Clinical Asthma Syndromes and Important Asthma Mimics

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Introduction

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Why Do Phenotypes Matter?

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Summary

Asthma is a heterogeneous disorder with multiple clinical phenotypes. Phenotypes can be grouped into clinical or physiological, trigger-defined, and inflammatory phenotypes. Treatment based on inflammatory phenotyping improves clinical measures of asthma morbidity. Further study of individual asthma phenotypes will improve understanding of their immunologic and pathologic characteristics and improve diagnosis and therapy. Because asthma is a common disorder with non-specific presenting features, other disorders are often misdiagnosed as asthma. A high index of suspicion for alternative diagnoses must be maintained when evaluating a patient who presents with clinical features suggestive of asthma, particularly if the patient presents with atypical symptoms or fails to respond to therapy. Key words: asthma; phenotypes; asthma, etiology; asthma, genetics; asthma, mimics; vocal cord dysfunction. [Respir Care 2008;53(5):568–580]

Introduction

Asthma is probably not a single disease, but rather a complex of multiple, separate syndromes that overlap. Several classification schemes have been proposed, but many are poorly characterized, with little known about the underlying pathophysiology. The recent development of tar-
Targeted asthma therapies have raised renewed interest in asthma phenotypes. However, there is no standardized method or agreed-upon classification system to define asthma phenotypes. Focus has recently shifted to classification of asthma based on immunopathology, specifically the cellular makeup of the inflammatory response. Studies have shown clinical improvement with management strategies that target inflammation rather than symptoms and peak flow.\(^1\)\(^2\) Better defining asthma phenotypes may improve understanding of the underlying pathobiology of the phenotypes and lead to targeted therapies for individual phenotypes. In this article we will explore the characteristics of 3 categories of asthma phenotypes: clinical phenotypes, trigger-defined phenotypes, and inflammatory phenotypes. We will then discuss conditions that commonly mimic asthma, with particular attention to chronic obstructive pulmonary disease (COPD) and vocal cord dysfunction.

The 2007 National Asthma Education and Prevention Program’s Expert Panel Report 3, Guidelines for the Diagnosis and Management of Asthma, defines asthma as “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.”\(^3\) This purposefully broad definition encompasses the many phenotypes of asthma, but poorly accentuates important differences. The current strategy of “lumping” asthma phenotypes together, with treatment based solely on asthma severity, hinders efforts toward therapy specifically targeted at the underlying etiology. Despite the call for a new taxonomy of asthma, there is no current consensus regarding categorization of asthma by phenotype. We believe that the categorization proposed in a recent review by Wenzel, the preeminent expert on asthma phenotyping, is the most comprehensive and descriptive.\(^4\) Wenzel describes 3 potential phenotypic categories: clinical or physiological, trigger-related, and inflammatory (Table 1).

Phenotype is defined as “the observable characteristics, at the physical, morphologic, or biochemical level, of an individual, as determined by the genotype and the environment.”\(^5\) This definition yields 2 key points: (1) phenotypic characteristics of asthmatic patients are only those that are observable, and (2) asthma phenotypes are determined by the complex interaction between environmental and genetic factors. Note that there is substantial overlap between phenotypic categories. An example of this is moderately persistent allergen-induced asthma in a child. One could phenotype based on severity, age of onset, type of trigger, or the underlying inflammatory phenotype. All of these approaches are valid, but the optimal approach would consider all of these phenotypes in an effort to get at the underlying pathobiologic mechanisms of asthma in this particular patient.

### Table 1. Potential Asthma Phenotypes

<table>
<thead>
<tr>
<th>Clinical or Physiological Phenotypes</th>
<th>Trigger-Related Phenotypes</th>
<th>Inflammatory Phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity-defined</td>
<td>Aspirin or nonsteroidal anti-inflammatory drug</td>
<td>Eosinophilic</td>
</tr>
<tr>
<td>Exacerbation-prone</td>
<td>Environmental allergens</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Defined by chronic airflow obstruction</td>
<td>Occupational allergens</td>
<td>Paucigranulocytic</td>
</tr>
<tr>
<td>Treatment-resistant</td>
<td>Menses</td>
<td></td>
</tr>
<tr>
<td>Defined by age at onset</td>
<td>Exercise</td>
<td></td>
</tr>
</tbody>
</table>

(Adapted from Reference 4.)

### Clinical Phenotypes

The clinically or physiologically defined phenotypes proposed by Wenzel include: severity-defined asthma, exacerbation-prone asthma, asthma defined by chronic airflow obstruction, treatment-resistant asthma, and asthma defined by age at onset.\(^4\)

### Severity-Defined

The severity-defined phenotype is advocated by the major national and international guidelines and therefore is among the most commonly used clinically.\(^3\)\(^6\) The Global Initiative for Asthma guidelines\(^6\) recommend classifying asthma as intermittent, mild persistent, moderate persistent, or severe persistent when making initial assessment and treatment decisions. Though severity-defined assessment may help develop an initial treatment strategy, it does not adequately predict the clinical course and response to therapy. Bateman and colleagues assessed the efficacy of escalating doses of either salmeterol/fluticasone or fluticasone in achieving symptom control, as defined by the Global Initiative for Asthma 2002 guidelines.\(^7\) Despite escalating doses of inhaled corticosteroids and rigorous follow-up, only 71% of patients were well-controlled and a mere 31% achieved total control in the salmeterol/fluticasone arm. An even lower success rate was achieved in the fluticasone arm. Though those authors concluded that the goal of guideline-derived asthma control was achieved in a majority of patients, a substantial minority did not achieve control, despite appropriate medication and follow-up.
Another disadvantage of severity phenotyping is disparity in the assessment of severity. Miller et al. compared physician assessment of asthma severity to those established by the National Asthma Education and Prevention Program and the Global Initiative for Asthma groups in 2,927 patients enrolled in the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens cohort. They found a clear lack of agreement among asthma severity assessment modalities, though patients considered to have severe asthma by all 3 assessments had greater health-care and medication usage. In conclusion, severity-defined phenotypes are widely used and have some utility in predicting health-care utilization and medication usage; however, they cannot adequately predict clinical course or response to therapy.

