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Asthma and COPD overlap (ACO)

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Definition

- patients with airway disease who have features of both asthma and COPD

- No single, universally accepted definition of ACO has emerged.

In 2015, GINA and GOLD released a joint statement describing what was then called ACOS, as "persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD", identifiable in clinical practice by the features shared with both asthma and COPD

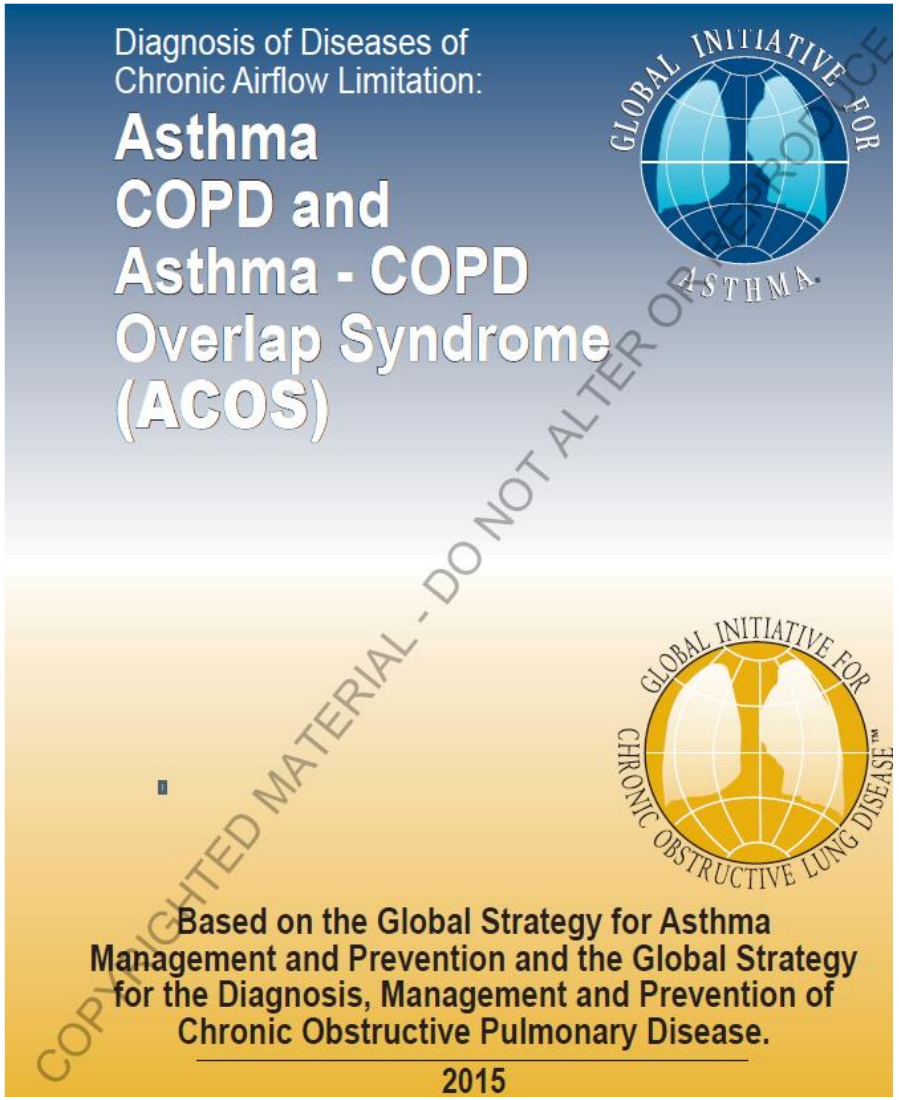


