

# Are Asthma and COPD a Continuum of the Same Disease?

Xavier Soler, MD, PhD<sup>a</sup>, and Joe W. Ramsdell, MD<sup>b</sup> San Diego, Calif

### INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

**Method of Physician Participation in Learning Process:** The core material for these activities can be read in this issue of the Journal or online at the *JACI: In Practice* Web site: [www.jaci-inpractice.org/](http://www.jaci-inpractice.org/). The accompanying tests may only be submitted online at [www.jaci-inpractice.org/](http://www.jaci-inpractice.org/). Fax or other copies will not be accepted.

**Date of Original Release:** July 1, 2015. Credit may be obtained for these courses until August 31, 2017.

**Copyright Statement:** Copyright 2015-2017. All rights reserved.

**Overall Purpose/Goal:** To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

**Target Audience:** Physicians and researchers within the field of allergic disease.

**Accreditation/Provider Statements and Credit Designation:** The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for

physicians. The AAAAI designates these educational activities for a maximum of 1 AMA PRA Category 1 Credit. Physicians should only claim credit commensurate with the extent of their participation in the activity.

**List of Design Committee Members:** Xavier Soler, MD, PhD, and Joe W. Ramsdell, MD

### Activity Objectives

1. To understand the concept of endotypes and obstructive airways disease.
2. To understand and use the rationale for the current classification system of obstructive airways disease.
3. To apply state-of-the-art diagnosis and treatment modalities for obstructive airways disease.

**Recognition of Commercial Support:** This CME has not received external commercial support.

**Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations:** The authors declare that they have no relevant conflicts of interest.

Asthma and chronic obstructive pulmonary disease (COPD) are common heterogeneous diseases with significant impact on morbidity, mortality, and health care costs. In most of the cases, the main features and pathophysiology differ substantially between both asthma and COPD, which allows differentiating both entities and providing appropriate treatment. The recognition of a subgroup of patients who present clinically with features of both conditions, asthma chronic obstructive pulmonary disease overlap syndrome, has reignited the question of whether asthma and COPD are different manifestations of the same disease or unique processes, the so-called Dutch hypothesis versus British hypothesis controversy. There is enough heterogeneity in the clinical and mechanistic profiles of these 3 diseases, and subsets of these 3 diseases, to suggest that a new

approach relying on the concept of endotypes of obstructive airways disease may be more useful. This characterization has provided the basis for opening new areas of research that may eventually lead to the development of new targeted drugs. This review focuses on the current knowledge of asthma, COPD, and asthma chronic obstructive pulmonary disease overlap syndrome phenotypes with emphasis on mechanisms of disease and how these may define endotypes, providing a more rational approach to research and clinical care. © 2015 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2015;3:489-95)

**Key words:** Asthma; COPD; Asthma-COPD; ACOS; Overlap

Asthma and chronic obstructive pulmonary disease (COPD) are among the most prevalent pulmonary disorders with significant economic and health burdens.<sup>1,2</sup> Historically, there has been controversy between the so-called Dutch hypothesis proposing that asthma and COPD are manifestations of the same basic disease and the “British hypothesis” suggesting that both diseases are distinct entities generated by different mechanisms.<sup>3</sup> This discussion is further complicated by a proposed new subgroup of patients termed the asthma chronic obstructive pulmonary disease overlap syndrome or ACOS<sup>4</sup> that can present clinically with features of both and is consistent with either hypothesis.<sup>5</sup> These core diagnoses are based on clinical phenotypes. We suggest that this discussion can be enhanced significantly by the concept of endotypes. *Endotype*—a contraction of

<sup>a</sup>Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of California San Diego, San Diego, Calif

<sup>b</sup>Division of General Internal Medicine, Department of Medicine, University of California San Diego, San Diego, Calif

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication April 3, 2015; revised manuscript received and accepted for publication May 29, 2015.

Corresponding author: Joe W. Ramsdell, MD, Division of General Internal Medicine, University of California San Diego, 200 West Arbor Dr, San Diego, CA 92103. E-mail: [jramsdell@ucsd.edu](mailto:jramsdell@ucsd.edu).

2213-2198

© 2015 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2015.05.030>

**Abbreviations used**

ACOS- asthma-chronic obstructive pulmonary disease overlap syndrome  
COPD- chronic obstructive pulmonary disease  
GINA- Global Initiative for Asthma Treatment  
ICS- inhaled corticosteroids  
LABA- long-acting beta agonist

endophenotype—is defined as a subset of disease driven by specific molecular mechanisms arising from an interaction between genetic and environmental factors, resulting in a particular disease process with a characteristic course and response to therapy.<sup>6</sup> Asthma and COPD may have different endotypes that contribute to their different manifestations and, therefore, because of different pathological and molecular origins, have different treatment responses.

## CLINICAL PHENOTYPES AND MECHANISTIC ENDOTYPES IN OBSTRUCTIVE AIRWAYS DISEASE

The 3 core types of obstructive airways disease are recognized through clinical manifestations (ie, phenotypes) and have been characterized in terms of histological patterns and biological mechanisms (viewed as being an interaction between genetic and environmental factors). The genetics of airways obstructive disease is emerging as a key factor in our understanding of the continuum of airways obstructive disease.

