	7.8	6.8	8.7	4.2	3.4	5.0	12.2	11.6	12.6
	Non-Hispanic Black	9.5	8.5	10.3	4.9	4.2	5.5	13.7	12.8	14.2

[a]Percent (the percent is calculated by dividing the weighted number of respondents identified as being within a specific category by the weighted total population that answered the relevant question(s)).

[b]Estimates for the races presented are for persons with one race recorded, except for the "multiple race" group which includes persons with more than one race recorded. When not otherwise mentioned, race groups include persons of Hispanic and non-Hispanic origin and those for whom Hispanic origin is unknown. Hispanic origin groups include people of any race.

[c]Estimates for age-adjusted to the year 2000 U.S. standard population to eliminate differences in observed percents that result from differences in age composition.

*Unreliable data.

Table 2
Estimated Current Prevalence of Self-Reported Asthma, Self-Reported Asthma Attack Prevalence, and Self-Reported Lifetime Asthma Diagnosis by Sex, Age 0–17 Years, and Race/Ethnicity (Annual Average 2006–2008; National Health Interview Survey – United States)[a,b]

Prevalence		*Current asthma prevalence*			*Asthma attack prevalence*			*Lifetime asthma diagnosis*		
Sex		*All*	*Male*	*Female*	*All*	*Male*	*Female*	*All*	*Male*	*Female*
Age	*Race/ethnicity*									
0–17	All	9.3	10.7	7.8	5.5	6.2	4.7	13.4	15.6	11.2
	White	8.2	9.6	6.7	4.9	5.7	4.0	12.1	14.2	9.9
	Black	14.6	16.5	12.7	8.1	9.0	7.2	19.2	21.7	16.6
	American Indian/Alaska Native	10.4	*	*	*	*	*	14.0	14.9	*
	Asian	5.8	7.3	4.3	3.9	4.9	3.0	10.2	11.7	8.8
	Native Hawaiian/other Pacific Islander	*	*	*	*	*	*	31.3	42.0	*
	Multiple race	13.6	14.6	12.6	8.2	7.6	8.8	19.1	22.2	15.9
	Hispanic	8.3	9.9	6.6	5.0	5.6	4.3	12.1	14.4	9.8
	Puerto Rican	18.4	23.6	13.0	10.8	13.2	8.3	23.5	28.3	18.5
	Mexican	7.0	7.8	6.2	4.2	4.4	4.1	10.7	12.1	9.2
	Non-Hispanic	9.6	10.9	8.1	5.6	6.4	4.8	13.8	15.9	11.6
	Non-Hispanic White	8.2	9.5	6.9	4.9	5.7	4.1	12.3	14.2	10.3
	Non-Hispanic Black	14.6	16.5	12.7	8.0	9.0	7.0	19.1	21.6	16.5

[a]Percent (the percent is calculated by dividing the weighted number of respondents identified as being within a specific category by the weighted total population that answered the relevant question(s)).

[b]Estimates for the races presented are for persons with one race recorded, except for the "multiple race" group which includes persons with more than one race recorded. When not otherwise mentioned, race groups include persons of Hispanic and non-Hispanic origin and those for whom Hispanic origin is unknown. Hispanic origin groups include people of any race.

*Unreliable data.

Table 3
Estimated Current Prevalence of Self-Reported Asthma, Self-Reported Asthma Attack Prevalence, and Self-Reported Lifetime Asthma Diagnosis by Sex, Age 18+ Years, and Race/Ethnicity (Annual Average 2006–2008; National Health Interview Survey – United States)[a–c]

Prevalence		*Current asthma prevalence*			*Asthma attack prevalence*			*Lifetime asthma diagnosis*		
Sex		*All*	*Male*	*Female*	*All*	*Male*	*Female*	*All*	*Male*	*Female*
Age	*Race/ethnicity*									
18+ (age-adjusted)	All	7.3	5.5	8.9	3.8	2.5	5.0	11.5	10.0	13.0
	White	7.2	5.5	8.9	3.8	2.5	5.0	11.5	10.0	13.0
	Black	7.8	5.7	9.5	3.9	2.5	5.0	11.9	9.8	13.5
	American Indian/Alaska Native	7.9	5.5	10.4	5.7	*	6.8	13.2	10.0	16.4
	Asian	4.5	4.1	5.0	2.3	2.2	2.3	8.6	7.9	9.1
	Native Hawaiian/other Pacific Islander	*	*	*	*	*	*	*	*	*
	Multiple race	15.1	11.2	19.1	8.9	5.4	12.1	21.0	16.7	25.2
	Hispanic	5.6	4.0	7.4	3.1	2.0	4.3	9.1	7.0	11.3
	Puerto Rican	12.8	7.0	18.2	7.6	3.7	11.1	21.1	16.8	25.1
	Mexican	4.2	2.6	6.0	2.3	1.3	3.3	7.0	4.8	9.4
	Non-Hispanic	7.6	5.9	9.2	3.9	2.6	5.1	12.0	10.6	13.3
	Non-Hispanic White	7.7	5.9	9.3	4.0	2.6	5.3	12.1	10.8	13.4
	Non-Hispanic Black	7.8	5.7	9.5	3.9	2.5	5.0	11.8	9.8	13.4

[a]Percent (the percent is calculated by dividing the weighted number of respondents identified as being within a specific category by the weighted total population that answered the relevant question(s)).

[b]Estimates for the races presented are for persons with one race recorded, except for the "multiple race" group which includes persons with more than one race recorded. When not otherwise mentioned, race groups include persons of Hispanic and non-Hispanic origin and those for whom Hispanic origin is unknown. Hispanic origin groups include people of any race.

[c]Estimates for age-adjusted to the year 2000 U.S. standard population to eliminate differences in observed percents that result from differences in age composition.

*Unreliable data.

Table 4
Estimated Annual Rate of Emergency Room Department Visits for Asthma as First-Listed Diagnosis, by Race/Ethnicity, Sex, and all Ages (Age-Adjusted) (National Hospital Ambulatory Medical Care Survey – NHAMCS – United States, Annual Average 2005–2007)[a,b]

Diagnosis			*Asthma*			
Year			*1996–1998*	*1999–2001*	*2002–2004*	*2005–2007*
Age	*Sex*	*Race/ethnicity*				
All ages (age-adjusted)	All	All races	73.2	65.1	63.7	58.1
		White	56.9	54.5	46.3	42.5
		Black	183.9	150.1	186.9	167.9
		Hispanic	74.6	55.7	65.7	64.8
		Non-Hispanic White	45.5	44.8	40.1	39.3
		Non-Hispanic Black	152.9	118.4	173.4	167.7
	Male	All races	66.3	56.3	60.0	50.3
		White	50.8	43.9	40.1	35.9
		Black	168.1	154.1	196.9	155.5
		Hispanic	63.2	61.2	64.3	50.4
		Non-Hispanic White	43.4	34.0	34.1	33.2
		Non-Hispanic Black	144.7	124.0	184.5	153.8
	Female	All races	78.8	73.2	67.1	65.8
		White	62.1	64.7	52.7	49.3
		Black	194.1	144.3	175.1	177.9
		Hispanic	87.6	50.4	68.9	79.1
		Non-Hispanic White	46.9	55.1	46.0	45.3
		Non-Hispanic Black	156.5	111.7	161.7	179.2

[a]Rate per 10,000.

[b]Estimates for age-adjusted to the year 2000 U.S. standard population to eliminate differences in observed percents that result from differences in age composition.

"Unreliable data": Relative standard error (RSE) is defined as the standard error divided by the estimate and is expressed as a percent of the estimated value. Estimates with a RSE greater than 30% or based on less than 30 records are not reliable and are not shown.

Table 5
Asthma Hospitalization Data: Estimated Rate of Hospital Discharges With Asthma as the First Listed Diagnosis per 10,000 Population, by Year, Sex, Race, Ethnicity, Age, and Region – National Hospital Discharge Survey, United States 1980–2004

Characteristic	*1980*	*1985*	*1990*	*1995*	*2000*	*2001*	*2002*	*2003*	*2004*
Sex									
Male	16.8	17.4	13.3	15.8	14.3	13.6	13.9	16.5	14.5
Female	19.9	22.0	21.9	18.7	18.7	18.6	19.4	23.0	18.9
Race[a]									
White	15.1	15.7	12.5	11.6	NA	NA	NA	NA	NA
Black	27.0	31.4	36.6	38.6	NA	NA	NA	NA	NA
Other	–	–	22.3	22.4	NA	NA	NA	NA	NA
Race[b]									
White	NA	NA	NA	NA	10.2	10.1	10.5	12.2	10.0
Black	NA	NA	NA	NA	31.0	31.2	35.7	39.9	33.5
Other races NTA	NA	NA	NA	NA	12.8	13.3[c]	10.0	18.1	19.0
Age									
<18 years	21.0	25.4	27.5	34.3	29.5	26.9	26.9	31.2	27.4
≥18 years	17.0	17.4	15.8	15.8	12.2	12.7	13.4	17.0	10.2
Age group (years)									
0–4	37.1	46.9	53.4	58.3	64.0	57.6	59.0	62.7	59.9
5–14	18.2	18.0	17.8	23.9	18.9	18.4	17.3	21.6	17.0
15–34	8.6	9.6	9.3	10.2	7.6	6.8	7.0	8.4	6.2
35–64	19.0	18.8	15.4	15.0	12.7	13.4	14.5	16.4	13.4
≥65	32.6	34.2	33.1	23.2	19.6	21.6	22.5	30.5	28.7
Region									
Northeast	19.6	21.3	22.6	28.2	21.1	20.7	20.6	31.0	23.7
Midwest	19.8	19.7	22.2	22.5	17.1[c]	16.0	15.9	19.8	16.7
South	17.8	20.8	16.9	17.8	16.8	18.0	17.7	17.4	15.7
West	16.9	17.3	15.4	14.4	12.2	13.9	13.6	14.7	13.8
Total	18.5	19.9	19.0	19.1	16.7	16.4	16.9	19.9	17.0

[a]Race categorized according to Statistical Policy Directive No. 15, Race and Ethnic Standards for Federal Statistics and Administrative Reporting (1977). Multiple race was not collected in these years. Unknown race was excluded. After 1999, there is no bridging variable to maintain historic coding therefore data are not available (NA).

