Clinical, functional and biomarkers criteria for the diagnosis of asthma-chronic obstructive pulmonary diseases overlap (ACO)

Ben Porath, Lilach Yael

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Lilach Yael Ben-Porat

CLINICAL, FUNCTIONAL AND BIOMARKERS CRITERIA FOR THE DIAGNOSIS OF ASTHMA-CHRONIC OBSTRUCTIVE PULMONARY DISEASES OVERLAP (ACO)

GRADUATION PAPER

Zagreb 2021

This graduation thesis was made at
the University Hospital Centre Zagreb, Clinic for Lung Diseases Jordanovac,
under the supervision of Prof. Dr. Sanja Popović-Grle

This paper was submitted for evaluation in the academic year 2020/2021.

Head of the Department: Academician Miroslav Samaržija

Mentor: Prof. Dr. Sanja Popović-Grle

Table of contents:

Abbreviations

ACO Asthma-COPD Overlap

AHR Airway Hyperresponsiveness

BDR Bronchodilator Response/Responsiveness

BD Bronchodilator

COPD Chronic Obstructive Pulmonary Disease

FAO Fixed Airflow Obstruction

FeNO Fraction of Exhaled Nitric Oxide

PPB parts per billion

FEV1 Forced Expiratory Volume in 1 Second

FVC Forced Vital Capacity

GINA Global Initiative for Asthma Committee

GOLD Global Obstructive Lung Disease Committee HR - Hazard Ratio ICS - Inhaled Corticosteroid

LABA Long-Acting Beta-Adrenoceptor Agonist

LAMA Long-Acting Muscarinic Antagonist

SABAs Short-Acting B2AR Agonists

GWAS Genome-Wide Association Studies

ICS Inhaled Corticosteroid

PR Pulmonary Rehabilitation

HRQoL Health-Related Quality of Life

1. Abstract

Keywords: chronic lung disease, asthma, chronic obstructive pulmonary disease (COPD), asthma-COPD overlap syndrome (ACO).

Asthma and chronic obstructive pulmonary disease (COPD) are two very common chronic lung diseases in the general population and are traditionally viewed as two distinct disease entities that can be easily differentiated by clinicians in the majority of cases. Both of them are characterized by a combination of multifactorial inflammatory processes and airway obstruction. In both diseases, the complexity of inflammatory processes affects the variable response to the given treatment among and scientific community, there is no doubt that despite the similarity between the two diseases and their affiliation with the group of obstructive lung diseases, the asthma treatment is different from COPD since the bronchoconstriction is usually reversible in asthma when on the other hand, COPD is characterized by progressive deterioration toward constant obstruction. Lack of distinction between these two diseases can lead to incorrect treatment that may even cause harm.

In recent years, the understanding has begun to form that there is a significant overlap in both the pathological and functional aspects of asthma and COPD, especially among the elderly population where characteristics of the two diseases can be found simultaneously and thus the concept of Asthma COPD overlap (ACO) was born as a new diagnosis. ACO patients have been shown to experience higher rates of exacerbations, higher healthcare utilization, and worse health-related quality of life but unfortunately, the systematic exclusion of patients who did not meet the criteria for pure asthma or COPD from the clinical trials has resulted in the fact that the information which available today regarding prevention, the understanding of risk factors and prediction for the development of ACO among patients with long term and uncontrolled asthma, is limited. As a result, the adjustment of treatment for these patients is not optimal.

Due to the facts outlined above, the purpose of this review is to summarize the main points of the most updated information that have concluded based on oriented studies that have been done with the ACO population of patients and to suggest additional lines of thought to cover the information gaps based on available data about asthma and COPD patients who share similar criteria to ACO patient. In hope that this paper will serve effectively every physician who might need to provide care for this spectrum of patients.

Sažetak

Ključne riječi: kronične bolesti pluća, astma, kronična opstruktivna plućna bolest (KOPB), sindrom preklapanja astme i KOPB-a (ACO).

Astma i kronična opstruktivna plućna bolest (KOPB) dvije su vrlo česte kronične bolesti pluća u opće populacije te se tradicionalno smatraju dvjema zasebnim bolestima koje kliničari u većini slučajeva mogu lako razlikovati. Obje su karakterizirane kombinacijom višefaktorskih upalnih procesa i opstrukcije dišnih putova. Kod obje bolesti složenost upalnih procesa utječe na varijabilni odgovor na dani tretman te među znanstvenom zajednicom nema sumnje da se - usprkos sličnosti dviju bolesti i njihovoj povezanosti s grupom opstruktivnih plućnih bolesti - liječenje astme razlikuje od KOPB-a jer je bronhokonstrikcija obično reverzibilna kod astme, dok s druge strane KOPB karakterizira progresivno pogoršanje prema stalnoj opstrukciji. Manjak razlike između ove dvije bolesti može dovesti do pogrešnog liječenja koje čak može naštetiti.

Posljednjih godina došlo je do razumijevanja da postoji značajno preklapanje i u patološkom i u funkcionalnom aspektu astme i KOPB-a, posebno među starijom populacijom gdje se karakteristike dviju bolesti mogu pronaći istovremeno, a time je i sindrom preklapanja astme i KOPB-a (ACO) rođen kao nova dijagnoza. Pokazalo se da ACO pacijenti imaju veću stopu pogoršanja, veću upotrebu zdravstvene zaštite i lošiju kvalitetu života povezanu sa zdravljem, ali nažalost, sustavno izuzeće bolesnika koji nisu udovoljili kriterijima za čistu astmu ili KOPB iz kliničkih ispitivanja rezultiralo je činjenicom da su danas dostupne informacije o prevenciji, razumijevanju čimbenika rizika i predviđanju razvoja ACO među pacijentima s dugotrajnom i nekontroliranom astmom ograničene. Kao rezultat, prilagodba liječenja za te bolesnike nije optimalna.

Zbog gore navedenih činjenica, svrha ovog pregleda je sažeti glavne točke najnovijih informacija zaključenih na temelju orijentiranih studija koje su rađene s ACO populacijom pacijenata i predložiti dodatne linije razmišljanja kako bi se obuhvatilo praznine u informacijama na temelju dostupnih podataka o bolesnicima s astmom i KOPB-om koji dijele slične kriterije kao i pacijenti s ACO-om, a u nadi da će ovaj rad učinkovito služiti svakom liječniku koji će možda morati pružiti skrb za ovaj spektar pacijenata.

2. Introduction

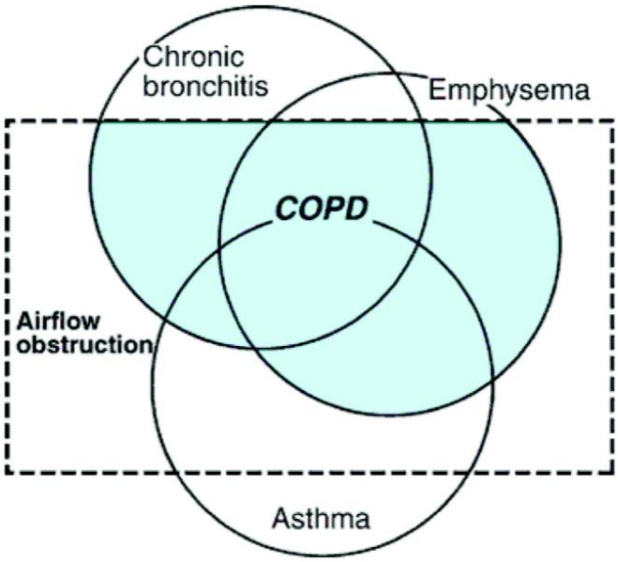
Asthma and chronic obstructive pulmonary disease (COPD) are two very common chronic diseases in the general population. Both are characterized by a combination of multifaceted inflammatory processes and airway obstruction. In both diseases, inflammatory processes affect the respiratory system from the small airways to the large ones, recruiting different cells and ranges of inflammation. The complexity of these processes affects the changing response to the treatment given. Air obstruction is mostly a reversal attack in asthma and on the other hand, in COPD it is characterized by a progressive course and a lack of complete reversibility. However, there is a significant overlap in both the pathological and functional aspects between these two diseases, especially among the elderly population where characteristics of the two diseases can be found simultaneously (1, 2).

The current definitions of asthma and COPD (3, 4, 5), are useful but limited in such a way that cannot describe the full spectrum of obstructive pulmonary diseases encountered by the attending physician in clinical practice. Moreover, the definition of asthma and COPD as two separate entities leaves a significant proportion of the patient population outside the existing definitions. This situation makes it difficult for both the individual level to influence the medical research in this important population, which constitutes a significant percentage of the patients of both the family doctor and the pulmonologist.

In contrast to the uncertainty regarding diagnosis, there is a consensus among researchers that patients who present with combined symptoms of asthma and COPD suffer from excessive flare-ups, a faster rate of deterioration in respiratory function, poorer quality of life, defined mortality, and higher health care consumption alone COPD (2, 6, 7, 8).

The prevalence of the phenomenon of overlapping diagnosis depends on age and sex. While the prevalence is less than 10% among those aged 50 and under 50, it is over 50% among women aged 80 and over (3, 4). This phenomenon of pathological and clinical processes overlapping between asthma and COPD has received many graphic descriptions (Image 1).

Further discussion about epidemiological, pathophysiological, and clinical characteristics of Asthma COPD overlap syndrome with a comparison to its differential diagnosis focusing mainly on asthma and COPD, will be discussed in the following chapters.



The classic Venn diagram is used to describe the overlap of the pathological and clinical features of chronic bronchitis, emphysema, and asthma. The subsets comprising chronic obstructive pulmonary disease (COPD) are shaded. Chronic bronchitis, emphysema, and airway obstruction are independent effects of cigarette smoking and may occur in various combinations. Patients with chronic bronchitis, emphysema, or both are not considered to have COPD unless they have airflow obstruction. Patients with asthma whose airflow obstruction is completely reversible do not have COPD, whereas those who develop a partially reversible airflow obstruction over time are considered to have asthma-COPD overlap).

2.1 COPD and Asthma Overview

The purpose of this chapter is to provide a brief overview of the characteristics, diagnosis, and treatment of asthma and COPD as distinct diseases, to create a background for future discussion and comparison of Asthma and COPD overlap (ACO) that defined as the coexistence of asthma and chronic obstructive pulmonary disease in patients with chronic airway obstruction and will elaborate in its detailed in the following chapters.