### ASTHMA

#### Clinical phenotype

Current asthma definitions and guidelines from the National Asthma Education and Prevention Program and the Global Initiative for Asthma Treatment (GINA) guidelines are available at [http://www.nhlbi.nih.gov/about/org/naep/naep\\_pd.htm](http://www.nhlbi.nih.gov/about/org/naep/naep_pd.htm) and [www.ginasthma.org](http://www.ginasthma.org), respectively.<sup>7,8</sup> The GINA 2014 definition of asthma states the following:

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

Asthma symptoms are intermittent in nature and may completely resolve for prolonged periods.<sup>9</sup>

The asthma clinical phenotype is predominantly an airway disease, generally without involvement of lung parenchyma. It is characterized primarily by airway hyperactivity, demonstrated by improvement in airflow in response to bronchodilator administration on spirometric testing or through worsening of airflow in response to various challenge tests. Gas exchange may be compromised during an asthma exacerbation but classically returns to normal in the interim.<sup>9-11</sup> Some patients with asthma may develop persistent airflow obstruction.<sup>12</sup> There are several clinically distinct but often clinically overlapping asthma syndromes based on clinical characteristics including allergic diathesis, exercise susceptibility, and susceptibility to bronchospasm with viral infections and cigarette smoking or other environmental factors.<sup>9</sup> There is increasing evidence that these asthma syndromes

represent different endotypes, each driven by specific biological mechanisms.<sup>4,13-17</sup>

#### Histologic/mechanistic factors

Prototypically, asthma is considered an allergic disease mediated by mast cells, eosinophils, T helper cells (CD4<sup>+</sup>) with predominant T<sub>H</sub>2 proinflammatory proteins, and natural killer cells and eosinophilic airway inflammation.<sup>13,14,18</sup> Over time, some patients with asthma develop airway thickening because of collagen deposition in the basement membrane underpinning the bronchial epithelium.<sup>14,19,20</sup> Recent studies, however, have highlighted the potential for multiple biological mechanisms associated with clinical asthma phenotypes. Neutrophilic or paucigranulocytic findings in sputum rather than eosinophilia have been reported to be common in a range of asthma severities,<sup>14,15,21,22</sup> suggesting that asthma is not a single disease mechanism with a variable presentation but rather several diseases with a common clinical phenotype.

Alternative endotypes to extrinsic/allergic asthma include exercise-induced bronchospasm, smokers with asthma, elderly patients with asthma, aspirin-sensitive patients with asthma, and patients with severe asthma, all of whom have a relative resistance to steroid treatment.<sup>23</sup> Many of these putative endotypes are associated with this neutrophilic or paucigranulocytic sputum profiles, suggesting different underlying mechanisms, and may be unresponsive to steroid therapy.<sup>13,14,23</sup> The endotype paradigm, therefore, may be particularly useful for directing treatment (eg, relative steroid resistance in smokers with asthma).<sup>14,24,25</sup>

#### Genetics

A number of genes have been associated with asthma (Figure 1)<sup>26</sup> or response to therapy, for example, beta-2 adrenergic receptor variants.<sup>27</sup> These relationships are complex and have not reached the point of clinical utility.<sup>28</sup>

### COPD

#### Clinical phenotype

COPD is defined as a chronic, progressive, irreversible, obstructive airways disorder secondary to substantial tobacco use or exposure to pollutants. To diagnose COPD, a post-bronchodilator spirometry should demonstrate an FEV<sub>1</sub>/forced vital capacity ratio of less than 0.7. COPD is inevitably associated with loss of lung function (and therefore, *obstructive* pulmonary disease).<sup>1</sup> The classical archetypes of COPD include chronic bronchitis, characterized by cough and sputum production, and emphysema, characterized by progressive dyspnea and parenchymal destruction, but a significant overlap is recognized.<sup>11</sup>

#### Histologic/mechanistic factors

Histologic changes characteristic in chronic bronchitis occur primarily in the airway (especially small airways) with relatively limited parenchymal destruction. Typically, goblet cell metaplasia and impaired mucociliary function contribute to excess mucus accumulation and worsening obstruction. Emphysema demonstrates mostly preserved airways structure but significant parenchymal damage leading to air trapping and dynamic airway obstruction. With the advent of modern chest imaging, computed tomography scanning has supplanted the histologic definition of emphysema. The density mask for severe emphysema in 5-mm-thin or thinner slices falls at approximately −950 HU, moderate emphysema at approximately −910 HU, and mild emphysema at approximately −850 HU.<sup>29</sup>