[b]Race categorized according to the 1997 revision of Statistical Policy Directive No. 15, Race and Ethnic Standards for Federal Statistics and Administrative Reporting. Race categories "white" and "black" are comprised of persons who indicated only a single race group. Other races NTA (not tabulated above)* includes Asian, American Indian and Alaskan Native, Native Hawaiian and Other Pacific Islander, persons reporting more than one race, and persons reporting their race as something other than those listed here or above. Unknown race was excluded. It is not possible to apply the 1997 revisions to the race categorizations to years before 2000; therefore, data were not available.

[c]The estimates are unreliable because the RSE of the estimate is 30–50%. For missing estimates, the RSE of the estimate exceeded 50% and the estimate was suppressed. All other RSEs are <30%. Except for age groups, rate is age-adjusted to the 2000 standard.

Table 6
Annual Rate of Deaths With Asthma as the Underlying Cause of Death Diagnosis by Race/Ethnicity, Sex, and Age Group 0–17 Years (United States, 1990–2007)[a,b]

Cause of death			*Asthma*					
		Year	*1990–1992*	*1993–1995*	*1996–1998*	*1999–2001*	*2002–2004*	*2005–2007*
Age	*Sex*	*Race/ethnicity*						
0–17	All	All	0.3	0.3	0.3	0.3	0.3	0.2
		White	0.2	0.2	0.2	0.2	0.1	0.1
		Black	0.9	0.9	1.0	0.9	0.9	0.8
		American Indian/Alaska Native	*	*	*	*	*	*
		Asian/Pacific Islander	*	*	0.3	*	*	*
		Hispanic	~	~	~	0.2	0.2	0.2
		Non-Hispanic White	~	~	~	0.2	0.1	0.1
		Non-Hispanic Black	~	~	~	0.9	0.9	0.9
	Male	All	0.3	0.4	0.4	0.3	0.3	0.3
		White	0.2	0.2	0.2	0.2	0.2	0.1
		Black	1.1	1.2	1.1	1.1	1.2	1.1
		American Indian/Alaska Native	*	*	*	*	*	*
		Asian/Pacific Islander	*	*	*	*	*	*
		Hispanic	~	~	~	0.2	0.2	0.2
		Non-Hispanic White	~	~	~	0.2	0.2	0.1
		Non-Hispanic Black	~	~	~	1.2	1.3	1.2
	Female	All	0.2	0.3	0.3	0.2	0.2	0.2
		White	0.2	0.2	0.1	0.2	0.1	0.1
		Black	0.6	0.6	0.8	0.6	0.6	0.6
		American Indian/Alaska Native	*	*	*	*	*	*
		Asian/Pacific Islander	*	*	*	*	*	*
		Hispanic	~	~	~	0.1	0.1	0.1
		Non-Hispanic White	~	~	~	0.2	0.1	0.1
		Non-Hispanic Black	~	~	~	0.6	0.6	0.6

Source: The National Vital Statistics System (NVSS).

[a]Deaths per 100,000 population.

[b]Cause of death is coded according to the appropriate revision of the International Classification of Diseases (ICD). Effective with deaths occurring in 1999, the United States began using the Tenth Revision of the ICD (ICD-10); during the period 1981–1998, cause of death was coded and classified according to the Ninth Revision (ICD-9).

*Unreliable data.

~Data not available.

Table 7
Annual Rate of Deaths With Asthma as the Underlying Cause of Death Diagnosis by Race/Ethnicity, Sex, and Age Adjusted 18+ Years, United States, 1997–2007[a–c]

Cause of Death			*Asthma*		
Year			*1999–2001*	*2002–2004*	*2005–2007*
Age	*Sex*	*Race/ethnicity*			
18+ (age-adjusted)	All	All races	2.1	1.8	1.5
		White	1.7	1.5	1.2
		Black	4.8	4.0	3.4
		American Indian/Alaska Native	2.3	1.6	1.4
		Asian/Pacific Islander	2.7	1.9	1.6
		Hispanic	2.1	1.6	1.2
		Non-Hispanic White	1.7	1.5	1.3
		Non-Hispanic Black	4.9	4.1	3.5
	Male	All races	1.6	1.4	1.2
		White	1.3	1.1	0.9
		Black	4.2	3.7	3.1
		American Indian/Alaska Native	*	*	*
		Asian/Pacific Islander	3.1	2.2	1.6
		Hispanic	1.6	1.3	1.0
		Non-Hispanic White	1.2	1.1	0.9
		Non-Hispanic Black	4.3	3.8	3.1
	Female	All races	2.4	2.0	1.8
		White	2.0	1.8	1.5
		Black	5.2	4.2	3.7
		American Indian/Alaska Native	*	*	*
		Asian/Pacific Islander	2.3	1.8	1.7
		Hispanic	2.4	1.9	1.4
		Non-Hispanic White	2.0	1.7	1.5
		Non-Hispanic Black	5.3	4.3	3.8

Source: The National Vital Statistics System (NVSS).

[a]Deaths per 100,000 population.

[b]Cause of death is coded according to the appropriate revision of the ICD. Effective with deaths occurring in 1999, the United States began using the Tenth Revision of the ICD (ICD-10); during the period 1981–1998, cause of death was coded and classified according to the Ninth Revision (ICD-9).

[c]Estimates for age-adjusted to the year 2000 U.S. standard population to eliminate differences in observed percents that result from differences in age composition.

*Unreliable data.

persisted (3.4 vs. 1.2/100,000 in 2005–2007). This is in contrast to the relative current asthma prevalence of 7.8% (95% CI = 7.3–8.4) for blacks compared to 7.2% (95% CI = 7.0–7.5) for white adults in 2006–2008.

In addition, the race/ethnicity groups of American Indian/Alaska Native (AIAN) (annual average rate of 2.3/100,000 in 1999–2001 and 1.4 in 2005–2007) and Asian/

Pacific Islander (API) (average annual rate of 2.7 in 1999–2001 and 1.6 in 2005–2007) also had greater relative death rates compared with whites. However, some of these differences must be interpreted with caution due to small sample sizes and/or missing data for some racial/ethnicity groups. In contrast to differences in the rate of emergency room visits, Hispanic adults did not have a greater mortality rate from asthma than white adults, with the same average annual rate of 1.2/100,000 for 2005–2007. As pointed out previously, this may be partly due to inadequately merging Hispanic subgroups into a single category ("Hispanic").

Disturbingly, the disparity for deaths was even more marked for the 0- to 17-year-old age group for blacks and Hispanics. The relative asthma death rate for blacks compared to whites ranged from 4.5 times higher (average annual rate of 0.9 vs. 0.2/100,000) in 1990–1992 and 8 times higher (average annual rate of 0.8 vs. 0.1/100,000) in 2005–2007. The death rate from asthma in Hispanics was twice as high as that of whites (rate 0.2 vs. 0.1/100,000) in 2005–2007. In contrast, the average annual current asthma prevalence for 0- to 17-year-old group was 14.6% (95% CI = 13.5–15.9) for blacks and 8.3% (95% CI = 7.5–9.2) for Hispanics compared to 8.2% (95% CI = 7.7–8.7) for whites for the period 2006–2008. Thus, there are significant race/ethnic disparities in morbidity and mortality from asthma.

SPECIFIC RACE/ETHNICITY DATA: ASTHMA IN CALIFORNIA

The California Health Interview Survey (CHIS) is the nation's largest state health survey and is conducted every 2 years. The latest survey (2007) randomly selected 53,611 households from every county in California *(15)*. CHIS conducts interviews in racial/ethnic groups often under-represented in other surveys (including Latinos and Latino ethnic groups), African-Americans, AIANs (urban and rural sub-samples) and Asians (including large sub-samples for Chinese, Filipinos, Japanese, Korean, Vietnamese, and South Asians). The CHIS interviews are conducted in English, Spanish, Chinese (Cantonese and Mandarin), Korean, and Vietnamese.