Asthma

Asthma is characterized as a disorder of chronic airway inflammation, airway hypersensitivity to a variety of stimuli, which belongs to the obstruction airway diseases group. Comparing to other chronic lung diseases such as COPD or Bronchiectasis. It is at least partially reversible, either spontaneously or with treatment. Asthma affects 3-5% of the U.S. population and is more common in children than in adults. Airway obstruction may be due to smooth muscle spasms in the walls of smaller bronchi and bronchioles, edema of the mucosa of the airways, increased mucus secretion, and/or damage to the epithelium of the airway (9).

The "classic" signs and symptoms of asthma are intermittent dyspnea, cough, wheezing, on by characteristic triggers, and relieved by bronchodilators. Although typical of asthma, and readily recognized in its classic presentation, these symptoms are nonspecific, making it sometimes difficult to distinguish asthma from other respiratory diseases and similar overlapping conditions. As a consequence, although sometimes the distinction between asthma and COPD could be clear such as in a case that chronic exercise limitation and persistent airflow obstruction in a middle-aged or older person with a history of more than 20 pack-years of cigarette smoking point to a diagnosis of COPD (10). Other criteria that assist to diagnose COPD, is pre- and post-bronchodilator pulmonary function testing that may confirm little or no reversibility of the airflow obstruction. At other times, however, the distinction is less clear, such as when patients with COPD exhibit episodic symptoms and a large reversible component to their airflow obstruction. Detection of these overlapping features of both asthma and COPD in some patients has led to a description of the condition, asthma-COPD overlap, that will be discussed in detail as the main theme of this review.

An additional clinical entity that shares common features with Asthma of bronchial hyperresponsiveness and airflow obstruction, known as Reactive airways dysfunction syndrome (RADS) refers to an airway disorder resulting from intense exposure to an inhaled chemical irritant or noxious gas. Reactive airways disease is an imprecise term that has been used to describe transient symptoms of cough and wheeze when confirmation of a diagnosis of asthma is lacking (11). More information about RADS will also be discussed further in the chapter about environmental and occupational exposures that are a possible cause for Asthma-COPD overlap syndrome and similar clinical presentations (9, 10, 11).

Asthma is diagnosed before the age of seven years in approximately 75 percent of cases (12). In most cases, children who have been diagnosed with asthma will experience a remission of

asthma symptoms around the time of puberty, with potential recurrence years later. But although new-onset asthma is less frequent in older adults compared to other age groups, it is important to mention that asthma may develop at any age; as such, Occupational asthma, aspirin-sensitive asthma (aspirin-exacerbated respiratory disease), and eosinophilic asthma are distinct syndromes that typically have their onset in adulthood. In most cases, children who have been diagnosed with asthma will experience a remission of asthma symptoms around the time of puberty, with potential recurrence years later. But although new-onset asthma is less frequent in older adults compared to other age groups, it is important to mention that asthma may develop at any age, as such, occupational asthma, aspirin-sensitive asthma (aspirin-exacerbated respiratory disease), and eosinophilic asthma are distinct syndromes that typically have their onset in adulthood. More information regarding adult-onset type of asthma is elaborated in Chapter 5 that compares Adult-Onset Asthma vs. Asthma–COPD Overlap Syndrome.

In addition to history-taking questions about the presence of symptoms earlier in life, historic clues that are highly suggestive of asthma include recurring, episodic symptoms, the presence of typical triggers (especially exercise, cold air, or allergen exposure), and personal or family history of allergic disease.

Physical examination may be normal in asthma, especially between attacks in stable asthma patients. The presence of abnormal findings (such as wheezing) is suggestive of asthma, although not specific. Asthmatic wheezing is typically composed of multiple high-pitched sounds audible most prominently during expiration. A nasal examination should be included to check for the pale, swollen mucosa of associated allergic rhinitis and for nasal polyps, which raise the possibility of aspirin-exacerbated respiratory disease (9).

Among the diagnostic tests, pulmonary function tests such as spirometry pre- and post-bronchodilator, bronchoprovocation testing (usually with methacholine), and peak expiratory flow (PEF) monitoring are the most helpful in diagnosing asthma. An obstructive pattern shown in spirometry is expiratory airflow obstruction with a reversible reduction in the forced expiratory volume in one second (FEV1), heightened sensitivity to bronchoprovocation agents such as methacholine or exercise, and variability over time of >20 percent in PEF are findings consistent with asthma (13-15). In addition, an increase in FEV1 of more than 12 percent from the baseline measurement following administration of 2 to 4 puffs of a quick-acting bronchodilator, is also suggestive of asthma, especially if post-bronchodilator spirometry is normal.

To exclude alternative diagnoses and for detection of potential asthma triggers, other laboratory studies are sometimes indicated, including blood tests (e.g., complete blood count with white blood cell differential, total serum immunoglobulin E, and allergen-specific immunoassays), skin testing for environmental allergies, and a chest radiograph.

When it comes to treatment and management of asthma, the goals of chronic asthma management may be divided into two domains: achieving good control of asthma-related symptoms and minimizing future risk (asthma exacerbations, suboptimal lung function, adverse effects of medication). The patient’s own goals such as maintenance of normal daily

activities, including work or school attendance and participation in athletics and exercise according to the medical condition, occupation, and age of the patient, should be incorporated into decision-making regarding asthma management.

Asthma control effectiveness can be judged, irrespective of medication use, based on the current level of symptoms, forced expiratory volume in one second (FEV1) or PEF values, and a number of exacerbations requiring oral glucocorticoids per year. (See "Initial assessment" above and "Initiating pharmacologic treatment" above.)

In cases of uncertainty about the diagnosis of asthma, poorly-controlled asthma, an episode of near-fatal asthma, and need for specialized diagnostic studies (e.g., allergy skin testing, bronchoscopy, evaluation for use of biologic agents) or treatment of comorbid conditions, it is appropriate to conduct a further clinical investigation by a specialist pulmonologist or allergist/immunologist.

Generally, all patients with asthma should have immediate access to an inhaled bronchodilator with a rapid onset of action for prompt relief of asthma symptoms. The gold standard for acute treatment is a short-acting beta-agonist (SABA; e.g., albuterol or levalbuterol) or an alternative approach is to use a combination low-dose glucocorticoid-formoterol inhaler (e.g., budesonide-formoterol 160 mcg-4.5 mcg), 1 inhalation as needed for quick relief of asthma symptoms. On the other hand, long-term pharmacological control is divided into different pharmacological combinations according to the level of severity as part of the personalized asthma management approach.

By that, for Intermittent (Step 1), (patients with mild asthma who have symptoms less than twice per month, FEV 1 is 80% and no risk of exacerbations): use of a combination inhaler that contains low-dose glucocorticoid and the fast-acting long-acting beta-agonist (LABA), formoterol, taken as needed for symptom relief (9). Mild persistent (Step 2): (Symptoms 3-6 times a week, nighttime symptoms 3-4 times a month and Lung function test FEV 1 is 80% or more), a regular (daily) use of low-dose inhaled glucocorticoid is recommended or a combination glucocorticoid-LABA inhaler, because regular use of inhaled glucocorticoids reduces the frequency of symptoms. Leukotriene modifiers are an alternative when avoidance of inhaled glucocorticoids is preferred, but efficacy is generally less.

Moderate persistent (Step 3): (Daily Symptoms, flare-ups may affect activity level, nighttime symptoms 5 or more times a month and FEV 1 is above 60% but below 80% of normal values): the preferred controller therapies are either low-doses of an inhaled glucocorticoid plus a LABA or medium doses of an inhaled glucocorticoid which has proven more effective in controlling asthmatic symptoms than an increased dose of inhaled glucocorticoids.
Severe persistent (Step 4 or 5): Symptoms that are continual and frequent nighttime symptoms, lung function test FEV 1 is 60% or less of normal values (9).

COPD

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as follows: "Chronic obstructive pulmonary disease (COPD) is a common, preventable, and

treatable disease that is characterized by persistent respiratory symptoms and airflow limitation as a contrary to asthma, which as mentioned above, consider as reversible airway obstruction lung disease, the cause for the persistent respiratory symptoms is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. The chronic airflow limitation that characterizes COPD is caused by a mixture of small airways disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. Chronic inflammation causes structural changes, small airway narrowing, and destruction of lung parenchyma. A loss of small airways may contribute to airflow limitation and mucociliary dysfunction, a characteristic feature of the disease" (16, 17).

In epidemiological terms, chronic obstructive pulmonary disease (COPD) is considered as a common respiratory condition characterized by airflow limitation and associated with high morbidity and mortality (18). More than 5 percent of the population are affected by COPD and it is the fourth-ranked cause of death in the United States, killing more than 120,000 individuals each year (16). The economic consequences from its high prevalence cause high resource utilization with frequent clinician office visits, frequent hospitalizations due to acute exacerbations, and the need for chronic therapy (e.g., supplemental oxygen therapy, medication) (19, 20).

Among the clinical features, it is important to note that the three main and most common symptoms which characterize COPD are dyspnea or reduced activity levels substantially, chronic cough, and sputum production that may develop independently and with variable intensity. When wheezing and chest tightness consider as less common comparing to asthma.

Typical initial presentation for COPD patients is the sedentary lifestyle of a person that at least have more than 40 years old, and patients with recurrent acute exacerbations such as dyspnea on exertion or cough. The physical examination of the chest varies with the severity of the COPD but is often normal in mild disease. Smoking and inhalational exposure history serve as an important risk factor for chronic obstructive pulmonary disease, other exposures including passive smoke and biomass fuel use also play roles (21). In consonance with the epidemiological data, the majority (about 80 percent) of patients with COPD in the United States have a history of cigarette smoking, when the amount and duration of smoking are to most important parameters to take into account when calculating the contribution to disease severity (22).

In addition to the direct symptoms described above, patients with COPD may experience weight gain (due to the breath on exertion activity limitations), weight loss (possibly due to dyspnea while eating), limitation of activity (including sexual), cough syncope, or feelings of depression or anxiety. Weight loss generally reflects a more advanced disease and is associated with a worse prognosis. However, the majority of COPD patients are overweight or obese.