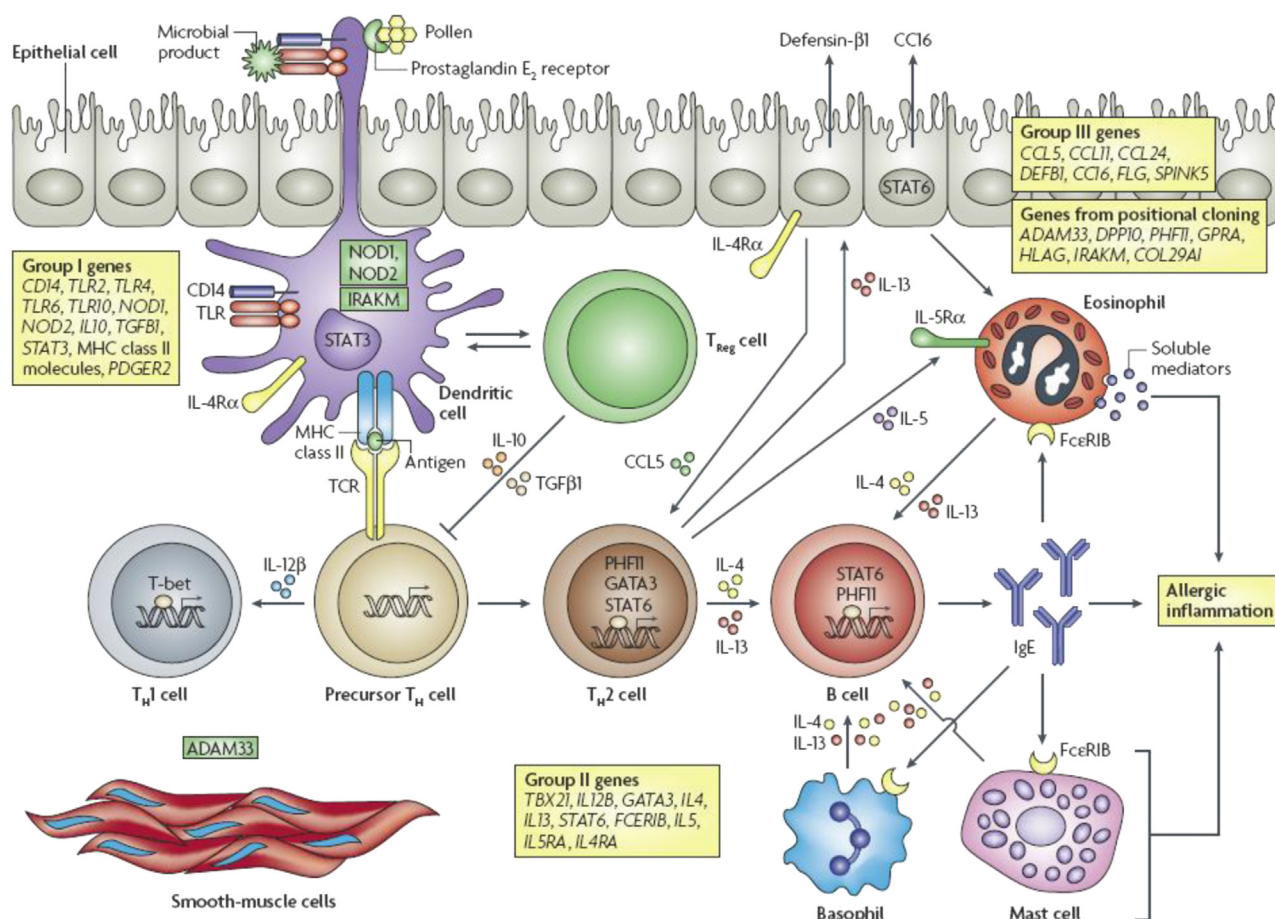


**FIGURE 1.** Representation of the most robust asthma candidate genes identified through association studies or positional cloning in a cell-based framework. From Vercelli.<sup>26</sup> Reproduced with permission.

The histological changes in both chronic bronchitis and emphysema are the result of repeated exposure to noxious stimuli (overwhelmingly cigarette smoke) that trigger an inflammatory response that continues after removal of the inciting stimulus.<sup>30</sup> Inflammatory mechanisms in COPD are characterized by macrophages, neutrophils, cytotoxic T lymphocytes (CD8<sup>+</sup>), and mast cells.<sup>28</sup> There may be associated “spillover” of the inflammatory response from the lungs into the systemic circulation, leading to potential downstream effects such as arterial stiffness and its consequences.<sup>13,14,31,32</sup>

The endotypes concept can also be usefully applied in COPD. A cross-sectional analysis of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study cohort recognized 5 clusters of patients with COPD that were clinically and biologically different.<sup>33</sup> These clusters differed with regard to outcomes, from milder patients with fewer deaths and hospitalizations (cluster A) to patients with lower FEV<sub>1</sub> and more frequent emphysema who experienced the highest exacerbation and hospitalization rates (cluster D). Interestingly, a cluster E was defined as intermediate for most variables that may represent a mixed group. Similarly, analysis of the COPDGene cohort identified 4 clusters: (1) relatively resistant smokers (ie, no/mild obstruction and minimal emphysema despite heavy smoking), (2) mild upper zone

emphysema-predominant, (3) airway disease-predominant, and (4) severe emphysema. All clusters were strongly associated with COPD-related clinical characteristics, including exacerbations and dyspnea.<sup>34</sup>

## Genetics

As in asthma, there is evidence that genetic variants may contribute to the phenotypic heterogeneity of COPD.<sup>35</sup> The mechanistic and genetic cause and effect consequences of alpha-1 antitrypsin deficiency are relatively well understood in emphysema; other genetic relationships in COPD are beginning to emerge but appear to be more complex.<sup>36</sup> Studies from pooled COPD genetic cohorts indicate that genetic imprints are associated with manifestations of COPD.<sup>37</sup> For example, analysis of the COPDGene cohort noted strong genetic associations between the mild upper zone emphysema group and rs1980057 near hedgehog interacting protein and between the severe emphysema group and rs8034191 in the chromosome 15q region.<sup>34</sup> Similar results from the ECLIPSE cohort support the robustness of the groupings, especially considering the differences in patient selection, cohort sizes, clinical features, and strategy used for clustering both ECLIPSE and COPDGene studies (Table 1).<sup>33</sup>