More specific ethnic data are collected in this survey, which is the largest, most complete database on asthma rates among different ethnic groups. The 2007 CHIS survey included data on lifetime prevalence, current or recent asthma symptoms, ED or urgent care use, hospitalizations, work or school absence, receiving an asthma action plan, use of a controller medication, confidence in asthma care, and other questions.

As in the NHIS data, lifetime asthma prevalence (*see* Fig. 3) was significantly higher in African-American children and adults than in white children and adults (African-American: children (ages 1–17 years) 23.6%; adults (ages 18 years and older) 18.9%; overall ages 1+ years 20.1%; compared with whites: children 14.9%; adults 14.7%; overall 14.8%). Compared to whites, greater lifetime asthma prevalence was found for those reporting $r \geq 2$ races (≥2 races, children 19.1%; adults 23.2%; overall 21.3%), American Indians and Alaska Natives (AIAN) (AIAN: overall 22.2%), and Native Hawaiian and other Pacific Islanders (NHPI: overall 16.1%). On the other hand, Latinos (Latinos: children 14.3%; adults 9.6%, overall 11.2%) and Asians (Asians: children 15.8%; adults 10.8%, overall 11.8%) had slightly lower lifetime asthma prevalence than whites.

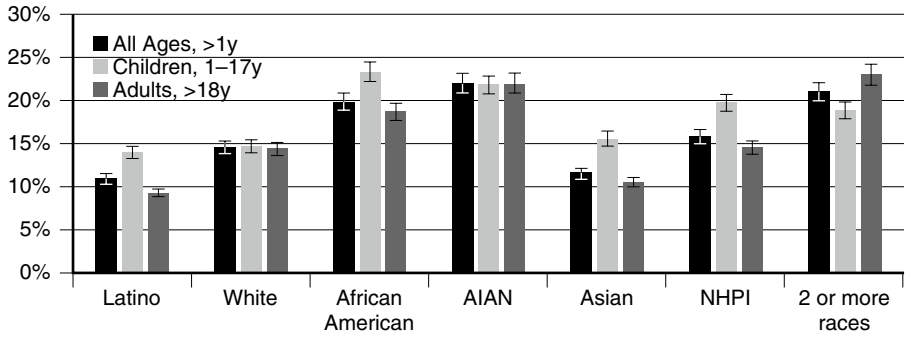

Fig. 3. Lifetime asthma prevalence by age groups and race/ethnicity in California, 2007. Graphs include 95% confidence interval bars. Note: *AIAN* American Indian and Alaska Native; *NHPI* Native Hawaiian and other Pacific Islander; Two or more races non-Latino. *Source*: 2008 California Health Survey *(15)*.

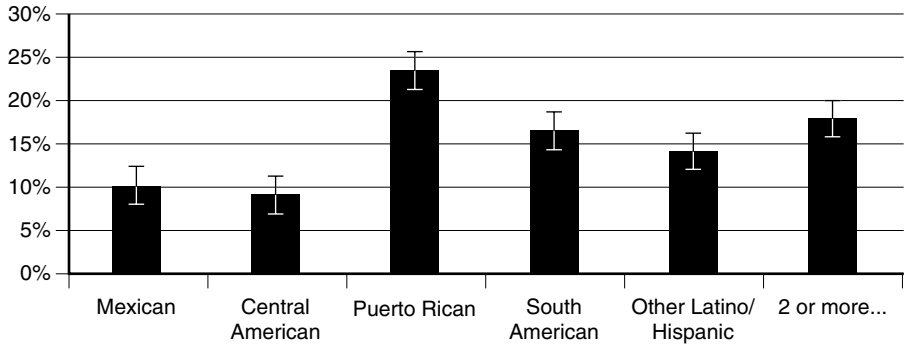

Fig. 4. Lifetime asthma prevalence by Latino ethnic groups, all ages, 2007. Graphs include 95% confidence interval bars. *Source*: 2008 California Health Survey *(15)*.

Though Latinos were found to have lower asthma prevalence rates in the CHIS survey, significant differences among Latino ethnic groups were seen. Puerto Ricans (overall 23.5%), two or more Latino/Hispanic group (18.0%) and South Americans (16.6%) were noted to have significantly higher prevalence than other Latino subgroups, including Mexicans (10.3%) and Central Americans (9.2%) (*see* Fig. 4).

The overall low prevalence of asthma among Latinos in California is a result of most Latinos in California being of Mexican heritage (84%). Thus, evaluating both the CHIS and the NCHS data about asthma prevalence in Hispanics would miss important differences among Hispanic subgroups.

Similarly, heterogeneous differences were seen among Asian-American subgroups in California. Filipinos (19.2%) had significantly higher overall lifetime prevalence compared with Vietnamese (11.5%), Japanese (11.2%), Chinese (10.0%), South Asians (8.5%), Koreans (5.0%), and other single/multiple Asians (9.5%) (*see* Fig. 5).

The CHIS cautioned that several issues might affect estimates of prevalence among ethnic subgroups including differences in asthma diagnosis due to financial or

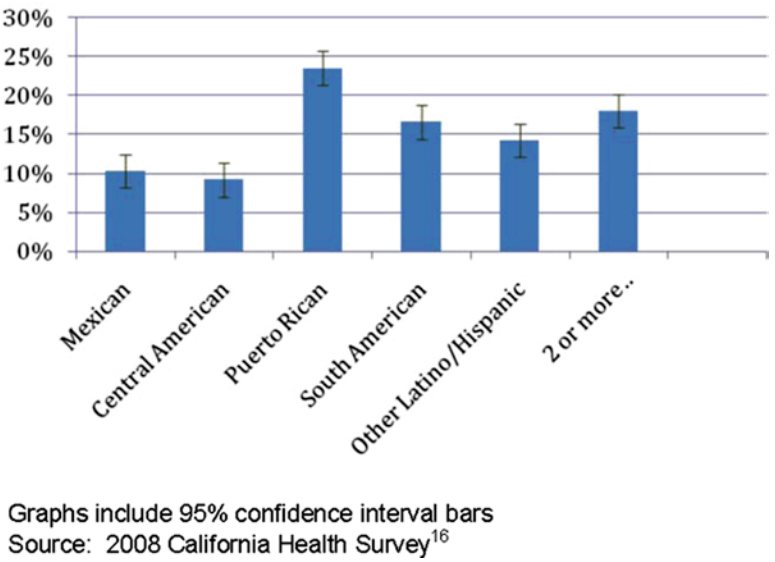

Fig. 5. Lifetime asthma prevalence by Asian ethnic groups, all ages, 2007. Graphs include 95% confidence interval bars. *Source*: 2008 California Health Survey *(15)*.

geographic access to health care, health care-seeking behaviors, physician practice patterns, and issues that particularly affect recent immigrants (barriers related to language, acculturation, and legal status). Thus, populations with higher poverty, no insurance or underinsurance might have underestimated prevalence rates.

In summary, the 2007 CHIS with its more specific race/ethnicity data reveals significant disparity in asthma lifetime prevalence and/or burden, as indicated by emergency room or urgent care visits for asthma *(16)* in racial/ethnic minority groups including African-Americans, Latinos, AIANs, Native Hawaiian and other Pacific Islanders, and ≥2 races. Furthermore, the Hispanic/Latino subgroups of Puerto Ricans and South Americans and the Asian subgroup of Filipinos had significantly higher degrees of asthma prevalence.

For children, similar results for lifetime prevalence variation among specific racial/ethnic subgroups were found in a California Healthy Kids Survey administered to California public school students from participating schools in the seventh, ninth, and eleventh grades. For Hispanic groups, there was a lifetime prevalence of 13.2% (95% CI 12.9–13.5) for Mexican Americans, 22.8% (95% CI 20.8–24.9) for Puerto Ricans, and 23.0% (95% CI 19.7–26.4) for Cubans. The lifetime prevalence for whites, non-Hispanic, was 20.2 (95% CI 19.9–20.5) in this study. For API subgroups, there was a range of 10.9% (95% CI 10.0–11.8) for Koreans up to 21% (95% CI 19.2–22.8) for Pacific Islanders and 23.8% (95% CI 22.7–24.9) for Filipinos *(17)*.

Thus, both California studies show that there is significant variation in racial/ethnic subgroups such that descriptions of asthma prevalence for "Hispanics" and "Asians" would be inaccurate for all subgroups of these racial/ethnic groups.

FACTORS CONTRIBUTING TO RACIAL/ETHNIC DISPARITIES IN ASTHMA

The etiology of racial/ethnic disparities in asthma prevalence, severity, and outcomes is complex and multifaceted. A study from New York State showed that hospitalization rates for asthma were highest in areas of greater poverty, unemployment, lower education, with higher proportions of blacks and Hispanics and in urban centers *(18)*. As many of these factors are strongly correlated, it is difficult to separate out the risk of attributable to race/ethnicity. Furthermore, there are likely genetic factors playing a role and these are discussed separately.

