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Clinical phenotypes of chronic obstructive pulmonary disease and asthma: Recent advances

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Asthma and chronic obstructive pulmonary disease (COPD) are prevalent obstructive lung diseases, both of which are characterized by airflow limitation. Although both represent distinct pathogenic entities, there can be significant clinical and physiologic overlap between the 2 disorders, creating potential management difficulties for clinicians. Although practice guidelines for both conditions outline diagnostic and management strategies, asthma and COPD are highly heterogeneous, and the symptoms of many patients remain poorly controlled despite adherence to current guidelines. Recent advances in phenotyping studies have elucidated heterogeneity in these airway diseases and might represent the best opportunity to enhance diagnosis, predict outcomes, and personalize treatments in patients with asthma and those with COPD. This review will focus on recent advances in describing phenotypic heterogeneity in asthma and COPD, including the evaluation of multiple clinical variables, molecular biomarkers, physiologic and radiologic data, and factors associated with disease progression and frequent exacerbations. (*J Allergy Clin Immunol* 2013;■■■:■■■-■■■.)

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Together, asthma and chronic obstructive pulmonary disease (COPD) comprise the 2 most prevalent chronic lung diseases worldwide.^{1,2} One of the essential challenges facing clinicians caring for patients with these 2 disorders is that although both share a spectrum of signs and symptoms and are characterized physiologically by expiratory airflow limitation, they represent distinct entities with apparently distinct pathogeneses. Thus, particularly in older patients, clinicians must carefully consider a number of variables in determining a correct diagnosis and appropriate treatment strategy. Clinical practice guidelines have

Abbreviations used

BMI:	Body mass index
BODE:	Body mass index, airflow obstruction, dyspnea, and exercise capacity
CAMP:	Childhood Asthma Management Program
COPD:	Chronic obstructive pulmonary disease
CT:	Computed tomography
ECLIPSE:	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
FVC:	Forced vital capacity
GOLD:	Global Initiative for Chronic Obstructive Lung Disease
HR:	Hazard ratio
ICS:	Inhaled corticosteroid
OR:	Odds ratio
SARP:	Severe Asthma Research Program
SGRQ:	St George's Respiratory Questionnaire

attempted to differentiate between the 2 diseases in clinically meaningful ways, typically incorporating some combination of epidemiologic and clinical characteristics to help differentiate the 2 disorders. However, there can be significant clinical and physiologic overlap between asthma and COPD, and therefore distinguishing between the 2 diseases and integrating clinical, physiologic, and inflammatory data to optimize outcomes remains a challenge.

One area of clinical investigation with the potential to have great clinical impact is the study of airways disease phenotypes. Phenotyping studies typically evaluate the interrelationship of multiple clinical, physiologic, inflammatory, and radiographic variables of disease (rather than focusing primarily on one physiologic variable, as is the case with current guidelines), and there has been a recent proliferation of data and scholarly reviews in the area of airways disease phenotyping.^{3,4} Herein, we focus on emerging data in this regard, with a particular focus on studies that have the potential to enhance efforts to diagnose, predict outcomes in, and refine treatments for patients with chronic airway diseases. These data will be applied to important disease characteristics of both asthma and COPD, including phenotypes related to underlying disease biology, radiologic manifestations, disease progression, and exacerbations.

GUIDELINE-BASED APPROACHES TO DIFFERENTIATING ASTHMA AND COPD

Guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) state that a clinical diagnosis of COPD

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should be considered in adult patients with dyspnea, chronic cough, sputum production, and a history of significant tobacco exposure. Typically, patients will present with cough, sputum production, or shortness of breath, and once such patients are identified, the diagnosis of COPD further necessitates the presence of a postbronchodilator FEV₁/forced vital capacity (FVC) ratio of less than 0.70 to demonstrate expiratory airflow limitation. The initial assessment of COPD is directed at determining disease severity by using airflow limitation, evaluating the effect of symptoms, and predicting disease course with regard to events such as exacerbations, hospital admissions, or death. Treatment is then linked to disease severity, with the goals of reducing symptoms, reducing exacerbation frequency and severity, and improving exercise tolerance and overall health status.²

Guidelines from the Global Initiative for Asthma indicate that asthma is a chronic airway inflammatory disorder with clinical manifestations that can be controlled with appropriate anti-inflammatory treatments. Patients typically present with symptoms such as episodic breathlessness, wheezing, chest tightness, and cough, and as in patients with COPD, evaluation of lung function is useful in assessing disease severity. In addition to measures of lung function, severity is based on assessment of daytime and nocturnal symptoms and frequency of bronchodilator use, and unlike COPD, asthma is described as being episodic in nature, both from the standpoint of symptoms and lung function impairment. As with COPD, treatment is linked to disease severity, with the ultimate goal being the achievement of clinical control of asthma, as reflected by the elimination of exacerbations, minimal symptoms and rescue β -agonist use, and maximal levels of activity and lung function.¹