Comorbid diseases to COPD are common presentation and include cardiovascular disease, anxiety, depression, bronchiectasis, lung cancer, and overlap presentation with asthma - this phenomenon will be discussed later as the main subject of this review (23). Physical

examination in the early stages may be normal or will reveal only prolonged expiration or wheezes on forced exhalation. As the disease progresses, hyperinflation (e.g., increased resonance to percussion), decreased breath sounds, wheezes, crackles at the lung bases, and/or distant heart sounds will be detected (24, 25) and when COPD is in its advanced stage, the radiological finding will reveal an increased anteroposterior diameter of the chest ("barrel-shaped" chest) and a depressed diaphragm with limited movement based on chest percussion.

Other physical examination findings include use of the accessory respiratory muscles of the neck and shoulder girdle, expiration through pursed lips, paradoxical retraction of the lower interspaces during inspiration (i.e., Hoover's sign) (26), cyanosis, asterixis due to severe hypercapnia, and an enlarged, tender liver due to right heart failure. Neck vein distention may also be observed because of increased intrathoracic pressure, especially during expiration. Although COPD leads to cyanosis, clubbing of the digits is not typical and suggests comorbidities such as lung cancer, interstitial lung disease, or bronchiectasis. An additional finding which is common in heavy smokers is yellow stains on the fingers due to nicotine and tar from burning tobacco (25, 27).

During evaluation and diagnosis of patients with COPD, chest radiography is typically performed to exclude alternative diagnoses since the differential diagnosis is broad and include the following (28):

1) Chronic Obstructive Asthma: this diagnosis is considered very difficult to differentiate from COPD, especially when asthma is present since childhood in addition to a long history of cigarette smoking. The reason for the importance of recognizing the coexistence of these diseases and distinguish between them is in devising a treatment plan that is adapted to reflect both underlying disease processes.

2) Chronic Bronchitis with Normal Spirometry: some smokers have a chronic productive cough but do not have airflow limitation on pulmonary function tests. They are not considered to have COPD, although they may develop COPD if they continue to smoke.

3) Bronchiectasis: shares many clinical features with COPD, including inflamed and easily collapsible airways and defined as a condition of abnormal widening of the bronchi that are associated with chronic or recurrent infection, shares many clinical features with COPD, including inflamed and easily collapsible airways, dyspnea and sputum production. It is established based on clinical characteristics of cough and sputum production and the presence of bronchial wall thickening and luminal dilatation on chest computed topographic (CT) scans.

4) Bronchiolitis Obliterans: known as Constrictive Bronchiolitis, most commonly seen following inhalation injury, transplantation (e.g., bone marrow, lung), or in the context of rheumatoid lung or inflammatory bowel disease and is characterized by submucosal and peribronchiolar fibrosis that causes concentric narrowing of the bronchiolar lumen. Symptoms include the progressive onset of cough and dyspnea associated with hypoxemia at rest or with exercise. CT scan includes centrilobular bronchial wall thickening, bronchiolar dilation, tree-in-bud pattern, and a mosaic ground-glass attenuation pattern.

5) Tuberculosis: considered as a risk factor for COPD and potential comorbidity (29). In an area endemic for tuberculosis, it was found that the overall prevalence of airflow obstruction was 31 percent among those with a history of tuberculosis compared with 14 percent among those without (29).

6) Heart Failure: as COPD, heart failure is a common cause for dyspnea among middle-aged and older patients accompanied by chest tightness and wheezing with fluid overload due to heart failure. Heart failure is usually differentiated from other lung pathology by the presence of fine basilar crackles, elevated brain natriuretic peptide levels, and radiographic evidence of increased heart size and pulmonary edema.

Furthermore, chest computed tomography is performed to diagnose abnormalities seen on the conventional chest radiograph and to exclude certain complications of COPD such as thromboembolic disease, lung cancer suspicion, or for evaluation of patients who are being considered for lung volume reduction surgery, or lung transplantation (28).

After using staging methods for assessment of exacerbation by the following methods:

1) COPD Assessment Test (CAT) which measures the impact COPD is having on a patient's wellbeing and daily life (See Table 1).

2) Modified British Medical Research (mMRC) via Breathlessness Scale (Table 2).

3) Global initiative for chronic Obstructive Lung Disease (GOLD) staging method that assesses the level of severity via FEV1 values (Table 3).

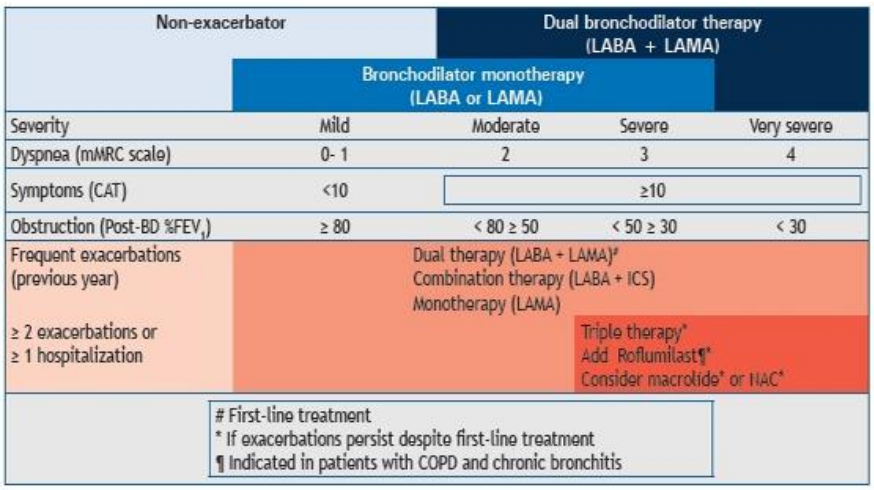
Treatment is dreamtime according to the level of severity and could be divide into pharmacological treatment and non-pharmacological. In early-milder stages smoking cessation encouragement, combined with nicotine replacement therapy, as well as pharmacotherapy with varenicline, bupropion, or nortriptyline, pulmonary rehabilitation via physiotherapy and physical activity can prevent deterioration (27). In addition, as a preventive step, annual flu and pneumococcal vaccines are recommended and long-term azithromycin therapy has been shown to reduce exacerbations of chronic obstructive pulmonary disease (COPD) (29). For advance stages oxygen therapy, surgical treatment, endoscopic treatment, and lung transplantation are used as part of the program treatment.

The major drugs that available for the treatment of COPD, a guide for the classification and treatment of COPD are presented by the following charts (23):

Drug	Dose, μg (except where otherwise indicated)	Duration of action, h
Short-acting β_2 agonist		
Fenoterol	MDI 100 and 200	4 a 6
Albuterol	MDI 100, 120, 200	4 to 6, 12
Long-acting β_2 agonist		
Formoterol	DPI 12	12
Salmeterol	MDI 25 and DPI 50	12
Indacaterol	DPI 150 and 300	24
Olodaterol	SMI 2.5	24
Short-acting anticholinergic		
Ipratropium (bromide)	MDI 20 e 40	6 to 8
Long-acting anticholinergic		
Glycopyrronium (bromide)	DPI 50	12 to 24
Tiotropium	SMI 2.5	24
Umeclidinium (bromide)	DPI 62.5	24
β_2 agonist plus short-acting anticholinergic		
Fenoterol/ipratropium	MDI 50/20	6 to 8
Albuterol/ipratropium	MDI 120/20	6 to 8
β_2 agonist plus long-acting anticholinergic		
Formoterol/aclidinium	DPI 12/400	12
Formoterol/glycopyrronium	MDI 9.6/14.4	12
Indacaterol/glycopyrronium	DPI 110/50	12 to 24
Vilanterol/umeclidinium	DPI 25/62.5	24
Olodaterol/tiotropium	SMI 2.5/2.5	24
Long-acting β_2 agonist plus inhaled corticosteroid		
Formoterol/beclomethasone	MDI and DPI 6/100	12
Formoterol/budesonide	DPI 6/200, 12/400, and 12/200 MDI 6/200	12
Formoterol/mometasone	MDI 5/50, 5/100, and 5/200	12
Salmeterol/fluticasone	DPI 5/100, 50/250, and 50/500 MDI 25/50, 25/125, and 25/250	12
Vilanterol/fluticasone	DPI 25/100	24
Phosphodiesterase-4 inhibitor		
Roflumilast	Tablet, 500 mg	24
Macrolide		
Azithromycin	Tablet or capsule, 250 and 500 mg	24
Mucolytic		
N-acetylcysteine	Powder, 200 and 600 mg; syrup, 30 mg/mL; and tablet, 600 mg	8 to 12

Main drugs for the treatment of COPD

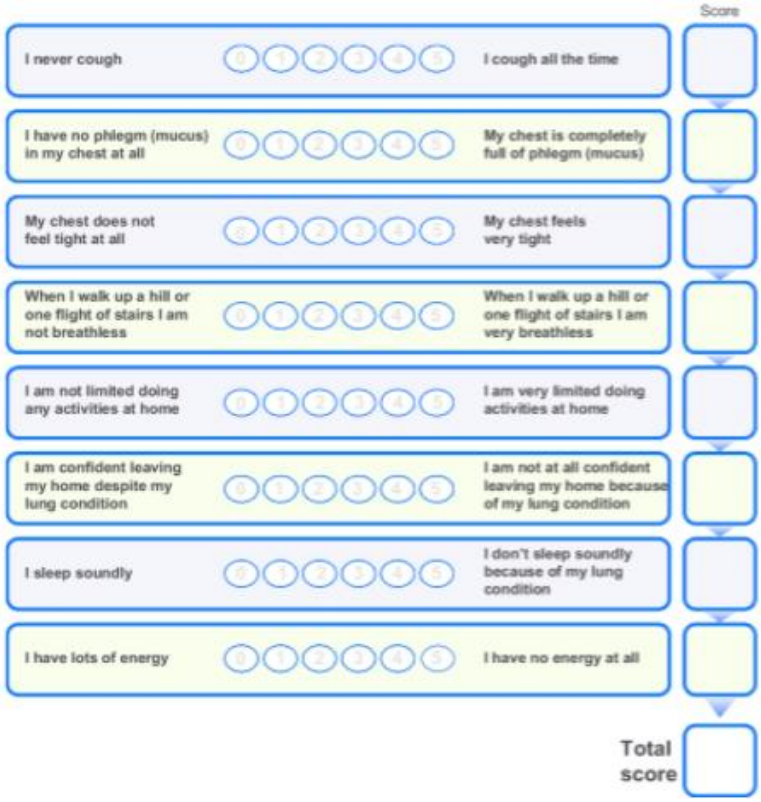
MDI: metered dose inhaler; DPI: dry powder inhaler; and SMI: soft mist inhaler. aIn bold, formulations currently available in Brazil. The others are, at the time of this publication, in the process of approval by the Brazilian National Health Oversight Agency or in the process of being released by the pharmaceutical industry.



