

Asthma diagnosis and treatment: Filling in the information gaps

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Current approaches to the diagnosis and management of asthma are based on guideline recommendations, which have provided a framework for the efforts. Asthma, however, is emerging as a heterogeneous disease, and these features need to be considered in both the diagnosis and management of this disease in individual patients. These diverse or phenotypic features add complexity to the diagnosis of asthma, as well as attempts to achieve control with treatment. Although the diagnosis of asthma is often based on clinical information, it is important to pursue objective criteria as well, including an evaluation for reversibility of airflow obstruction and bronchial hyperresponsiveness, an area with new diagnostic approaches. Furthermore, there exist a number of treatment gaps (ie, exacerbations, step-down care, use of antibiotics, and severe disease) in which new direction is needed to improve care. A major morbidity in asthmatic patients occurs with exacerbations and in patients with severe disease. Novel approaches to treatment for these conditions will be an important advance to reduce the morbidity associated with asthma. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

Key words: *Asthma, asthma diagnosis, asthma management, asthma heterogeneity*

In 1991, the National Institutes of Health released the “Guidelines for the diagnosis and management of asthma.”¹ The US guidelines have undergone revisions, and the 2007 report² continues to provide recommendations on the diagnosis and treatment of asthma, which represent ongoing efforts to advance the effectiveness of asthma care. These recommendations reflect a consensus of available data and expert opinion and continue to undergo a continuous “sifting and winnowing” to provide the best information to optimize asthma care.

Similar asthma guidelines have appeared at international levels and in individual countries and, in many cases, are components used to plan and implement asthma care by the health care

Abbreviations used

BHR: Bronchial hyperresponsiveness
EPR: Expert Panel Report
FENO: Fraction of exhaled nitric oxide
FVC: Forced vital capacity
ICATA: Inner-City Anti-IgE Therapy for Asthma
ICS: Inhaled corticosteroid
LABA: Long-acting β -agonist
SARP: Severe Asthma Research Program

industry, health care practices, and patient education, as well as treatment. Although the guidelines have been incorporated into most aspects of asthma care, their story is continually undergoing revision based on new information about asthma in general and experience from appropriate well-designed clinical trials. Despite all efforts to provide a comprehensive and complete guideline for asthma care, gaps remain in our current knowledge on approaches to the diagnosis and treatment for all levels of asthma severity and patients of all ages.³

From a personal perspective and from the literature, key gaps exist in the treatment of asthma that will serve as research targets in the future. In approaching my topic, “filling the information gaps,” I will use the guidelines as a source of direction on the diagnosis and management of asthma and, based on their recommendations, point out selective gaps where new information and guidance could lead to a more effective way to diagnose and treat this disease. My comments will focus primarily on adults (ie, ≥ 12 years of age), not because other age brackets are less important but because my experience comes primarily from an adult perspective.

ASTHMA HETEROGENEITY

A major advance to fill the gaps in the diagnosis and selection of treatment for asthma in individual patients has been a recognition and description of asthma heterogeneity.⁴⁻⁷ Clinically, the recognition that asthma is a heterogeneous disease has been apparent for decades. Guidelines have also noted this aspect of asthma by defining multiple levels of severity and dividing patient groups into categories of intermittent and persistent, with the latter being further subdivided into mild, moderate, and severe.^{1,2} Although these classifications were arbitrary when originally proposed, they suggest clinical portraits of subpopulations that are based on reasonable and relevant clinic parameters: symptoms, lung function, and need for rescue medication. Another component and key aspect to the categorization of asthma phenotypes has been the incorporation of the dose of medication or medications needed to achieve disease control.⁴ With a greater formalization of clinical criteria to classify asthma or characterize phenotypes,

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CLUSTER ANALYSIS: 5 CLUSTERS

	Cluster 1 n=110	Cluster 2 n=321	Cluster 3 n=59	Cluster 4 n=120	Cluster 5 n=116	P-value
Corticosteroid Use (%)						<0.0001
None	45%	31%	14%	15%	5%	
Low-moderate dose ICS	38%	40%	37%	18%	16%	
High dose ICS*	10%	28%	49%	63%	78%	
Oral or Systemic CS**	11%	10%	17%	39%	47%	
Total Controllers(%)†						<0.0001
None	41%	26%	10%	12%	4%	
≤ 2	41%	46%	35%	33%	28%	
≥ 3	19%	29%	54%	56%	67%	
Health Care Utilization Pst Yr †						<0.0001
None	67%	61%	41%	38%	32%	
≥ 1 Urgent Visit and/or ED	20%	25%	34%	39%	42%	
≥ 3 Oral CS burst/yr	11%	19%	36%	46%	42%	
Hospitalization	7%	9%	15%	23%	28%	

FIG 1. Demographics and clinical characteristics of the SARP subjects evaluated in the cluster analysis.

*High-dose ICS dose equivalent to 1000 fluticasone propionate daily or greater. **Chronic oral corticosteroids (CS) of 20 mg/d or greater or other systemic steroids in the past 3 months. †Controllers include leukotriene receptor antagonists, ICSs, LABAs, theophyllines, oral corticosteroids, or omalizumab. *P* values are from χ^2 analysis of ranked ordinal composite variables. Adapted from data reported in Moore et al.⁸

significant advances are ongoing to recognize and incorporate these features into the diagnosis and treatment of asthma.

Using subjects enrolled in the National Institutes of Health–supported Severe Asthma Research Program (SARP), Moore et al⁸ performed a cluster analysis on 726 adult asthmatic patients who represented multiple levels of disease severity. The cluster modeling method was used to identify unique groups (ie, clusters) of asthmatic patients and was based on 34 core variables. Although limitations exist with this approach, it is an instructive exercise to illustrate asthma heterogeneity and how the recognition of individual patient profiles can be of potential benefit to the diagnosis and eventual management of asthma (Fig 1).⁸

As expected, patients with more severe disease have a greater level of symptoms, lower lung function, more frequent need and use of health care, and larger amounts and doses of medication to maintain disease control (clusters 3, 4, and 5).⁸ From these analyses, it became possible to link the influence or association of disease onset, atopic status, body mass index, and pulmonary physiology, including improvement after attempts with maximal bronchodilation (≤ 8 puffs of albuterol), to patient patterns of asthma. Because pulmonary function was a major feature that led to patient placement in individual clusters, the SARP framework to define heterogeneity should be viewed as an initial step in the use of cluster analysis as a prospective manner to improve asthma control by developing personalized or stratified management programs that are linked to specific disease features and also to identify patients who are potentially at greater risk for adverse outcomes.