**Exacerbation-Prone**

A subgroup of asthmatics predisposed to frequent and sometimes severe exacerbations despite adequate treatment has been recognized for decades. The term “brittle asthma” was coined in 1977 to describe this phenotype. Understanding the underlying pathogenesis of this phenotype is paramount, as this group of patients is at high risk for hospitalization and death. This may be partially explained by the fact that patients with exacerbation-prone asthma also seem to have a blunted perception of dyspnea, which delays recognition of an exacerbation. The prevalence of this phenotype is poorly defined because of difficulties in standardizing the definition of exacerbation-prone asthma and in controlling for differences in patient adherence to therapy, but greater than 40% of patients with severe asthma in the Severe Asthma Research Program database were reported to have exacerbation-prone asthma.

Multiple risk factors for exacerbation-prone asthma have been identified. Over 90% of these patients are atopic, as measured via skin-prick testing. Low forced expiratory volume in the first second (FEV₁), African race, early age of onset, and a history of exacerbation in response to aspirin, nonsteroidal anti-inflammatory drugs, or premenstrually were all independent predictors of a severe exacerbating phenotype in a logistic regression analysis of the Severe Asthma Research Program database. Relative immunoglobulin deficiency, chronic sinus disease, and exacerbations provoked by certain foods have also been proposed as risk factors. Psychological conditions such as depression and anxiety are associated with exacerbation-prone asthma, although it is unclear if this relationship simply reflects psychological disease as a risk factor for poor adherence to therapy.

The make-up of the inflammatory response in exacerbation-prone asthma is not well-defined. Wenzel and colleagues performed endobronchial biopsies in 34 cortico-steroid-dependent patients with severe asthma. They found 2 distinct inflammatory milieus: 14 patients had nearly absent eosinophils; the remainder were considered eosinophil-positive. Both groups had similar baseline FEV₁ and bronchodilator response, but the eosinophil-positive group had more intubations than the eosinophil-negative group (12/20 vs 1/14, p < 0.001). Another recent study, by Qiu et al., assessed endobronchial biopsy specimens from patients with severe asthma exacerbations. They found both bronchial neutrophilia and eosinophilia. Given the above studies, it seems that the baseline level of eosinophilic inflammation plays a key role in exacerbation-prone asthma. Further studies are needed to clarify this issue.

**Asthma With Chronic Airflow Obstruction**

Asthma has classically been thought of as a disorder characterized by reversible airflow obstruction; however, irreversible obstruction develops in a portion of both adult and pediatric asthma patients. It is estimated that 35–50% of adult asthmatic patients have irreversible airway obstruction. Despite having reduced baseline pulmonary function, these patients may have only moderately symptomatic disease. Fixed obstruction is believed to develop from chronic airway inflammation and subsequent remodeling.

Studies of the pediatric population reveal that asthmatic children with fixed obstruction are more often male, less predisposed to exacerbations, have less reversibility of airway obstruction, and are less likely to be atopic, compared to asthmatic children without fixed obstruction.

Jang and colleagues compared 49 adult patients with fixed airway obstruction to 533 asthmatics without. They found that, compared to those without fixed obstruction, adult asthmatics with fixed obstruction had longer duration of disease, were older, had a lower percentage of sputum eosinophils, a lower rate of atopy, lower body mass index, and a greater response to short-acting bronchodilators, and all those differences were statistically significant. Another study of adults with severe asthma compared 37 patients with fixed obstruction to 29 patients without. That study found that greater age and longer disease duration were associated with fixed obstruction. After controlling for age and duration, only peripheral blood eosinophilia and bronchial wall thickening on high-resolution computed tomography (HRCT) were independently associated with persistent airflow obstruction. It seems from the available data that fixed airflow obstruction in adults may be a marker of longstanding disease, whereas in younger patients it may represent a more distinct phenotype. Further study of adult asthmatics with persistent airflow obstruction is warranted to clarify this issue.
Treatment-Resistant Asthma

Control of airway inflammation with corticosteroids is the cornerstone of asthma management. In the majority of asthmatics, suppression of airway inflammation and symptom control are achieved with inhaled or oral corticosteroids. However, 5–10% of patients do not adequately respond to glucocorticoid therapy. Glucocorticoid-resistant asthma most commonly occurs in severe asthma, but may be seen in all levels of asthma severity. There are multiple molecular mechanisms of glucocorticoid resistance, including reduced number of glucocorticoid receptors, reduced affinity of the ligand for glucocorticoid receptors, reduced ability of glucocorticoid receptors to bind to deoxyribonucleic acid, and increased expression of inflammatory transcription factors, which compete for deoxyribonucleic-acid binding. Some asthmatics may not respond to glucocorticoid therapy because of an absence or different type of airway inflammation. An absence of sputum eosinophils or a high number of sputum neutrophils may predict poor response to corticosteroids.

Substantial progress has been made toward understanding the underlying inflammatory cascade in patients with corticosteroid-resistant asthma. Multiple mechanisms have been proposed, including mutations of the glucocorticoid receptor gene, which can lead to altered pharmacokinetics and defects in ligand binding. Other factors thought to contribute to glucocorticoid resistance include immunomodulation via T regulatory cells, cytokines, cigarette smoking, genetic variation, recurrent infections, and neutrophilia. This opens the door for new therapies targeted at these underlying inflammatory mediators. For an in-depth discussion of the mechanisms and therapeutic implications of corticosteroid resistance, see the excellent update by Ito and colleagues.

Asthma Defined by Age at Onset

There seems to be a distinct phenotypic difference between the majority of asthmatics with childhood-onset and those with adult-onset asthma. Miranda and colleagues compared 50 patients with severe asthma whose disease onset was prior to age 12, to 30 patients with late-onset asthma of similar severity. The early-onset patients had significantly more allergen sensitivity and more allergic symptoms. Late-onset asthmatics had worse lung function than early-onset asthmatics, despite having a shorter duration of disease. Hsu et al compared asthma characteristics in 504 asthmatic patients divided into groups based on age of onset. They found a higher incidence of allergic rhinitis in younger patients. They also noted worse pulmonary function in older patients. However, they did not control for duration of disease. In general, patients with early-onset asthma are more likely to have atopy, eczema, and a family history of asthma.