Classification and pharmacological treatment of COPD

LABA: long-acting β2 agonist; LAMA: long-acting anticholinergic; mMRC: modified Medical Research Council dyspnea scale; CAT: COPD Assessment test; %FEV1: percent predicted FEV1; BD: bronchodilator; ICS: inhaled corticosteroid; and NAC: N-acetylcysteine.

Table 1:



Evaluative questions from the COPD Assessment Test (CAT).

COPD Assessment Test and the CAT logo is a trade mark of the GlaxoSmithKline group of companies. © 2009 GlaxoSmithKline group of companies. All rights reserved. Last Updated: February 24, 2012. Abbreviation: COPD, chronic obstructive pulmonary disease.

Table 2:

mMRC Breathlessness Scale

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

Table 3:

Classification of Severity of Airflow Limitation in COPD

In patients with	
GOLD 1: Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2: Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3: Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4: Very Severe	$FEV_1 < 30\%$ predicted

COPD stages and GOLD criteria by Minesh Khatri, MD on July 17, 2019.

3. ACO Epidemiology

Since the definition for ACO is controversial, it is difficult to establish an exact disease burden for ACO and the prevalence of ACO varies according to the definition used.

Data based on estimations that account on self-reported physician diagnosis or a combination of spirometry and symptom reporting suggest that the prevalence of ACO in the general population is between 2 to 3 percent when the estimations for asthma and COPD for the same general population being roughly 5 to 17 percent for asthma and 2 to 12 percent for COPD (30), although the prevalence of diagnosed patients with ACO among those who already have COPD may reach to 25 percent (31) and among asthmatic patient prevalence estimates for ACO range from 10 to 31 percent (32).

Studies suggest that ACO patients tend to be female, with lower education, lower socioeconomic status but higher body mass index (BMI) comparing to COPD patients (32, 33, 34). ACO patients may have poorer disease control concerning lung function, exacerbation rates, and respiratory symptoms than those with asthma or COPD without overlap although there is no clear evidence for longer-term outcome regarding lung function and mortality, apparently due to the significant heterogeneity of patients encompassed by this umbrella term (35, 36).

4. Etiology and Pathogenesis

As part of the question of whether ACO deserves a distinct definition as an independent disease with a different clinical approach, the elementary question when considering the pathogenesis of ACO should be discussed: whether it is the result of a unique pathogenic process, or the result of additive pathologic processes of asthma and COPD coexisting in the same patient., although even the pathogenesis of COPD itself is hotly debated. Similarly, the pathologic mechanisms underlying asthma are heterogeneous.

Currently, two main hypotheses suggest explanations for the etiology of ACO: the first and the well-known one is thought to be proposed by Orie and Sluiter in 1961.

The Dutch Hypothesis suggests that both asthma, chronic bronchitis, and pulmonary emphysema (COPD) stem from a single disease entity, that occurs as a result of the same genetic factors (atopic status, promotion of airway hyperactivity), and only presents different clinical phenotypes due to different environmental factors (allergens, smoking, and infections) (37).

The second hypothesis, the British Hypothesis, proposed in 1965 by Charles Fletcher, who described it as “a disease in which asthma and COPD occur as a result of different mechanisms triggered by different pathogeneses”, meaning separate origins for asthma and COPD, each with its characteristic inflammatory drivers and treatment, including allergic inflammation in the former and factors such as chronic bacterial infection in the latter (37, 38). In the Dutch hypothesis worldview, ACO would lie in between asthma and COPD on the same continuous spectrum contrast with the British hypothesis, where unique factors would drive a specific type of inflammation that would make ACO distinct from asthma and COPD.

When analyzing the etiology of progression from asthma to COPD as a mixed disease, it is easy to conclude that tobacco smoking in an asthmatic patient might trigger increased neutrophilic inflammation, fixed airflow obstruction, and eventually, COPD (39) Contrast, patient with primarily COPD combined atopic future will develop airway hyperresponsiveness and type 2-mediated airway inflammation. Allergen sensitization has been reported in older COPD patients (40).

5. ASTHMA PROGRESSION TOWARDS ACO VS. ADULT ONSET ASTHMA DIFFRENCES AND SIMILARITES:

When analyzing the patient population who have been diagnosed with ACO (asthma chronic obstructive pulmonary disease overlap), in a purpose to trace the risk factors and characterize the pathological starting point of these patients, it was found that asthma in the elderly is considered as a specific phenotype at high risk of progression towards ACO and around 20% of old patients with asthma are affected by ACO (41).

The progression remains poorly characterized at the population level, mainly because it is difficult to define ACO in epidemiological studies., Furthermore, according to major and minor risk factors criteria that were set for ACO diagnosis (42), people who have adult onset of asthma and are older than 40 years of age but documented history of asthma before 40 years of age, have a higher risk of progression towards ACO especially if they are active smokers and strongly if at least 10 pack-years of tobacco smoking is documented.

Another fact that was detected is that patients with a history of atopic or allergic rhinitis, and peripheral blood eosinophil count of ≥300 cells μL, which consider a more complicated asthma presentation, have higher chances to progress towards ACO (43).

With saying that, it is important to point on the fact that differences between asthma–COPD overlap (ACO) and adult-onset asthma are poorly understood, and diagnostic error may lead to inappropriate medical management.

First, to stand on the key differences among them, it is worth mention again the assumption which claims that ACO can develop by two different pathways: either the patient with COPD develops asthma-like symptoms and/or typical characteristics of asthma (for example, high reversibility of the airways) or the patient with asthma continues to smoke and eventually develops non-reversible airway obstruction indicating COPD (44, 45). There is also a third pathway suggested, in which a patient with asthma develops non-reversible airway obstruction without a smoking history (46). However, a history of exposure to tobacco smoking (or biomass fuels) has been considered a requirement for COPD diagnosis.

On the other hand, asthma that starts in adulthood is often non-atopic, more severe, and associated with a fast decline in lung function (47) incidence among adults is as high as 12 cases per 1,000 person-years which consider higher than the ACO number of diagnosed cases (48, 49). Many risk factors responsible for the onset of asthma in adulthood have been recognized and similarly to ACO, it seems that female sex hormones are associated with adult-onset asthma (49) as well as obesity (50) and stress.

Lastly, CO most clearly differs from adult-onset asthma several laboratory and diagnostic tests results including lower levels of pulmonary diffusing capacity, higher levels of blood neutrophils and serum IL-6, greater reversibility of the airways (despite equal medication for asthma), and a greater number of comorbidities than asthmatic patients without COPD. Due to that, measurements of the diffusing capacity could be considered a useful clinical tool to facilitate the identification of ACOS patients among those with asthma alone (51).

On the whole, the physicians have to carefully explored the clinical signs and symptoms in adults with severe asthma and to be guided by the characteristics that have early stages the possibility of asthma progression toward ACO.

6. Risk Factors

As mentioned previously, under the epidemiology section, sociodemographic and lifestyle risk factors with significant links to the incidence of asthma and COPD overlap syndrome included older age, less education, unemployment, obesity, rural residency, and a history of tobacco use. The next text will elaborate on another main two factors: The genetic and occupational-environmental contribution and which have not been studied extensively for ACO.

6.1 Environmental and Occupational Exposures

The development and exacerbation of asthma and chronic obstructive pulmonary disease may be affected by pollutants in rural and urban environments, according to data presented at the annual conference of the American Academy of Allergy, Asthma, and Immunology.

Pollutants in the air in the workplace or substances that cause respiratory irritation in families about asthma and the overlapping characteristics between asthma and chronic obstructive pulmonary disease. The syndrome of overlap between asthma and chronic obstructive pulmonary disease was first included in the GINA (Global Asthma Initiative) guidelines in 2015 and includes prolonged airflow restriction with several characteristics commonly described in asthma patients and several characteristics described in patients with chronic obstructive pulmonary disease (52, 53).

Experts explain that does not mean a single disease but a heterogeneous range of diseases. A person's interaction with the environment in the workplace, in rural and urban areas, may further affect lung disease. They mainly emphasize the importance of occupational exposure to pollutants that may contribute to the development of the overlapping syndrome.

In a study that included more than 6,000 participants with asthma living in Canada, 630 (10.4%) were diagnosed with overlapping asthma and chronic obstructive pulmonary disease, with an increase in air pollution accompanied by an increased chance of developing overlapping syndrome (2.78 odds ratio).

While air pollution was not accompanied by a defined risk of developing overlapping syndrome, a link was found between a body-evident index, low levels of education, living in a rural area, and smoking habits.

Farmers in rural areas have previously been described as having the asthma-like syndrome, which includes some degree of airflow obstruction and reversal, which may worsen with smoking with possible overlap between asthma and chronic obstructive pulmonary disease. Farmers may also experience asthma flares while working and those working with drinking animals are at higher risk of developing chronic bronchitis and/or chronic obstructive pulmonary disease, presently for farmers working with a crop. Interestingly, occupational exposure to dust and fumes has also been shown to increase the risk of developing COPD (54, 55). However, the role of occupational exposures in the development of ACO is not known.

To prevent overlapping asthma syndrome and chronic obstructive pulmonary disease, researchers recommend stopping tobacco use, reducing the use of indoor flammable substances, medical follow-up programs, and examining reducing exposure to substances that cause respiratory excitement with terror levels to ensure that so much remains and tell what is allowed (52, 53).

6.2 Genetic Features of COPD Asthma Overlap Syndrome

Improved knowledge of genetic variants associated with co-existing asthma and COPD can contribute to an understanding of the underlying molecular pathways, clarifying whether the genetic determinants of illness in this patient group are distinct from those in COPD or asthma alone. This knowledge could also help to determine the oriented management strategies for those with co-existing asthma and COPD. By that, Genome-wide association studies (GWAS) examine variants across the genome agnostically, to identifying variant-trait associations that inform understanding of disease biology, and by extension, potential treatment strategies. GWAS has identified a considerable number of loci associated with the risk of asthma or COPD in European populations (54, 55). Some GWAS have specifically studied ACO, including a GWAS of ACO compared to COPD alone (55) and a meta-analysis of asthma and COPD GWAS (56). At least twenty loci outside of the HLA (human leukocyte antigen) region have been identified as associated with both asthma and lung function or COPD at a threshold of $p<5\times10-8$, but have not been specifically described as ACO loci: these include signals in/near *IL1RL1* on chromosome 2 (57, 58), *STAT6* on chromosome 12, and *GSDMB/THRA* on chromosome 17 (59,60). There are also several overlapping loci in the HLA region, including the first shared signal to be identified, *HLA-DQB1/HLA-DQA2* (58).