**TABLE I.** Top results for the genomewide association analysis of those with severe COPD versus smoking controls in COPDGene non-Hispanic white (NHW) and African-American (AA), ECLIPSE, National Emphysema Treatment Trial/Normative Aging Study (NETT/NAS) and Genetics of Chronic Obstructive Lung Disease (GenKOLS) (Norway) studies

| Locus | Nearest gene(s) | SNP        | Risk allele | Frequency |      | Meta-analysis    |                        |
|-------|-----------------|------------|-------------|-----------|------|------------------|------------------------|
|       |                 |            |             | NHW       | AA   | OR (CI)          | P value                |
| 15q25 | <i>CHRNA3</i>   | rs12914385 | T           | 0.42      | 0.19 | 1.39 (1.29-1.51) | $2.70 \times 10^{-16}$ |
| 4q31  | <i>HHIP</i>     | rs13141641 | T           | 0.59      | 0.89 | 1.39 (1.28-1.51) | $3.66 \times 10^{-15}$ |
| 4q22  | <i>FAM13A</i>   | rs4416442  | C           | 0.42      | 0.54 | 1.36 (1.26-1.47) | $9.44 \times 10^{-15}$ |
| 11q22 | <i>MMP3/12</i>  | rs626750   | G           | 0.83      | 0.74 | 1.36 (1.23-1.51) | $5.35 \times 10^{-9}$  |
| 14q32 | <i>RIN3</i>     | rs754388   | C           | 0.83      | 0.85 | 1.33 (1.2-1.48)  | $6.69 \times 10^{-8}$  |
| 1q41  | <i>TGFB2</i>    | rs4846480  | A           | 0.75      | 0.65 | 1.26 (1.16-1.37) | $1.25 \times 10^{-7}$  |

ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; OR, odds ratio; SNP, single nucleotide polymorphism.

The TGFB2 locus became genomewide significant ( $P < 5 \times 10^{-8}$ ) when results from the International COPD Genetics Network were included. RIN3 reached genomewide significance for moderate-to-severe COPD. Significance  $P$  value  $\geq 5 \times 10^{-8}$ .

Modified from Cho et al.<sup>37</sup> With permission.

## ASTHMA-COPD OVERLAP SYNDROME

### Clinical phenotype

ACOS was defined as the presence of persistent airflow limitation with features typically of asthma and COPD.<sup>4,10,38</sup> In 2014, GINA and the Global Obstructive Lung Disease published a joint document on ACOS (available for free download at <http://www.ginasthma.org/documents/14>).<sup>39</sup> The ACOS prevalence is unclear because of different definition criteria, with reported rates of COPD between 13% and 55%.<sup>4,40-42</sup> Compared with patients with either asthma or COPD, patients with ACOS experience frequent exacerbations, poor quality of life, increased use of health care resources, a more rapid decline in lung function, and high mortality.<sup>41-43</sup> Although there is currently no general agreement on criteria for ACOS, the Spanish Respiratory Society suggested a combination of major or minor characteristics that could be used clinically (Table II).<sup>10</sup>

### Histologic/mechanistic factors

Patients with ACOS present 3 main mechanistic characteristics that are interrelated: (1) enhanced bronchial and systemic eosinophilic inflammation, (2) increased reversibility of airflow (compared with COPD), and (3) increased response to inhaled corticosteroids (ICS) (compared with patients with COPD alone).<sup>44,45</sup> As with COPD, smoking is a critical factor in all types of ACOS. Cigarette smoke typically increases neutrophils and (modestly) eosinophils<sup>46</sup> and is associated with a pulmonary inflammatory response driven by  $T_H1/T_H17$  cytokines such as IL-8 and TNF, and leukotriene B<sub>4</sub>.<sup>47,48</sup> Although this appears to suggest an underlying mechanism distinct from typical eosinophilic inflammation seen in allergic asthma, this relationship is not straightforward.<sup>45</sup> For example, hallmarks of asthma such as eosinophil cationic protein-1 and eotaxin-1 are associated with bronchodilator responsiveness in patients with COPD.<sup>49</sup> Furthermore, smokers with asthma often demonstrate sputum eosinophilia as opposed to smokers without asthma in whom neutrophils predominate with only modestly increased eosinophils.<sup>45,50,51</sup> Taken together, this may indicate heterogeneity of host inflammatory reaction to cigarette smoke among nonobstructive ("normal") smokers, nonsmokers with asthma, smokers with asthma, patients with COPD who lack bronchial reactivity, and patients with COPD who demonstrate bronchial reactivity. Finally, smoking causes a disruption in the balance between acetylated deacetylated histones, the glucocorticoids pathway,<sup>52</sup> resulting in increased (or persistent) inflammation

**TABLE II.** Criteria proposed by the the Spanish Respiratory Society\* to diagnose ACOS

| Major                                                                          | Minor                                                                         |
|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| 1. Highly positive bronchodilator test result ( $\geq 15\%$ and $\geq 400$ cc) | 4. Positive bronchodilator test ( $\geq 12\%$ and $\geq 200$ cc) <sup>†</sup> |
| 2. Sputum eosinophilia                                                         | 5. Elevated IgE level                                                         |
| 3. History of asthma <sup>‡</sup>                                              | 6. History of atopy                                                           |

Two major criteria, or 1 major and 2 minor criteria are necessary for diagnosis.

\*Modified from Soler-Cataluna et al.<sup>10</sup>

<sup>†</sup>On 2 occasions.

<sup>‡</sup>Before the age of 40 y.

in both COPD and asthma.<sup>8,53-57</sup> This can lead to impaired responses to steroids in both asthma and COPD.<sup>58,59</sup>

Finally, aging may also be a risk factor for ACOS. Normal aging of the lung is associated with increased airway hyper-responsiveness, greater asthma severity, and reduced response to steroids among others, which may also contribute to the increased prevalence of ACOS with age.<sup>11</sup>