Adult-onset asthma is a term often used to refer to a distinct asthma phenotype that develops later in life. This group is often atopic, predominantly female, and has greater asthma severity than those with early-onset asthma. Smoking and chronic rhinosinusitis appear to be risk factors for adult-onset asthma. Adult-onset asthma may have distinct clinical subtypes based on the underlying endogenous or exogenous trigger. Examples include aspirin sensitivity, chronic infection from respiratory pathogens, occupational asthma, and asthma due to inhalation of irritants.

Trigger-Related Phenotypes

Wenzel proposed the following trigger-related phenotypes: allergic asthma, occupational asthma, aspirin-induced asthma, menses-related asthma, and exercise-induced asthma.

Allergic Asthma. The majority of asthma has an allergic basis. Allergic asthma commonly begins in childhood, but can present at any age and is seen in a large proportion of adult asthmatics. Recent studies reported similar inflammatory responses in atopic and nonatopic asthma, and for this reason questioned the value of phenotyping in asthma. However, other studies have seen distinct differences in immunopathology between atopic and nonatopic asthma.

Further study is warranted to better elucidate the inflammatory cascade of allergic asthma, as this will probably lead to new targeted asthma therapies. Some progress has already been made. Immunoglobulin E (IgE) is a key mediator of the inflammatory reactions of allergic disease. Omalizumab, a humanized monoclonal anti-IgE antibody, has been developed to treat severe, persistent asthma. Omalizumab binds to IgE molecules, thus preventing free IgE from binding to IgE receptors. Multiple clinical trials have found that omalizumab reduces exacerbations. The success of anti-IgE therapy illustrates the promise of further study of the underlying pathobiology of various asthma phenotypes in the development of new therapies.

Occupational Asthma. Asthma is the most common occupational respiratory disorder in industrialized nations, accounting for 9–20% of adult asthma cases. Asthma exacerbated by the workplace is termed work-aggravated asthma, whereas the term occupational asthma describes asthma caused by workplace exposure. Occupational asthma has 3 distinct subphenotypes, defined by the underlying mechanism. It may be a nonimmunologically mediated, rapid response to irritant chemicals, such as smoke or chlorine exposure. This subphenotype is referred to as reactive airways dysfunction syndrome. Occ-
cupational asthma may also be immunologically mediated. If the causal agent is of high molecular weight, the underlying inflammatory response is IgE-mediated, similar to that seen in allergic asthma syndromes. Response to low-molecular-weight triggers also results in an immunologically-mediated response, although the involvement of IgE is variable. Though the mainstay of therapy for occupational asthma is avoidance of the asthma trigger, better understanding of the inflammatory mechanisms of these distinct subphenotypes may lead to improvements in therapy.

Aspirin-Induced Asthma. In 1968, Samter and Beers described the classic triad of aspirin intolerance, sinusitis with nasal polyps, and asthma. This well-described, homogenous asthma phenotype is now commonly referred to as aspirin-induced asthma. The prevalence of aspirin-induced asthma in adult asthematics is 3–5% when based on patient history alone, but is much higher when aspirin challenge is prospectively performed. A systematic review of articles on aspirin-induced asthma reported a prevalence of 21% in adult asthmatic patients diagnosed via oral provocation testing. Rhinorrhea and nasal congestion generally precede onset of asthma and aspirin sensitivity by 1–5 years in aspirin-induced asthma. Ingestion of aspirin or certain nonsteroidal anti-inflammatory drugs will result in an acute asthma attack accompanied by rhinitis and conjunctival injection within 3 hours of drug ingestion. The asthma associated with this phenotype is often severe and poorly responsive to corticosteroids.

The mechanism of aspirin-induced asthma is believed to be “shunting” of arachidonic acid metabolism away from prostanoid production, leading to increased leukotriene production and resultant bronchoconstriction. Genetics studies have identified mutations in the leukotriene pathway in patients with aspirin-induced asthma, although these mutations alone do not explain the adult onset of disease. It is likely that an environmental factor is required to activate the pathologic response in aspirin-induced asthma.

Menses-Related Asthma. The association between the menstrual cycle and asthma is poorly understood. The prevalence of self-reported perimenstrual worsening of symptoms in women visiting out-patient clinics is around 30–40%, although there has been substantial variability among the studies. Reports that have examined the phase of the menstrual cycle on emergency department visits are mixed. Skobeloff et al found more presentations during the perimenstrual period, whereas Zimmerman and colleagues found more visits during the preovulatory phase. A third study found more visits in both the preovulatory and perimenstrual phases, as compared to the periovulatory and postovulatory phases of menses. Those authors concluded that both the preovulatory and perimenstrual phases may trigger asthma exacerbations in some women. Although the incidence of menses-related asthma is poorly defined, it does seem to play a causal role in asthma exacerbations in some women and has been implicated in near-fatal asthma exacerbations. The mechanisms underlying menses-related asthma exacerbations are unclear. Estrogen and progesterone can act as pro-inflammatory or anti-inflammatory hormones. Fluctuations in the levels and ratio of estrogen and progesterone may play a role. More research is needed on the relationship of menses to asthma and the influence of sex hormones on airway inflammation.

Exercise-Induced Asthma. Exercise is the most commonly reported trigger of bronchospasm, affecting 50–90% of known asthmatics. Exercise-induced bronchospasm also occurs in up to 10% of patients without known asthma or atopy. Though exercise-induced asthma is often regarded as a distinct asthma phenotype, it is unclear if exercise-induced bronchospasm occurs as a general response in all asthmatic patients or if there truly is a subset of asthmatics predisposed to exercise-induced bronchospasm alone.

The pathogenesis of exercise-induced bronchospasm is poorly understood. The prevailing hypothesis is that the hyperventilation of dry air results in evaporative water loss on the airway surface and the resultant hyperosmolar environment releases inflammatory mediators, resulting in bronchoconstriction and mucus production in asthmatic patients. Exercise-induced asthma and exercise-induced bronchospasm in nonasthmatic athletes may be distinct entities. It is unclear to what extent inflammation plays a role in development of exercise-induced bronchospasm in nonasthmatic patients. Further study is needed to clarify the differences in pathobiology between inflammatory responses in asthma and exercise-induced bronchospasm in the nonasthmatic patient.