As measured by genome-wide genetic correlation, studies have shown a strong genetic overlap between ACO and COPD, ACO and severe asthma, and ACO and asthma. Furthermore, a genetic correlation was found between ACO and blood eosinophil counts. Increased eosinophil levels have been associated with exacerbations in asthma and COPD (61, 62).

Additionally, an intergenic signal on chromosome 5, rs80101740 has been identified and had not previously been associated with asthma, COPD, or lung function.

The following signals identified as a novel for ACO: *GLB1, FAM105A, PHB, TSLP* are known signals for asthma or allergic disease but not COPD. It is assumed that these loci also have a role in fixed airflow obstruction. All these four signals have been associated with both child- and adult-onset asthma, and therefore could serve as an opportunity to intervene in early life to prevent serious long-term sequelae (60) One ACO signal (*IL17RD*) is a known locus for lung function and COPD, and additional findings have demonstrated the relevance of this locus in reversible airflow obstruction. Taken together, these loci could represent targets for intervention, potentially to prevent the development of fixed airflow obstruction.

Another two signals had previously been reported as associated with asthma and either COPD or lung function, including the *HLA-DQB1* locus, the first one that identified as being associated with both asthma and COPD, and a signal at *C5orf56*, encoding interferon regulatory factor I (*IRF1*) antisense RNA.

In summary, via genome-wide association study of asthma-COPD overlap to date, eight signals identified as associated with ACO and the findings suggest a spectrum of shared

genetic influences from variants that predominantly influence asthma, to those which predominantly influence fixed airflow obstruction.

The focus of current studies is on variants that tend towards an intermediate phenotype with features of asthma and fixed airflow obstruction, with pathways implicating innate and adaptive immunity and potentially bone development, as well as signals for which the biology is as yet unclear. Further understanding of the biology of these signals is likely to be important for therapeutics to prevent the development of fixed airflow obstruction among people with asthma (54).

7 Complications/ Clinical Sequelae of ACO

7.1 Lung Cancer

COPD is known as a well-established independent risk factor for lung cancer. In contrast, meta-analyses have shown mixed results about the potential association between asthma and lung cancer, but the least is known about the relationship between Asthma COPD Overlap (ACO) and lung cancer risk.

By data from National Lung Cancer Screening Trial (NSLT), which has conducted a large randomized lung cancer screening trial, a comparison of lung cancer risk among patients with ACO vs. COPD and other conditions associated with airway obstruction was done. The study included 13,939 patients, all with at least 30 pack-years of smoking. Patients divided into five groups based on their spirometry results:

1) Smokers without airway obstruction,
2) Preserved Ratio Impaired Spirometry (PRISm, a ratio of forced expiratory flow in 1 second [FEV1] over forced vital capacity [FVC] ≥0.7 and FEV1,
3) History of childhood asthma,
4) COPD patients (FEV1 /FVC<0.7).
5) ACO (Patients have to have a history of childhood asthma and FEV1 /FVC <0.7).

The study used Poisson regression to compare adjusted lung cancer risk among these groups and the results have shown that: the incidence rate of the lung. The results have shown that the incidence rate of lung cancer per 1,000 person-years was 13.2 (95% confidence interval [CI]: 8.1-21.5), 11.7 (95% CI: 10.5-13.1), 1.8 (95% CI: 0.6), and specifically 7.7 ACO patients had increased lung cancer risk compared to asthmatic smokers (incidence rate ratio [IRR]: 4.5, 95% CI: 1.3-16.0) and normal spirometry smokers (IRR: 2.4, 95% CI: 1.3-4.3) and a similar risk of lung cancer. It is important to note that according to the results, patients with ACO did not differ from COPD regarding lung cancer subtype, histological grade, tumor size, or clinical stage ($p>0.05$ for all comparisons).

In a conclusion, patients with ACO have an increased independent risk of lung cancer that appears to be similar to those with COPD and higher than the risk of asthmatic smokers and normal-spirometry smokers. This suggests that ACO is an independent risk factor for lung cancer that should be considered when making decisions about lung cancer screening (63).

7.2 Infections

As previously mentioned, the frequency of acute exacerbations in ACO may be higher than in either disease alone. In the COPDGene cohort, patients with ACO were more likely to be frequent exacerbations (which defined as 2 or more exacerbations in the year before study enrollment) and almost twice as likely to have a history of severe exacerbation than in either disease alone (64).

As a consequence, ACO may be associated with increased mortality and a higher rate of hospitalization compared with either asthma or COPD.

Unfortunately, there is no documented data with information regarding which pathogens lead to the exacerbation among patients with ACO, but since this syndrome considers as a severe

presentation and combination of both asthma and COPD, it will be reasonable to assume that a combination of the same infective complications will appear in ACO the next paragraph will elaborate the infections that are typical for patients who suffer from severe asthma and COPD complications.

Regarding COPD, studies consistently find that patients with COPD are at an increased risk of respiratory infections. Most COPD exacerbations are caused by respiratory infections, particularly involving rhinoviruses (RVs), influenza viruses, Haemophilus influenza, and Streptococcus pneumonia. Recent reports demonstrated a causal role for viral infection in 29%–44% of COPD exacerbations, Pseudomonas aeruginosa and other Gram-negative bacilli infect patients with advanced COPD, often prolonging COPD-related hospitalizations.

Studies suggest that antibiotics are effective, although primarily in patients admitted to the hospital, thus representing patients with more severe exacerbations. Although, the question of antibiotic efficacy for different clinically well-defined subgroups of COPD exacerbation as well as the choice of the most appropriate antibiotic for these subgroups is uncertain. Antibiotics may also be efficacious in exacerbation prevention. Recent studies on the efficacy of macrolides for the prevention of COPD exacerbations demonstrated promising results and due to that prophylactic treatment with azithromycin is recommended for COPD patients with recurrent pneumonia. Nevertheless, questions on the risk-benefit ratio of macrolides, efficacy in subgroups of COPD patients, and long-term effects remain unanswered.

From the asthma aspect, it would be appropriate to mention that atopic conditions can increase the risk of infection with several types of organisms in different infection, among them, researches have shown that asthmatic patients had an increased risk of Staphylococcus aureus colonization as measured by nasal swab (both methicillin-sensitive and methicillin-resistant S. aureus) based on 2001-2002 NHANES participants older than 1 year OR, 1.2; 95% CI, 1.0-1).

In addition, a population-based epidemiologic study showed a significantly increased risk of community-acquired Escherichia coli bloodstream infection (BSI) in persons with asthma compared with those without asthma (65). Furthermore, previous studies showed significantly increased risks of invasive pneumococcal disease (IPD) and pneumococcal pneumonia in patients with asthma compared with those without asthma (11-17% of the population-attributable risk percent for asthma in invasive pneumococcal diseases) (4) Additionally, on the association of asthma increased risks of serious pertussis, 50 Streptococcus pyogenes upper respiratory infections, 40 recurrent/persistent otitis media, 30 H1N1 influenzas, 56 and herpes zoster were also detected (66, 67, 68).

Study regarding asthma and viral infections showed that, although asthma status was not associated with the risk of rhinovirus or other viral infections, asthma exacerbations are most commonly caused by viral respiratory tract infections, and although asthmatic children are the most susceptible population, exacerbations and asthma flaring as a consequence of viral infection can occurs also in adults.

Virtually, any respiratory tract virus can provoke an asthma exacerbation, but rhinovirus (i.e., the common cold virus) is the most prevalent and has served to highlight the presence of individual patient susceptibility to infections (69).

From the aspect of the medical treatment which includes the use of inhaled corticosteroid (ICS) for asthma, COPD and ACO together, it is important to take into consideration that this treatment has been reported to increase the risk of infections such as pneumonia in patients with chronic obstructive pulmonary disease, but this finding has not been established in patients with asthma (70, 71). Interestingly, it seems that it even decreased the risk of pneumonia as an adverse event in patients with asthma (hazard ratio, 0.52; 95% CI, 0.36-0.76), based on data from many clinical trials (72, 73).

7.3 Spontaneous Pneumothorax

Similar to the shortage of clinical data related to infectious complications which have proven as unique to the ACO, there is no available documented data for spontaneous pneumothorax - complication rates among ACO patients. Due to that, this rearview will lean on data that collected from observation on COPD patients only from the assumption that ACO patient will have similar clinical presentation:

According to the definition of Spontaneous pneumothorax, it considers as the presence of air in the pleural cavity without a history of trauma. This is a significant clinical problem that needs immediate and definitive management. COPD is one of the most prevalent causes for pneumothorax and it is attributed to the second type of spontaneous pneumothorax- which is defined as pneumothorax that presents as a complication of underlying lung disease (74).

From a cohort study that was done on COPD patients that admitted with pneumothorax during six-year period, to assess the frequency of pneumothorax in the COPD and describe its clinical profile (75), it was found that the rate of pneumothorax secondary to COPD was 67% while most of the patients were men, mean age 59± 8 years, and the notion of smoking was found in 100% among the diagnosed patients. Additionally, it was found that 52% of the patients had previous emphysema and 35% of them had a recurrence of pneumothorax, six patients died in an array of acute respiratory failure. Furthermore, based on an additional study, COPD seems to be the most common pre-existing lung disease responsible for pneumothorax (73).

From these findings, researchers concluded that pneumothorax represents a factor of mortality for patients suffering from COPD and surgical treatment is needed to prevent a recurrence.

8. Diagnosis and Evaluation

8.1 Systematic Approach to Diagnosing a Patient with Respiratory Symptoms

As a first step, the clinician should determine if the clinical picture correlates with a diagnosis of chronic lung disease as a general group, before even considering ACO. The following findings should raise suspicion of chronic lung disease: prolonged cough, chronic phlegm, shortness of breath, "wheezing", recurrent respiratory infections, previous report about a diagnosis of asthma or COPD, previous treatment of inhalers, smoking, exposure to harmful environmental/occupational factors (76).