DIAGNOSIS OF ASTHMA

The first step to effective management of asthma is a correct diagnosis. The guidelines identify “key points” for the diagnosis of asthma (Table I); these include episodic symptoms and airflow obstruction, which is at least partially reversible.² In most cases the diagnosis of asthma is straightforward and accurate. The diagnosis of asthma is, however, most often based largely on subjective

TABLE I. Key points: diagnosis of asthma

- To establish a diagnosis of asthma, the clinician should determine that (EPR-2, 1992) — - episodic symptoms of airflow obstruction or airway hyperresponsiveness are present - airflow obstruction is at least partially reversible - alternative diagnoses are excluded. - Recommended methods to establish the diagnosis are (EPR-2, 1997) — - detailed medical history - physical examination focusing on the upper respiratory tract, chest, and skin - spirometry to demonstrate obstruction and assess reversibility, including in children ≥ 5 years of age. Reversibility is determined either by an increase in FEV₁ of $\geq 12\%$ from baseline or by an increase of $\geq 10\%$ of predicted FEV₁ after inhalation of a short-acting bronchodilator - additional studies as necessary to exclude alternate diagnoses.

features, such as clinical symptoms. However, objective criteria are needed to incorporate key features of airway pathophysiology: hyperresponsiveness and reversibility of airflow obstruction. These measures, however, are not readily performed in office settings or documented at the time of an initial evaluation and initiation of treatment. Therefore, the diagnosis of asthma is very often based on a clinical history and a patient’s response to a medication, such as a bronchodilator or a therapeutic trial with a long-term controller, which may not be accurate in all patients. Asthma is a heterogeneous disease, and this heterogeneity might also complicate the diagnosis of asthma in some patients, particularly at the extremes of mild and severe disease.

REVERSIBILITY OF AIRFLOW OBSTRUCTION IN ASTHMATIC PATIENTS

Guidelines recommend that spirometric measurements (FEV₁, forced vital capacity [FVC], and FEV₁/FVC ratio) be obtained

before and after the administration of a short-acting bronchodilator to demonstrate reversible airflow obstruction.² There is general agreement that reversibility in asthma is demonstrated by a minimum of a 12% improvement in FEV₁ (over baseline values) and at least a 200-mL differential.⁹ Despite the objectivity and quantitation found with pulmonary function measurements and the observation that reversibility is part of asthma, the guidelines go on to state the following¹: “Although asthma is typically associated with an obstructive impairment that is reversible, neither this finding nor any other single test or measure is adequate to diagnose asthma.”

To evaluate the effectiveness of performing pulmonary function measurements in a primary care setting to assist in the diagnosis of obstructive lung disease, Schneider et al¹⁰ obtained spirometric results as part of the workup in 219 adult patients who were being seen with complaints compatible with obstructive lung disease (ie, asthma or chronic obstructive pulmonary disease). All patients being evaluated for obstructive lung disease underwent spirometry to evaluate the sensitivity and specificity of spirometry with this diagnostic approach. Their findings are relevant to the general applicability, predictability, and specificity of spirometry to confirm the diagnosis of asthma. Many (41.1%) of the patients were eventually given a diagnosis of asthma. The sensitivity for diagnosing airflow obstruction in asthmatic patients in this population was 29%, but the specificity was 90%, with a positive predictive value of 77% and a negative predictive value of 53%. The authors speculated on reasons for the low level of sensitivity of spirometry to identify asthma and indicated that many patients had mild-to-moderate disease at the time of evaluation; because lung function was normal, reversibility was unlikely to occur under these conditions. Their observations identify the importance of realizing that pulmonary physiology can be entirely normal in many patients who indeed have asthma, and although this is particularly relevant to childhood asthma, it also occurs in adults.¹¹ Therefore the addition of provocation testing might be necessary to assist in the diagnosis of asthma.¹⁰

The high degree of variability of pulmonary function in asthmatic patients is well illustrated by reviewing the SARP cluster data.⁸ Subjects in cluster 1, for example, had a mean baseline FEV₁ of 102% of predicted value and an FVC of 112% of predicted value. Given these normal spirometric values, it was not surprising that the improvement in FEV₁, even followed with 8 puffs of albuterol (90 µg per puff), did not reach 12% in many patients, despite the existence of asthma. However, the FEV₁/FVC ratio was less than 80% in cluster 1, indicating that airflow obstruction exists even in patients with mild asthma and suggesting that the use of spirometry should be expanded beyond FEV₁ alone to recognize the presence of obstructive airway disease.

In contrast, patients in cluster 5 had a very different pattern of pulmonary function, with a mean FEV₁ of 43% of predicted value, which improved to 58% of predicted value after bronchodilation. The studies by Schneider et al¹⁰ and Moore et al,⁸ with a cluster analysis, illustrate the wide heterogeneity that exists in asthmatic patients in terms of airflow obstruction and demonstrate that reversibility assists in the diagnosis of asthma, but may not be possible in a significant number of individuals.

BRONCHIAL HYPERRESPONSIVENESS

Bronchial hyperresponsiveness (BHR) is another characteristic feature of asthma.¹² What gaps currently exist with provocation

TABLE II. Detection of AHR by direct and indirect activators of airway contraction

Indirect (Variable)	Direct (Persistent)
Hypertonic Aerosols (Hypertonic Saline, Mannitol)	• Methacholine
• Adenosine Monophosphate (AMP) (Mediator Release)	• Histamine
	
Airway Smooth Muscle Contraction	

testing to diagnose asthma? As noted in the Expert Panel Report (EPR) 3, “a positive methacholine bronchoprovocation test is diagnostic for the presence of airway hyperresponsiveness,” which, the report goes on to state, “can be present in other conditions as well (allergic rhinitis, cystic fibrosis, post-viral syndromes, and normals).² Thus a test that is positive for hyperresponsiveness can be consistent with other diseases, whereas a negative test may be of greater value as it may serve to rule out asthma.”