Are there ACOS endotypes? This is not as straightforward as with asthma or COPD. Clinically, the ACOS phenotype appears to be patients with COPD with increased bronchial reversibility and/or patients with asthma with a history of smoking who developed non—fully reversible airway obstruction at an older age.<sup>44</sup> Such patients have been reported to manifest increased sputum eosinophilia.<sup>5</sup> Based on these observations, 3 biological clusters have recently been reported in ACOS: (1) asthma predominant with eosinophilic inflammation and elevated  $T_H2$  mediators; (2) COPD predominant with elevated proinflammatory cytokines; and (3) asthma-COPD overlap group with chronic bronchitis, increased bacterial colonization, elevated sputum IL-1b and TNF- $\alpha$  levels, and sputum neutrophilia.<sup>5</sup> There are suggestions of mechanistic differences among patients with ACOS. Fractional exhaled nitric oxide levels correlate with airway inflammation in COPD, similar to asthma,<sup>60</sup> and normal fractional exhaled nitric oxide levels may predict lack of steroid response.<sup>61</sup> Furthermore, higher fractional exhaled nitric oxide levels may be a common finding in patients with ACOS compared with other COPD phenotypes.<sup>62</sup> It remains to be seen whether these represent endotypes that will be clinically useful.<sup>41</sup>

### Genetics

The genetic determinants of ACOS are emerging. A genomewide analysis of non-Hispanic white subjects in the

COPDGene cohort identified single nucleotide polymorphisms in the genes *CSMD1* (rs11779254;  $P = 1.57 \times 10^{-6}$ ) and *SOX5* (rs59569785;  $P = 1.61 \times 10^{-6}$ ) and the meta-analysis identified single nucleotide polymorphisms in the gene *GPR65* (rs6574978;  $P = 1.18 \times 10^{-7}$ ) associated with COPD and asthma overlap.<sup>63</sup> It has been suggested that signatures of airway epithelial gene expression alterations in asthma are upregulated in some subjects with COPD and can identify an ACOS-like subgroup with T<sub>H</sub>2 mechanistic signatures and characterized by increased severity and “asthma-like” features (including a favorable corticosteroid response).<sup>64</sup>

## MANAGEMENT RECOMMENDATIONS

Management recommendations such as GINA, the National Asthma Education and Prevention Program, and the Global Obstructive Lung Disease for asthma and COPD are widely available. Short-acting beta agonist for symptomatic relief is the common first step for all patients with obstructive airways disease. ICS are the usual first-line choice for persistent asthma, with a long-acting beta agonist (LABA) as the preferred add-on treatment,<sup>8</sup> whereas a LABA or long-acting muscarinic antagonists may be preferred in COPD, with ICS as a later add-on help to reduce exacerbations.<sup>1</sup> This approach is based on extensive clinical experience combined with numerous well-designed clinical trials. However, the approach to patients with ACOS or smokers with asthma is more problematic. Subjects with asthma are generally excluded from trials of COPD, and guidelines applicable to asthma have been developed almost exclusively from studies that exclude smokers such that neither of these guidelines can be extrapolated to patients with ACOS.<sup>65</sup> The rationale for this exclusion is based on the understandable desire to avoid confounding asthma studies with other smoking-induced lung diseases. The net result, however, is a paucity of scientific information on treatment options for those patients with ACOS or other endotypes of obstructive airways disease who fall outside of the classic clinical archetypes.<sup>66</sup>

Given the importance of ICS in the treatment of asthma and COPD, and the effects of cigarette smoke on steroid responsiveness, clinicians are left with a uniquely difficult choice in the management of patients with ACOS. In addition to symptomatic treatment with short-acting beta agonists in addition to ICS for persistent symptoms, the Gaining Optimal Asthma Control study endorses the current National Asthma Education and Prevention Program recommendation of the addition of a LABA.<sup>67</sup> Beyond that (and without much scientific evidence), current consensus recommendations suggest that patients with ACOS may benefit from a treatment plan similar to that used in asthma.<sup>24,39,66,68</sup> However, a retrospective study of patients with ACOS found no benefit of ICS use on FEV<sub>1</sub> decline, incidence of severe exacerbations, or overall mortality in 125 patients with ACOS.<sup>69</sup> Despite several limitations of the study, it emphasizes the need to properly identify those patients who may, or may not, benefit from this treatment. Uncertainties regarding the safety of the use of LABA alone in ACOS have led to the recommendation that ICS should always be used with a LABA.<sup>66</sup> In cases of worsening symptoms in the face of maintenance ICS plus LABA, the consensus recommends moving up to triple therapy with ICS, LABAs, and a long-acting muscarinic antagonist, leukotriene receptor antagonists, or theophylline. Antimuscarinic agents such as ipratropium have long been known to

be bronchodilators in both asthma and COPD.<sup>70</sup> There is reason to believe that antimuscarinic agents may be useful add-on therapy for asthma in general and for smokers with asthma in particular.<sup>71</sup> The long-acting antimuscarinic agent tiotropium is effective add-on therapy in patients with asthma inadequately controlled by ICS alone, and has been demonstrated to be an effective add-on therapy for patients with a combined diagnosis of COPD.<sup>45,66,72</sup> Leukotriene receptor antagonists effectively antagonize the binding of the sulfido-peptide leukotriene D<sub>4</sub> to its CysLT<sub>1</sub> and have been shown to be effective in smokers with asthma.<sup>73</sup> Cigarette smoking increases urinary leukotriene E<sub>4</sub> concentration, suggesting a mechanism for this beneficial effect. The response to the leukotriene receptor antagonist montelukast in smokers was associated with pretreatment sputum levels of eosinophils. Although patients with concomitant asthma and COPD have an increased number and severity of exacerbations,<sup>63</sup> the role of phosphodiesterase 4 inhibitors such as roflumilast or macrolides has not been investigated, and further clinical studies are warranted. Finally, theophylline increases intracellular histone activity, which modulates corticosteroid activity and the efficacy of ICS.<sup>14,74-77</sup> Interestingly, low-dose theophylline is able to restore histone deacetylase 2 function, impaired *in vitro* in relative corticoid-resistant subjects (eg, smokers with asthma),<sup>28</sup> so may eventually be used in patients with ACOS. The preferred add-on treatment or even initial treatment for patients with ACOS and smokers with asthma is still a matter of research.