For many minorities, coexistent low SES affects asthma outcomes through factors including decreased or limited access to health care (e.g., lack of insurance or transportation to health-care facilities), poor access to support groups, and inability to afford medications.

Low SES is an independent and important variable for poor asthma management and outcomes *(19)*. SES may be conceptualized as a chronic multidimensional state. Comparing studies of SES and asthma is difficult due to differences in indicators of SES, asthma diagnosis, healthcare access, and lower response rates amongst impoverished and minority populations across studies. A few studies have suggested that SES differences might account for most, if not all, of the race/ethnicity-associated differences in asthma. For example, Weitzman et al. evaluated data from the 1981 NHIS and found that the increased prevalence of asthma in black and poor children was accounted for by a variety of social and environmental characteristics such as maternal smoking, low birth weight, large family, smaller home size, and young maternal age *(20)*. In a cross-sectional analysis in Boston, income, area of residence, and level of education accounted for a large proportion of the increased prevalence for blacks and Hispanics.

Studies within and outside of the United States have still shown increased asthma morbidity (severe symptoms, suboptimal asthma care, increased ED use, and increased hospitalization) in black and Hispanic children. The NHIS in the United States attempted to analyze the independent and joint effects of race/ethnicity and SES on asthma prevalence. The difference in asthma prevalence between non-Hispanic black children and non-Hispanic white children was only significant among the very poorest families, suggesting that social and environmental issues play an important role, as genetic effects should be seen across all income levels *(16)*.

U.S. national data from 1991 to 1996 show that SES and race/ethnicity exert independent effects on asthma mortality. Asthma mortality rates among blacks in the highest income quintile were nearly 400% greater, 1.29 vs. 0.26/100,000, and almost 200% greater in the lowest income quintile, 1.52 vs. 0.51/100,000, compared to whites aged 5–34 years *(21)*. In addition to increased mortality, epidemiologic data indicate that, after correction for socioeconomic and environmental factors, racial/ethnic differences still remain for asthma hospitalizations *(22)*.

Compared to non-Latino whites, other racial/ethnic groups have lower rates of employment-based insurance and higher uninsured rates which contribute to disparities in health status. Latinos have the highest uninsured rates which are largely due to low education and income, as well as lack of citizenship. Almost one in four nonelderly

African-Americans is not insured and there is a lot of variability in education, income, immigration status, and insurance among other ethnic minorities.

Another effect of low SES is inadequate medical care, including under- or improper diagnosis, inadequate recognition of asthma severity, and under-prescription of controller medications. In addition to SES, other potential risk factors for asthma disparities include allergy, environmental exposures and air pollution, obesity, low birth weight, prematurity, increased upper respiratory tract infections for those living in poverty, smoking rates and stress or psychosocial comorbidities.

Environmental exposures are highly likely to contribute to asthma disparities. Both birthplace and duration of residency in the United States have been associated with increased asthma prevalence in Mexican-American adults, indirectly implicating environmental risk factors, particularly in early life *(23)*. Similar findings have been reported for Mexican-American children *(24)*. Racial/ethnic differences in allergic diseases such as atopic asthma have been found for both children and adults. In the United States, compared to white adults, Asians had an increased risk of atopic conditions (e.g., asthma with hay fever) and blacks had an increased risk of nonatopic asthma. More specifically, Asians born in the United States had a higher risk of allergic conditions than those born outside the United States. Similar findings for Asians have been reported in Australia *(25)*. Thus, nongenetic conditions such as social and/or environmental factors and possibly acculturation may be important in determining risk of asthma and atopy in immigrants.

Among children in the Third National Health and Nutrition Survey (NHANES III), Mexican Americans and African-Americans were more likely to be sensitized to cockroach and dust mite than whites. Increased risk of sensitization to cockroach and dust mite allergen has also been shown in Puerto Ricans living in the United States. These findings suggest that there may be ethnic/racial differences in susceptibility to allergen sensitization. These differences in allergen sensitization may partly explain ethnic/racial disparities in asthma morbidity, as certain allergies (e.g., to cockroach) have been associated with increased disease severity.

Other potential environmental risk factors include air pollution, exposure to tobacco smoke (ETS), diet, and stress. Smoking is more common among people of lower SES and varies significantly across ethnic groups. ETS is a known risk factor for childhood asthma and thus differing rates of smoking among ethnic groups may contribute to asthma disparities *(26)*. The effects of outdoor population have been less well studied; however, nonwhites are more likely to live in areas of elevated air pollution *(27)*. Obesity has been associated with asthma in several populations and this link could be due to many factors including diet, exercise, genetics, and SES. Blacks and Hispanics have been shown to have higher rates of overweight among children with asthma. Closely linked to obesity is diet, which in turn is also closely linked to SES *(28)*. Fast food consumption has also been associated with asthma and bronchial hyperresponsiveness and Vitamin D deficiency (which is more common in African-Americans) has been recently associated with increased asthma morbidity *(29)*. Furthermore, amongst families living in poverty, there are increased rates of depression, mood and anxiety disorders, stress from exposure to crime and violence, and illicit drug use. Maternal stress in early life, independent of low SES, has been associated with increased risk of childhood

asthma *(30)*. Mental health problems of caretakers and children have been associated with increased asthma hospitalizations and symptoms.

Underutilization of inhaled corticosteroids is common in racial/ethnic minorities. The Multicenter Airway Research Collaboration study (MARC) found that inadequate prescription of inhaled steroids for members of ethnic minorities was prevalent among ED physicians, who often provide asthma care for these patients. The explanation for this pattern is unclear but may relate to unfamiliarity with controller medications and/or perceptions of cost. Similar racial/ethnic differences in ED discharge prescriptions are seen amongst adults. This difference in anti-inflammatory prescriptions filled by minority populations is larger among those who have not received specialist care.

A discrepancy in controller/preventative asthma medication use across ethnic groups has been shown outside of the ED *(31)*. In general, rates of long-term controller medication use for persistent asthma in children are lower than what is suggested by current guidelines. Having Spanish-speaking parents, African-American ethnicity and lack of health insurance have been associated with reduced use of controller medications. Among children enrolled in different health plans across three U.S. states, blacks and Latinos had lower use of preventative asthma medications than whites, even after adjusting for asthma severity and indicators of SES. Since financial access to health care (including prescription coverage) was adequate, this suggests nonfinancial barriers to use of preventive therapy exist for minorities *(32)*. In the National Asthma Survey, Hispanic and black children were less likely to be on controller medications and blacks had significantly higher daily beta-agonist use and health-care utilization despite adjusting for symptom severity, household income, and other potential confounders. These results and other findings suggest that symptoms alone may under-represent asthma control in certain minorities.

Similar racial/ethnic disparities exist in medical care. The National Survey of Children's Health showed that having no usual source of medical care was a barrier to healthcare access in Latinos, African-Americans, and Native Americans. Whereas lack of insurance was a common problem in Latinos and Native Americans, this was not the case in African-Americans *(33)*. Minority populations are more likely to use the ED as the primary site of care for their asthma, likely because of factors including type of health insurance, marital status, asthma severity, and lack of access to primary care medical home. This may result in inadequate overall asthma care because ED facilities are less likely to focus on chronic disease management, including asthma action plans and disease-specific education. White children are more likely to have asthma action plans than black or Hispanic children, leading to under-utilization of controller medications *(34)*. This is thought to be due to language barriers and/or SES and as such, interventions enhancing literacy and asthma self-management skills of minority children have been shown to improve asthma outcomes.

Another explanation for lower rates of inhaled steroids use among African-Americans is that physicians underestimate disease severity and thus under-treat members of this ethnic group. Individual patients' perceptions and parental perceptions and expectations of their child's asthma, as well as belief in the benefits and fear of adverse effects of inhaled corticosteroids play an important role adherence to medications *(35)*. Despite these potentially modifiable barriers, adherence in a study on adults with asthma was primarily affected by immutable factors such as income, education, having commercial insurance, and recent symptoms *(36)*.

In summary, current evidence suggests that increasing the use of preventive medications in minority populations could help reduce racial/ethnic disparities in asthma. Indeed, studies have indicated that asthma status and severity had no difference in measurements of quality of life in young urban children, indicating that other factors, such as the social and emotional milieu, are also important in understanding the adaptation and functioning to a chronic disease such as asthma within the context of low SES.

INTERVENTION STRATEGIES

While there are many studies on the impact of culture-specific asthma education programs on asthma-related outcomes in minorities, few have been clinical trials. A Cochrane review of four studies showed greater effect of culture-specific programs compared with usual or generic programs in improving asthma knowledge in children, and caregivers, asthma control in children, improving self-reported asthma-related quality of life in adults, and reducing asthma exacerbations of ED visits and hospitalizations in children *(37)*.

A different Cochrane review evaluated the effectiveness of an indigenous health-care worker (IHW) to improve asthma outcomes. Two small randomized, controlled trials showed benefit in several outcomes, including asthma knowledge in parents and children, parents' asthma skills score, and days of school loss. However, no differences were noted in asthma exacerbations. As noted by the authors, this area should be subject to further randomized controlled trials *(38)*.

