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PERSPECTIVES

GOLD 2021 Strategy Report: Implications for Asthma–COPD Overlap

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Abstract: In its 2021 strategy report, the Global Initiative for Chronic Obstructive Lung Disease states: "we no longer refer to asthma-COPD overlap (ACO), instead we emphasize that asthma and COPD are different disorders, although they may […] coexist in an individual patient. If a concurrent diagnosis of asthma is suspected, pharmacotherapy should primarily follow asthma guidelines, but pharmacological and non-pharmacological approaches may also be needed for their COPD." What does this mean for the treating physician? In this review, we explore the implications of this new guidance on treating patients with chronic obstructive pulmonary disease, arguing for a personalized approach to treatment.

Keywords: COPD, asthma, asthma–COPD overlap, inhaled corticosteroid, bronchodilator

ACO: No Longer Fit for Purpose?

The coexistence of asthma and COPD in the same patient is not a new concept, with references in the literature dating back to the 1760s.[1] First coined by Gibson et al in 2009,[2] asthma–COPD overlap (ACO) has gathered much global interest in the past decade, resulting in >350 publications on the subject within the past 5 years alone (PubMed search string as of 09 March 2021: "asthma-COPD overlap"). So why, despite this increased knowledge and interest in ACO,[3] has Global Initiative for Chronic Obstructive Lung Disease (GOLD) chosen to revise its position?[4] The answer to this may lie in the lack of a unified definition for ACO. In 2015, a Global Initiative for Asthma (GINA)/GOLD joint publication was developed by the Science Committees of both GINA and GOLD based on a review of available literature.[5] It defined ACO syndrome as characterized by persistent airflow limitation, with several features usually associated with asthma and several features usually associated with COPD. However, it also acknowledged that a specific definition was not possible due to the lack of evidence. Some consensus documents, such as those from Spain[6,7] and the Czech Republic,[8] describe ACO using diagnostic criteria, though the latest update to the Spanish document does not include ACO.[9] Similarly, ACO was addressed in the 2017 update of the Canadian Thoracic Society position statement[10] on the treatment of COPD, but was not included in the 2019 update due to a lack of evidence.[11] Since the 2015 GINA/GOLD consensus document was published,[5] there have been some attempts to work towards a consensus definition.[12] However, research into ACO has been limited, with no randomized controlled trials conducted and no clear consensus on how to define or diagnose the condition.

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Some physicians and researchers still consider ACO to be a specific syndrome,[13] and use of the term may have been helpful in some situations for primary care providers to ensure that characteristics of asthma in patients with COPD are identified and addressed.[14] However, the inclusion of heterogeneous populations of patients under the same term and the absence of clinical trial data to guide treatment may make treatment decisions challenging.[13] Many physicians and researchers see ACO as a theoretical construct with no clear biologic grounds and an imprecise definition that encompasses both long-standing asthmatics who smoke and develop chronic airflow obstruction, and patients with COPD who have blood eosinophilia or greater reversibility after a bronchodilator test.[7] Where lack of clarity in the definition of a disease exists, so too does a lack of confidence in its diagnosis and treatment. Some consensus documents contain precise classification criteria for ACO which can be used to assess prevalence in specific countries.[6,8] However, the lack of an internationally accepted definition means that accurate comparisons of the disease epidemiology cannot be made between countries. Our own systematic review of seven studies, which included a total of >36,700 patients across 20 countries, revealed a relatively low prevalence of 1.8–15.9%.[15–21] However, interpreting these studies is complicated by a lack of consistency in terms of patient selection (diagnostic criteria), definitions of pulmonary function impairment, and concomitant medication received by patients.[22] In short, the complexities surrounding the definition and diagnosis of ACO may be the driving force behind the recent change in the GOLD 2021 strategy report. The consequence of all this for primary care physicians is potential confusion and a lack of clarity on how to treat patients with COPD who show features of asthma. In the following section, we consider how best to treat this complex patient population.

Differential Diagnosis and Tailored Treatment

In no longer referring to the term "ACO" and increasing the emphasis on a treatment approach tailored to COPD and/or asthma,[4] GOLD puts the focus on personalized medicine – a concept gaining traction across many disease areas. Personalized medicine targets the individual needs of patients on the basis of the genetic, biomarker, phenotypic or psychosocial characteristics that distinguish them.[23] In essence, the new GOLD 2021 strategy report endorses a personalized approach, acknowledging that there are cases where COPD and asthma can coexist, and in these cases, "pharmacotherapy should primarily follow asthma guidelines"[4] (ie, use of inhaled corticosteroids [ICS]). However, in a new patient presenting with respiratory symptoms, it is important not to simply assume COPD with concomitant asthma without careful consideration of the presenting features.[4] The features of COPD and asthma are summarized in Table 1.