## FUTURE RESEARCH

The endotype paradigm for obstructive airways disease provides a roadmap for future research. Investigations into the consequences of biological mechanisms and genetic variability on clinical phenotypes will lead to a more rational identification and characterization of the 3 core archetypes of obstructive airways disease and suggest more rational and targeted therapy. To that end, basic mechanistic studies and proposed endotypes need to strive to link with clinical phenotypes and proposed endotypes in the theoretical rationale. Likewise, clinical trials should be designed to scrupulously phenotype all participants and embed mechanistic studies from biological samples collected during the course of the clinical trials. Recognizing unique mechanistic (eg, steroid resistance with smoking) and genetic (eg, alpha-1 antitrypsin deficiency, beta receptor heterogeneity) factors represent the ultimate approach to targeted, effective treatment. In this context, the endotypes paradigm offers a solid theoretical basis for designing future research.

## DUTCH OR BRITISH?

Based on mechanistic data reviewed herein, it would appear that a rationale for extrinsic/allergic asthma and COPD as different diseases is scientifically sound. In clinical practice, most cases present with a typical phenotype and are diagnosed without much difficulty, but the subgroup of subjects with overlapping symptoms or other atypical presentations can be challenging to characterize and treat. Historically, the treatment of asthma has focused on symptom relief and on underlying mechanisms (eg, ICS to reduce inflammation). The treatment of COPD, however, has generally focused primarily on symptom relief. In this context and as a practical matter, cautions regarding the use of LABAs as solo treatment in asthma suggest that safety issues may

ultimately drive a more careful consideration of the unique features of obstructive airways diseases. In this context, the expansion of our understanding of the underlying mechanism and genetics of obstructive airways disease would seem to render both the Dutch and the British views of obstructive lung disease moot. Furthermore, if specifically targeted new treatments are to be developed with the hope of modulating underlying disease, mechanistic and genetic differences in the various forms of airways disease must be pursued.

## SUMMARY

Asthma, COPD, and (perhaps) ACOS are prevalent, heterogeneous, and challenging obstructive lung disorders. Careful characterization of patient subpopulations is required to better understand heterogeneous diseases and to properly manage therapy. The paradigm of endotypes is useful for identifying potentially distinct molecular mechanisms to inform research and clinical care. To this end, it would be useful to abandon both the Dutch and the British hypotheses in favor of the paradigm that diseases of airways obstruction are a collection of endotypes, driven by unique biological/genetic mechanisms.