Table 1. Four Examples of Patients with Obstructive Airway Disease.*

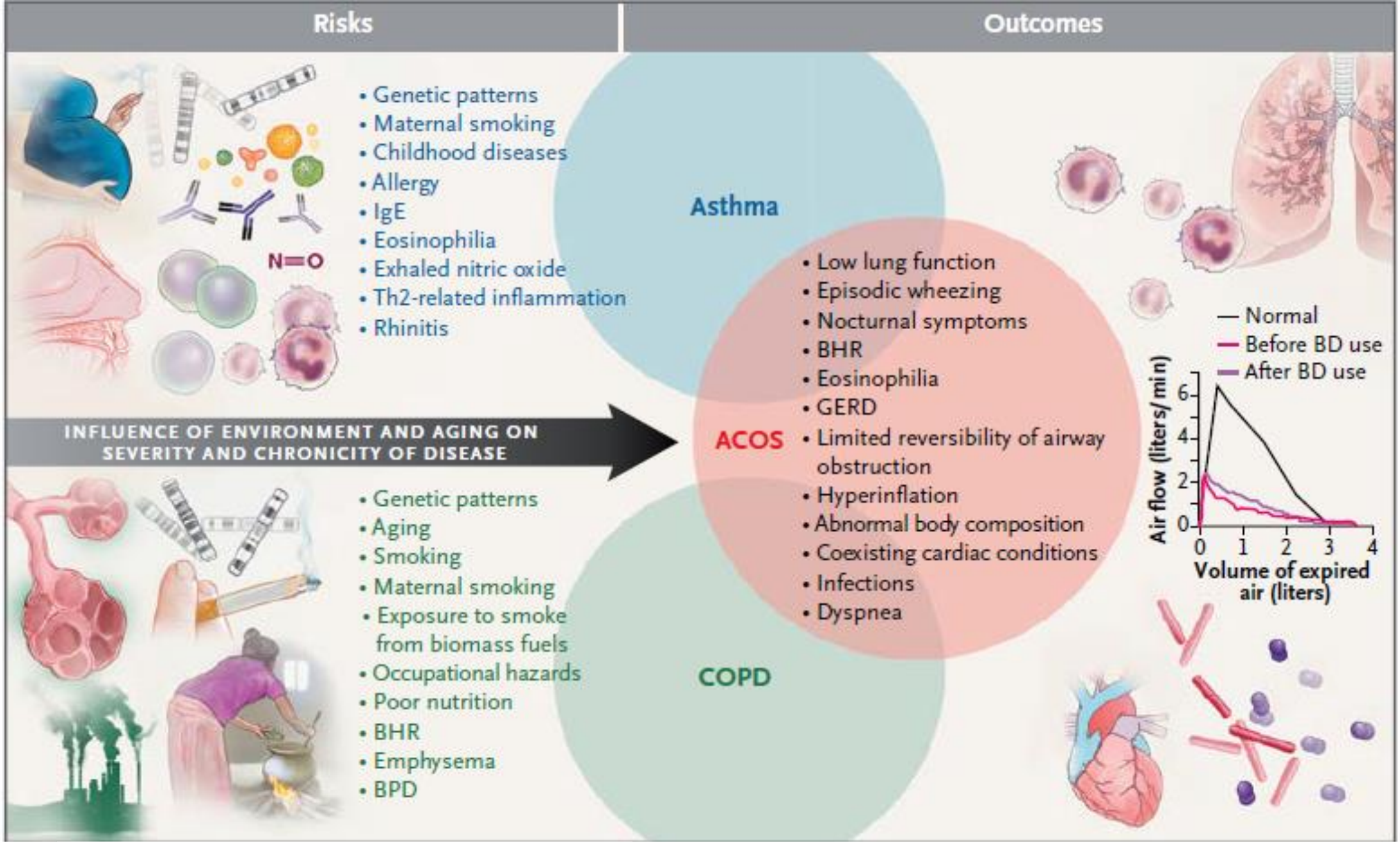
Characteristic	Patient with "Easy" Asthma	Patient with "Easy" COPD	Patient with ACOS Stemming from Asthma	Patient with ACOS Stemming from COPD
Age (yr)	21	65	45	45
Atopy	Yes	No	Yes	Yes
Current smoker	No	Yes	No	Yes
Pack-years	0	95	0	20
Dyspnea	Recurrent	Chronic	Chronic with flares	Chronic with flares
Wheezing	Yes	No	Yes	Yes
Reversible airway obstruction	Yes	No	No	Yes
Bronchial hyperresponsiveness	Yes	No	Yes	Yes or no