Although practice guidelines are useful in applying general principles to large numbers of patients in primary care settings, specialty physicians are often expected to provide expertise in circumstances in which the guidelines do not apply or where there is question about the appropriate diagnosis, treatment, or both, a phenomenon that often arises because of the potential heterogeneity of the 2 disorders. Heterogeneity in asthmatic patients has long been recognized in a number of features, including degree of airflow limitation, bronchodilator responsiveness, frequency of exacerbations, and response to therapies, particularly inhaled corticosteroids (ICSs). Recently, phenotype-based approaches to asthma have moved to include features such as airway inflammatory cell types and various molecular pathways in concert with clinical characteristics. COPD also represents a heterogeneous disorder, with at least 2 clinical subgroups (chronic bronchitis and emphysema) having been recognized for decades.⁵ COPD can be further characterized by other factors, such as the degree, type, and distribution of emphysema, or nonspirometric physiologic parameters, such as diffusing capacity and hyperinflation. As with asthma, novel investigations to classify COPD phenotypes based on exacerbation frequency, radiologic parameters, and inflammatory biomarkers are currently underway.

CLINICAL PHENOTYPING IN PATIENTS WITH COPD AND PREDICTION OF MORTALITY

One approach to phenotyping in patients with COPD involves the use of clinical, physiologic, and radiologic data to elucidate factors that dictate disease heterogeneity and therefore might be relevant to diagnosis, prognosis, or both. The application of analytic approaches, such as cluster analysis, has advanced the

study of phenotypes, facilitating the identification of unique groups of related variables in an attempt to identify factors that might relate to both underlying disease biology and clinically relevant outcomes.⁶ Such approaches are typically hypothesis independent and use data obtained from large cohorts of well-characterized patients to identify relationships between clinical variables and outcomes.

In one example of such an approach, Burgel et al⁷ used principal component analysis to assess the relationship between 8 COPD-related variables in a cohort of 322 French patients: age, smoking history, FEV₁ percent predicted, body mass index (BMI), exacerbation frequency, shortness of breath (evaluated by using the modified Medical Research Council scale), overall health status (measured by using the St George's Respiratory Questionnaire [SGRQ]), and depressive symptoms (measured by using the hospital anxiety and depression scale). The study population was 77% male, with a median age of 65 years and a median FEV₁ of 48.9% of predicted value.⁷ Their analysis revealed separate, independent disease clusters (ie, phenotype groups). The first cluster consisted of comparatively young subjects (median age, 58 years) with severe airflow limitation, low BMI, increased symptoms, poor quality of life, poor lung function, and frequent exacerbations. A second phenotype was composed of older subjects (median age, 68 years) with mild airflow limitation and minimal symptoms but who exhibited a high prevalence of comorbidities, such as diabetes, coronary artery disease, and hypertension. The third and fourth clusters both had moderate-to-severe airflow limitation but differed on age, frequency of comorbidities, BMI, and dyspnea. The authors concluded that variables other than FEV₁ are important in classifying subsets of patients with COPD and subsequently went on to validate the utility of this classification approach against mortality over a 3-year follow-up study.⁸ The longitudinal follow-up study identified a relationship between phenotype and mortality, showing that subjects classified in cluster 1 (ie, those who were younger with severe airflow limitation, frequent exacerbations, and low BMI) had the greatest mortality, with those in cluster 2 having the lowest mortality. Although additional investigation is warranted to identify the mechanisms of increased mortality in these various clusters, the clusters can aid in the identification of novel predictors of mortality in patients with COPD.

Although hypothesis-free methods, such as those described above, have the potential advantage of identifying novel combinations of clinical variables, further study will be necessary to determine whether they yield results that perform any better than prognostic tools based on pre-existing clinical knowledge. One example of a useful prognostic algorithm based on pre-existing knowledge (and therefore, to some extent, hypothesis driven) is the BODE index, as reported by Celli et al,⁹ in which BMI (B), airflow obstruction (O), dyspnea (D), and exercise capacity (E) were combined in a multidimensional index. This index was found to be a better predictor of both respiratory mortality and all-cause mortality than FEV₁ alone, and subsequent applications of the BODE index have demonstrated that longitudinal change in the value is predictive of mortality in patients with severe emphysema,¹⁰ that it is predictive of hospitalization for COPD exacerbations,¹¹ and that it changes with clinical intervention (eg, pulmonary rehabilitation).¹² The success of the BODE index in predicting both outcome and response to therapy in patients with COPD suggests that there is a role for other methods of determining phenotypic subsets that can be used to assess prognosis

in patients with COPD. Once further studies are done to validate these subgroups, trials that evaluate the relationship between phenotype and outcomes, such as mortality or response to therapeutic interventions, will become possible.