## REFERENCES

- Vestbo J, Hurd SS, Agustí AG, Barnes PJ, Buist SA, Calverley P, et al. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013;187:347-65.
- Boulet LP, FitzGerald JM, Reddel HK. The revised 2014 GINA strategy report: opportunities for change. *Curr Opin Pulm Med* 2015;21:1-7.
- Barnes PJ. Against the Dutch hypothesis: asthma and chronic obstructive pulmonary disease are distinct diseases. *Am J Respir Crit Care Med* 2006;174:240-3.
- Louie S, Zeki AA, Schivo M, Chan AL, Yoneda KY, Avdalovic M, et al. The asthma-chronic obstructive pulmonary disease overlap syndrome: pharmacotherapeutic considerations. *Exp Rev Clin Pharmacol* 2013;6:197-219.
- Ghebre MA, Bafadhel M, Desai D, Cohen SE, Newbold P, Rapley L, et al. Biological clustering supports both "Dutch" and "British" hypotheses of asthma and chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2015;135:63-72.
- Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet* 2008;372:1107-19.
- Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143-78.
- National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol* 2007;120:S94-138.
- Abramson MJ, Perret JL, Dharmage SC, McDonald VM, McDonald CF. Distinguishing adult-onset asthma from COPD: a review and a new approach. *Int J Chron Obstr Pulmon Dis* 2014;9:945-62.
- Soler-Cataluna JJ, Cosío B, Izquierdo JL, López-Campos JL, Marín JM, Agüero R, et al. Consensus document on the overlap phenotype COPD-asthma in COPD [in English, Spanish]. *Arch Bronconeumol* 2012;48:331-7.
- Soriano JB, Davis KJ, Coleman B, Visick G, Mannino D, Pride NB. The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. *Chest* 2003;124:474-81.
- Broekema M, Timens W, Vonk JM, Volbeda F, Lodewijk ME, Hylkema MN, et al. Persisting remodeling and less airway wall eosinophil activation in complete remission of asthma. *Am J Respir Crit Care Med* 2011;183:310-6.
- Robinson DS, Hamid Q, Ying S, Tsiocopoulos A, Barkans J, Bentley AM, et al. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med* 1992;326:298-304.
- Fahy JV. Type 2 inflammation in asthma—present in most, absent in many. *Nat Rev Immunol* 2015;15:57-65.
- Gibson PG, Simpson JL, Saltos N. Heterogeneity of airway inflammation in persistent asthma: evidence of neutrophilic inflammation and increased sputum interleukin-8. *Chest* 2001;119:1329-36.
- Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218-24.
- Lötvall J, Akdis CA, Bacharier LB, Bjerner L, Casale TB, Custovic A, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011;127:355-60.
- Barnes PJ. The cytokine network in asthma and chronic obstructive pulmonary disease. *J Clin Invest* 2008;118:3546-56.
- James AL, Wenzel S. Clinical relevance of airway remodelling in airway diseases. *Eur Respir J* 2007;30:134-55.
- Brewster CE, Howarth PH, Djukanovic R, Wilson J, Holgate ST, Roche WR. Myofibroblasts and subepithelial fibrosis in bronchial asthma. *Am J Respir Cell Mol Biol* 1990;3:507-11.
- Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999;160:1001-8.
- McGrath KW, Icitovic N, Boushey HA, Lazarus SC, Sutherland ER, Chinchilli VM, et al. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. *Am J Respir Crit Care Med* 2012;185:612-9.
- Barnes PJ. Corticosteroid resistance in patients with asthma and chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2013;131:636-45.
- Bujarski S, Parulekar AD, Sharafkhan A, Hanania NA. The asthma COPD overlap syndrome (ACOS). *Curr Allergy Asthma Rep* 2015;15:509.
- Peters MC, Mekonnen ZK, Yuan S, Bhakta NR, Woodruff PG, Fahy JV. Measures of gene expression in sputum cells can identify TH2-high and TH2-low subtypes of asthma. *J Allergy Clin Immunol* 2014;133:388-94.
- Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol* 2008;8:169-82.
- Reihnsaus E, Innis M, MacIntyre N, Liggett SB. Mutations in the gene encoding for the beta 2-adrenergic receptor in normal and asthmatic subjects. *Am J Respir Cell Mol Biol* 1993;8:334-9.
- Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. *Nat Rev Immunol* 2008;8:183-92.
- Hoffman EA, Simon BA, McLennan G. State of the art: a structural and functional assessment of the lung via multidetector-row computed tomography: phenotyping chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2006;3:519-32.
- Rutgers SR, Postma DS, ten Hacken NH, Kauffman HF, van Der Mark TW, Koëter GH, et al. Ongoing airway inflammation in patients with COPD who do not currently smoke. *Thorax* 2000;55:12-8.
- Agusti A, Faner R. Systemic inflammation and comorbidities in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2012;9:43-6.
- Sinden NJ, Stockley RA. Systemic inflammation and comorbidity in COPD: a result of 'overspill' of inflammatory mediators from the lungs? Review of the evidence. *Thorax* 2010;65:930-6.
- Rennard SI, Locantore N, Delafont B, Tal-Singer R, Silverman EK, Vestbo J, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints. Identification of five chronic obstructive pulmonary disease subgroups with different prognoses in the ECLIPSE cohort using cluster analysis. *Ann Am Thorac Soc* 2015;12:303-12.
- Castaldi PJ, Dy J, Ross J, Chang Y, Washko GR, Curran-Everett D, et al. Cluster analysis in the COPDGen study identifies subtypes of smokers with distinct patterns of airway disease and emphysema. *Thorax* 2014;69:415-22.
- Lee JH, Cho MH, Hersh CP, McDonald ML, Crapo JD, Bakke PS, et al. COPDGen and ECLIPSE Investigators. Genetic susceptibility for chronic bronchitis in chronic obstructive pulmonary disease. *Respir Res* 2014;15:113.
- Stockley RA. Alpha1-antitrypsin review. *Clin Chest Med* 2014;35:39-50.
- Cho MH, McDonald ML, Zhou X, Mattheisen M, Castaldi PJ, Hersh CP, et al. NETT Genetics, ICGN, ECLIPSE and COPDGen Investigators. Risk loci for chronic obstructive pulmonary disease: a genome-wide association study and meta-analysis. *Lancet Respir Med* 2014;2:214-25.
- O'Donnell DE, Aaron S, Bourbonneau J, Hercowitz P, Marciniuk DD, Balter M, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update. *Can Respir J* 2007;14:5B-32.
- Asthma COPD and asthma-COPD overlap syndrome (ACOS). <http://www.ginasthma.org/documents/14>. Accessed June 4, 2015.
- Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax* 2009;64:728-35.
- Hardin M, Silverman EK, Barr RG, Hansel NN, Schroeder JD, Make BJ, et al. COPDGen Investigators. The clinical features of the overlap between COPD and asthma. *Respir Res* 2011;12:127.
- Menezes AM, Pérez-Padilla R, Nadeau G, Wehrmeister FC, Lopez-Varela MV, et al. PLATINA Team. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. *Chest* 2014;145:297-304.