As a result of the environmental exposures in urban settings, inner-city inhabitants with asthma are exposed to multiple indoor allergens (e.g., cockroach, rodents) and irritants, such as environmental tobacco smoke. Most inner-city children with moderate to severe asthma are sensitized to multiple indoor allergens. The Inner-City Asthma Study Group evaluated a multi-faceted, home-based, environmental 1-year intervention for urban children with asthma. The intervention was individualized and comprehensive. A successful reduction in allergen burden was achieved, which included an approach based on social learning theory. This reduction was remarkable, in contrast to previous studies, which often targeted only one allergen or environmental factor such as cockroach or tobacco smoke. The success of this study's approach emphasizes the importance of the intervention strategy, especially in such a high-risk population. Moreover, the reductions achieved were associated with reduced asthma morbidity. Continued improvement, compared to the control group, was noted in days of symptoms and caretaker sleep loss in the postintervention follow-up year *(39)*. The National Cooperative Inner-City Asthma Study multifaceted intervention program has been analyzed to be cost-effective when compared with usual care *(40)*.

Other intervention strategies have been evaluated in inner-city populations, including an individualized approach with an asthma counselor, school-based programs (e.g., the Breathmobile™ program), patient and family asthma education (including addressing patient and family beliefs, attitudes and behaviors), comprehensive healthcare provider education programs, community-based social networking and education, a citywide asthma management program, enhanced access to specialty care, and structured transition from acute care to outpatient care *(19)*. In addition, a recent systematic Expert Panel 3 guideline-based approach was noted to improve asthma control in adolescents and young adults *(41)*.

On the other hand, an evaluation of a more general program of community health centers in the United States participating in quality-improvement collaboratives, The Health Disparities Collaboratives sponsored by the Health Resources and Services Administration, did not find improvement in urgent care or hospitalizations for asthma, though greater increase in use of asthma anti-inflammatory medications was noted *(42)*. This study evaluated diabetes and hypertension outcomes, in addition to asthma.

Because of the complexity of factors affecting asthma outcomes in minorities, comprehensive, multi-faceted intervention strategies will be needed to reduce asthma disparities. This will involve addressing (1) access to care; (2) adherence to asthma guidelines, including increased use of controller medications and asthma action plans, and practice policies; (3) health provider/clinician factors such as bias/stereotyping and cultural competence; (4) individual/family factors such as health beliefs, adherence with therapy, and health literacy; and (5) social/environmental factors such as allergen burden, environmental pollutants and environmental tobacco smoke, stress/violence, and depression. A framework of asthma disparities model with implications for research and clinical practice has been proposed *(43)*.

GENETICS

Genetic variation, alone or interacting with environmental exposures, is very likely to contribute to ethnic disparities in asthma. Asthma is a complex and heterogeneous disease with estimates of heritability from twin studies between 36 and 79% *(44)*. Despite a recent explosion in the number of studies of asthma genetics (including genome-wide association studies), relatively few of these studies have been conducted purely in ethnic minorities.

CULTURALLY COMPETENT CARE

Many racial/ethnic minority populations face unique health-care barriers in addition to those imposed by low SES including language and communication challenges, different customs, taboos, folk beliefs, and religious concepts. To help overcome these barriers, health-care delivery systems and providers need to avoid medical ethnocentrism and develop awareness, understanding, and acceptance of racial and ethnic differences in order to be more effective health-care providers for diverse populations.

These issues have been acknowledged in the NHLBI Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, with a section on "Racial and Ethnic Disparity in Asthma" *(45)*.

Poor patient/provider communication may lead to disease underestimation and therefore inadequate treatment and poor clinical outcomes. Potential factors in poor communication include patient health literacy, health beliefs, adherence, physician's expectations, bias and stereotyping, concordance/discordance in provider/patient race, communication skills and styles, and type of health-care system *(46)*.

Appropriate and sensitive attitudes, behaviors, and policies are vital for effective, cross-culturally appropriate and effective health-care delivery. Some examples of asthma-specific culturally competent care will be mentioned. Further details are available in the review by George *(47)* and the section enclosed within this chapter listing selected books on culturally competent care.

An example of health-care barrier is communication not only because of language, but also the specific expressions used for the condition being assessed. For example, the language and perception of and response to breathlessness and its management vary among racial/ethnic groups. For example, in a study evaluating description of airway obstruction by induced bronchoconstriction, African-Americans reported symptoms of breathing discomfort with upper airway descriptors. A Puerto Rican relative might be noted to fan or blow on a patient in the belief of providing oxygen or relief of dyspnea. Having a clear, understandable, and culturally sensitive dialog between patient and health-care provider is required for more effective symptom assessment, monitoring, and management *(48)* (see also Lipson and Dibble in selected books).

Many cultures use medicinal teas and herb supplements. Awareness and asking about these may elicit information about different patients' beliefs. This may lead to a better acceptance and understanding of the role of prescription medications. In addition, effective communication may elicit information on potentially harmful therapies being used, such as use of ginseng, which can cause bronchoconstriction, or royal jelly (bee saliva and pollen), which can lead to anaphylaxis in bee-allergic patients.

Awareness of religious beliefs, such as possible abstinence of oral and inhaled medications during the fasting month of Ramadan for Muslims, may help the provider and patient arrive at a more effective, alternative treatment program. In addition, there are a number of cultural beliefs regarding body function, such as the "hot–cold" theory of health and disease and the "cleansing model" of body function (in which sputum production, coughing, sneezing, and rhinorrhea act as natural cleansing mechanisms). Consequently, believers would feel that agents that might decrease mucus drainage such as topical corticosteroids and antihistamines might be counterproductive.

Asians, Islamic, East Asians, and Latinos perceive asthma as a "cold" disease. Puerto Rican mothers have been reported to dress their children and heat their homes warmly as an attempt to treat this "cold" disease. In addition, other home-based remedies commonly used in Puerto Rican communities for asthma exacerbations might include rubbing the chest and back, use of Vicks VapoRub or alcanfor (camphor rubs), having the child rest and kept calm, the administration of fluids, and prayer. Awareness of the belief in this humoral, "hot–cold," theory may then help the provider to avoid use of an inhaler with a "cold" blue casing and prescribe one with a "warm" orange casing instead. Sensitivity to the issues of alternative health viewpoints should improve understanding, communication, and allow for a more culturally consistent and acceptable medical care plan.

Systematic reviews of the effectiveness of cultural competence training interventions designed to improve the quality of healthcare in racial or ethnic minorities have shown evidence that such interventions are effective *(49)*. A prospective cohort study of childhood asthma in five health plans revealed that certain policies could predict higher quality of care (e.g., decreased under-prescription of preventive medication, parental ratings of care) for children with asthma in managed Medicaid. The policies included promotions of cultural competence, asthma reports to clinicians, and access and continuity. Cultural competence policies evaluated in this study included recruitment of ethnically diverse or bilingual nurses and providers, attempts to minimize cultural barriers through printed materials, provision of cross-cultural or diversity training, and training in communication skills. In addition, communication-related practices such as access to interpreters and low-literacy health education materials were also assessed *(50)*.

Thus, culturally competent strategies can be effective in helping to reduce the disparity in asthma health care and outcomes in racial/ethnic minorities. These strategies must include improvement over barriers to effective communication, understanding and acceptance of patients' health beliefs, and more effective approaches to improvement in treatment adherence.

CONCLUSIONS

Asthma disparities have significant direct and indirect economic as well as societal costs, and represent an important challenge. Research on the effects of specific genotypes, gene–environment interactions, environmental exposures, health-care quality improvement, symptom perception and adherence, responses to therapy and culturally competent care should lead to better understanding and treatment for different racial/ethnic minority groups. Understanding the reasons for these disparities may and should lead to more specific recommendations for improved prevention, disease modification, greater specificity in treatment with pharmacogenetics, and improved management of all persons with asthma. A comprehensive approach by government, researchers, health-care providers and organizations, pharmaceutical companies, community and racial/ethnic organizations, and patients will be necessary in order to overcome the disproportional burden of asthma in minorities. Improved health-care access, culturally appropriate communication and interventions, adequate education and empowerment, and improvement of living conditions within the context of a supportive community environment can reduce current asthma disparities.

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18 Asthma, Health Care, and the Law

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KEY POINTS

- In 2010 the projected direct cost for health care expenditures for asthma is $15.6 billion, including $5.5 billion for hospital care. For the uninsured, the cost of preventative and emergency treatment can be staggering. The Patient Protection and Affordable Care Act seeks to increase access to insurance coverage. It currently protects children from being denied insurance coverage on the basis of asthma as a pre-existing condition; this protection will expand to include adults in 2014. Likely problems with the law for patients include political factions attempting to defund or overturn some or all parts of the law, and ever-increasing insurance premiums coupled with plans that offer no more than the minimum-mandated coverage. Additionally, because the law is looking to reduce Medicare expenditures, Accountable Care Organizations would receive payment for improving the quality of health care and reducing costs. This change in reimbursement and the movement to larger group cooperation has the potential to challenge a physician's ability to effectively advocate for more expensive but more effective treatments.
- Improper or out-of-date asthma treatment can lead to malpractice claims. The standard of care is becoming a national standard based on the level of care that would be rendered by a specialist in the same or similar circumstances. In certain instances the standard of care may require physicians to provide treatment or services for which

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insurance companies will not provide reimbursement. It is important for physicians to keep up with the literature and disease management protocols. Because many problems arise from patients not receiving or not understanding medical instructions, documented informed consent is extremely important.