In order to make a confident diagnosis of concomitant asthma, we must consider the patient with COPD and ask how asthma was diagnosed. Misdiagnosis between COPD and other respiratory diseases – especially asthma – is common and may lead to inadequate treatment.[24] For the treatment of asthma, the most effective medication currently available remains low- or high-dose ICS,[25] whereas for COPD, the cornerstone of treatment is inhaled long-acting bronchodilators (alone or in combination), with ICS reserved as an add-on therapy for patients who are highly symptomatic, have a severe exacerbation history and high eosinophil count.[4] But what about patients with a history of asthma (perhaps diagnosed in childhood) who are not currently receiving any treatment – not even short-acting bronchodilators for symptomatic relief? Is it appropriate to treat these patients with ICS? Confusing a history of asthma with concomitant (and clinically relevant) asthma on presentation might lead physicians to favor a treatment choice that covers both diagnoses, even if their asthma was a feature early in life but is no longer clinically relevant.[26] Because primary care physicians often lack resources to help differentiate COPD from asthma such as spirometry, FeNO, full pulmonary function tests and computed tomography scans, they may rely on the historical diagnosis of asthma to guide their treatment choices, choosing to cover all bases by prescribing bronchodilators together with ICS. A current prescription for asthma medication or a history of asthma exacerbations in the years preceding consultation may therefore be the best confirmatory signals for asthma; if these are not available, re-assessment of bronchodilator responsiveness and eosinophil count should be carried out (Figure 1). Ultimately, using diagnostic markers that have a high specificity gives a high degree of confidence in "ruling in" or identifying the presence of a particular trait,[27] such as asthma.

According to GINA, one of the diagnostic criteria for asthma is a post-bronchodilator increase in forced expiratory volume in 1 second (FEV_1) of >12% and 200 mL from baseline (indicating reversible airflow limitation),

Table 1 Summary of Characteristics of COPD and Asthma

	COPD	Asthma
Definition	Disease characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by environmental exposure to noxious particles or gases	Disease usually characterized by chronic airway inflammation causing respiratory symptoms that vary over time, and variable expiratory airflow limitation
Symptoms	Dyspnea, cough, sputum production	Wheezing, dyspnea, chest tightness, cough
Risk factors	Smoking, occupational exposures, environmental exposures	Smoking, family history of asthma or allergy, history of allergic rhinitis or eczema, childhood respiratory infection, exposure to irritants
Spirometry	Post-bronchodilator FEV_1/FVC <0.70	Positive bronchodilator reversibility (in adults: increase in FEV_1 of >12% and >200mL 10–15 mins after salbutamol)
Indicators	Age >40 years; dyspnea, chronic cough and/or chronic sputum production; recurrent lower respiratory tract infections; exposure to environmental risk factors; family history of COPD	Symptoms vary over time and in intensity; symptoms triggered by infections, exercise, allergen or irritant exposure; respiratory symptoms in childhood; family history of allergy or asthma
Comorbidities	Cardiovascular disease, lung cancer, osteoporosis, anxiety and depression, metabolic syndrome and diabetes, GERD, bronchiectasis, obstructive sleep apnea and cognitive impairment	Obesity, GERD, anxiety and depression, food allergy and anaphylaxis, rhinitis, sinusitis and nasal polyps
Role of blood eosinophils	Predict response to ICS	Predict future exacerbations and possible undertreatment
Other disease markers	Decline in FEV_1 or markers of chronic hyperinflation	Sputum eosinophils and FeNO levels

Note: Data from these studies.[4,25]

Abbreviations: COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroids.

with an increase of >15% and 400 mL providing greater confidence in the diagnosis.[25] In line with this, the GINA/GOLD publication[5] and other consensus documents[7] define a post-bronchodilator increase in FEV_1 of 400 mL from baseline (ie, marked reversibility) as compatible with a diagnosis of ACO, but unlikely to be indicative of COPD, suggesting that this threshold might be useful for differential diagnosis. However, reversibility may not be the most reliable diagnostic tool, as large-scale studies have shown that bronchodilator responsiveness is at least as common in COPD as in asthma. Thus, measures of reversibility alone may be of limited value for differentiating between patients with asthma and COPD, and those with both.[28]