The 2 major classes of stimuli of BHR include direct and indirect activators of airway smooth muscle contraction (Table II).¹³ Direct agonists include methacholine and histamine, which act directly on airway smooth muscle to cause bronchial constriction. In asthmatic patients the PC₂₀ value is small (<8–16 mg/mL) and the overall contractile response is often more intense, particularly in severe disease.^{12,13} It has been proposed that methacholine hyperresponsiveness in asthmatic patients reflects structural changes in the airway that result in a heightened contractile response. Although the threshold PC₂₀ response to methacholine that reflects BHR in asthma is 8 to 16 mg/mL,¹² BHR to methacholine occurs over a wide range of concentrations and can be influenced by treatment¹⁴ or airway remodeling.^{15,16}

Indirect stimuli (ie, inhaled mannitol, which is now approved by the US Food and Drug Administration [FDA] as Aridol [Pharmaxis, Frenchs Forest, Australia]) cause airflow obstruction secondary to mast cell activation. In contrast to methacholine, the changes in airway caliber to hypertonic solutions, such as mannitol, are believed to reflect airway inflammation.^{17,18} There exist obvious advantages and limitations to each approach, but their overall use can be an important assessment to aid in the diagnosis of asthma, particularly in the presence of normal lung function.¹³

The division of provocative stimuli into direct and indirect categories is artificial because the response to methacholine and histamine is also influenced by airway inflammation.

Clinical experience with mannitol is limited because its widespread availability is new. To provide guidance to the use of various provocative tests for BHR, Anderson et al¹⁷ compared mannitol and methacholine to predict exercise-induced bronchospasm and a subsequent clinical diagnosis of asthma. Three hundred seventy-five subjects were enrolled, but at the time of enrollment, the investigators were not aware whether the patient

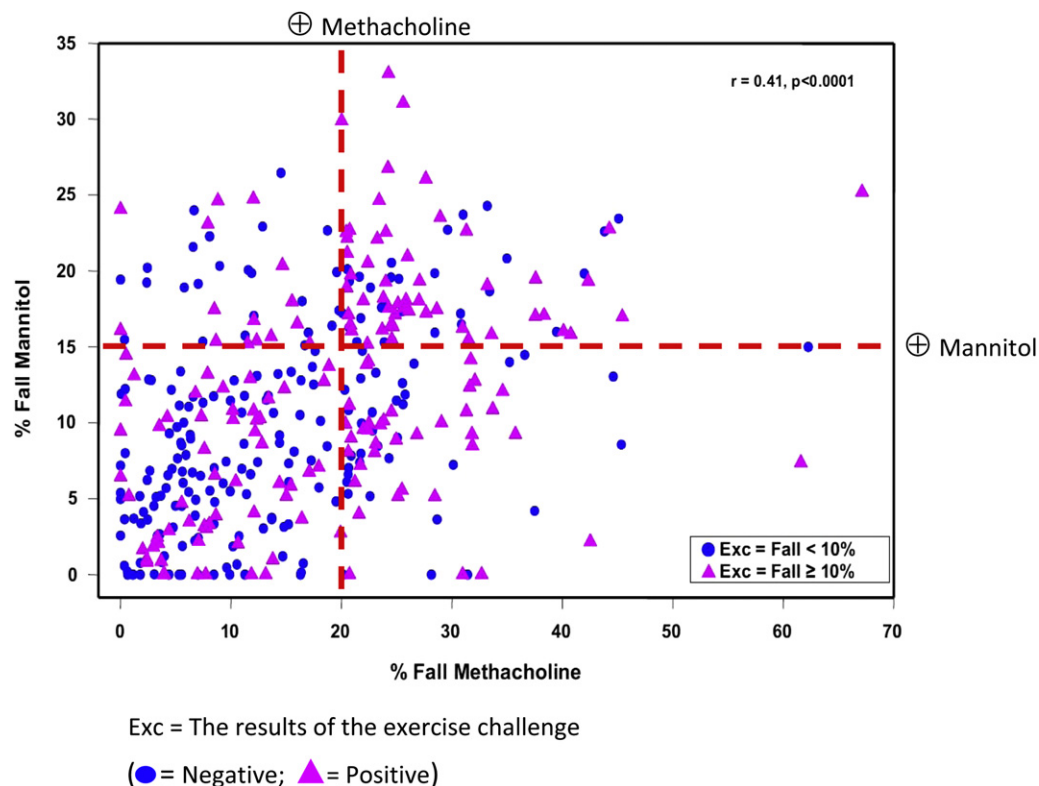


FIG 2. The maximum percentage decrease in FEV₁ for mannitol and methacholine in subjects in the per-protocol populations. Reproduced with permission from Anderson et al.¹⁷

had asthma. Each patient underwent 2 standard exercise challenges along with a methacholine and mannitol provocative test. The recruited subjects were also evaluated by a physician for the presence of asthma, which was based on a history of a bronchodilator response, skin test results to detect allergen sensitization, and exercise test results.

The maximum decrease in FEV₁ to mannitol and methacholine was variable among the recruited subjects and between the 2 testing agents (Fig 2).¹⁷ Although there was a significant overlap between these 2 provocative testing approaches, there was also variability in the responses to mannitol and methacholine and exercise-induced bronchospasm amongst individual patients. This variability to provocative challenges suggests that patients might have a positive response to mannitol and not methacholine and *vice versa*, which possibly reflects the predominant contributing factor to the underlying BHR.

These experiences raise a number of questions. Should patients undergo provocation with both direct and indirect stimuli to gain greater insight into what airway features might drive their hyperresponsiveness (ie, inflammation or structural changes) or whether asthma exists? It is unlikely that this approach will be used frequently, but the availability of 2 different stimuli provides the clinician with options should 1 test result be negative, but a high level of clinical suspicion for asthma remains.