EXACERBATION PHENOTYPING IN PATIENTS WITH COPD

As the disease progresses, the natural history of COPD is marked by exacerbations, which cause worsening of airflow limitation and increased symptoms in the context of infection, an increase in underlying airway inflammation, or both. COPD exacerbations negatively affect quality of life and accelerate the overall decrease in lung function, increasing both morbidity and mortality.¹³⁻¹⁵ Given the importance of these events in the natural history of COPD, it is important to recognize and identify patients at risk for exacerbations. One study that has provided significant insight into exacerbation susceptibility is by the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) investigators.¹⁶ This observational study tested the hypothesis that there is a frequent exacerbation phenotype of COPD by following 2138 patients, monitoring exacerbation frequency over a period of 3 years. The investigators made a number of interesting observations. First, they were able to identify a subgroup of patients who had increased susceptibility to COPD exacerbations (ie, were “frequent exacerbators”) and observed that this susceptibility was not solely dependent on disease severity as defined by lung function. Second, they determined that susceptibility to exacerbation was best predicted by a history of previous exacerbations, which was defined as 2 or more exacerbations in the 12 months before the study. Additionally, more frequent exacerbations were associated with greater impairment in health status, a history of gastroesophageal reflux disease, and increases in white blood cell counts.¹⁶ These factors help to identify a subgroup of subjects in whom treatments should be focused not just on improving lung function and symptoms but also on preventing exacerbations.

It is also possible that evaluating patients during the course of COPD exacerbations can yield information that helps differentiate groups of patients from each other. Bafadhel et al¹⁷ explored whether it was possible to use cluster analysis to define biological phenotypes occurring during exacerbations of COPD, as well as to determine whether there were biomarkers that were associated with these phenotypes. To do this, they used a prospective observational design to follow a group of patients with COPD of wide-ranging severity over 12 months. Within their cohort, they were able to identify 182 exacerbations in 86 separate patients. Cluster analysis revealed that there were 4 separate biologic exacerbation clusters, which the investigators termed “bacterial predominant,” “viral predominant,” “eosinophilic predominant,” and “pauci-inflammatory.” Fifty-five percent of exacerbations were associated with a positive sputum culture for bacteria, with sputum IL-1 β and C-reactive protein identified as biomarkers associated with this cluster. Twenty-nine percent of exacerbations were associated with viral infections, most commonly with rhinovirus. In this subset of patients, serum chemokine ligand 10 was the best biomarker for distinguishing the presence of viral infection at the time of the exacerbation. Twenty-eight percent of exacerbations involved sputum eosinophilia of greater than 3%, which was found to be associated with peripheral blood eosinophil levels of greater than 2%. Using combinations of these biomarkers,

investigators were subsequently able to prospectively validate combinations of these biomarkers with regard to their ability to predict membership in the exacerbation phenotype clusters.

An additional study, by the Phenotype and Course of COPD study investigators,¹⁸ has provided useful information with regard to subclassifying groups of patients with COPD exacerbations. The Phenotype and Course of COPD investigators recruited 342 subjects with COPD who were hospitalized with their first exacerbation; 3 months after discharge, an extensive panel of clinical, physiologic, radiographic, and inflammatory biomarker data were collected and used in a cluster analysis approach to provide data that were then validated prospectively against clinical outcomes and mortality. The investigators identified 3 distinct COPD groups: one (“severe respiratory COPD”) characterized by airflow limitation (mean FEV₁, 38% of predicted value), one (“moderate respiratory COPD”) marked by milder degrees of airflow limitation (mean FEV₁, 58% of predicted value), and a third (“systemic COPD”) with similarly milder airflow limitation but a greater proportion of comorbidities, including obesity, cardiovascular disease, and diabetes. With regard to outcomes, patients in the severe respiratory COPD group were more likely to be hospitalized for COPD (hazard ratio [HR], 3.28; $P < .001$) and demonstrated higher all-cause mortality (HR, 2.36; $P = .018$) than the other 2 groups. Additionally, consistent with an important effect of comorbidities, the systemic COPD group had a higher risk of admissions because of cardiovascular disease than did the other 2 groups (HR, 2.87; $P = .014$).¹⁸ Although further studies and larger groups of patients will be required to validate findings such as those described herein, investigative approaches such as these help define phenotypic heterogeneity in COPD exacerbations and might provide insight into underlying mechanisms that could be targeted with regard to both prevention and treatment.