- Asthma can be an expensive disease for physicians bearing financial risks under a managed care contract or under projected reimbursements for health care organizations. Accordingly, when negotiating medical care contracts or evaluating ACO arrangements, the population affected by asthma should be identified, the asthma treatment separately calculated, and a carve-out for asthma negotiated. Whenever physicians gain financially by rendering less care under a managed care contract on ACO reimbursement plans, there is a potential ethical dilemma. This dilemma can be resolved for asthma patients by prescribing appropriate disease management measures, which may entail short-term costs, especially pharmaceutical expenses, but in the end, will save money on the overall cost of the patients' care. This chapter outlines available measures if governmental or health plan authorizers will not authorize the appropriate cure. Some health plans financially incentivize physicians to render a prescribed regimen for asthma patients. These so-called pay-for-performance protocols may help educate physicians on updated treatment modalities in the short run and may provide low levels of increased reimbursement. The incentives are expected to disappear rather quickly, and of course, there is a risk that the treatments prescribed by the standing protocols may be inappropriate or ineffective for a given patient.
- Air pollution – indoors and outdoors – can create suffering for patients with asthma. To help protect individuals with respiratory problems, governments at all levels have enacted clean air laws regulating everything from car emissions to tobacco smoke. Courts have also provided remedies for asthmatic victims of air pollution. Notably, part of the justification for a recent tobacco settlement was to pay for the care of patients with asthma whose condition was caused or exacerbated by smoking or second-hand smoke.
- This chapter also discusses policies, especially those involving drug and genetic testing, and the need to harmonize those policies with the privacy rights of patients with asthma.
- The Americans with Disabilities Act or the Federal Rehabilitation Act will protect individuals with asthma (especially those with severe cases) from job discrimination, and will ensure their access to insurance, although there is currently still a strong conflict regarding insurance access.
- Finally, this chapter offers legal information for physicians who must render expert opinions regarding the scope of an asthmatic's disability or its cause.

INTRODUCTION

This chapter raises and highlights some of the legal issues associated with asthma, from the perspective of both patients and physicians. As with all medical conditions, especially those defined as disabilities, the possible topics are so numerous that complete treatises could be and have been written on such subjects. Therefore, the author has chosen to focus on only a few specific legal issues pertaining to asthma. This chapter includes a broad discussion of some of the anticipated consequences of the Patient Protection and Affordable Care Act as well as a brief discussion of the legal implications of reimbursement mechanisms for physicians treating asthma patients.

Developments in this area are very fluid, so physicians are encouraged to contact the Patient-Physician Alliance and lawyers specializing in physician advocacy. Because asthma may be considered a disability, this chapter also outlines some of the key legal issues associated with all disabilities, including discrimination, access to health service, insurance coverage, denials of claims for medical treatment, and actions for professional liability. Moreover, it is important to note that, although federal law may cover many of the legal issues, state law may apply and often is more stringent than federal law, and it may provide additional remedies for the same conduct. Therefore, anyone with particular legal questions should consult a local health care lawyer who is familiar with particular state laws regarding disabilities, such as asthma. For further information, the reader is encouraged to review the Web site of The National Conference of State Legislatures, which allows visitors to search for information on current state asthma-related bills and laws: www.ncsl.org.

HEALTH CARE REFORM AND ASTHMA CARE

The passage of the Patient Protection and Affordable Care Act in March 2010 represented an attempt to broaden insurance access. Starting immediately, children who suffer from asthma can no longer be excluded from health insurance plans due to pre-existing conditions. In 2014, the law will expand to prevent insurance plans from excluding adults with pre-existing conditions as well.

Although the elimination of pre-existing condition exclusions represents a significant advance in insurance accessibility for patients with asthma, the health reform bill does not present doctors or patients with a complete resolution of patient care issues. One of the main things the bill does not address is the increasing cost of health insurance. Health insurance companies have been raising premiums, deductibles, and co-pays while reducing coverage. Unfortunately, the bill does little to prevent them from continuing to do so. Furthermore, the subsidies provided in the bill which were designed to help lower-income Americans pay for insurance are fixed amounts rather than a percentage of the total premium; so as health premiums rise, the subsidies become less relevant. Patients may opt for lower premium/higher deductible plans as they are priced out of the market for better plans. The increase in insurance costs presents a very real problem for patients, especially for patients with low incomes. Although mandatory insurance may provide asthma sufferers with maintenance treatments, the ever-increasing cost of care and the problem of under-insurance may leave asthma patients unable to afford necessary emergency room visits, hospitalizations, or expensive pharmaceutical regimens.

Unfortunately, reaction to the bill remains divided and its future is somewhat murky. In response to the health care reform bill, many large employers have indicated they will elect to pay the mandatory fines instead of offering health insurance to their employees.[1] The exit of the employers from the insurance market will leave patients to trying to deal

[1] Cook, Bob, "More employers consider dropping health coverage, report says" American Medical News 20 June 2011, http://www.ama-assn.org/amednews/2011/06/20/bisa0620.htm.

with well-funded, politically powerful insurance companies one-on-one. Health and Human Services has also shown willingness to provide waivers of the minimum annual benefit included in low cost plans for large employers. The only way for individuals to gain control of their care going forward is to gain a voice with the strength to compete with the fiscal resources of big health care. By uniting the interests of health care providers and consumers, organizations such as the nonprofit Patient-Physician Alliance provide a vehicle through which individuals can work together to shape health care reform on a local and national level.[2]

THE INCREASING INSTANCE OF ASTHMA AND ITS LEGAL IMPLICATIONS FOR ENVIRONMENTAL LAW

With asthma rates growing, the legal implications of the disease are widespread. Asthma is viewed as a barometer of our environmental health. It presents physical symptoms that reflect how clean our air and the surrounding environment may be at any given time. As a result, numerous laws at the state and local levels are being passed to help ensure a clean breathing environment for individuals who may suffer from asthma or severe allergies.

In the work environment, there are much stricter Occupational Safety and Health Administration regulations to prevent job-related asthma. Public buildings, even apartment dwellings, are being subjected to tighter ventilation and air-filtering requirements. Air polluters, such as oil refineries and others, have to pay asthma sufferers for major accidents or long-term polluting activities. Recently, indoor air quality (especially related to mold, which is a known cause of asthma) has also been the subject of increased attention from courts and government agencies. Mold especially poses a risk for renters who may not be able to control the abatement measures used by the landlord. State landlord/tenant law will provide the recourse available to asthmatics whose homes become infested with mold.

For more information and updates on the subject, consult the Environmental Protection Agency's Web site at: www.epa.gov/iaq/index.html. The heightened awareness of asthma and its personal and social costs is improving the quality of the environment for those who do not suffer from the disease, as well as for those who do.

SUCCESSFUL MANAGEMENT OF ASTHMA AND PREVENTION OF MALPRACTICE

As the medical standards for managing asthma improve, the standard of care for asthma diagnosis and treatment is being elevated. The National Asthma Education Prevention Program (NAEPP) released its Expert Panel Report 3 in 2007, providing evidence-based guidance on the management and treatment of asthma. Although continuous updates regarding treatment standard result in better treatment for patients, it also means that physicians throughout the country are expected to adhere to the accepted

[2] http://www.patientphysicianalliance.org.

improving standards. However, because there is no single standard for treatment, physicians must never rely on a single source. The law provides that:

> *A physician is negligent if [he/she] fails to use the level of skill, knowledge, and care in diagnosis and treatment that other reasonably careful [insert type of medical practitioners] would use in the same or similar circumstances. This level of skill, knowledge, and care is sometimes referred to as "the standard of care."*
>
> *— Judicial Council of California Civil Jury Instructions (CACI) 501, Mathew Bender & Co. (2010).*

Although the standard of care references the locality where the physician practices, a failure by local physicians to adhere to national and accepted standards is not an excuse for malpractice. Furthermore, primary care physicians who attempt to care for and manage asthma will be held to the same standards as allergists or rheumatologists. As national standards emerge for disease management, it will be the responsibility for all physicians who are treating asthma patients to be up to date regarding those standards. This does not mean that practitioners must accept every new proposed treatment, only those which have become accepted in practice or recommended by leading national standard setting academies, associations, or organizations. The law provides that:

> *A [physician] is not necessarily negligent just because [he/she] chooses one medically accepted method of treatment… and it turns out that another medically accepted method would have been a better choice.*
>
> *— (CACI, 506, Matthew Bender & Co. [2010]).*

Physicians should be aware that if they do not follow mainstream and standard procedures, they are more likely to be second-guessed by experts at trial.