USE OF BIOMARKERS IN THE DIAGNOSIS OF ASTHMA

Airway inflammation is a characteristic feature of asthma and is believed to contribute to the underlying disease severity and

target of treatment.¹⁹ Fraction of exhaled nitric oxide (FENO) levels reflect airway inflammation and provide a biomarker for this process and a high probability that the use of inhaled corticosteroids (ICSs) will be effective treatment.²⁰

FENO measurement has a number of advantages: it is noninvasive, can be quantitated, and reflects the probable presence of airway inflammation. The use of FENO measurement in the clinical management of asthma is less clear.²¹ Smith et al²² and Shaw et al²³ evaluated the effectiveness of titrating the ICS dose in patients with asthma by monitoring levels of FENO versus a treatment adjustment based on symptoms. Smith et al²² found that FENO levels were a helpful guide to aid in safely and effectively achieving a lower ICS dose in a well-defined cohort of asthmatic patients. Shaw et al²³ also assessed the use of FENO levels as a guide to ICS treatment in an 8-month-long study in which the ICS dose was adjusted by either an assessment of FENO levels or symptoms. Although the frequency of exacerbations was less in the FENO-monitored treatment group, the differences were not striking (Fig 3).²³ Similar conclusions were drawn by Szefer et al²⁴ in a large inner-city cohort of patients that compared treatment adjustments with measures of FENO and guideline-based care versus guideline-based care alone. Finally, a Cochrane meta-analysis²¹ of 6 studies available for analysis reached the conclusion that the benefit of a FENO-based approach to guide treatment was modest at best.

There are situations, however, in which FENO measurement might provide benefit and identify subpopulations of asthmatic patients requiring greater attention in treatment. Dweik et al²⁵ compared FENO measurements in 175 patients with severe and 271 patients with nonsevere asthma who were enrolled in

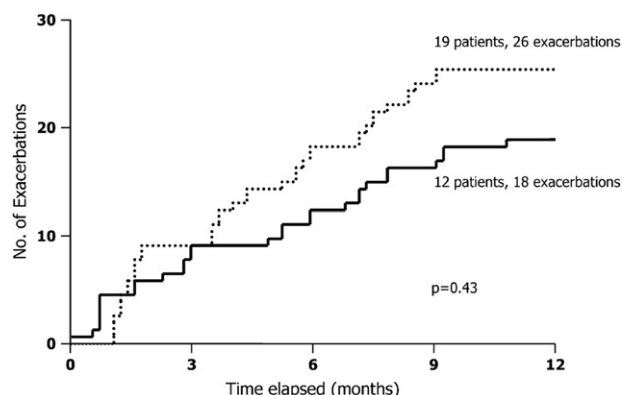


FIG 3. Cumulative exacerbations in the control (dotted line) and FENO (solid line) groups. Excerpted from Shaw et al.²³ Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society.

SARP. The proportion of patients with increased FENO levels in these 2 divisions of asthma severity was similar at about 60%. However, patients with asthma and an increased FENO level (>35 ppb) had some distinct characteristics: greater airway reactivity (bronchodilation and methacholine responsiveness), more of an allergic pattern of inflammation (sputum eosinophils), more evidence of atopy, and more pulmonary hyperinflation but a decreased awareness of their symptoms. In addition, patients with severe asthma, who had persistently high FENO levels, had the greatest degree of airflow obstruction and hyperinflation, as well as the most frequent use of emergency care. The ability to measure FENO levels has been an advance in asthma, but its implementation in the diagnosis and management of asthma is not fully established and remains a gap to be filled.

USE OF SPUTUM EOSINOPHIL MEASUREMENT IN THE DIAGNOSIS AND MANAGEMENT OF ASTHMA

The ability to induce, collect, and analyze sputum provides another noninvasive method to assess and monitor airway inflammation.^{26,27} The routine use of sputum analysis to determine eosinophil counts in the diagnosis and management of asthma is limited by the complexity of the procedure for collection and sample analysis. The application of sputum analysis in clinical trials has, however, provided insight into the role that eosinophils might play in asthma and under what conditions this biomarker might prove most helpful to direct treatment.

Sputum eosinophil counts increase with allergic inflammation, indicate a higher probability of a positive response to ICSs, and often correlate with pretreatment levels of disease severity.²⁸ Sputum eosinophil counts have also served as a biomarker to regulate asthma treatment, particularly as a reflection of the patient at risk for exacerbations.²⁹ A study by Green et al³⁰ found that treatment directed toward reducing sputum eosinophil counts versus a guideline-based approach alone led to a significant reduction in asthma exacerbations over a 12-month period. Subsequent studies with anti-IL-5^{31,32} have also shown that reducing sputum eosinophil counts significantly decreases but does not eliminate asthma exacerbations. These observations suggest that an eosinophil–airway epithelium interaction exists that either reflects an increase in the susceptibility of a particular patient for a respiratory tract virus to provoke an exacerbation or directly contributes as a risk

factor for exacerbations. Treatment directed toward a reduction in sputum eosinophil counts reduces exacerbations but not other airway parameters.

NEWER BIOMARKERS TO DEFINE ASTHMA HETEROGENEITY

Woodruff et al³³ conducted an innovative set of experiments to determine whether clinical heterogeneity in asthmatic patients is reflected in the heterogeneity of molecular mechanisms related to the presence of T_H2 inflammation. Bronchial epithelial cells were obtained from asthmatic patients and healthy control subjects, cultured with IL-13, and subsequently subjected to microarray analysis for patterns of gene expression to assess this possibility. Three genes had relatively greater expression in epithelial cells from asthmatic patients (ie, periostin; chloride channel regulator 1 (*CLCA1*), and serpin peptidase inhibitor, clade B, member 2 [*SERPINB2*]) when compared with activated epithelial cells from healthy subjects (Fig 4).³³ An analysis of lavage fluid from these same patients found greater levels of the T_H2 cytokines IL-5 and IL-13 in asthmatic patients with increased periostin expression, but there was considerable variability in the levels of these cytokines in individual subjects. The identified patients were treated for 2 weeks with ICSs to determine whether there were clinical relationships to treatment responsiveness in subjects with a T_H2-high profile (periostin expression and increases in lavage fluid IL-5 and IL-13 levels). A significant improvement in FEV₁ occurred in the T_H2-high but not the T_H2-low patients (Fig 5).³³ Although these data are preliminary, they do point to the intriguing possibility that an *a priori* expression of genetic markers identifies an asthma phenotype with a greater likelihood to respond to a particular treatment, in this case ICSs. The possible contribution of periostin as a predictive treatment biomarker has been extended in a study to evaluate lebrikizumab, an mAb directed agonist IL-13, in asthmatic patients whose disease was inadequately controlled by ICSs.³⁴ Patients who received anti-IL-13 had a significant improvement in FEV₁ over the placebo-treated group. Moreover, Corren et al³⁴ found that patients with higher levels of periostin were more likely to have a greater improvement in FEV₁ with anti-IL-13. Further research to identify whether other markers will serve to enhance the effectiveness of patient selection programmed to respond to specific treatments is needed.³⁵