REVIEW ARTICLE

Jeffrey M. Drazen, M.D., *Editor*

The Asthma–COPD Overlap Syndrome

N ENGL J MED 373;13 NEJM.ORG SEPTEMBER 24, 2015


Risks
Outcomes
• Genetic patterns
• Maternal smoking
• Childhood diseases
• Allergy
• IgE
• Eosinophilia
• Exhaled nitric oxide
• Th2-related inflammation
• Rhinitis
N=O
Asthma
• Low lung function
• Episodic wheezing
• Nocturnal symptoms
• BHR
• Eosinophilia
• GERD
ACOS
• Limited reversibility of airway obstruction
• Hyperinflation
• Abnormal body composition
• Coexisting cardiac conditions
• Infections
• Dyspnea
INFLUENCE OF ENVIRONMENT AND AGING ON SEVERITY AND CHRONICITY OF DISEASE
• Genetic patterns
• Aging
• Smoking
• Maternal smoking
• Exposure to smoke from biomass fuels
• Occupational hazards
• Poor nutrition
• BHR
• Emphysema
• BPD
COPD
Normal
Before BD use
After BD use
Air flow (liters/min)
Volume of expired air (liters)

ATS/NHLBI WORKSHOP

American Thoracic Society/National Heart, Lung, and Blood Institute Asthma–Chronic Obstructive Pulmonary Disease Overlap Workshop Report

- A major conclusion of the workshop is that ACO, like asthma and COPD, does not represent a single discrete disease entity
- patients, for instance, who have a long-standing history of asthma, in addition to having a modest smoking history and fixed airflow obstruction
- Patients with COPD who have features of asthma, such as bronchodilator responsiveness and peripheral eosinophilia, could also be described as having ACO

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

2019 REPORT

- In contrast, the 2020 GOLD Strategy update abandoned use of the term “asthma COPD overlap” arguing that asthma and COPD are different disorders that may share common features such as eosinophilia or some degree of reversibility
- asthma and COPD may coexist in an individual patient and that, if concurrent diagnoses are suspected, pharmacotherapy should primarily follow asthma guidelines although COPD specific therapy approaches may also be needed in some patients.