8.2 History Taking

In a view of the multiplicity of overlapping characteristics between asthma and COPD, it is advisable to focus on the characteristics that allow the best choice between these two diseases. Building a list of characteristics that support asthma or COPD - from a careful history that includes the estimation of severity, frequency, and duration of respiratory symptoms (as dyspnea, cough, sputum), tolerance to physical activity, and exercise limitation.

As asthma background considers as a strong predisposition for ACO progression, patients should be asked about any prior diagnosis or symptoms of asthma or allergic rhinitis and if asthma was diagnosed previously. Attention should be pay to the timing of appearance to expand the investigation for differential diagnosis to other obstructive pulmonary diseases comparing with ACO (See discussion under differential diagnosis section, chapter 9). Importantly, a detailed history should be obtained regarding potential occupational, vocational, or domestic exposures to fumes or dust, particularly tobacco smoke as these parameters increase significantly the chances for ACO diagnosis.

Despite the lack of a solid definition for ACO characteristics, the Global Initiative for Asthma (GINA) identifies several clinical features that support the diagnosis of ACO, including (77): age of onset ≥40 years, history of diagnosed asthma at some point, history of atopy or allergy, respiratory symptoms (as exertional dyspnea) are refractory and persistent.

The airflow limitation is partially reversible: post-bronchodilator forced expiratory volume in one second/forced vital capacity (FEV1/FVC) <0.7 or lower limit of normal and bronchodilator increase in FEV1 >12 percent and 400 mL.

Exposure to a risk factor (e.g., ≥10 pack-years tobacco smoking or equivalent indoor/outdoor air pollution).

As a general rule, the physical examination in people who are suffering from obstructive lung disease can be normal between flares, but evidence of hyperinflation and other characteristics of chronic lung disease/respiratory failure might be present.

Patients with coexisting asthma and COPD present similarly to pure asthma or COPD, manifesting signs and symptoms of obstructive lung physiology.

Abnormal findings on lung auscultation such as tubers, wheezing or decreased breath sounds, wheezes, crackles at the lung bases, and/or distant heart sounds are findings that correlate

with COPD features. Other physical examination findings that may appear in severe cases include use of the accessory respiratory muscles of the neck and shoulder girdle, expiration through pursed lips, paradoxical retraction of the lower interspaces during inspiration (Hoover's sign) (78, 79). Furthermore, in severe cases, the patient may adopt positions that relieve dyspnea, such as leaning forward with arms outstretched and weight supported on the palms or elbows. This posture may be evident during the examination or may be suggested by the presence of calluses or swollen bursae on the extensor surfaces of forearms, it is important to note that the clinical cause for this description comes from the presence of COPD in its advanced stages and is not unique to ACO (80). In addition, because a significant proportion of the ACO patients are smokers, during the total body physical examination yellow stains on the fingers due to nicotine and tar from burning tobacco can be detected and indicates heavy cigarette smoking.

8.4 Clinical Tests

Spirometry

Examination of lung function is essential in the procedure of the patient with suspected chronic lung disease. To delay misdiagnosis and incorrect treatment, it must be performed at an early stage of the patient's evaluation. Evidence for an obstructive pattern in lung function (FEV1 / FVC ratio <0.7) can confirm clinical suspicion of an obstructive pulmonary disease but its absence does not rule out asthma. Moreover, it is recommended that lung functions be performed before and after treatment with bronchodilators to evaluate airway responsiveness as an additional measure in an attempt to differentiate between asthma, COPD, and overlap syndrome. Although it is common to assume that among those who are suffering from asthma, a definite reactivity will be measured (increase in FEV1 by 200 ml and 12% after treatment with bronchodilators) and on the other hand, COPD patients will have a permanent obstructive disorder The COPD and at the same time, there will be asthma patients who in the guarantee of the years will develop a permanent obstructive disorder.

In light of all this, although a lung function test is a necessary condition for confirming a suspected obstructive pulmonary disease, the test results should always be examined in the patient's clinical context and in cases where they are doubtful, so the test should be repeated under optimal conditions and even use provocative tests as an exercise-induced stress test or methacholine challenge test (81).

Radiological Findings

A chest radiograph is frequently obtained as part of the evaluation of persistent respiratory symptoms or an exacerbation, generally, the radiological findings for any chronic lung disease can present as: normal, abnormal findings on chest X-ray or computed tomography (CT), which include, among others: air confinement, airway thickening, tissue permeability, and the presence of bullae. Findings aimed at differential diagnoses such as bronchiectasis, pulmonary infections (tuberculosis), interstitial lung diseases, or heart failure are sometimes exposed.

In ACO patients, a chest radiograph may reveal hyperinflation but generally does not help with differentiating among asthma, COPD, and ACO because hyperinflation can be present in all of them. In the case of diagnostic uncertainty, high-resolution computed tomography may help the diagnostic process.

Small airway disease in the absence of emphysema could still be consistent with ACO, although asthma (without COPD) and other diagnoses such as *bronchiolitis obliterans* should be considered (see 'Differential diagnosis' below). While some emphysema may be present in ACO, severe emphysema is more consistent with COPD

Imaging can reveal that along with ACO small airway disease in the absence of emphysema could still be consistent, but in that case, it is recommended to take into consideration other diagnoses such as *bronchiolitis obliterans* should be considered (see more elaboration under Differential diagnosis section). Likewise, some emphysema may be present in ACO, and severe emphysema is more consistent with COPD (82). Recent interesting radiological findings have suggested that patients with ACO have less emphysema on high-resolution computed tomography (HRCT) of the thorax than patients with COPD alone (83,84) but found to have greater variations in air trapping after bronchodilator administration. These findings can serve as proof of a distinct phenotype for ACO on CT densitometry compare to COPD. Additionally, a recent clinical study concluded that patients with ACO have greater airway wall thickness and higher pulmonary microvascular density on CT than COPD patients (85).

The following images present the radiological findings of computed tomography scan which suggests ACO radiological characteristics (86).

Figure 1. Axial Images of the CT Scan of the Chest Showing Thickened Airways

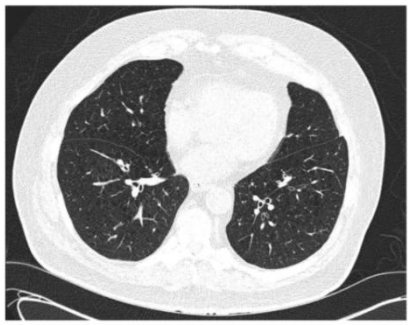


Figure 2. Axial Images of the CT Scan of the Chest Showing Upper Lobe Emphysema

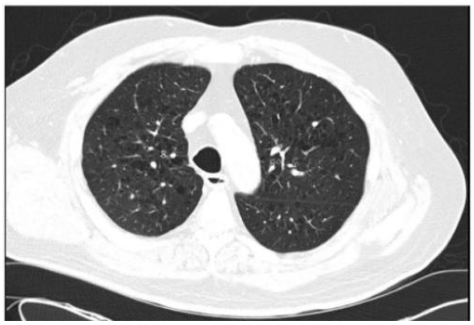
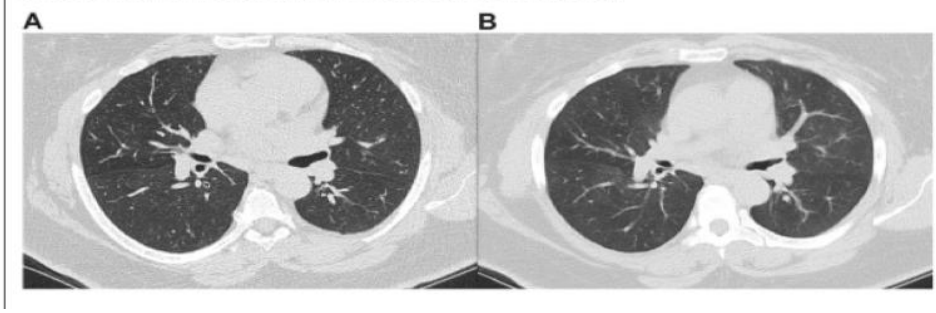


Figure 3. Axial Images of a CT Scan of the Chest During Inspiration (A) and During Expiration (B) Showing Air Trapping



Laboratory-Inflammatory Biomarkers

Eosinophilia

It is well known and accepted that eosinophilia of the bronchial wall, bronchoalveolar lavage, fluid, sputum, and blood is a hallmark of allergic asthma and typically, asthma is characterized by inflammation predominantly involving eosinophils, whereas COPD is characterized by inflammation by neutrophils. Elevated sputum eosinophil counts, if available, are more common in asthma or ACO more than in COPD, and it could serve as an additive criterion toward ACO diagnosis.

An elevated total serum immunoglobulin E (IgE; >100 international units/mL), elevated peripheral blood eosinophil count (>300 cells/microL), combined with evidence of allergic disease (eg, skin testing or immunoassays for perennial allergen sensitivity) may point a clinician towards asthma or ACO diagnosis (87).

When eosinophilia is present in patients with COPD, is associated with increased with noninfectious exacerbation rate (88, 89) and therefore, may identify an ACO-like subpopulation of patients with COPD, and in a cluster analysis of pooled asthma and COPD patients, a cluster resembling ACO was found to have the highest mean IgE level but unfortunately, the significant overlap between the blood eosinophil counts of patients with ACO, asthma, and COPD may limit its discriminatory power (90).

Eosinophilia serves also as a biomarker for treatment response monitoring and consider as a more useful tool than a diagnostic biomarker. An appropriate absolute or relative (percentage) threshold to define "eosinophilia" is required but currently, there is no consensus on what this threshold should be. According to the subanalysis by blood eosinophils in clinical trials on COPD patients, the threshold of 2% has been used to demonstrate a superior response to ICS (91, 92, 93).

Antigen-specific IgE

Although total serum IgE and antigen-specific IgE levels are also elevated in those with allergic asthma, a cross-sectional study analyzing prospectively, demonstrated that the presence of antigen-specific IgE also was observed more frequently in those with ACO (94, 95) and that consider as an indication for the suggestion that at least some patients with ACO are allergen-sensitized.