GAPS IN ASTHMA TREATMENT

Stephen Holgate's article in the "Asthma: current status and future directions" series describes advances in asthma treatment and the patient stratifications for which current or new interventions might be of greatest benefit.³⁶ In addition to selecting the "right patient for the right medication," there are other significant gaps in this area.

Stepwise approach for managing asthma

For further details on the stepwise approach for managing asthma, see Fig 6.² As discussed in EPR-3, treatment recommendations for step 1 to 3 approaches are and have been derived from well-designed, randomized, placebo-controlled trials. Although discussion currently exists at step 3 as to whether a medium-dose ICS versus a low-dose ICS plus a long-acting β -agonist

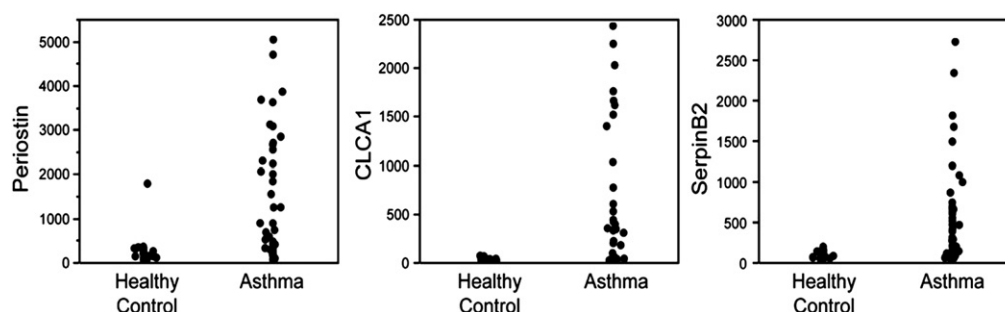


FIG 4. Relative expression of 3 genes induced by IL-13. Relative expression levels (normalized fluorescence units) of periostin (*POSTN*), chloride channel regulator 1 (*CLCA1*), and serpin peptidase inhibitor, clade B, member 2 (*SERPINB2*) in healthy control subjects ($n = 28$) and patients with asthma ($n = 42$). Reproduced from Woodruff et al.³³ Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society.

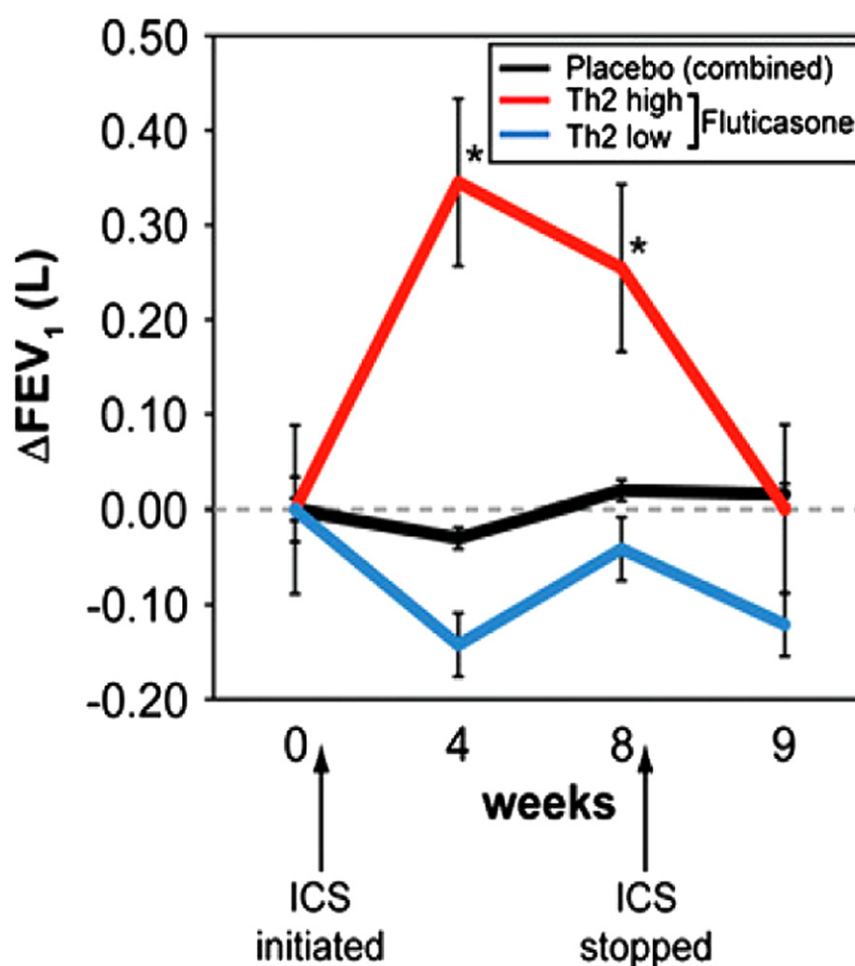


FIG 5. Responsiveness of patients with T_H2-high asthma to inhaled steroids. FEV₁ was measured at baseline (week 0), after 4 and 8 weeks of daily fluticasone (500 mg twice daily), and 1 week after the cessation of fluticasone (week 9). There was no significant change in FEV₁ in response to placebo at any time point in either group. Reproduced from Woodruff et al.³³ Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society.