RADIOLOGIC PHENOTYPING OF PATIENTS WITH COPD

Ongoing large cohort studies in which imaging data are being obtained provide the opportunity to link radiologic phenotypes with disease status and outcomes in patients with COPD. One such study that has recently facilitated significant advances in this regard is the COPDGene study, a multicenter observational study designed to identify genetic factors associated with COPD. Participants in this study undergo inspiratory, whole-lung, volumetric multidetector computed tomographic (CT) scanning¹⁹ with measurement of total lung emphysema percentage. Using these data in an analysis of 1002 COPDGene participants, Han et al²⁰ were able to determine that both bronchial wall thickness and total lung emphysema percentage were predictive of COPD exacerbation frequency in a continuous fashion independent of the severity of airflow limitation. For example, in participants with 35% or greater total emphysema, each 5% increase in emphysema was associated with a 1.2-fold increase in the rate of exacerbations. Additionally, each 1-mm increase in airway wall thickness was associated with a 1.8-fold increase in the annual exacerbation rate. The authors concluded that CT might be a useful tool for identifying subgroups of patients with COPD at greatest risk for acute exacerbations.²⁰

Secondary pulmonary hypertension is a common comorbidity in patients with advanced COPD, and pulmonary vascular disease is recognized as an important risk factor for COPD exacerbations.

To determine whether radiologic data could be used to predict exacerbation risk associated with vascular disease, investigators from the COPDGene and ECLIPSE groups hypothesized that CT metrics of pulmonary vascular disease could be used to predict exacerbation risk. They evaluated the association of pulmonary artery enlargement, determined as the ratio of pulmonary artery diameter to aortic diameter, with severe COPD exacerbations. Three thousand six hundred ninety patients with GOLD-defined moderate-to-very-severe COPD were included in the analysis and were divided into 2 groups based on the pulmonary artery/aortic diameter ratio, with the group having a ratio of greater than 1.0 considered to demonstrate evidence of relative pulmonary artery enlargement. In the study population a pulmonary artery/aortic diameter ratio of greater than 1.0 was associated with a significantly increased risk of a severe exacerbation in the prior year (odds ratio [OR], 7.44; 95% CI, 6.23-8.89). Investigators also found significant associations between severe exacerbations and younger age, African American race, need for supplemental oxygen, congestive heart failure, and other comorbidities and markers of disease severity. In a follow-up cohort a pulmonary artery/aortic diameter ratio of greater than 1.0 was also predictive of future exacerbations (OR, 4.56; 95% CI, 3.73-5.58).²¹

Of note, severe COPD exacerbations have also been shown to be associated with increased risk of adverse cardiovascular and cerebrovascular events, a phenomenon demonstrated by Donaldson et al.²² Their analysis of data from more than 25,000 primary care patients in England and Wales indicated that there was a 2.27-fold increase in the risk of myocardial infarction in the first 5 days after a COPD exacerbation and a 1.26-fold increase in stroke in the first 49 days thereafter. A similar phenomenon was reported by Halpin et al²³ using data from the UPLIFT trial; in this population the risk of non-lower respiratory tract-related serious adverse events was increased 3.22-fold in the 30 days before or after a COPD exacerbation, with the increased risk decreasing somewhat to 2.36-fold when the time window was expanded to 180 days. Thus, given that transient worsening of comorbid (particularly cardiovascular) conditions might lead to symptoms that mimic those experienced during COPD exacerbations and given the proximity of these other events to COPD exacerbations in these 2 studies, it is important to consider the possibility of misclassification in cross-sectional and retrospective studies of COPD exacerbations and plan for careful evaluation and adjudication of clinical events in prospective cohort studies.

Radiographic data are also associated with other important clinical features of COPD. In a separate report by Martinez et al,²⁴ the COPDGene investigators evaluated the relationship between quantitative chest CT metrics and both health status (SGRQ) and BODE index scores in 1200 subjects. Increases in CT measures, including airway wall thickness, wall area percentage, and luminal perimeter, predicted increased disease effect, as reflected by SGRQ scores, better than the emphysema percentage, whereas emphysema was more strongly related to the score on the BODE index. Using data from the Multiethnic Study of Atherosclerosis lung study, Barr et al²⁵ reported the relationship between percentage of emphysema, airflow limitation, and left ventricular filling in patients with COPD. In this study investigators found significant associations between cardiac magnetic resonance imaging measures of left ventricular structure and function and both percentage of emphysema on chest CT and airflow limitation, as reflected by the FEV₁/FVC ratio. Together, these articles suggest that CT scan data can be used not only to

determine the extent of the disease but also to predict the risk of future exacerbations and provide additional meaningful data with regard to disease severity and comorbidities.