43. Miravittles M, Soriano JB, Ancochea J, Muñoz L, Duran-Tauleria E, Sánchez G, et al. Characterisation of the overlap COPD-asthma phenotype: focus on physical activity and health status. *Respir Med* 2013;107:1053-60.
44. Barrecheguren M, Esquinas C, Miravittles M. The asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS): opportunities and challenges. *Curr Opin Pulm Med* 2015;21:74-9.
45. Fabbri LM, Romagnoli M, Corbetta L, Casoni G, Busljetic K, Turato G, et al. Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003;167:418-24.
46. Jensen EJ, Pedersen B, Narvestad E, Dahl R. Blood eosinophil and monocyte counts are related to smoking and lung function. *Respir Med* 1998;92:63-9.
47. Fauler J, Frolich JC. Cigarette smoking stimulates cysteinyl leukotriene production in man. *Eur J Clin Invest* 1997;27:43-7.
48. Thornton WH Jr, Adelstein EH, Edes TE. Leukotriene B4 is measurable in serum of smokers and nonsmokers. *Clin Chem* 1989;35:459-60.
49. Miller M, Ramsdell J, Friedman PJ, Cho JY, Renvall M, Broide DH. Computed tomographic scan-diagnosed chronic obstructive pulmonary disease-emphysema: eotaxin-1 is associated with bronchodilator response and extent of emphysema. *J Allergy Clin Immunol* 2007;120:1118-25.
50. Sunyer J, Springer C, Jamieson B, Conover C, Detels R, Rinaldo C, et al. Effects of asthma on cell components in peripheral blood among smokers and non-smokers. *Clin Exp Allergy* 2003;33:1500-5.
51. Bass DA. Behavior of eosinophil leukocytes in acute inflammation, II: eosinophil dynamics during acute inflammation. *J Clin Invest* 1975;56:870-9.
52. Adcock IM. Molecular mechanisms of glucocorticosteroid actions. *Pulm Pharmacol Therapeut* 2000;13:115-26.
53. Barnes PJ. Inhaled corticosteroids are not beneficial in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161:342-4. discussion 344.
54. Ito K, Lim S, Caramori G, Chung KF, Barnes PJ, Adcock IM. Cigarette smoking reduces histone deacetylase 2 expression, enhances cytokine expression, and inhibits glucocorticoid actions in alveolar macrophages. *FASEB J* 2001;15:1110-2.
55. Ito K, Caramori G, Lim S, Oates T, Chung KF, Barnes PJ, et al. Expression and activity of histone deacetylases in human asthmatic airways. *Am J Respir Crit Care Med* 2002;166:392-6.
56. Cosío BG, Mann B, Ito K, Jazrawi E, Barnes PJ, Chung KF, et al. Histone acetylase and deacetylase activity in alveolar macrophages and blood monocytes in asthma. *Am J Respir Crit Care Med* 2004;170:141-7.
57. Barnes PJ. Reduced histone deacetylase in COPD: clinical implications. *Chest* 2006;129:151-5.
58. Alsaedi A, Sin DD, McAlister FA. The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review of randomized placebo-controlled trials. *Am J Med* 2002;113:59-65.
59. Keatings VM, Jatakanon A, Worsdell YM, Barnes PJ. Effects of inhaled and oral glucocorticoids on inflammatory indices in asthma and COPD. *Am J Respir Crit Care Med* 1997;155:542-8.
60. Donohue JF, Herje N, Crater G, Rickard K. Characterization of airway inflammation in patients with COPD using fractional exhaled nitric oxide levels: a pilot study. *Int J Chron Obstruct Pulmon Dis* 2014;9:745-51.
61. Dummer JF, Epton MJ, Cowan JO, Cook JM, Condliffe R, Landhuis CE, et al. Predicting corticosteroid response in chronic obstructive pulmonary disease using exhaled nitric oxide. *Am J Respir Crit Care Med* 2009;180:846-52.
62. Papi A, Romagnoli M, Baraldo S, Braccioni F, Guzzinati I, Saetta M, et al. Partial reversibility of airflow limitation and increased exhaled NO and sputum eosinophilia in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;162:1773-7.
63. Hardin M, Cho M, McDonald ML, Beaty T, Ramsdell J, Bhatt S, et al. The clinical and genetic features of COPD-asthma overlap syndrome. *Eur Respir J* 2014;44:341-50.
64. Christenson SA, Steiling K, van den Berge M, Hijazi K, Hiemstra PS, Postma DS, et al. Asthma-COPD overlap: clinical relevance of genomic signatures of type 2 inflammation in COPD. *Am J Respir Crit Care Med* 2015;191:758-66.
65. Lange P, Scharling H, Ulrik CS, Vestbo J. Inhaled corticosteroids and decline of lung function in community residents with asthma. *Thorax* 2006;61:100-4.
66. Miravittles M, Soler-Cataluna JJ, Calle M, Molina J, Almagro P, Quintano JA, et al. Spanish guideline for COPD (GesEPOC): update 2014. *Arch Bronconeumol* 2014;50:1-16.
67. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;170:836-44.
68. Magnussen H, Bugnas B, van Noord J, Schmidt P, Gerken F, Kesten S. Improvements with tiotropium in COPD patients with concomitant asthma. *Respir Med* 2008;102:50-6.
69. Lim HS, Choi SM, Lee J, Park YS, Lee SM, Yim JJ, et al. Responsiveness to inhaled corticosteroid treatment in patients with asthma-chronic obstructive pulmonary disease overlap syndrome. *Ann Allergy Asthma Immunol* 2014;113:652-7.
70. Higgins BG, Powell RM, Cooper S, Tattersfield AE. Effect of salbutamol and ipratropium bromide on airway calibre and bronchial reactivity in asthma and chronic bronchitis. *Eur Respir J* 1991;4:415-20.
71. Soler X, Ramsdell J. Anticholinergics/antimuscarinic drugs in asthma. *Curr Allergy Asthma Rep* 2014;14:484.
72. Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, et al. National Heart, Lung, and Blood Institute Asthma Clinical Research Network. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010;363:1715-26.
73. Lazarus SC, Chinchilli VM, Rollings NJ, Boushey HA, Cherniack R, Craig TJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med* 2007;175:783-90.
74. Welte T, Miravittles M, Hernandez P, Eriksson G, Peterson S, Polanowski T, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;180:741-50.
75. Nadeem NJ, Taylor SJ, Eldridge SM. Withdrawal of inhaled corticosteroids in individuals with COPD—a systematic review and comment on trial methodology. *Respir Res* 2011;12:107.
76. van der Valk P, Monninkhof E, van der Palen J, Zielhuis G, van Herwaarden C. Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. *Am J Respir Crit Care Med* 2002;166:1358-63.
77. Wouters EF, Postma DS, Fokkens B, Hop WC, Prins J, Kuipers AF, et al. COSMIC (COPD and Seretide: a Multi-Center Intervention and Characterization) Study Group. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. *Thorax* 2005;60:480-7.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.