(LABA) is best, these concerns center primarily on a perceived safety issue with LABAs rather than the well-documented evidence of greater effectiveness with combination therapy.^{37,38} However, there remains interpatient and inpatient variability

as to which treatment selection is best for an individual patient and the methods to determine this outcome.³⁹ Advancing asthma treatment to step 4 to 6 care, especially at the latter 2 increments, is less well defined.

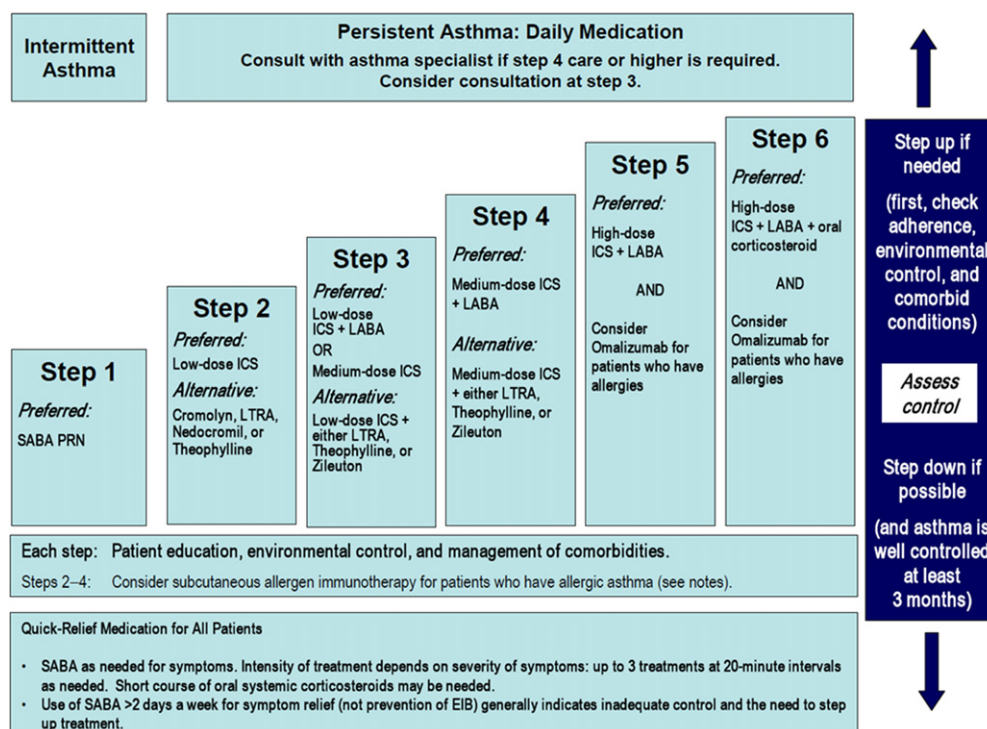


FIG 6. Stepwise approach for managing asthma in youths older than 12 years and adults. Excerpted from the National Asthma Education and Prevention Program's "Expert panel report 3: Guidelines for the diagnosis and management of asthma."² LTRA, Leukotriene receptor antagonist; SABA, short-acting β -agonist.

Thomas et al⁴⁰ have recently discussed the "Approaches to stepping-up and stepping-down care in asthma." The majority of their discussion centers appropriately on the extensive experience and evidence in decision making for step-up care and what factors should be considered in making these choices. Experience with step-down care is far less extensive.^{41–44} The need to be more fully informed about step-down care has become more important, especially in the United States because the FDA has recently proposed a step-down from LABA use in patients when their symptoms are well controlled with LABA-ICS combination therapy.^{37,38} Three separate studies have shown that stepping off of LABAs when asthma control appears stable, however, has resulted in a loss of asthma control.^{45–47}

Addressing when and what treatment to reduce during a step down is more complex. In the Gaining Optimal Asthma Control study, Bateman et al⁴⁸ reported that treatment escalation with either ICSs or ICSs plus LABAs led to greater levels of asthma control in many but not all enrolled subjects and was achieved by using a step up in therapy. Although the Gaining Optimal Asthma Control study was not designed to evaluate step-down care, many patients continued to show a gradual and continual improvement in asthma control throughout the study whether taking ICSs or ICSs-LABAs. Therefore a number of gaps exist in defining the approach to step-down care: the timing for such decisions, the specific treatment (eg, ICSs vs LABAs), and what end point to use to make this decision (eg, symptoms, lung function, or exacerbations).

Asthma exacerbations

Asthma exacerbations are recognized as an important clinical manifestation of asthma and an obvious target of treatment.

Although initial attention had focused on these events in patients with severe asthma, patients at all levels of disease severity are at risk for exacerbations.⁴⁹ Exacerbations of asthma vary in severity but, by current definition, represent a need for treatment with systemic corticosteroids.⁵⁰ As appropriately noted in the American Thoracic Society/European Respiratory Society report on asthma control and exacerbations, this aspect of asthma might be the most important outcome for patients because exacerbations pose the greatest risk to patients and families, cause stress on health care systems, and lead to the greatest cost, both directly and indirectly, on the health care system.⁵⁰ Many factors contribute to exacerbations, as will be discussed in a later contribution to this series by Dr Sebastian Johnston, but respiratory tract infections are the primary precipitant.⁴⁹ Prevention of asthma exacerbations is a central goal in all guideline documents, but the degree to which this can be achieved is variable both with current treatments and individual patients.

Because of the importance of asthma exacerbations to maintaining disease control, clinical trials are now designed to assess the efficacy of asthma treatments to prevent exacerbations rather than focusing solely on lung function or symptoms. Appropriate dosing with ICSs, ICS-LABA combinations, or leukotriene antagonists all reduce exacerbations, with combination treatment with ICSs and LABAs emerging as being most effective in the majority of patients.³⁹ Despite an overall improvement in decreasing asthma exacerbations, elimination of these events has yet to be completed.