PHENOTYPES RELATED TO PHYSIOLOGIC PROGRESSION OF COPD

Historically, the rate of decrease in FEV₁ has been the most widely used means to monitor disease progression in patients with COPD. Although the classic Fletcher-Peto curve defined susceptibility phenotypes of patients with COPD based on rate of lung function decrease over time,²⁶ the variables that predict which patients will progress rapidly and which will not are still not well understood. To address the issue of intersubject variability in the rate of lung function decrease, Nishimura et al²⁷ used a 5-year prospective follow-up study of patients with COPD in Hokkaido, Japan, to identify variables that might influence the rate of COPD progression. In their population, which represented a broad spectrum of COPD severity, the investigators evaluated a number of important clinical variables, including lung function and CT scan results at baseline, as well as twice-yearly lung function and clinical outcomes over the follow-up period. The investigators were able to divide the cohort into 3 groups: one with sustained lung function, one with a slow rate of lung function decrease (approximately 30 mL/y decrease in FEV₁), and a third with a rapid rate of lung function decrease (approximately 60 mL/y decrease in FEV₁). Interestingly, emphysema severity on CT scan but not FEV₁ percent predicted differed significantly between the 3 groups. Patients with sustained lung function demonstrated less evidence of emphysema and had higher numbers of circulating eosinophils, whereas those who were rapid progressors had the highest proportion of emphysema on CT scans and the lowest transfer coefficient for carbon monoxide.

Data from the ECLIPSE cohort have been analyzed to identify both variability in and determinants of the rate of lung function decrease in patients with COPD.²⁸ In this longitudinal study of 2164 patients with COPD between the ages of 40 and 75 years with a mean $\pm$ SD FEV₁ of 48% $\pm$ 16% of predicted value, the mean rate of decrease in postbronchodilator FEV₁ was 33 $\pm$ 2 mL/y. However, there was significant between-subject heterogeneity in this rate of decrease, as represented by a between-subject SD of 59 mL/y. Absolute rates of decrease lessened as disease severity increased. The rate of FEV₁ decrease was affected by smoking status and exacerbation frequency but was not influenced by age, sex, or comorbid cardiovascular disease. Baseline bronchodilator responsiveness was associated with a greater rate of lung function decrease, as was a greater degree of emphysema on CT scans. However, when the investigators evaluated a comprehensive panel of serum or plasma biomarkers (including C-reactive protein, IL-6, IL-8, fibrinogen, TNF- α , Clara cell secretory protein 16, and surfactant protein D), although many were associated with FEV₁ at baseline, only Clara cell secretory protein 16 was associated with rate of decrease. Thus the investigators were able to identify CT-identified emphysema, bronchodilator response, exacerbations, and current smoking status as predictors of the rate of lung function decrease. However, these variables alone are unlikely to explain the observed heterogeneity of decrease, and (disappointingly) the addition of biomarkers of systemic inflammation does not appear to enhance the ability to identify those at greater risk of accelerated progression.

These data are interesting in that therapies provided to patients with airflow limitation that are effective with regard to improving outcomes, such as shortness of breath, quality of life, and exacerbations, have demonstrated mixed results^{29,30} with regard to their ability to affect the rate of lung function decrease and mortality in patients with COPD. These studies are often performed in unselected populations of patients with COPD, however, and it is possible that different outcomes could be observed in selected subpopulations. Thus there is a need for studies that identify variables other than lung function to improve risk assessment in patients with COPD.

INFLAMMATORY PHENOTYPES IN ASTHMATIC PATIENTS

Asthma has long been recognized as a heterogeneous condition, and as reviewed elsewhere,³¹ substantial progress has been made in describing biologically meaningful phenotypes, many of which have implications for clinical management. One of the earliest approaches to phenotyping asthma in a clinically relevant manner was to use the inflammatory cell composition of induced sputum. To do this, Green et al³² performed a randomized trial comparing guideline-based therapy with therapy targeted to normalizing airway eosinophils in patients with moderate-to-severe asthma ($n = 74$). Over the 12-month study period, successful targeting of the sputum eosinophil percentage was associated with a reduction in severe asthma exacerbations, with 35 exacerbations observed in the sputum group versus 109 in the guideline management group ($P = .01$), an effect achieved with a similar daily dose of inhaled steroids between the 2 groups. However, there is heterogeneity in the degree of eosinophilic inflammation, with noneosinophilic asthma also reported to represent a distinct and less glucocorticoid-responsive asthma phenotype.³³