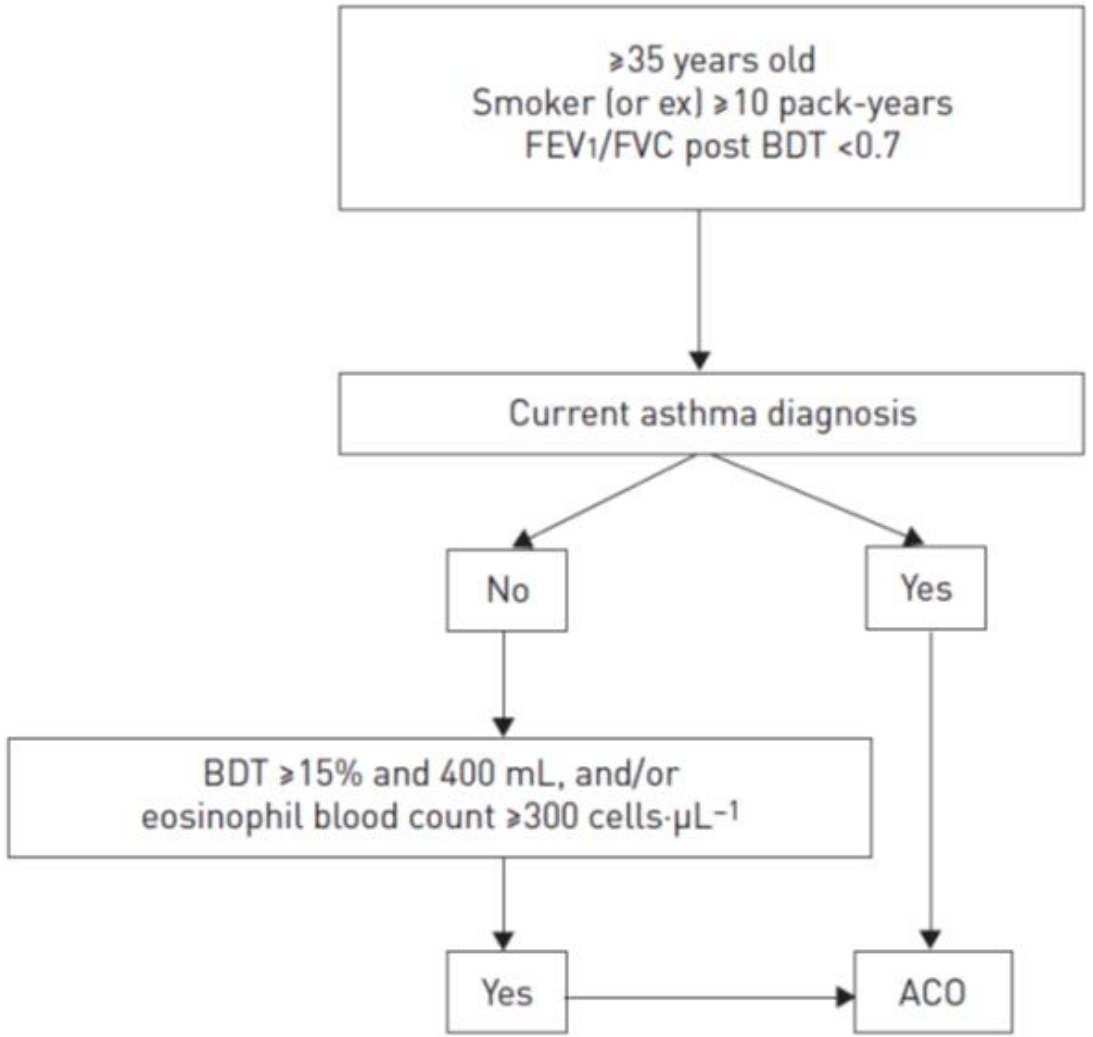
Study	Major criteria	Minor criteria	Diagnosis
Gibson, 2009 [1]	■ Clinical symptoms of chronic airway disease, $FEV_1/FVC < 70\%$ ■ $FEV_1 < 80\%$ ■ Bronchial hyper-responsiveness defined as a PD15 < 12 mL (provocative dose of hypertonic saline that induces a 15% fall in FEV_1)		3 major criteria

Soler-Cataluna, 2011 [2]	COPD plus: ■ Positive bronchodilator test defined by increase in FEV_1 $\geq 15\%$ and ≥ 400 mL ■ Sputum eosinophilia ■ History of asthma	COPD plus: ■ High total serum IgE ■ Personal history of atopy ■ Positive bronchodilator test, ie, increase in FEV_1 $\geq 12\%$ and ≥ 200 mL over baseline on ≥ 2 occasions	2 major criteria **OR** 1 major criteria **AND** 2 minor criteria

Global Initiative for Asthma (GINA). Diagnosis and initial treatment of asthma, COPD, and asthma-COPD overlap: A joint project of GINA and GOLD updated April 2017

Miravittles, 2017 [8]	■ Age > 35 years ■ Postbronchodilator $FEV_1/FVC < 70\%$ ■ ≥ 10 pack years tobacco smoke	■ Current diagnosis of asthma ■ No current diagnosis of asthma but a bronchodilator response to albuterol ≥ 15% and 400 mL and/or blood eosinophils ≥ 300 cells/microL	3 major criteria **AND** 1 minor criteria

Miravitlles M, Alvarez-Gutierrez FJ, Calle M, et al. Algorithm for identification of asthma-COPD overlap: consensus between the Spanish COPD and asthma guidelines. Eur Respir J 2017; 49.