Recently, as asthma management has improved and the standard of care has become better defined, the number of claims for failure to diagnose or promptly treat asthma has increased. Particularly, there has been an increase in the number of claims alleging failure to properly instruct the patients and their families on how to handle asthma emergencies. Educating patients in the management of asthma is an essential part of the standard of care. Unfortunately, due to time constraints placed on practitioners and an unwillingness on the part of insurance companies to pay for time spent on patient education, education may be a lower priority than other treatment issues. Financial disincentives must not prevent practitioners from providing patient education. Physicians undertaking asthma care, therefore, should consider using instruction sheets and computer training resources. Doctors should always document their patient instructions in the chart. Emergency rooms and other departments that receive asthma patients must also be current in their methods of recognizing and treating asthma-related problems. In short, the practice of good medicine will lead to fewer malpractice claims, but the message is that everyone in the profession must keep up with treatment protocols and new medical developments in the field.

Increasingly, to meet the standard of care, physicians must be aware of numerous specific environmental triggers for each patient. Home visit programs may offer an effective way for physicians to incorporate environmental risk factor management along with traditional treatment and prevention. Unlike efforts to alleviate single risk factors, environmental intervention tailored to each person's allergic sensitization and environmental

risk factors has been shown to improve outcomes.[3] In 2010, HHC's Woodhull Medical and Mental Health Center in Brooklyn was selected to receive U.S. Environmental Protection Agency's (EPA) 2010 *National Environmental Leadership Award in Asthma Management* for its home visit program. The Boston Public Health Commission, the University of the District of Columbia, and other non-profit asthma education organizations have also introduced trial home visiting projects to address environmental triggers. As part of these programs, health care workers visit the homes of children with severe asthma and work to identify suspected environmental effects at the child's home or school and work with patients and their families to eliminate them. The federal government has endorsed the use of home environmental assessments: the EPA released a sample home environment checklist with action items as guidance for providers who want to include home visits as part of their treatment protocols.[4] With positive results stemming from home-visit studies, the standard of care for asthma sufferers is likely to evolve to include mandatory home visits.

Although careful, onsite examination of all potential environmental triggers for each patient is ideal, there are many practical factors which may make home visits difficult for health care providers. Because home visit programs are still being studied, there are no comprehensive training programs for physicians interested in instituting home visits. Physicians or group practices will likely use dedicated nurses or other allied health workers to conduct the visits, thus making the practice responsible for creating its own training, policies, and procedures, all of which must fall within the standard of care. A physician who does not see a large number of asthma patients may not have the time or resources available to institute a comprehensive home visit program, but may find himself or herself liable for the failure to do so. In addition, because insurance reimbursement has not yet caught up to the latest advances in care, physicians may be held legally responsible for the failure to provide home environmental assessments despite their inability to receive reimbursement for such services.[5]

ASTHMA MANAGEMENT AND MEDICAL ECONOMICS

Treating asthma emergencies can be expensive. Not only do patients with blocked airways require expensive emergency room treatment, but also, if help is not provided in time, there can be serious complications, including brain damage, leading to costly long-term deficits and high levels of care. Patients face increasing insurance costs, restrictive formularies, and exclusions for pre-existing conditions all of which act to reduce access to the best treatment and specialists. There has been a push to compensate physicians based on "pay-for-performance," rewarding healthcare practitioners who

[3] Morgan, Wayne, M.D., C.M., Crain, Ellen, M.D. Ph.D., et al. "Results of a Home-Based Environmental Intervention among Urban Children with Asthma" New England Journal of Medicine Volume 351:1068-1080, 9 September 2004.

[4] http://www.epa.gov/asthma/pdfs/home_environment_checklist.pdf.

[5] The EPA has created an informational brochure for health plans interested in implementing home visits, which can be found at: http://www.epa.gov/asthma/pdfs/implementing_an_asthma_home_visit_program.pdf.

meet certain standards for quality and efficiency. These rewards are often coupled with disincentives which reduce or eliminate payment for increased costs or errors. The movement toward pay-for-performance may encourage physicians to choose set treatment regimens; however, treatments are not one-size-fits-all, and a physician who chooses to treat a patient outside of the set regimen may lose financial incentives. Regardless of set regimens or the potential loss of income from deviating from those regimens, physicians must choose the most effective treatments for each individual patient in order to avoid malpractice.

Whether or not pay-for-performance works remains to be seen; the administrative component required by the system has prevented pay-for-performance from demonstrating real cost-savings. Most importantly, the pay-for-performance system encourages physicians to avoid high-risk patients in cases where payments are tied to outcome improvements. When dealing with chronic conditions, such as asthma, pay-for-performance may seriously restrict the number and quality of physicians willing to provide treatment.

Increased patient access to insurance, even the prospective increases contemplated by the Affordable Care Act, is not a panacea; in this age of managed care, health insurers and managed care organizations, including physicians' medical groups and independent physician associations, can be forced to bear the cost of care and treatment, depending on their contracts with health care organizations. Physicians who contract for the care of patients with asthma or patients with potential asthma – whether they be primary care physicians or specialists – should expressly negotiate a clause in their contracts singling out the asthma risk and ensuring that it is both identified and properly reinsured through stop-loss insurance.

Insurance company authorizers may try to limit or impede the physicians' aggressive management of asthma to save short-term costs, particularly pharmaceutical costs. Successful management of the disease not only means treatment of patients, but it also means, under managed care or capitation, controlling an important economic risk in the patient population. In this instance, good medicine equals good disease management, which, in turn, equals good economics. Patients are entitled to appropriate care, and physicians are ethically and in most states legally bound to advocate appropriate care for patients, even if health plan authorizers say, "No." Physicians must appeal and take all steps possible to convince medical directors to provide appropriate care. If medical directors refuse to authorize appropriate care, physicians should write letters to the medical director documenting their concerns and stating clearly that any adverse consequences of the medical decisions made by medical directors will be the responsibility of the director. Some physicians who have failed to gain authorization have gone so far as to report medical directors to the state licensing board for violation of the state Medical Practice Act. If the health plan tries to retaliate against the treating physician for advocating good patient care, the doctor may have statutory and common-law protection, depending on the state in which he practices. Medical associations throughout the country will often help their members in such situations.

From the patient's perspective, asthma can be difficult to diagnosis. Unfortunately, physicians often miss the diagnosis, particularly if they are in a rushed managed care environment. Patients who suspect that they have asthma but do not receive close medical supervision should contact the American Lung Association.

PATIENTS WITH ASTHMA AND PRIVACY

The US Constitution, as well as state constitutions such as California's, guarantees an individual's right to privacy as a part of the "penumbral" or understood rights under the Constitution. California's constitution expressly guarantees the right of privacy to all its citizens. Notwithstanding these constitutional guaranties, the abuse of drugs has led to widespread practice of drug testing on the job, in sports, and in other venues. Under many circumstances, especially where motor skills are required or competition is involved, drug testing has been allowed by the courts. Readers may recall that in 1972 an Olympic swimmer from the United States was deprived of his medal because he tested positive for a drug test after having taken drugs for his asthma.[6] Obviously, we will see legal activity in the future to balance the rights of patients with asthma with our drug and drug testing policies.

Fortunately for patients, some recent developments have increased the access to treatment. One practical legal problem previously faced by patients with asthma is the increasing ban on inhalers, especially in schools. As a result, many children and young people were required to leave their inhaler with the school nurse or some other school official, risking an attack without the medication at hand. As of 2010, South Dakota became the final state to pass legislation allowing students to carry and use their inhalers to self-medicate within school campuses. Schools may prefer to treat inhalers like other medications and request that inhalers are left with an official; however, this may not be the best solution for each child with asthma. Parents should familiarize themselves with the laws of their state and ascertain the school district's self-carry requirements to determine if the student is capable of complying with the appropriate policies. Treating physicians may be required to assist in the determination whether a child is ready to participate in a program that allows them to carry and administer their medication.

Asthma is a disease with multiple genetic risk factors as well as environmental triggers. Advances in genetic testing have lowered the costs of such testing dramatically. Not only have states like California begun to turn their attention to the collection and use of genomic data in asthma research,[7] but recently widespread distribution of an over-the-counter genetic test kit was announced.[8] Genetic testing, however, raises many unsolved legal and ethical issues. There is little current federal regulation about how genetic tests should be reviewed for accuracy, reliability, and use. Because many chronic conditions are linked to multiple genes or gene–environment interactions, testing may be unreliable or reveal untreatable diseases. Until further genomic research is done, the use of simple genetic testing is of very limited use for diagnostic or preventive purposes

[6] Patrick, Dan "DeMont redeemed after 29 years" 6 December 2001 http://espn.go.com/talent/danpatrick/s/2001/0202/1057642.html.

[7] See "Asthma's Future in Utah: How will genomics play a role? July 2006 Workplan" http://health.utah.gov/genomics/pages/projects/asthmaconference/Workplan%20with%20notes%20-%20FINAL.pdf.