Inflammatory Phenotypes

Inflammation is recognized as a key component of asthma pathology, but until recently little attention was paid to the heterogeneity of the cellular make-up of the inflammatory response in asthma. In a 1999 study, Wenzel and colleagues distinguished 2 distinct inflammatory subtypes on mucosal biopsies of patients with severe asthma, which led to the suggestion of distinct inflammatory phenotypes. Since this exciting development, much attention has been focused on the use of noninvasive procedures to determine the inflammatory phenotype in asthma. This approach has already led to important therapeutic advances. We will now review the 3 major inflammatory phenotypes proposed by Wenzel on the basis of the predominant cell type:
eosinophilic asthma, neutrophilic asthma, and paucigranulocytic asthma.

**Eosinophilic Asthma.** Early studies of immunopathology in patients with mild asthma suggested that eosinophilic inflammation was the characteristic abnormality. Indeed, up to 80% of corticosteroid-naive, and more than 50% of corticosteroid-treated, asthmatics with symptomatic disease have an abnormally high sputum eosinophil count. There is some evidence that sputum eosinophilia may predict response to corticosteroids. There is also good evidence that sputum eosinophilia can be used to guide asthma therapy. Zacharasiewicz et al assessed sputum eosinophils in children with stable asthma undergoing inhaled-corticosteroid dose reduction. They found that steroid reduction was successful in all children with no sputum eosinophils. Green and colleagues compared a management strategy targeted at reducing the sputum eosinophil count to < 3% with a traditional management strategy based on symptoms and peak flow readings. Patients managed relative to sputum eosinophil count experienced fewer exacerbations and had fewer hospital admissions than the traditional-management group.

Persistent sputum eosinophilia despite corticosteroid therapy in severe asthma is associated with adult-onset disease and aspirin sensitivity. This subgroup of patients with severe asthma and refractory eosinophilic airway inflammation may represent a distinct asthma phenotype, although this is a subject of ongoing debate. In a study in The Netherlands, ten Brinke and colleagues assessed the response of 22 patients with severe asthma and sputum eosinophilia (> 2%) despite treatment with high-dose inhaled corticosteroids or long-term oral prednisone to intramuscular injection of high-dose triamcinolone. They found significant improvement in the level of sputum eosinophils, use of rescue inhalers, and FEV₁ in the patients who received the intramuscular triamcinolone, independent of whether they were taking daily oral corticosteroids. The response to corticosteroids led those authors to conclude that this group did not constitute a distinct asthma phenotype, although one could argue that the significantly blunted corticosteroid responsiveness is a distinguishing feature favoring this as a discrete phenotype. Regardless, that article has therapy implications, because it indicates that a trial of high-dose intramuscular steroid therapy may be warranted in patients with severe asthma and persistent sputum eosinophilia. Given the evidence that assessment of inflammatory phenotype has both prognostic and therapeutic implications, this strategy will probably be increasingly utilized.

**Neutrophilic Asthma.** A distinct clinical phenotype associated with neutrophilic asthma has not yet been defined. Green and colleagues compared 60 patients with neutrophilic asthma to 199 patients with eosinophilic asthma. Compared to their eosinophilic counterparts, the patients with neutrophilic asthma were more likely to be nonatopic, female, and to have middle-age asthma onset. Other studies have suggested an association with smoking, exposure to low-molecular-weight occupational sensitizers, and obesity. All of these associations require further epidemiologic study. Neutrophilic asthma is most commonly reported in patients with severe asthma, and has been found on autopsies of patients who died from asthma attacks. There are differences in airway remodeling between eosinophilic and neutrophilic asthma, and neutrophilic asthma may be associated with the development of irreversible airflow obstruction. This is supported by studies that showed an association between elevated sputum neutrophil count and fixed obstruction in asthma. When compared to patients with severe eosinophilic asthma, patients with neutrophilic asthma experience fewer and less severe exacerbations. As mentioned above, the effectiveness of corticosteroid therapy in eosinophilic asthma is well-established. Multiple uncontrolled studies and a single double-blind placebo-controlled study found decreased responsiveness to corticosteroid therapy in noneosinophilic asthma. It would be premature at this point to conclude that neutrophilic asthma does not respond to corticosteroid therapy. Studies of the effectiveness of corticosteroid and alternative therapies in neutrophilic asthma are required to develop optimal treatment strategies.

**Paucigranulocytic Asthma.** Studies suggest that asthma can exist without an identifiable influx of inflammatory cells. It is unclear if this represents a true phenotypic variant or inadequate sampling. Patients with paucigranulocytic asthma may be symptomatic despite high doses of steroids, which implies that variant forms of inflammation or other pathologic mechanisms may be responsible for the symptoms. Further study is required to elucidate the underlying pathobiology of this poorly understood condition.

**Why Do Phenotypes Matter?**

Developing new asthma phenotypes is useful only if it leads to novel insights into the underlying nature of the disease, which will in turn provide important prognostic and therapeutic information. Currently there is substantial overlap between the clinical and immunologic phenotypes. Further research into the immunology and genetics of asthma should help to better define the links between the various asthma phenotypes.

**Asthma Mimics**

Given the heterogeneity of asthma syndromes, it is imperative to make an accurate diagnosis. Some general hall-
marks apply to all asthma phenotypes. First, asthma symptoms typically include some combination of wheezing, chest tightness, cough, and dyspnea. When the disease is inadequately controlled, these symptoms are often worse in the early morning hours. Identifiable triggers, such as cigarette smoke, allergens, cold air, and exercise, typically provoke symptoms. The symptoms are accompanied by airflow obstruction, which is at least partially reversible. Though the above symptoms are generally associated with asthma, any process that narrows the intrathoracic airways or increases airway resistance can cause similar symptoms and must be considered in the differential diagnosis of asthma. Alternative diagnoses are particularly important to consider when the presentation is atypical for asthma or the response to treatment has been suboptimal. It is also important to keep in mind that many of these disorders can co-exist with and complicate asthma, rather than being simply mistaken for asthma.