Patients are provided with an action plan to combat the drift toward an exacerbation to reduce asthma morbidity during a loss of asthma control. Initial recommendations in action plans were to double the dose of ICS; this approach has not proved

effective.^{51,52} In contrast, quadrupled doses of ICSs might be of benefit.^{53,54} In addition, O'Byrne et al⁵⁵ evaluated the effect of increasing the daily frequency of a combination product, budesonide-formoterol, versus regular use of either an ICS or the combination product. Episodic increases in combination therapy as asthma control was being lost, presumably reflecting a pending exacerbation, were more effective than the other regimens. This preventative approach is now followed in many parts of the world and reduces, but does not fully eliminate, asthma exacerbations.

These studies suggest that the mechanisms underlying a loss of control during an asthma exacerbation, particularly with respiratory tract infections, are not fully regulated by corticosteroid treatment. Preventing exacerbations is a major unmet need.

As noted previously, sputum eosinophil counts indicate a risk for exacerbations or patients more vulnerable to an exacerbation.³⁰ To pursue that possibility, Halder et al³¹ identified 61 patients with severe asthma who, despite the use of high-dose ICSs and in some circumstances oral corticosteroids, had sputum eosinophilia and a history of frequent exacerbations. Twenty-nine of the identified subjects received mepolizumab (anti-IL-5) with their usual treatment over the next 12 months, and the others received a placebo. No changes in lung function were noted, but treatment with anti-IL-5 led to an approximate 50% reduction in exacerbations. Sputum eosinophil counts also decreased with anti-IL-5.

A study involving children living in US inner cities evaluated the addition of omalizumab to guideline-directed treatment: the Inner-City Anti-IgE Therapy for Asthma (ICATA) study.⁵⁶ In this clinical trial 419 subjects were enrolled; all had active asthma, IgE sensitization to a perennial allergen, and IgE levels within treatment dosages for omalizumab. A treatment algorithm was developed by using guideline recommendations, and individual patient treatment programs were continuously adjusted throughout the study based on the level of disease control. After an enrollment period to improve and stabilize asthma control, patients were given, in a randomized, placebo-control fashion, either omalizumab or placebo and then followed for the next 60 weeks. As noted in previous omalizumab trials in children and adults, anti-IgE recipients had fewer symptom days, less of a need for ICSs to maintain control, and a decrease in the frequency of exacerbations.⁵⁷⁻⁶⁰

Because this trial took place over a year, the effects of treatment on seasonal patterns of asthma, including exacerbations, could be evaluated, in particularly the effect of treatment on "September" exacerbations (Fig 7).⁶¹ Based on data from Canada⁶¹ over approximately 20 years, hospitalization rates for asthma in children were found to spike in September and coincide with the time when children return to school. The early fall is a time for an increase in respiratory tract infections, particularly rhinoviruses, and likely relates to the close proximity of children in school for enhanced virus transmission.⁴⁹ Furthermore, as noted by Johnston et al,⁶¹ September is also a time of significant allergen exposure, which might be a risk factor for exacerbations. In the ICATA study there was a virtual elimination of the "September epidemic" of asthma exacerbations in those patients who received omalizumab (Fig 8).⁵⁶ It is important to note that not all asthma exacerbations were prevented, but primarily those associated with seasonal flares, this was the first time a treatment demonstrated this effect. Because recovery of virus, predominantly rhinovirus, was unaffected by omalizumab treatment, the effectiveness of anti-IgE

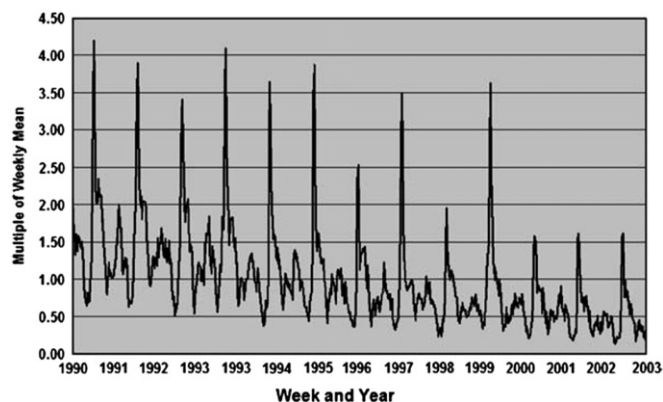


FIG 7. The cycle of asthma hospitalization of children aged 5 to 15 years from April 1990 to March 2003 as multiples of the weekly mean number of hospitalizations over the whole period. Excerpted with permission from Johnston et al.⁶¹

might be the result of reducing a patient's susceptibility for a cold to provoke asthma.

These findings raise a number of speculations regarding risk factors for exacerbations and new approaches to prevent these episodes. At least in the highly allergen-sensitized population studied in the ICATA study, IgE-dependent processes have emerged as a major predisposing factor for wheezing with a cold. When allergen exposure is high (ie, cockroach allergen in the case of ICATA patients), the IgE-sensitized patient might have an enhanced susceptibility to the asthma-provoking effects of a respiratory tract infection. Guideline-directed treatment, although effective in most aspects of asthma control, might not regulate the virus-associated events, which lead to an exacerbation. To gain more effective control of exacerbations might require identification of targets that are directly linked to exacerbations and can be regulated by specific interventions and also include an identification of the patients most at risk for these events because not all patients have exacerbations with a respiratory tract infection.

Antibiotics

The NAEPP's EPR-3 does not recommend routine antibiotic use for asthma treatment in the absence of a bacterial infection²; however, this recommendation is based largely on studies well over 30 years old.⁶² Recent surveys have found that the use of antibiotics for patients seen in emergency departments for asthma is frequent and approaches 20%.^{63,64} There has also been a shift in the types of antibiotics prescribed during acute asthma episodes and the age brackets in which this practice is most likely applied. There is now greater use of macrolides versus other antibiotics, with the increase in antibiotic use greatest in the infant to 9-year-old group.