Fraction of exhaled nitric oxide (FeNO)

The same cross-sectional study that has mentioned above found that patients who belonged to the ACO category, had a high level of FeNO, which measured by breath analysis and quantifies nitric oxide gas, were registered (95). Another study found that a cutoff of >55 ppb in the FeNO threshold adequately differentiated patients with ACO from patients without ACO, but since it is a very high threshold, only 6% of the diagnosed ACO patients were met this criterion. Another suggestion for a lower cutoff at >22.5 ppb, achieved broader cover with results of sensitivity of 70% and a specificity of 75% (95), therefore, it seems that although FeNO may be high in a subset of patients, the trade-off between specificity and

sensitivity may limit the usefulness of FeNO for ACO diagnosing. Consequently, it is important to note that since each of these laboratory values suffers from low sensitivity and/or specificity, it would be more resalable to have combined all these tests with the clinical and radiological findings to improve diagnostic accuracy for ACO.

Succinctly, given the multiplicity of overlapping characteristics between asthma and COPD, it is advisable to focus on the characteristics that allow the best choice between these two diseases and the option for ACO progression.

Building a list of characteristics that support asthma or COPD - from a careful history that includes the subject's age, symptoms (time of onset, course, variability, seasonality, duration), medical history, exposure to secondary factors including smoking, previous diagnoses, nonresponse to the current treatment, can build the diagnostic profile that supports the existence of asthma or COPD.

A positive answer to three or more of the features listed for asthma or COPD, in the absence of an alternative diagnosis, is a supportive factor in making a correct diagnosis. However, as is often the case in medicine, in the absence of findings to send a diagnosis and on the other hand, positive findings can lead to a misdiagnosis. For example, the absence of allergic symptoms in non-allergic asthma (non-eosinophilic asthma / neutrophilic asthma) or the presence of atopic features in a patient who will develop COPD later in life. Given a similar number of asthma and COPD characteristics in the subject, the existence of the overlap syndrome should be considered.

The following table summarizes the diagnostic futures of ACO in comparison to COPD and asthma as an independent clinical presentation (78):

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	FEV1 may be improved by therapy, but post-BD FEV1/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.

*BD-bronchodilator, AHR-airway hyperresponsiveness

Lastly, the clinician should evaluate the degree of certainty of the diagnosis; in the absence of pathogenic characteristics, the clinician must make a conscious and informed assessment of the data presented to him when determining the effect. When there is doubt about the diagnosis, it should be remembered that the lack of proper treatment will lead to greater potential harm to the patient. For example, misdiagnosis of COPD is treated with asthma while giving long-acting beta-agonists (LABA) treatment without co-administration of corticosteroids so constant evaluation of the diagnosis based on the treatment response and biomarkers monitoring is essential, especially in the case of overlapping diseases presentation.

9. Differential Diagnosis

Besides the common clinical features that ACO shares with advanced stages of COPD and severe asthma, as chronic pulmonary diseases with obstructive characteristics, the differential diagnosis of ACO includes other airway diseases such as bronchiectasis, obliterative bronchiolitis, central airway obstruction, and diffuse panbronchiolitis that should take into consideration during the diagnostic process (93).

In the next section, each of these diseases will be presented with an emphasis on its similarities vs differences from the clinical characteristics of ACO:

1) Bronchiectasis: as ACO, bronchiectasis is also an obstructive lung disease with the presence of chronic inflammatory secretions and colonization of microbes which leads to a condition of abnormal widening of the bronchi with airflow obstruction (due to airway collapse). Bronchiectasis should be suspected based on prominent symptoms of a cough that is productive of mucopurulent sputum, recurrent chest infections, and sometimes hemoptysis. The diagnosis is usually established radiographically based on characteristic findings of bronchial wall thickening and luminal dilatation seen on CT scans (94).

2) Diffuse panbronchiolitis: an inflammatory lung disease of unknown cause. It is a severe, progressive form of bronchiolitis characterized by bronchiolitis and chronic sinusitis The isolation of Haemophilus influenzae and Pseudomonas aeruginosa in the sputum enhance disease recognition. This disease is well recognized mainly in Japan and East Asia. "Diffuse" in the disease name refers to the distribution of the lesions throughout both lungs and "pan" refers to the pathologic finding that the inflammation involves all layers of the respiratory bronchioles. Similar to ACO, a prominent clinical feature is a cough productive of copious amounts of sputum and the average age of onset: 40 areas old but range is broader: 1st–7th decade of life (92-94).

3) Obliterative bronchiolitis: also known as bronchiolitis obliterans, considers as a clinical syndrome marked by progressive dyspnea and cough with the absence of parenchymal lung disease on radiographic studies. It is characterized by concentric fibrotic narrowing of the bronchiolar lumen. The most common etiology for Obliterative bronchiolitis is due to post-viral illness, inhalation injury, in the context of rheumatic disease, or due to a primary noninfectious pulmonary complication of allogeneic hematopoietic stem-cell transplantation and lung transplantation. Symptoms include the progressive onset of cough and dyspnea associated with hypoxemia at rest or with exercise Similar to the symptoms that also characterize asthma ACO and COPD. Radiological often include centrilobular bronchial wall thickening, bronchiolar dilation, tree-in-bud nodularity, and a mosaic pattern of attenuation of lung tissue density (95).

4) Central airway obstruction: as the trachea and mainstream bronchi, it can be caused by numerous benign and malignant processes and the morbidity is significant and if left untreated, death from suffocation is a frequent outcome. These phenomena should take into consideration during the diagnostic process of ACO since it can mimic COPD with slowly

progressive dyspnea on exertion followed by dyspnea with minimal activity. A flow-volume loop, which can be insensitive, and computed tomography with three-dimensional reconstruction can be helpful, but direct visualization is the gold standard for diagnosis (96).

10 Treatment and Prevention

10.1 Pharmacotherapy

After completing the patient's evaluation according to the steps that have mentioned in the last section, the clinician should recommend starting initial treatment.

Because most clinical studies in asthma and COPD have excluded patients with ACO and lack of solid clinical evidence makes it difficult to determine appropriate treatment strategies, the recommendations for pharmacotherapy outlined by the joint Global Initiative for Asthma/Global Initiative for COPD statement on ACO and rely only on expert opinions, roundtable discussions, and strategy documents and they are as the following (97):

Initial management

When the differential diagnosis supports the presence of asthma or ACO or when there is significant uncertainty about the diagnosis of COPD, the initial treatment approach will be similar to that for asthma with the inclusion of inhaled glucocorticoids (ICS), with a stepwise adjustment based on the response to medications, starting with low to moderate doses since clinical evidence suggests that there is a relationship between greater blood eosinophil levels and ICS response in COPD (98, 99). Importantly, an effort to identify triggers for the flares has to be made to limit the patient’s exposures, saying that, smoking cessation is particularly important in patients with ACO since it will contribute to symptom control and will stop the progression of asthma and COPD independently. Furthermore, it was shown that smoke exposure the response to ICS (100, 101).

For urgent need, patients with ACO should have immediate access to an inhaled bronchodilator with rapid onset of action as short-acting beta-agonist, short-acting muscarinic antagonist, or combination of them. Long-acting muscarinic antagonists are effective in both asthma and COPD and should be considered in ACO as an add-on treatment. Additionally, ICS in this population has been recommended to target airway inflammation and because these patients have concomitant airway obstruction, it is recommended that managing their symptoms should include adding one or more long-acting bronchodilators, often with the initial addition of a LABA.

In this context, a noteworthy note to mention is that LABA and/or LAMA therapy consider as a starting choice for maintenance therapy in COPD (102,103), but LABA monotherapy is avoided in asthma due to evidence for an increase in respiratory-related deaths and asthma-related deaths. As a consequence, ICS-LABA combination inhalers can be used in ACO, but LABA monotherapy should be avoided. Furthermore, a case-control study has demonstrated that prescription of ICS-LABA therapy was associated with a significantly lower mortality

rate and lower amount of hospitalization comparing to patients who received LABAs alone (103).

Medical management for moderate to severe cases

In a case that patients treated with ICS/LABA but continue to have symptoms, an additional long-acting bronchodilator, such as a LAMA is recommended to add. Tiotropium bromide is the most commonly used LAMA in case of refractory symptoms of ACO because it is the only one currently approved for the treatment of asthma (103).

The next level of treatment for refractory cases and frequent exacerbations is triple inhaled therapy (ICS/LABA/LAMA) has been effective in both asthma and COPD and therefore should be considered in cases of moderate ACO cases (104). But if after this adjustment of inhaler therapy is still not effective in these patients, advanced therapies such as the use of biological treatment based on phenotyping and identification of treatable traits may be considered.

The patients who belong to this category of severe ACO symptoms should be evaluated for features, such as sensitivity to perennial allergens, elevated total serum IgE, and/or peripheral blood eosinophilia, since the elevation of these markers may identify patients who will have a good response to one or more of the biologic agents that have been developed for severe asthma, which in the absence of enough data about patients with ACO, use as a comparison model and the treatment for ACO cases that is recommended to be the same as for severe asthma (105). The use of these therapies demonstrated a significant reduction in the need to use systemic corticosteroids, reduction in exacerbations, emergency room visits, and improvements in quality of life for these patients (106, 107) monoclonal antibodies targeting T2 inflammation in severe asthma have thus far been the most successful, and 5 different monoclonal antibodies are now approved for the treatment of severe allergic and eosinophilic asthma. Only a few studies for biological treatment for ACO patient have been conducted, among them Omalizumab (an anti-IgE monoclonal antibody), has been studied the most in patients with overlapping features and it was found that patients with and without overlapping features had similar improvements in exacerbation rates and asthma control (108) An analysis from Australian Xolair Registry that demonstrated data from patients who had a diagnosis of COPD in addition to severe asthma, based on either physician assessment, demonstrated improved asthma control and health-related quality of life (QOL) scores, with 48 weeks of Omalizumab treatment but without significant change in FEV1 (103, 113, 114). Additionally, since IL-5 is a key mediator in eosinophil differentiation, maturation, and tissue migration and play the main role in asthma exacerbation, several anti-IL-5 and anti-IL-5Ra monoclonal antibodies such as benralizumab, mepolizumab, and reslizumab, are approved as add-on maintenance treatment in patients with severe asthma and eosinophilia (108-117) when benralizumab specifically have shown a good clinical respond for COPD as well (118).

The anti-IL-4Ra antibody dupilumab, that targets both the IL-13 and IL-4 pathways, (which are cytokines that play a role in allergic inflammation via recruitment of mast cells and eosinophils to sites of inflammation and also induce goblet cell metaplasia) (117) As with the anti-Ige therapy,anti-IL-4Ra antibody improves lung function and reduces exacerbations in

severe asthma, with greater benefit seen in patients with higher blood eosinophil levels 119))although, for COPD and/or ACO, the efficacy is not established.