When the predominant symptom is chronic cough rather than wheezing or dyspnea, several conditions are often confused with asthma. Pertussis causes a prolonged period of cough commonly misdiagnosed as new-onset asthma. Although the cough associated with pertussis is classically described as occurring in sporadic paroxysms of severe cough, often followed by gagging or emesis, these symptoms may be absent in patients previously immunized against the disease. The diagnosis is important to consider to prevent spread to other susceptible individuals.47

Cystic fibrosis is the second most common chronic inflammatory airway disease among whites. The classical presentation of malabsorption may not be present, and some patients will not present until adolescence or early adulthood. Cystic fibrosis should be suspected when signs of airway disease persist despite high-dose systemic corticosteroids.

Gastroesophageal reflux disease and post-nasal drip (upper-airway cough syndrome) often present with chronic cough, but are not usually associated with airway obstruction.

Other less common causes of cough in patients with documented obstruction include chronic bronchitis, tracheomalacia, and primary ciliary dyskinesia.47

When a patient complains of “wheezing,” keep in mind that people often use “wheezing” to describe any rattling noise during breathing, so stridor and other airway obstruction sounds might be misclassified as wheezing. Even when the term is applied correctly, we know that several disorders other than asthma may be the cause. COPD and vocal cord dysfunction will be discussed in detail, as these are most likely to be mistaken for asthma. Less common masqueraders include congestive heart failure, central airway obstruction, and bronchiectasis. There are often clinical clues that are very helpful in differentiating these syndromes. Table 2 lists conditions that less commonly mimic asthma and the keys to differentiating them. Table 3 lists diseases that are uncommonly mistaken for asthma.

**Chronic Obstructive Pulmonary Disease**

COPD can be difficult to differentiate from asthma because both present with dyspnea, wheezing, or cough. Both have associated airflow obstruction. COPD is typically categorized by fixed obstruction, and asthma by completely reversible obstruction. However, patients with COPD can have airway hyperresponsiveness and reversibility, and patients with chronic asthma can develop fixed defects. In addition, both diseases are common, especially in the elderly, so they may co-exist. Some may argue that distinction is not necessary, as the underlying physiology and goals of treatment are similar. Although they are indeed both characterized by chronic inflammation, the initial triggers and type of inflammatory response differ, so management and prognosis differ.

Historical clues may be useful. COPD is typically a disease of elderly patients who have a substantial smoking history, and COPD may be characterized by a history of chronic or recurrent infections. Asthma can develop at any age, but is more common in younger patients with a history of atopy. The pattern of symptoms and response to triggers, particularly exercise, are often distinct. COPD develops and progresses gradually, with little day-to-day variation in baseline symptoms. Asthma patients, however, often feel well at baseline and then become acutely symptomatic in response to a trigger or inhaled irritant.48

Symptoms during exercise are common in both. Exertional symptoms in patients with COPD often parallel oxygen demand and are caused by hypoxemia. They occur with a fairly predictable level of activity and resolve with rest. On the other hand, exercise-induced bronchospasm occurs after several minutes of vigorous exercise, peaks after 20–30 min, then gradually resolves. In addition, there is often a refractory period of several hours in which additional exercise will not induce symptoms.48,49

Symptom-defined questionnaires have been developed to capitalize on the potential of these historical clues to differentiate asthma from COPD. Their derivation has been somewhat limited by the lack of an accepted standard for the diagnosis of patients with chronic airflow obstruction and incomplete reversibility. Nonetheless, several factors appear to have significant predictability for the diagnosis of COPD, including greater age, greater exposure to tobacco smoke, worsening cough, worsening dyspnea, dyspnea-related disability or hospitalization, more daily sputum, a history of colds “going to the chest,” and use of medication to help with dyspnea.50

Pulmonary function testing may also help distinguish asthma from COPD. Both are characterized by hyperinflation and airflow obstruction, with a variable degree of
reversibility. A post-bronchodilator FEV$_1$ increase of > 12% is a common criterion for reversibility, although an increase of 15% is thought to be more indicative. However, reversibility based on an increase in baseline FEV$_1$ has poor specificity for asthma, and its diagnostic utility has been questioned. Defining reversibility as an increase in percent-of-predicted FEV$_1$ is a better discriminator; a percent-of-predicted FEV$_1$ increase of 15% has a specificity of 1 for asthma. The diffusing capacity of the lung for carbon monoxide, corrected for alveolar volume, is typically normal or increased in asthma but decreased in COPD. Bronchoprovocation testing, especially methacholine challenge, has an excellent negative predictive value for asthma. Bronchial hyperreactivity is neither sensitive nor specific for asthma; it is seen in up to two thirds of patients with COPD, especially those with a baseline FEV$_1$ < 70% of predicted. Other inflammatory airway diseases, such as cystic fibrosis, and other forms of bronchiectasis can also have associated airway hyperresponsiveness. Therefore, methacholine challenge may be most helpful for discriminating mild-to-moderate asthma from mild COPD.

Table 2. Less Common Asthma Masqueraders

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Presentation</th>
<th>Key to Differentiating From Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>Dyspnea on exertion, paroxysmal nocturnal dyspnea, occasionally wheezing, bronchial hyperreactivity Cardiac risk factors</td>
<td>Examination findings: rales, edema, gallop rhythm Chest radiograph Electrocardiogram Echocardiogram</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Dyspnea, occasionally wheezing Pulmonary embolus risk factors: oral contraceptive use, history of deep venous thrombosis, pregnancy, hypercoagulable state, immobility</td>
<td>Unilateral rales, leg edema, cord Ventilation-perfusion scan Spiral computed tomography</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Dyspnea, cough, gastrointestinal complaints Airflow obstruction Infertility Poor growth</td>
<td>Sweat chloride test Deoxyribonucleic acid analysis</td>
</tr>
<tr>
<td>Bronchiolitis obliterans</td>
<td>Cough, dyspnea Irreversible airflow obstruction</td>
<td>Bronchoscopy with bronchoalveolar lavage Transbronchial biopsy</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Cough, dyspnea unresponsive to bronchodilator or corticosteroid Recurrent pneumonia</td>
<td>High-resolution computed tomography</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis</td>
<td>Dyspnea after chronic exposure to organic antigen (eg, moldy hay, birds) Restriction on spirometry</td>
<td>Resolution of symptoms after removal from exposure Precipitating antibodies</td>
</tr>
<tr>
<td>Aspiration gastroesophageal reflux disease</td>
<td>Recurrent pneumonia Pulmonary fibrosis</td>
<td>Overnight esophageal pH probe Barium swallow High-resolution chest computed tomography</td>
</tr>
<tr>
<td>Central airway obstruction</td>
<td>Dyspnea, expiratory wheezing Symptoms not episodic No diurnal variation</td>
<td>Symptoms improve with inhalation of helium-oxygen mixture Bronchoscopy</td>
</tr>
<tr>
<td>Extrathoracic obstruction</td>
<td>Dyspnea, stridor, inspiratory wheezing Truncation of the inspiratory portion of the flow-volume loop</td>
<td>Laryngoscopy</td>
</tr>
</tbody>
</table>

(Adapted from Reference 48.)