The renewed interest in antibiotic use in asthma follows a number of observations, including a potential role for *Chlamydia* and *Mycoplasma* organisms in asthma in general and exacerbations in particular.^{65,66} In addition, Bisgaard et al⁶⁷ isolated airway bacteria during wheezing episodes in children, and the rate of this association was similar to that of viral isolation. Also, there is evidence that macrolides might have anti-inflammatory effects against virus-provoked responses, which

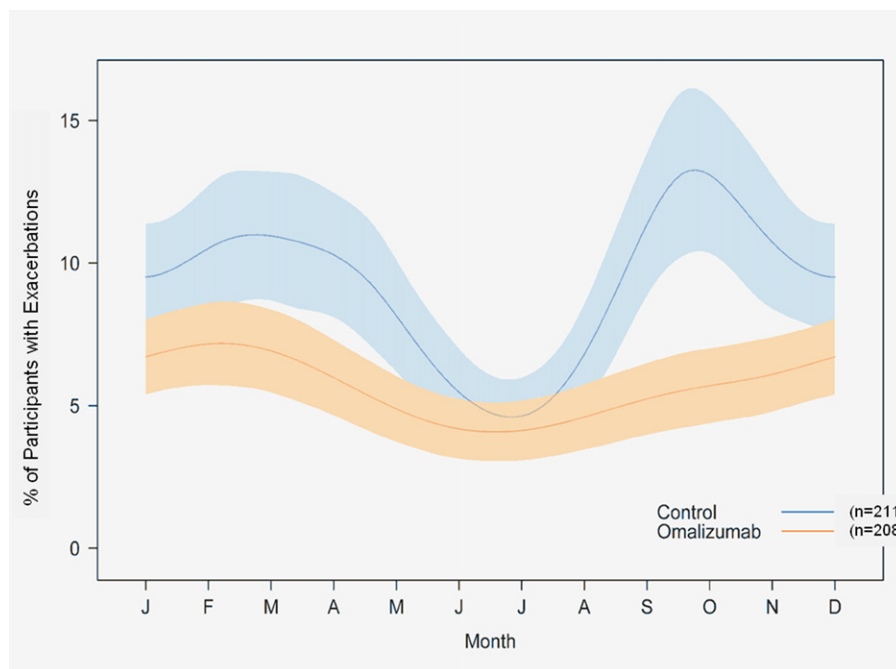


FIG 8. Seasonal variation in days with symptoms, frequency of exacerbations, and dose of inhaled glucocorticoids in patients treated with omalizumab (orange) versus placebo (blue). Reproduced with permission from Busse et al.⁵⁶

are independent of antimicrobial activity.⁶⁸⁻⁷⁰ Moreover, macrolides might have an effect on neutrophilic inflammation, which is the cellular characteristic of inflammation associated with an acute viral infection.⁷¹⁻⁷³ The relationship of bacterial infection to asthma and use of macrolide treatment, however, has been complicated by the report of Sutherland et al.⁷⁴ In this prospective trial investigators evaluated the effectiveness of treatment with clarithromycin for 16 weeks versus placebo in fluticasone-treated patients who had also undergone evaluation for the presence of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* by means of PCR in bronchial specimens. The number of PCR-positive subjects was small, thus limiting an assessment of the effectiveness of an antibiotic intervention in this subgroup. Overall, the addition of clarithromycin to ICSs did not further improve asthma control. Because the use of antibiotics is on the increase in asthmatic patients, this question is of considerable interest and potential importance.

Severe asthma

Patients with severe asthma have the greatest degree of morbidity and require the greatest amount of health care dollars.^{75,76} In contrast to patients with less severe asthma, disease control is often not achieved despite the use of multiple medications. The reasons for this compromise in response to conventional treatments are not fully identified but likely relate to a composite of mechanisms, including underlying inflammation, airway remodeling, and distinct genetic patterns.⁷⁷⁻⁷⁹

SARP investigators identified 5 distinct clusters in their cohort; patients who segregated to clusters 4 and 5 in particular had the most severe disease.⁸ More than 50% of patients in these clusters required 3 or more controller medications for asthma treatment. Despite this use of up to 3 controllers, more than 40% of patients

had 3 or more bursts of oral prednisone per year, and nearly one quarter required hospitalization in the preceding year. These data indicate a critical need for new avenues of treatment, which, at present, are limited for these high-risk groups.

Hanania et al⁸⁰ evaluated omalizumab in patients using combination treatment of high-dose fluticasone (1000 µg/d) and salmeterol (ie, guideline steps 5 and 6 care). Compared with patients who received placebo, omalizumab treatment led to a 25% reduction in asthma exacerbations. These data support EPR-3 recommendations to consider anti-IgE in steps 5 and 6 care. What is missing from studies evaluating omalizumab in asthma treatment is an identification of the patient profile most likely to experience benefit from this intervention.

Holgate³⁶ stressed that asthma is a complex disease and that a first step to successfully implementing new treatments is to identify the phenotypes or strata that express the target of interest and their relevance to underlying disease. With omalizumab, the underlying target is IgE-linked events, and for mepolizumab, it is the IL-5-dependent pathways with a persistence of eosinophils despite optimal treatment. Now there is evidence that an overexpression of the gene product periostin might be a treatment reflecting the predominance of the T_H2 pathway to the clinical disease. Moreover, in patients with virus-provoked asthma, evidence exists that deficiencies in interferon production to respiratory viruses might be a major risk factor for exacerbations with respiratory tract infections.^{49,81-83} Replacement of this deficiency in asthmatic subpopulations might provide considerable benefit that is not achieved with current interventions. A significant gap in fulfilling our goals to achieve optimal asthma control for all patients rests in the need to identify the mechanism, or mechanisms, that cause asthma in individual patients. Only when this information is available will the gaps in diagnosis and management disappear.

SUMMARY

Asthma remains a common respiratory tract disease for patients of all ages. However, asthma is now recognized to have many phenotypes. Although steps in the diagnosis of asthma do not usually present difficulty, the emerging recognition that asthma is heterogeneous and has distinct phenotypes will help to improve the limitations that currently exist. In addition, guideline-directed care provides a framework for an evidence-based approach to treatment that, in many patients, is highly effective and successful. A number of key gaps exist that prevent attempts to achieve and maintain asthma control, including exacerbations and the presence of severe disease. Advances in these 2 areas promise to fill these gaps, and with improvements should come a significant reduction in asthma morbidity, a goal of all involved in patient care.

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