[8] The test was pulled from drugstore chains when the FDA alerted the manufacturer that the test met the legal definition of a "device" and thus fell under the purview of the FDA. Tests currently remain available online. See http://www.ama-assn.org/amednews/2000/10/02/hlsb1002.htm. Genetics help predict asthma drug response. By Victoria Stagg Elliott, amednews staff. 2 Oct 2000.

and brings with it more cause for concern than utility. Current testing can, however, reveal how well an individual may respond to certain medications used for asthma, and in this regard may prove very helpful.

Ethically, the long history of misuse of genetic information in the United States (including the forced sterilization of individuals having presumed genetic "defects" such as mental retardation, mental disease, epilepsy, blindness, and hearing loss) raises concerns about the widespread use of genetic testing. In the 1970s, 12 states mandated sickle-cell anemia screening programs for African-Americans. At the time, prenatal diagnosis was next to impossible, and there were no definitive treatments to protect affected individuals. Finding a compelling public health interest served by these laws is extremely difficult. Their deleterious effects were much clearer; persons whom testing revealed to have the usually benign sickle cell trait had trouble receiving life or health insurance and were subjected to workplace discrimination. Genetic testing for asthma could lead to similar unfair discrimination.

Numerous studies have demonstrated that a large majority of Americans do not want insurers or employers to have their genetic information, and that they are increasingly concerned about the risk of genetic discrimination. "Workers fear that employers will use genetic information to lower their insurance and sick leave costs by weeding out individuals who have traits linked to inherited medical conditions. There is both hard and anecdotal information indicating that employees' fears are not baseless, and that the problem will only get worse as technology develops," notes Paul Miller of the U.S. Equal Employment Opportunity Commission.[9] Fear of discrimination often prevents persons from seeking testing although insurance companies may provide reimbursement for genetic testing, many patients still choose to pay cash in advance of genetic testing and only submit to their insurance company if their test is negative.

Supplementing a patchwork of state laws, in 2008, Congress passed the Genetic Information Nondiscrimination Act which protects individuals from discrimination on the basis of genetic information by employers or health insurance companies. GINA does not apply to employers with less than 15 employees, nor does it prevent health insurers from making decisions based on an individual's current symptoms or diagnosis. The law does not currently protect individuals from other adverse insurance determinations, such as the denial of life insurance, based on genetic information.

Potential misuse of genetic testing samples or results does not end with simple discrimination; some testing companies include contractual terms allowing them to sell the test information to third parties. Individuals have no control over who is purchasing their data, or to what purpose it may be used, and because of the nature of DNA, total privacy can never be assured.

Until genetic testing can ensure concrete benefits for asthma patients or greater legal protections are created, the need to protect individual privacy will usually outweigh the benefits of genetic testing.

[9] Faces of Genetic Discrimination: How Genetic Discrimination Affects Real People authored/published by *National Partnership for Women & Families on behalf of the Coalition for Genetic Fairness*. http://www.geneticalliance.org/ksc_assets/documents/facesofgeneticdiscrimination.pdf.

PATIENTS AND THE AMERICANS WITH DISABILITIES ACT

Research reveals no case in the country that has yet held that asthma is a disability as defined in the Americans with Disabilities Act (ADA).[10] The statutory definition of a disability, however, appears to apply to asthma. Under the ADA, a person is considered to be disabled and protected if:

- He or she has a record of having, or is regarded as having, a physical or medical impairment.
- That impairment substantially limits one or more of the person's major life activities.

A "physical or medical impairment" is defined as any physiological disorder or condition, cosmetic disfigurement, or anatomical loss affecting one or more of several body systems, or any mental or psychological disorder. Determination as to whether an impairment constitutes a disability is made on an individual basis depending on each individual's circumstances. Such conditions as chronic fatigue syndrome, depression, diabetes, epilepsy, heart disease, high blood pressure, hypersensitivity to substances (such as cigarette smoke), learning disorders, mental retardation, migraine headaches, schizophrenia, shortness, stress disorders, and obesity have been held to be disabilities. Logically, asthma would similarly be considered to be a disability when other elements of the definition of disability are met.

The impairment must also affect one or more of the affected person's "major life activities," which are the activities that the average person can perform with minimal or no difficulty on a daily basis. Such activities would include caring for oneself, eating, drinking, walking, speaking, breathing, learning, hearing, and working, among others. The 2008 amendments to the ADA expanded the class of major life activities to specifically include working. The life activities which are impaired must not simply be restricted or limited, but rather the person's impairment must "substantially limit" performance of "major life activities." Therefore, the ADA applies only to those impairments that are permanent or chronic or that have long-term effects; temporary, non-chronic impairment with short duration and little or no permanent impact would not be covered by the ADA. The determination as to whether a person's impairment rises to the level of a disability within the meaning of the ADA must also take into account corrective mitigating measures, including medication. There is, however, no absolute and truly objective method for applying this requirement of the law. Because of this, asthma patients seeking accommodations or redress for discrimination under the ADA must be prepared to have their cases evaluated based on their specific situations.

The Equal Employment Opportunity Commission, which is the federal governmental agency empowered to enforce the disability discrimination laws, emphasizes that each

[10] While many cases have held that the impairment suffered by asthmatic plaintiffs does substantially limit major life activities, *Moran v. Premier Educ. Group, Lp*, 599 F.Supp.2d 263 (D. Conn., 2009) which in denying the employer's request for summary judgment found that there was "sufficient material facts in dispute to warrant precluding summary judgment on the basis that the [asthmatic] Plaintiff does not suffer from a disability."

case must be evaluated on its own merits. The episodic nature of asthma would not be a bar to its being classified as a disability, because the onset is unexpected, unanticipated, and not under the control of the individual. Even though the disability may be medically controlled, it may still fall within the zone of protection of the ADA. Claims of disability discrimination based on asthma have been both allowed and denied by the courts depending upon the specific facts at issue. The ADA and the Federal Rehabilitation Act provide protection for persons with disabilities against discrimination in the workplace.

Under the ADA, equal job opportunity is guaranteed and the employer must make reasonable accommodations to ensure that the disabled person can take the job if he or she is otherwise qualified. Much has been written about the ADA and its effect on employers. From physicians' and patients' points of view, it is simply important to be aware that asthma should not limit the employability of an individual except under conditions that may trigger attacks.

The ADA also protects the rights of patients with asthma to health care services. As with all public accommodations, Title 3 of the ADA prohibits discrimination in the delivery of healthcare, requires the removal of any barriers to receiving health care, and mandates that construction and alterations consider the disabilities of patients. Building codes are increasingly strict regarding air filtration, and physicians specializing in rheumatology and asthma treatment should pay attention to the environmental accommodations that they make to their patients with asthma.

The ADA and the Federal Rehabilitation Act may also affect physicians who are contracting for managed care or for payment through ACOs. As noted, physicians should negotiate special arrangements for patients with asthma to avoid assuming unsupportable financial risks. The language of those provisions as they relate to asthma and other patients with disabilities should be carefully worded, so as not to be construed as discriminatory, i.e., a refusal by the doctors to provide access to medical care for these individuals. Healthcare providers are prohibited from withholding medical benefits and treatment services for patients with disabilities, so arrangements for such patients should be anticipated during contract negotiations.

There now exists a conflict in the laws regarding whether insurance companies are required to provide coverage as a public accommodation without discrimination to the disabled. The Sixth Circuit, in its opinion in *Parker v. Metropolitan Life Insurance Company*, clearly states that places that do not have physical boundaries, which would include insurance-benefit plans, are not to be considered public accommodations and are not subject to Title 3 of the ADA. Other case law, however, from other Circuits, holds that insurance is a public accommodation.

Employees may also be held liable for ADA violations if they deny insurance benefits to their employees based on disability. The discrimination must be showed to be disparate treatment. In sum, the ADA and the Federal Rehabilitation Act – and corresponding state laws protecting the disabled – may help patients gain access to care, access to insurance, and access to employment with reasonable accommodations to ensure a helpful working environment for them. Physicians may be called on to advocate for their patients to obtain the benefits of these laws, and they are encouraged to do so.

CONCLUSION

The legal concerns and recourses for asthma sufferers and their healthcare providers continue to grow. Patients are generally protected from discrimination by federal and state laws, and physicians are required to treat the ailment. New laws have been enacted to allow asthmatic children a broader access to insurance, while states now recognize and have begun to offer legal remedies for asthmatics who face environmental triggers at home and in public. The standard of care for treatment continues to change, and a physician treating asthma patients must stay educated about emerging studies and treatment plans. Medical economics, insurance, and physician compensation will play an ever greater role in the treatments a physician is able to prescribe; however, available compensation does not affect the standard of care. Under managed care contracts and under ACO arrangements, physicians should not assume the financial risk of catastrophic asthma treatment. That risk should be separately negotiated and separately insured with stop-loss insurance. New disease management techniques should be used carefully to ensure better, more timely, and less costly treatment. In turn, the economic risk, under managed care, will be lowered. Physicians with questions are encouraged to contact non-profit physician advocacy groups such as the Patient-Physician Alliance with any questions about the intersection of medical economics and patient care.

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