Table 3. Uncommon Asthma Masqueraders

<table>
<thead>
<tr>
<th>Pulmonary infiltration with eosinophilia</th>
<th>Tropical cosinophilia</th>
<th>Löffler syndrome</th>
<th>Chronic eosinophilic pneumonia</th>
<th>Idiopathic hypereosinophilic syndrome</th>
<th>Allergic bronchopulmonary aspergillosis</th>
<th>Churg-Strauss syndrome</th>
<th>Metastatic carcinoid</th>
<th>Systemic mastocytosis</th>
<th>Lymphangioleiomyomatosis</th>
</tr>
</thead>
</table>

(Adapted from Reference 48.)
Methacholine acts primarily through direct stimulation of the airway smooth-muscle cells. Other provoking stimuli, such as adenosine, act indirectly through the release of inflammatory mediators or stimulation of neural pathways. In this setting, airway hyperresponsiveness is linked to the degree of airway inflammation and is measured through the number and degree of activation of inflammatory cells. Mast-cell-derived mediators have been implicated in the bronchial response to adenosine in both asthma and COPD. Standardized cutoff values for significant bronchial responsiveness to adenosine have not been established, but the degree of responsiveness directly relates to allergic airway inflammation and atopy. Although chronic exposure to tobacco smoke often invokes an inflammatory pattern similar to that seen in patients with asthma, adenosine-inhalation challenge testing may prove useful in separating nonsmoking COPD patients from asthma patients in the future.

Finally, radiographic imaging may provide clues that distinguish COPD from asthma. Lung hyperinflation is often present in both diseases, but bullous disease indicates COPD. HRCT is more sensitive in identifying macroscopic emphysematous changes and may be particularly useful in discriminating asthma from COPD in patients who have some degree of fixed airflow obstruction. In a series of 516 patients with chronic airflow obstruction, HRCT had a sensitivity of 81% for the presence of isolated COPD.

Both asthma and COPD are highly prevalent diseases in the elderly, which makes it difficult to distinguish them in this population. Not uncommonly, asthma is either misdiagnosed or underdiagnosed in this population. Perhaps this is due to the common perception that asthma is a disease of childhood and young adulthood or because the perception of dyspnea is blunted in some elderly patients. Dyspnea in elderly patients may also be incorrectly attributed to deconditioning or the general aging process. Asthma will present in a less typical pattern in older patients with an absence of allergic disease, absence of nocturnal or early-morning symptoms, and a less complete response to bronchodilator. Elderly patients are more likely to have a history of cigarette smoking, which confounds diagnosis. Most importantly, adults who have had a longstanding history of asthma, especially if it has been unrecognized and under-treated, are more likely to have a component of fixed airway obstruction. The tendency, therefore, is for elderly patients with asthma to be misdiagnosed with COPD. In one study, the main correlates to this were older age and disability. In another study of elderly asthma and COPD patients, a history of heavy cigarette smoking, a decreased diffusing capacity, the presence of more prominent lung hyperinflation, and chronic hypoxemia favored the diagnosis of COPD. Atopy and a greater response to bronchodilator favored the diagnosis of asthma, which reveals that the factors used to discriminate the 2 diseases are not different than those used in younger patients. Even in older patients who present with a similar degree of fixed airway obstruction and airway hyperresponsiveness there are distinct characteristics that help distinguish asthma from COPD. These patients have lower residual volume and higher diffusing capacity and PaO2. They have more eosinophils in peripheral blood, sputum, bronchoalveolar lavage fluid, and airway mucosa, and fewer neutrophils in sputum and bronchoalveolar lavage fluid. Asthma patients have significantly higher exhaled nitric oxide and lower emphysema score on HRCT. Although these historical clues and pulmonary function and radiographic features are generalizations and not necessarily applicable to all patients, the majority of patients with fixed airflow obstruction can often be appropriately diagnosed with asthma or emphysema, and not grouped under the general heading of COPD. Table 4 summarizes the defining characteristics. Figure 1 proposes a diagnostic algorithm.

Vocal Cord Dysfunction

Paradoxical vocal cord motion, also known as vocal cord dysfunction, is an increasingly recognized cause of dyspnea. This disorder is characterized by paroxysmal adduction of the vocal cords, resulting in airway restriction. Symptoms generally occur during exercise or times of stress, but may present without a clear precipitant. Patients commonly report shortness of breath, wheezing, and cough. Chest pain, choking sensation, and voice changes may also occur. Patients with vocal cord dysfunction are often misdiagnosed with asthma initially, which can lead to adverse effects from high-dose corticosteroids, hospitalizations, and psychological disorders. Extreme cases may result in intubation or tracheostomy. Lack of sputum production and minimal symptom improvement in response to bronchodilators are more likely to be reported in vocal cord dysfunction; however, historical features are inadequate to discriminate the 2 disorders.

The prevalence of vocal cord dysfunction in the general population is unknown. A prospective trial with 1,025 patients with dyspnea found an incidence of 2.8%. Morris et al found a prevalence of 12% in military patients evaluated for unexplained dyspnea. The prevalence in that study is probably higher than would be found in a cohort of patients with exertional dyspnea from the general population, for 2 reasons. First, the military bars entry to people with a history of asthma, which decreases the likelihood that unexplained dyspnea in the Morris study was due to asthma. Second, mandatory physical training probably results in asymptomatic patients seeking specialty evaluation at a higher rate than in the general population. Though early reports on vocal cord dysfunction described dramatic presentations of dyspnea and stridor, often re-
sulting in hospitalization, vocal cord dysfunction is increasingly recognized as an ambulatory disorder characterized by milder presentations of exertional dyspnea. Further study is required to determine the true prevalence of this probably underreported disorder.