Recently, induced sputum data from 995 adult asthmatic participants in Asthma Clinical Research Network studies were analyzed to determine the prevalence of noneosinophilic airway inflammation. Sputum eosinophilia (defined as $\geq 2\%$ eosinophils) was found in 36% of ICS-naïve subjects and 17% of ICS-treated subjects. The investigators noted the absence of eosinophilia frequently, even in subjects with asthma whose disease was suboptimally controlled. In serial analyses of ICS-naïve participants, 22% had persistent eosinophilia, with sputum eosinophilia present at every measurement; 31% had intermittent eosinophilia; and 47% were persistently noneosinophilic. The authors concluded that approximately half of patients with mild-to-moderate asthma have persistently noneosinophilic disease, a phenotype that responds suboptimally to currently available anti-inflammatory therapy.³⁴

Bronchoscopy allows more targeted sampling of the airway than induced sputum and thus might have a role in identifying clinically relevant asthma phenotypes. Good et al³⁵ undertook a systematic study of bronchoscopic phenotyping in patients with refractory asthma. In their analysis of 58 patients, the investigators identified distinct clinical subsets to which therapy could be directed, including tissue eosinophilia, subacute bacterial infection, and comorbid gastroesophageal reflux. Directed therapy in these different groups (eg, omalizumab, macrolide antibiotics, or proton-pump inhibition) resulted in improvements in asthma control test scores and FEV₁.

In another biopsy-based phenotyping study performed in the context of clinical care, Wenzel et al³⁶ used surgical lung biopsy

(performed through video-assisted thoracoscopic surgery) to guide treatment decisions in specific refractory asthma cases. In this study 10 of 19 patients demonstrated pathologic findings in the small airways that were consistent with asthma, with the additional finding of interstitial nonnecrotizing granulomata. These findings occurred in the absence of features of hypersensitivity pneumonitis; the majority of cases had a family history of autoimmune disease, and in 9 of the 10 patients, the use of immunomodulatory agents (eg, azathioprine and mycophenolate) led to clinical improvements and a reduction in the need for glucocorticoids. Additional studies are needed to validate these clinical phenotypes in other populations and test the interventions in a controlled manner, but these findings suggest that direct evaluation of lung tissue can have a more expanded clinical role in the care of refractory asthma than is currently appreciated.

Other rigorous studies have used bronchoscopic sampling of airway epithelial cells to facilitate molecular phenotyping of the disease, with identification of pathways of direct relevance to pathogenic mechanisms. Woodruff et al³⁷ used genome-wide expression profiling of airway epithelial cells to identify a T_H2-based molecular signature in 42 patients with mild-to-moderate asthma, with 28 healthy control subjects for comparison. Expression of known IL-13-regulated genes (eg, periostin; chloride channel, calcium activated, family member 1 [*CLCA1*]; and serpin peptidase inhibitor, clade B, member 2 [*SERPINF2*]) as markers of T_H2 inflammation was used to define the phenotype. Patients were classified as having “high” or “low” T_H2 signatures based on expression of these surrogate biomarkers in airway epithelial cells. In this study 22 (52%) of 42 patients with mild-to-moderate asthma demonstrated a T_H2-high profile, whereas 20 (48%) demonstrated a T_H2-low profile that was similar to that of the control population with regard to these biomarkers. T_H2-high patients demonstrated higher expression of IL-5 and IL-13 in airway epithelium and had greater airway hyperresponsiveness, greater blood and bronchoalveolar eosinophilia, greater presence of airway mast cells, and greater serum IgE levels. T_H2-high asthmatic patients also demonstrated more airway remodeling with subepithelial fibrosis and higher mucin gene expression compared with that seen in the T_H2-low phenotype. The T_H2-high phenotype was also more ICS responsive, demonstrating significant improvements in FEV₁ compared with control subjects at 4 and 8 weeks’ follow-up, a finding not observed in T_H2-low participants. This observed heterogeneity of T_H2-driven phenotypes in asthmatic patients suggests that additional pathogenic pathways are important in asthmatic patients and might explain why a significant number of these patients’ symptoms remain poorly controlled despite treatment with ICSs.

CLUSTER ANALYSES TO IDENTIFY ASTHMA PHENOTYPES

Although focusing on molecular signatures in phenotyping asthma is attractive, it requires biologic samples, which are not always readily available in clinical practice. As described in patients with COPD, investigators have focused on phenotyping asthma by clustering patients using several more easily determined clinical variables. Halder et al³⁸ used K-means cluster analysis to identify phenotypically similar groups in 3 independent asthma populations. The variables selected included age of onset of asthma, sex, atopic status, BMI, peak expiratory airflow variability, sputum eosinophil counts, and symptom scores. This

study compared cluster analysis in a group of 184 patients with mild-to-moderate asthma managed in primary care with a group of 187 patients classified as having refractory asthma in secondary care.