≥35 years old
Smoker (or ex) ≥10 pack-years
FEV1/FVC post BDT <0.7
Current asthma diagnosis
No
Yes
BDT ≥15% and 400 mL, and/or
eosinophil blood count ≥300 cells·μL−1
Yes
ACO

Feature	Asthma	COPD	ACOS
Age of onset	Usually childhood onset but can commence at any age.	Usually > 40 years of age	Usually age ≥40 years, but may have had symptoms in childhood or early adulthood
Pattern of respiratory symptoms	Symptoms may vary over time (day to day, or over longer periods), often limiting activity. Often triggered by exercise, emotions including laughter, dust or exposure to allergens	Chronic usually continuous symptoms, particularly during exercise, with 'better' and 'worse' days	Respiratory symptoms including exertional dyspnea are persistent but variability may be prominent
Lung function	Current and/or historical variable airflow limitation, e.g. BD reversibility, AHR	FEV_1 may be improved by therapy, but post-BD $FEV_1/FVC < 0.7$ persists	Airflow limitation not fully reversible, but often with current or historical variability
Lung function between symptoms	May be normal between symptoms	Persistent airflow limitation	Persistent airflow limitation
Past history or family history	Many patients have allergies and a personal history of asthma in childhood, and/or family history of asthma	History of exposure to noxious particles and gases (mainly tobacco smoking and biomass fuels)	Frequently a history of doctor-diagnosed asthma (current or previous), allergies and a family history of asthma, and/or a history of noxious exposures
Time course	Often improves spontaneously or with treatment, but may result in fixed airflow limitation	Generally, slowly progressive over years despite treatment	Symptoms are partly but significantly reduced by treatment. Progression is usual and treatment needs are high
Chest X-ray	Usually normal	Severe hyperinflation & other changes of COPD	Similar to COPD
Exacerbations	Exacerbations occur, but the risk of exacerbations can be considerably reduced by treatment	Exacerbations can be reduced by treatment. If present, comorbidities contribute to impairment	Exacerbations may be more common than in COPD but are reduced by treatment. Comorbidities can contribute to impairment
Airway inflammation	Eosinophils and/or neutrophils	Neutrophils ± eosinophils in sputum, lymphocytes in airways, may have systemic inflammation	Eosinophils and/or neutrophils in sputum.

If ≥3 items are present for either asthma or COPD, the patient is likely to have that disease
A similar number of items for asthma and COPD is suggestive for ACO

EPIDEMIOLOGY

- It is difficult to establish an exact disease burden for ACO when no single definition has emerged

- the prevalence of ACO in the general population is between 2 to 3 percent, with estimates for asthma and COPD in these same populations being roughly 5 to 17 percent for asthma and 2 to12 percent for COPD

EPIDEMIOLOGY

- ACO patients tend to be female and have a higher BMI, lower socioeconomic status, and lower education level than patients with COPD

- patients with ACO may have poorer disease control with respect to lung function, exacerbation rates, and respiratory symptoms than those with asthma or COPD without overlap

Hardin M, Silverman EK, Barr RG, et al. The clinical features of the overlap between COPD and asthma. Respir Res 2011; 12:127

Vaz Fragoso CA, Murphy TE, Agogo GO, et al. Asthma-COPD overlap syndrome in the US: a prospective population-based analysis of patientreported outcomes and health care utilization. Int J Chron Obstruct PulmonDis 2017; 12:517

CLINICAL FEATURES

- age 40 years or older
- respiratory symptoms including exertional dyspnea, persistent partially reversible airflow obstruction (without normalization of obstruction
- history of atopy and/or allergies
- clinical features may include ≥10 pack-years tobacco smoking and documented history of asthma before the age of 40 year
- As with both asthma and COPD, periodic exacerbations of these symptoms have been described in ACO

Laboratory

- Elevated total serum immunoglobulin E (IgE; >100 international units/mL)
- Elevated peripheral blood eosinophil count (>300 cells/microL)
- evidence of allergic disease (eg, skin testing or immunoassays for perennial allergen sensitivity) may point a clinician to asthma or ACO.