Vocal cord dysfunction primarily affects young patients; the average age at diagnosis is 14.5 years in children and 33 years in adults. Women are more commonly affected; there is a 2-to-1 female predominance. Numerous factors are associated with vocal cord dysfunction, including psychiatric disease, history of sexual abuse, gastroesophageal reflux disease, and irritant exposure. Vocal cord dysfunction may co-exist with asthma; the reported rate range is 12–56% in studies of patients with vocal cord dysfunction.

Vocal cord dysfunction is diagnosed via direct visualization of the vocal cords, preferably while the patient is symptomatic. Complete adduction of the vocal cords during inspiration, with formation of a posterior glottic chink, is diagnostic. Paradoxical movement during expiration may also be observed. In asymptomatic patients, symptoms may be elicited by having the patient speak, pant, breathe deeply, or exercise. The spirometry flow-volume loop may provide ancillary information in the diagnosis of vocal cord dysfunction (Fig. 2). Although normal in the majority of asymptomatic patients, the flow-volume loops of symptomatic patients and approximately 25% of asymptomatic patients demonstrate blunting of the inspiratory limb of the flow-volume loop, consistent with variable extrathoracic obstruction.

The primary treatment for vocal cord dysfunction is speech therapy, the goal of which is teaching the patient to control the laryngeal area and maintain a patent airway while breathing. Limited data demonstrate the efficacy of this technique. Sullivan and colleagues found that 95% of female athletes treated with speech therapy were able to adequately control their symptoms. Other proposed therapies include psychotherapy, biofeedback, and inhaled anticholinergic medications. It is also important to control irritating factors such as gastroesophageal reflux and rhinitis with post-nasal drip.

A high index of suspicion is required to diagnose vocal cord dysfunction. Given the similarities in presenting symptoms, it is often difficult to distinguish vocal cord dysfunction from asthma. Clinicians should consider vocal cord dysfunction in any patient with a history of asthma and continued symptoms despite treatment. In addition, it is imperative to keep in mind that vocal cord dysfunction may coexist with asthma, so one should be careful about abruptly stopping medications in a poorly responsive asthmatic with a new diagnosis of vocal cord dysfunction.

**Summary**

Asthma is a heterogeneous disorder. By accentuating the unique characteristics of asthma phenotypes, further insight into the underlying pathobiologic mechanisms of

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**Table 4. Comparison of Asthma, Chronic Obstructive Pulmonary Disease, and Vocal Cord Dysfunction**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asthma</th>
<th>COPD</th>
<th>Vocal Cord Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Any age</td>
<td>Elderly smokers</td>
<td>Adolescents and young adults</td>
</tr>
<tr>
<td>Classic symptoms</td>
<td>Wheezing, dyspnea, cough, which worsen at night</td>
<td>Dyspnea on exertion</td>
<td>Dyspnea, chest tightness, and stridor</td>
</tr>
<tr>
<td>Relationship of symptoms to the respiratory cycle</td>
<td>Exhalation &gt; inhalation</td>
<td>Exhalation &gt; inhalation</td>
<td>Inhalation &gt; exhalation</td>
</tr>
<tr>
<td>Localization of symptoms</td>
<td>Deep in chest</td>
<td>Deep in chest</td>
<td>Upper chest, throat</td>
</tr>
<tr>
<td>Physical examination findings during symptoms</td>
<td>Expiratory wheezing (posterior chest)</td>
<td>Expiratory wheezing (posterior chest)</td>
<td>Inspiratory wheezing or stridor, upper chest</td>
</tr>
<tr>
<td>Chest radiograph findings</td>
<td>Hyperinflation</td>
<td>Hyperinflation and hyperlucency</td>
<td>Normal</td>
</tr>
<tr>
<td>Pulmonary function test results</td>
<td>Increased lung volumes, reversible airflow obstruction, and normal or increased $D_{LCO}$</td>
<td>Increased lung volumes, irreversible airflow obstruction, and decreased $D_{LCO}$</td>
<td>Normal lung volumes, extrathoracic airflow obstruction, and normal $D_{LCO}$</td>
</tr>
<tr>
<td>Response to corticosteroids</td>
<td>Good</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Response to bronchodilators</td>
<td>Good</td>
<td>Modest</td>
<td>Poor</td>
</tr>
</tbody>
</table>

*Substantial overlap in clinical presentation is possible. This is a guide to the most common presentations of isolated disease.

COPD = chronic obstructive pulmonary disease

$D_{LCO}$ = diffusing capacity of the lung for carbon monoxide

(Adapted from Reference 48.)
this complex disease will be gained and will lead to improved therapies. Given the varied phenotypic presentations of asthma, other diseases are commonly misdiagnosed as asthma. Clinicians must maintain a high index of suspicion for diseases that mimic asthma, particularly when the patient presents atypically or fails to respond to therapy.

ACKNOWLEDGMENTS

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REFERENCES

Discussion

Rubin:* In the army you see a lot of vocal cord dysfunction. We’ve got another issue in the very young children: it’s been my observation that we see an overdiagnosis of asthma, particularly in children under the age of 4. Now it may be that they want to do something, and they open up their cabinet; they see bronchodilators, they see inhaled corticosteroids in their sample cabinet, and if you’ve got a hammer, everything looks like a nail. So children who have colds, upper airway noises, congestion, “ruttles” is what Mark Everard has called it,1 children with frequent cough or who get lots of viruses are often put on these medications. Those who have a brilliant response may well have asthma and we never see them in a referral clinic. Those who get referred to us, more often than not, do not. So rather than being masqueraders, perhaps misdiagnosis or overdiagnosis. September-exercise-induced asthma is similar, where children have been couch potatoes over summer break, they get back to school, they start exercising and they’re not up to the standard that they were in the springtime before they took the summer break.

The other comment relates to anti-neutrophil therapy. You alluded to the use of inhibitors of TNF [tumor necrosis factor] alpha, and there’ve been some small studies,2 but, more to the point, there are quite a few studies of low-dose macrolide antibiotics3,4 that showed that the 14- and 15-member macrolides, in low dose, will modulate the immune system, probably through ERK 1/2 [extracellular signal-regulated kinase], and will have a specific effect on neutrophils. They’re the standard of care for cystic fibrosis now and for diffuse panbronchiolitis, but they’ve also been shown to be extremely effective in patients who have steroid-resistant asthma. It may be that those who are steroid-resistant are a marker for those who are primarily neutrophilic.