Analysis revealed 2 clusters common to both populations: one characterized by early-onset atopic asthma with eosinophilia and another characterized by obese noneosinophilic asthma. The mild-to-moderate asthma group also contained a third unique cluster characterized by very mild disease and a lack of eosinophilia. The refractory asthma group contained 2 unique clusters: a symptom-predominant asthma cluster with little eosinophilic inflammation (these tended to be female subjects with late-onset asthma who were often obese) and an eosinophilic inflammation-predominant asthma cluster with little symptoms (these tended to be male subjects with late-onset asthma). The authors further demonstrated that the use of an inflammation-guided treatment strategy in a separate cluster of 68 patients with refractory asthma resulted in a significant reduction in exacerbation frequency (3.5 vs 0.38 exacerbations per patient per year, $P = .002$) in an inflammation-predominant cluster and allowed a reduction in ICS dose in a symptom-predominant cluster.

Using a similar analytic approach, Moore et al³⁹ evaluated 726 subjects with severe persistent asthma from the Severe Asthma Research Program (SARP) to identify 5 different clusters of asthma phenotypes based on lung function, age of onset, atopy, sex, symptoms, and medication use. Clusters 1, 2, and 4 were identified as having early-onset atopic asthma but differed based on severity, medication use, and health care use. Cluster 1 had normal lung function and little health care use, whereas cluster 2 had normal lung function and increased medication use and health care use. Cluster 4 was characterized by childhood onset, atopic disease, and marked reduction in baseline lung function with significant reversibility but high health care use. Clusters 3 and 5 consisted of nonatopic subjects who were predominately women with late-onset disease and associated obesity. Cluster 3 had moderate reductions in lung function and frequent steroid use, whereas cluster 5 had the most severe reduction in lung function, high health care use, and significant morbidity. One important aspect of this study was the creation of a decision tree using prebronchodilator FEV₁, postbronchodilator FEV₁, and atopic status with an 80% accuracy in correctly classifying subjects to their cluster. These 3 variables can easily be determined in clinical practice to phenotype patients and thus predict disease severity and treatment response, although trials in these stratified populations remain to be done.

Asthma is an equally heterogeneous condition in childhood, and similar cluster analyses with clinical variables collected from children 6 to 17 years of age enrolled in SARP have been used to identify phenotypes and determine how children with severe asthma might be distributed throughout the clusters. Fitzpatrick et al⁴⁰ identified 4 clusters in 161 children enrolled in SARP. The first cluster had relatively normal lung function and less atopy, although a second cluster had more atopy, more health care use, more symptoms, and slightly lower lung function. A third cluster had even lower lung function, more comorbidities, and more bronchial hyperresponsiveness, whereas cluster 4 had the lowest lung function and greatest amount of symptoms and medication use. They determined that asthma duration, number of medications, and baseline lung function predicted cluster membership, with children with severe asthma being distributed across all clusters. Interestingly, none of these clusters corresponded to conventional

or guideline-based definitions of severe asthma, especially because of the influence of atopy and duration of asthma in defining cluster phenotypes, suggesting a potential role for clinically meaningful phenotyping to refine asthma management in children.

PHENOTYPES RELATED TO ASTHMA PROGRESSION

Some patients with asthma experience a progressive decrease in lung function similar to that observed in patients with COPD, possibly because of variations in disease persistence, patterns of inflammation, and airway remodeling. The rate of lung function decrease in asthmatic patients is variable, possibly because of differences in phenotype. Data from the Childhood Asthma Management Program (CAMP) have provided insight in this regard. Using data from the CAMP study to perform a secondary analysis, Covar et al⁴¹ identified factors associated with a 1% loss in postbronchodilator FEV₁ per year in children with asthma. Approximately 26% of those enrolled in CAMP experienced lung function decrease at this accelerated rate, and younger age, male sex, and higher postbronchodilator FEV₁ percent predicted were found to be associated with this accelerated progression. Biomarker assessment at a single CAMP site revealed that eosinophilic airway inflammation (observed during the period of the study) was also associated with accelerated lung function decrease.

EXACERBATION PHENOTYPING IN ASTHMATIC PATIENTS

Exacerbations in asthmatic patients, as is the case in those with COPD, are associated with loss of lung function. Bai et al⁴² followed 93 adults with moderate-to-severe asthma over 11 years to assess the effects of exacerbations on lung function. There were 186 exacerbations in 60% of the subjects enrolled in this study over the 11 years, and subjects with frequent exacerbations had lower lung function, with an accelerated decrease in FEV₁ (32 vs 15 mL). Although the authors were not able to identify specific mechanisms of accelerated lung function decrease, this study highlights a clear link between excessive decrease in lung function and frequent exacerbations.