- Elevated sputum eosinophil counts, if available, are more common in asthma or ACO than COPD

Pulmonary function tests

- Measurement of spirometry pre- and postbronchodilator is an essential component of the evaluation of airway disease and is used to confirm airflow limitation (forced expiratory volume in one second/forced vital capacity [FEV_1/FVC] <0.7).
- After inhaled bronchodilator, the FEV_1/FVC may occasionally be ≥0.7 in patients with ACO, but this is unusual and more typical of asthma

DIFFERENTIAL DIAGNOSIS

- **Bronchiectasis**
- **Obliterative bronchiolitis**
- **Central airway obstruction**
- **Diffuse panbronchiolitis**

treatment

- **Nonpharmacologic therapy**
  - **Smoking cessation**
  - **Vaccination**
  - **Inhaler technique**
  - **Allergen avoidance**
  - **Pulmonary rehabilitation**

Pharmacotherapy

- regular therapy with a regimen that includes ICS in low to moderate doses
- ICS are considered appropriate in ACO, as they are a mainstay of asthma therapy
- All patients with ACO should have immediate access to an inhaled bronchodilator with a rapid onset of action (eg, short-acting beta agonist, short-acting muscarinic antagonist, or combination) for as-needed symptom relief.

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. vbs://ginasthma.org (Accessed on October 22, 2019).

Pharmacotherapy

- LABA monotherapy should be avoided, as in asthma

- **LABA-ICS** – A randomized, open-label, crossover study in 16 patients with ACO (defined as the combination of fixed airflow obstruction with airway hyperresponsiveness demonstrated by methacholine inhalation challenge) demonstrated a significant improvement in forced expiratory volume in one second (FEV_1) after four weeks of once daily fluticasone furoate/vilanterol, compared with a run-in phase of twice daily fluticasone propionate-salmeterol

Ishiura Y, Fujimura M, Shiba Y, et al. A comparison of the efficacy of oncedaily fluticasone furoate/vilanterole with twice-daily fluticasone propionate/salmeterol in asthma-COPD overlap syndrome. Pulm Pharmacol Ther 2015; 35:28.

Triple therapy (LAMA-LABA-ICS)

- A randomized, open-label crossover pilot study in 17 patients with ACO found that adding umeclidinium(LAMA) to fluticasone furoate/vilanterol (ICS/LABA) achieved a greater improvement in forced expiratory volume in one second (FEV_1) after four weeks, than continuing fluticasone furoate/vilanterol without umeclidinium

Ishiura Y, Fujimura M, Ohkura N, et al. Effect of triple therapy in patients with asthma-COPD overlap . Int J Clin Pharmacol Ther 2019; 57:384

Biologic agents

- Patients with persistent symptoms or exacerbations despite triple inhaled therapy should be evaluated for features that might suggest benefit from one of the biologic agents (eg, omalizumab, mepolizumab, benralizumab,reslizumab) that have been developed for asthma (eg, sensitivity to perennial allergens, elevated total serum IgE, and/or peripheral blood eosinophilia).
- While awaiting data in patients with ACO, expert typically use the same criteria that are used in severe persistent asthma when selecting among biologic agents

CONCLUSION

- ACO is likely not a single disease, nor even a syndrome from a clinical or mechanistic perspective

- Research efforts are needed to better understand asthma and COPD phenotypes and what types of biomarkers (physiologic, radiologic, or biologic) help to distinguish patients that are most responsive to specific therapies