So, what is the harm in treating a patient with COPD and suspected (but unconfirmed) or historical (and no longer clinically relevant) asthma with an ICS? It has been suggested that the main reason for diagnosing concomitant asthma in patients with COPD is to identify those who are likely to have a better response to ICS.[7] This is the correct motive, as the effectiveness of ICS (normally prescribed in combination with a long-acting β_2-agonist [LABA]) in preventing exacerbations is well established.[29] But how should these patients be identified? Rather than relying on a historical diagnosis of asthma or bronchodilator responsiveness (as discussed), blood eosinophilia may be a more useful guide. In the MAJORICA study, for example, 27.4% of 603 patients with COPD fulfilled the 2015 GINA/GOLD definition of ACO.[30] These patients were more frequently treated with ICS and had a better prognosis relative to patients with COPD alone in terms of healthcare utilization (emergency department visits and all-cause hospitalizations). Assessment of the heterogeneity of these patients classified under the ACO umbrella showed that the prognosis of patients with eosinophilic COPD (COPD-Eo) differed from that of patients with a previous diagnosis of asthma.[30] Thus, from a practical point of view, distinguishing patients with

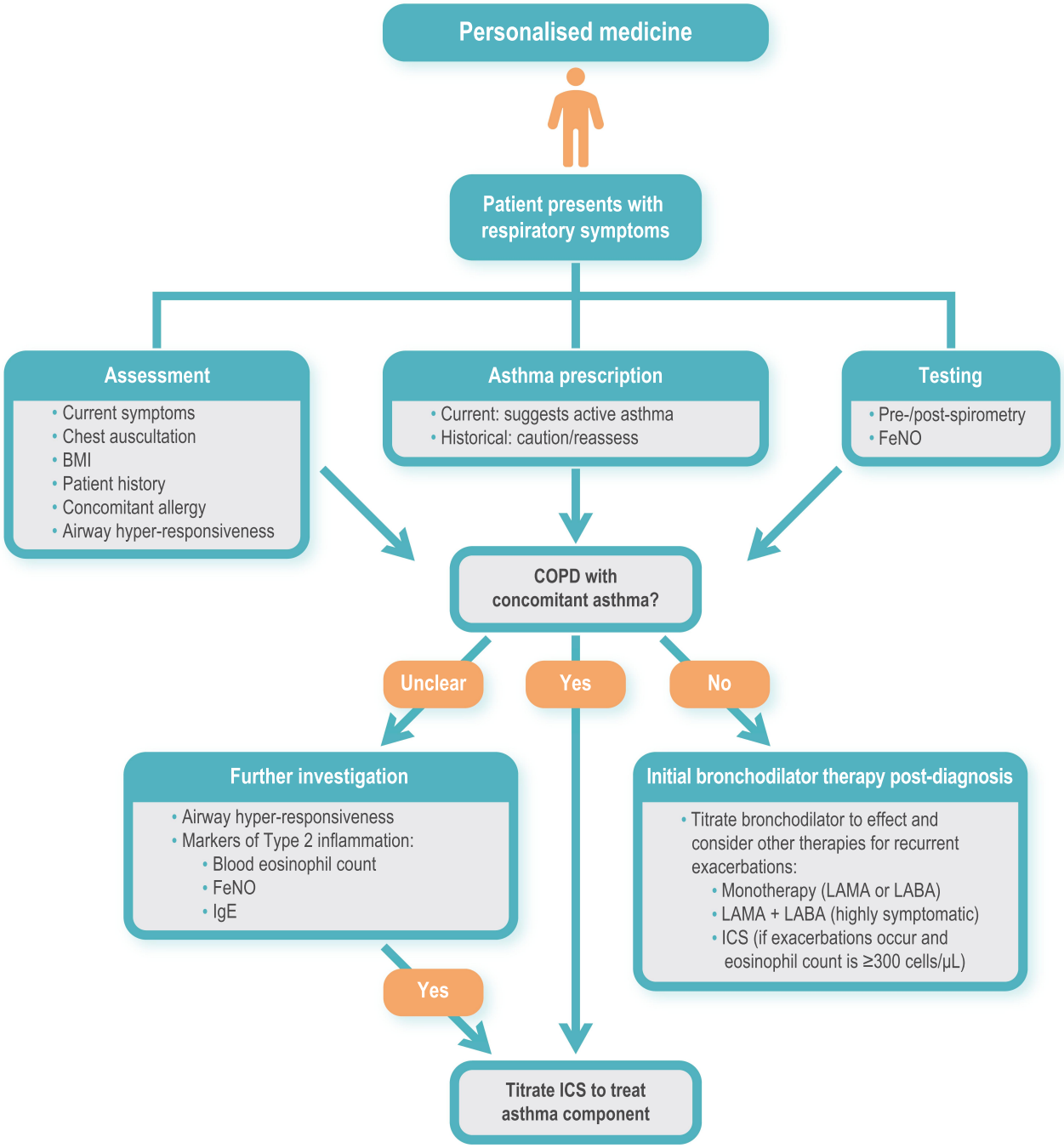

Figure 1 Assessments to guide treatment choice for patients with COPD presenting with asthma symptoms.
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist.