More recently, Wu et al⁴³ conducted a *post hoc* analysis of diary cards completed by subjects enrolled in the CAMP study to identify factors predictive of severe exacerbations, which were defined as an asthma episode requiring oral steroids for greater than 3 days, hospitalization, or an emergency department visit. The authors found that persistent asthma symptoms were associated with a risk of severe exacerbations, and the strongest predictors of a severe exacerbation were a previous exacerbation requiring 3 days or greater of oral steroid use in the prior 3 months, an emergency department visit or hospitalization in the previous year, lower FEV₁/FVC ratio, greater bronchial responsiveness, and higher eosinophil counts. This study highlights phenotypic factors associated with severe asthma exacerbations and therefore the need to focus on symptoms, exacerbation risk, and impairment in the management of asthma in children.

PHENOTYPIC OVERLAP BETWEEN ASTHMA AND COPD

Some patients with COPD demonstrate features that overlap with asthma.⁴⁴ Diagnostic criteria for this "phenotypic overlap"

have been proposed, including positive bronchodilator response, eosinophilia in sputum, personal history of asthma before age 40 years, high total IgE level, and a personal history of atopy.⁴⁵ It is important to recognize that this group of patients has been systematically excluded from many clinical trials, and therefore evidence about their management is limited despite the fact that this phenotypic group tends to have more frequent exacerbations and more health care use. The COPDGene investigators used data from 915 subjects in the COPDGene cohort with moderate-to-very-severe COPD using GOLD criteria and found that 119 had criteria for the diagnosis of both COPD and asthma. Participants who met the criteria for this overlap phenotype were younger and more likely to be African American, with less smoking history and a greater degree of gas trapping on expiratory CT scans. Additionally, these subjects with the overlap phenotype were more likely to experience frequent exacerbations (OR, 3.55; 95% CI, 2.19-5.75) and had worse disease-related quality of life than those with COPD alone, suggesting that this population is an important subset of patients for clinicians to recognize.⁴⁶ As noted above, authors for the ECLIPSE investigators noted that those patients with bronchodilator reversibility experience a more precipitous decrease in lung function than those without when followed over a 3-year period.²⁸ Given that bronchodilator responsiveness is a hallmark of asthma, this could suggest that the “overlap” population is one in whom therapy with ICSs (as recommended in asthma) is more likely to demonstrate significant benefit.

PHENOTYPING AND FUTURE IMPLICATIONS FOR THERAPY

Whereas the treatment of asthma has the use of anti-inflammatory therapies (particularly ICSs) as its cornerstone, with prolonged bronchodilation brought to bear in more advanced disease stages, in the treatment of COPD, prolonged bronchodilation is at the forefront of management. Although treatment of these 2 disorders is comprehensively reviewed in guideline documents,^{1,2} the data reviewed above could be construed to suggest that the identification of clinical, cellular, and molecular phenotypes might expand the context in which clinicians apply currently available therapies, especially when patients do not fit guideline-based approaches. Particularly in those with severe asthma, therapy with biologic agents targeted to IgE is now available, and drug development programs are underway to target other important mechanisms identified through phenotyping approaches, including eosinophilic, neutrophil-predominant, and paucigranulocytic disease, as well as disease mediated by IL-5, IL-4, and IL-13. Phenotypic approaches to COPD management have identified patients with upper lobe-predominant emphysema as candidates for lung volume reduction surgery. More recently, the identification of a “frequent exacerbator” phenotype has led to therapeutic approaches designed to reduce exacerbations, including chronic macrolide antibiotic therapy and phosphodiesterase E4 inhibition.

In conclusion, it is likely that further elucidating the heterogeneity of COPD and asthma through clinical and biologic phenotyping will allow greater understanding of pathogenic mechanisms and more directed management, especially when patients are not controlled with first-line modalities. Because the diversity of phenotypes of each condition is better understood, clinicians will be presented with opportunities to evolve from a “one size fits all” approach to personalized approaches, with the

ultimate goal of improving care and reducing potential adverse effects from unnecessary therapies.

What do we know?

1. Asthma and COPD are common conditions with significant phenotypic heterogeneity and potential for clinical overlap.
2. Phenotypic heterogeneity in patients with asthma or COPD can be defined on the basis of clinical, physiologic, molecular, and radiographic variables.
3. Careful assessment of phenotypes in patients with asthma and those with COPD has potential implications for patient management, potentially allowing a more personalized approach to patient care.

What is still unknown?

1. The most appropriate methods for identifying novel clinical phenotypes
2. The stability of different phenotypic characteristics over time
3. Whether the identification of specific phenotypes will allow more targeted approaches that enhance the efficacy of current and future therapies for COPD and asthma

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