I know that Richard Martin in Denver has suggested that this may be due to chronic infection by mycoplasma and chlamydia,5 but most have interpreted these data not to be chronic infection but that there is an infection leading to inflammation due to these intercellular organisms, recurrent inflammation, something that is provoking a neutrophilic response. Neutrophil life may be prolonged by

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*Bruce K Rubin MD MEngr MBA FAARC, Department of Pediatrics, Wake Forest University School of Medicine, Winston Salem, North Carolina.
corticosteroids, and by giving something that will lead to neutrophil death, you can solve it. So there are some very good data that suggest that anti-neutrophil therapy may be effective, particularly in those patients who have steroid-resistant asthma.

**Donohue:** I’m intrigued by the studies of females in their 50s who have non-eosinophilic asthma. You said that they were smokers in the past, but we have a lot of trouble diagnosing COPD in women in their 50s. Ken Chapman did a study of gender bias,1 which was replicated by Marc Miravitlles in Spain,2 in which 192 doctors considered case scenarios. If the patient was a 52-year-old female with a smoking history, but she stopped smoking, her FEV1 was 60% of predicted, and her post-bronchodilator FEV1 increased to 70%, only 41% of the physicians said it was COPD, but that patient was male 69% said it was COPD. So there’s a barrier to diagnosing COPD in that age group, and now it’s confounded by this group. How big is the non-eosinophilic asthma group?


**Moores:** The series I saw said anywhere up to 30% overall. I don’t know that I have the data to break that down into the over-40 or over-45 age group, but in general it can be up to 30%, or higher if they’ve seen corticosteroids for any reason. Perhaps we change the natural history or perhaps initially there was something else going on and they responded to that component—sort of a mixed granulocytic and the eosinophils are now gone and you are left with a neutrophil-predominant inflammation. So it can be higher in that group.

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**MacIntyre:** Like you, I tend to be more in the ICU [intensive care unit] and the definition conundrum reminds me of ARDS [acute respiratory distress syndrome], where it’s a syndrome rather than a specific diagnosis. But at least in ARDS we have a consensus definition that people can use to communicate. Is there a consensus among asthma experts on the definition of asthma? What should we be calling it? . . . There is a deafening silence around the room. It seems to me that neutrophil asthma with some chronic airflow obstruction sounds like COPD with hyperreactive airways, or maybe it’s asthma with some chronic bronchitis.

**Martinez:** If you define love, I’ll define asthma.

**Moores:** It seemed so simple when I was a fellow, but it’s really not that simple. I don’t think that the Venn diagram of emphysema, chronic bronchitis, and asthma that I showed is the correct representation really, and putting them on a continuum or a line wouldn’t quite make it fit either. But, as you said, that line sort of matches the question of whether it’s asthma with a degree of COPD (or chronic bronchitis) or is it chronic bronchitis with airway reversibility? Or does it matter? Maybe what we really need to understand is reversing what’s there, and then what’s the underlying inflammatory process, and targeting that inflammatory process rather than worrying about whether it’s asthma with COPD or COPD with asthma.

**Pierson:** Is sudden asphyxic asthma a distinct clinical entity? I’m referring to the situation where the medics get called because the person’s in extremis and gets intubated, but by the time they’re in the emergency room or the ICU, it’s all better.

**Moores:** I wouldn’t say that doesn’t exist, but when they get better that quickly I suspect vocal cord dysfunction. That’s a classic description and pre-

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*David J Pierson MD, Division of Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle, Washington.
sentation of someone with acute paradoxical vocal cord motion, especially if it’s on both inspiration and expiration. Obviously all you have to do is bypass the vocal cords and the problem’s gone. If you intubate them and they’re suddenly fine and don’t have any evidence of airways resistance or persistent air trapping or airflow obstruction, it’s probably vocal cord dysfunction.

**MacIntyre:** Has anybody ever died of vocal cord dysfunction? Or do you get so hypoxic or hypercarbic and pass out that the stimulus to vocal cord dysfunction is gone and it reverts itself?

**Moores:** You shouldn’t be able to die from vocal cord dysfunction, unless whatever’s causing the spasm persists because it’s not psychological or it’s not something that can be controlled. People with vocal cord dysfunction often also have other somatic or maybe conversion disorders. There’s a disproportionate number of them in the military and in health care. They tend to have complications, they get themselves in trouble, they like being intubated, they like having central lines, and then they have other nosocomial problems as well.

**Donohue:** The people who have died of sudden asphyxic asthma are of historical interest. We rarely see it any more, but they are reputed to have very few eosinophils at autopsy: more neutrophilic cells are found. Another thing I’ve noticed in managing these patients is that a lot of them are really hard to intubate, because they seem to have upper-airway obstruction. I didn’t think of it as vocal cord dysfunction, but more as laryngospasm in that group. They’re really hard to intubate.

**Moores:** It could be laryngospasm related to the asthma. It could be laryngospasm alone. I think vocal cord dysfunction is an umbrella term, and some of them are paradoxical vocal cord motion that can be controlled with speech therapy, but others are true reactions to something else in the environment, which speech therapy won’t affect at all.

**Stoloff:** Part of the problem with vocal cord dysfunction is that often the patient has received multiple courses or continuous corticosteroids, and they’ve been called steroid-resistant or steroid-sensitive before someone recognizes or figures out that it’s vocal cord dysfunction. So the complication is much more the duration and amount of medication, and other ancillary emergency room visits or hospitalizations for supposed exacerbations of asthma that were never really asthma, or were not well differentiated; that is far more the issue in that population.

**Moores:** True. However, when you identify such a patient, don’t abruptly stop the asthma medications, because asthma often coexists with vocal cord dysfunction, so gradually taper the medications down. A lot of these patients come off the medications completely because it never was asthma, but in some of them there was a component of asthma, but it’s a lot less resistant than it seemed, so you can get away with a much lower dose of medication.

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*Stuart W Stoloff MD, Department of Family and Community Medicine, University of Nevada, Reno, Nevada, representing Monaghan/Trudell Medical.*