COPD-Eo from those with a historical diagnosis of asthma may help to determine which patients would benefit most from ICS (though referral to a specialist center may be required to ascertain this). In abandoning the term ACO (in line with GOLD), it may be more useful then to consider T helper type 2 (Th2) in the blood as a surrogate marker (ie, treatable trait) of airway eosinophilia.[30] Increased levels of Th2 are associated with increased severity of COPD and "asthma-like" features (including a favorable corticosteroid response), suggesting that Th2 inflammation is important in a COPD subset that cannot be identified by a clinical history of asthma alone.[31] Additionally, serum levels of immunoglobulin E antibody and fractional exhaled nitric oxide are

useful biomarkers in identifying the Th2 asthma phenotype (Figure 1).[32,33]

Prescription of ICS for patients who do not have clinical features suggesting steroid responsiveness is associated with certain risks. Singh et al have estimated that the relative risk of severe pneumonia in patients with COPD was significantly higher when treated with ICS (1.57 [95% confidence interval 1.41–1.75]).[34] Pneumonia is a well-documented side effect of ICS,[35] but there are others, including tuberculosis,[36] osteoporosis with potential airflow obstruction,[37,38] diabetes,[39] adverse metabolic effects,[40] glaucoma,[41] cataracts[42] and disruption of the lung microbiome,[43] and mycobacteria-associated bronchiectasis,[44] Therefore, the clinician must evaluate the risk–benefit ratio in each patient before the prescription of an ICS, taking the time to make a careful differential diagnosis to identify those patients with asthmatic features who are most likely to benefit (Figure 1).[7]

The similarities shared by COPD and asthma have the potential to confound diagnosis, but it is important to recognize that there are differentiating features – from etiology, symptoms, type of airway inflammation, inflammatory cells and mediators, consequences of inflammation, response to therapy, and disease course.[45] GOLD 2021 still recognizes that asthma and COPD may coexist in a patient; however, estimates of ACO prevalence vary (as previously discussed) and some evidence suggests that asthma is over-diagnosed in patients with COPD.[18] The following basic principle therefore holds true: if there are features of COPD, then the recommendations of GOLD should be followed, namely treat first with bronchodilators based on the GOLD ABCD classification (monotherapy or dual therapy), reserving treatment with ICS for patients in group D only, ie, those who are highly symptomatic (modified Medical Research Council grade 2 or COPD Assessment Test score ≥10) and have a history of two or more exacerbations per year (or one or more exacerbation leading to hospitalization).[4] Furthermore, use of ICS (in the form of LABA/ICS or LAMA/LABA/ICS) in these patients should only be considered if they have an eosinophil count higher than 300 eosinophils/μL (Figure 1), with the benefits of use in patients with levels between 100 and 300 less clear, and <100 possibly causing harm.[46] However, the potential instability of eosinophil counts over time must be considered, as evidence from a large, population-based study suggests that the stability of blood eosinophil counts is significantly lower in patients with COPD compared with control subjects (85% stability after 6 months, declining to 65% at 2 years and progressively thereafter), with age and sex having a significant impact. Thus, more frequent reassessment of eosinophilia in patients with COPD may be advisable.[47] In asthma, tiotropium can be added to LABA/ICS to help improve lung function and prevent exacerbations,[25] and single-device triple therapies (combining other long-acting muscarinic antagonists with LABA/ICS) are now available in Europe and the USA.[48,49] For both COPD and asthma, non-pharmacologic management (vaccination, smoking cessation, trigger management, exercise, diet, inhaler technique and adherence to therapy) must also be considered as part of the holistic management of their disease.[4,25]

For a patient with COPD, a diagnosis of concomitant asthma must be thoroughly considered and based on an individualized assessment – in order to weigh up the benefits and risks of treating the individual with ICS. The use of ICS should also be considered in patients with eosinophilic COPD, taking into account the number of exacerbations and their triggers. For all other patients with COPD, disease management should follow guideline recommendations for the use of bronchodilator therapy.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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