When discussing anti-inflammatory drugs for ACO it is worth mentioning that macrolides antibiotics have been useful in various chronic pulmonary diseases, as a chronic and prophylactic treatment. Since only a few data on the use of macrolides in ACO exist and no study has evaluated prospectively the effects of macrolides was done, the treatment protocol suggestion relay on evidence from studies in both asthma and COPD populations.

Even for the treatment of asthma and COPD, the mechanisms explaining the benefits are incompletely understood, but practically in the clinical field, several trials have been shown to provide benefits from macrolides regarding exacerbations and other outcomes such as reduction of airway reactivity and remodeling (120). Furthermore, some evidence also suggests that these medications may alter gene expression (121).

10.2 Adjuvant Therapies for Prevention of ACO Exacerbation

Macrolides

The contribution of the macrolides as an anti-microbial agent is very efficient against infections with atypical pathogens which may contribute to exacerbations and uncontrolled symptoms, among patients with chronic obstructive lung diseases. Additionally, some evidence links the T2 inflammatory responses and airway remodeling as an immunological reaction to toxins from *Mycoplasma pneumoniae* which can be prevented by using macrolides (122).

Macrolides are considered medications that can affect various inflammatory pathways. For example, clarithromycin has a role in the suppression of the IL-13 mediated production of mucus by goblet cells (123-124).

As a result of these benefits, several clinical trials support the chronic use of azithromycin in COPD as a prophylactic agent but careful risk vs. benefit evaluation should be done before initiating this therapy due to the significant increase of antimicrobial resistance (125, 126).

Lastly, concerning ACO, since most of these patients have high pack-year smoking exposure, the anti-inflammatory properties of macrolides that have been described above, can be particularly beneficial in reduction to the extent of inflammation induced by smoke exposure.

Vaccinations

Pneumococcal vaccination is recommended for patients older than 65 years, in the time interval of at least one year between each dose. For COPD patients it has been shown to reduce the likelihood of flares and exacerbations (127). Annual influenza vaccination has been beneficial in both asthma and COPD and should be also given to ACO patients (128).

10.3 Pulmonary Rehabilitation

In addition to a regular physical activity program, pulmonary rehabilitation (PR) via respiratory physiotherapy has been well established to alleviate the signs and symptoms of various pulmonary conditions and after the patient's symptoms have stabilized and flares have reduced. Another goal of this treatment is to optimize functional capacity and improve exercise tolerance (129). The benefit of PR as well as its efficacy has been reported previously in both COPD and asthma patients (130, 131). However, as for the other aspect of the clinical approach to ACO patients, the efficacy of a comprehensive PR program in ACO patients is largely unknown since very few studies have been done on this population (132-135).

The PR program that has been conducted in the ACO population includes stretching of upper and lower extremity muscles, breathing exercises, supervised endurance and resistance training, diaphragmatic and pursed-lip breathing (136, 137), self-management, and patient education for relaxation techniques to control dyspnea, smoking cessation, and nutritional guidelines as per the individualized recommendation of the nutritionist and avoidance of triggers. These exercises have been found to reduce respiratory rate and improve tidal volume as well. Few investigations demonstrated an improvement in pulmonary function (137). A short-term PR program in ACOS patients results in favorable changes in the functional capacity, and improvement in health-related quality of life (HRQoL). However, short-term PR was not sufficient to register changes in pulmonary function in these patients, and based on recent studies (138) that found no significant improvement in PFT following four and eight weeks of PR in COPD patients, it is recommended to plan longer period of PR for ACO patient to achieve symptomatic improvement.

10.4 Lifestyle Modifications

Patients who are suffering from ACO should avoid the stimuli that may trigger exacerbation in their pulmonary functions. As most of these patients have an atopic condition that provokes an asthma attack, it is recommended to limit the exposure to pollutants, stimuli, and allergens, according to their allergic status of the patients (139-140) such as:

Smoke

Encouraging smoking cessation is an essential step in the management of ACO for all individuals who smoke. Similarly, avoidance of exposure to other sources of smoke and irritant inhalants at home or work is necessary as well.

Allergenic plants

Breathing symptoms such as wheezing, shortness of breath, chest tightness, and chronic cough which get worse at certain times of the year, may indicate a reaction to seasonal plant pollen especially if a rash is present. During periods when the allergen load is heavy it is recommended to limit the length of staying outdoors and to use an air conditioner with a HEPA filter.

Dust mite

Dust mites are another common cause of allergies among asthma chronic obstructive pulmonary disease, and ACO patients. To reduce the amount of dust that accumulates in the house home, it is recommended to replace the carpets with tile or parquet flooring. Additionally, washing all bedding and clean all carpets of the patient regularly and vacuuming the house regularly and installing filters in the heating and cooling systems, and replace them regularly to avoid the accumulation of the dust mite.

Animal skin cells

Pet allergy is an allergic reaction to proteins found in an animal's skin cells, saliva, or urine, animal skin cells are incident microscopic parts of skin and hair, and constitute a common allergen. If there is a suspect that the pet triggers breathing symptoms, it is recommended to keep shower the pet regularly, avoiding its stay inside the bedroom, and in severe cases, consider referral to desensitization immunotherapy (139).

Mold

Mold is another common cause of allergic reactions and triggers asthma attacks. Even if the patient is not allergic to mold, its inhalation can lead to a fungal infection. A study published in the Journal Respiratory European indicates that the presence of healthy fungi was more common among people suffering from chronic obstructive pulmonary disease than among people not suffering from this disease (140). Mold thrives in a humid environment, due to this fact, it is recommended to check the patient's home regularly for signs of mold, especially around taps, showerheads, pipes, and roofs. maintaining about 40 percent humidity indoors using air conditioners, dehumidifiers and vents can prevent mold colonization. When mold is detected, it is advisable to evacuate and treat it by a professional worker.

Chemical sensitivity

Many household cleaners that produce strong vapors can irritant the airways especially in a patient with a chronic lung condition. Bleach, bathroom cleaners, oven cleaners, and polishing sprays are common causes. For these patients, avoiding usage of these capable materials in enclosed spaces that are not sufficiently ventilated and do not mix different products. The recommended alternative would be gentle solutions of soap and water and other eco-friendly products to perform cleaning tasks (141).

Diet adjustment as a preventative treatment

Although no definitive data regarding an optimal diet for ACO patients are available, several dietary options can be considered in terms of COPD prevention and/or progression and the available scientific evidence indicates that some foods and nutrients especially those with antioxidant and anti-inflammatory properties balanced dietary patterns are associated with better pulmonary function, less lung function decline, and reduced risk of COPD exacerbation.

Interestingly, in many studies, specific dietary patterns and/or nutrients exerted benefits on lung function and the risk of COPD, but not asthma, although the general recommendation

for asthma patient is to eat food which is rich with vitamins C and E as they serve as an anti-oxidants and may help to reduce the collateral damage from the chronic inflammatory state that asthma crests (142-143). In addition, clinical evidence shows that a diet high in total and saturated fat increases the expression of genes involved in airway inflammation in people with asthma, and diets enriched with omega-6 fatty acids hinder the incorporation of omega-3 fatty acids into plasma and tissue lipids (144). Avoidance of salty foods also have proved as beneficial: it was found that a low-sodium diet maintained at least for 1 to 2 weeks decreased bronchoconstriction in response to exercise in individuals with asthma, although the evidence does not yet support a benefit of a low-sodium diet on either the prevalence or severity of asthmaf (145).

Regarding alcohol consumption - it was found that consumption of alcohol has an association with the development of new-onset asthma in adults (146). Furthermore, epidemiologic studies found that subjects with low alcohol consumption (up to 30 g/day) had higher levels of FEV1, lower prevalence of COPD symptoms, and a decreased risk of COPD compared to non-consumers.

Another important fact that should take into consideration when diet modification for advanced COPD patients\ACO patients is planning: These patients have poor diet quality and nutrient deficiencies in COPD, which leads to poorer antioxidant content, that was correlated with impaired lung function and risk of having COPD (147-149). Moreover, lower energy intake (accompanied by elevated resting energy expenditure), unbalanced intake of macronutrients (e.g., low proteins), and defective intake of several micronutrients (minerals and vitamins, e.g., iron, calcium, potassium, zinc, folate, vitamin B6, retinol, niacin) have been documented in COPD patients as a consequence to disease-specific factors such as symptoms like dyspnea, fatigue, anxiety, depression, anorexia, periodontal disease, loss of taste, poor dentition, dysphagia, poor chewing and swallowing ability-all of them damage the optimal eating habits in those patients (147).

Lastly, because there is strong evidence of associated chronic lung diseases with cardiovascular pathology and other comorbidities like diabetes and obesity (150), many scientific organizations recommend prudent/Mediterranean-like diets as healthy dietary patterns to decrease the general risk for morbidity and mortality from all of these diseases together. As already mentioned above, the Mediterranean-like diets loaded with plant-based foods and healthy fats, help to preserve lung function and prevent COPD or its evolution over time. As a consequence, it can be concluded that this diet helps to prevent the progression or exacerbation of ACO (148-151).

11. Summary

The existence of individuals who present a chronic respiratory disease with some characteristics of asthma combined with some chronic obstructive pulmonary disease (COPD) has been recognized for many years, although the clinical recognition of this so-called asthma-COPD overlap (ACO) has emerged only in recent years. The reason for the official clinical recognition among the scientific community as a result of excessive use of inhaled corticosteroids (ICS) in COPD and the findings of different studies, which suggest that only COPD patients with some characteristics of asthma or with a particular type of inflammation, predominantly eosinophilic, will respond to ICS.

At the same time, western medicine has begun to adopt a holistic and personalized approach to the patient and his disease to tailor the treatment to each person according to the potential for recovery and his response to the treatment. By that, the pharmacogenomics and biological treatments have added to the standard corticosteroids and LABA medications regime. In addition, these patients are offered a preventative treatment plan which includes maintaining a free environment from allergens that may worsen the disease pattern, adhering to a diet that will reduce the inflammatory response level in the airways, smoking cessation, and maintaining physical fitness that will contribute for the improvement of lung function.

It is important to note that since ACO is an understudied population treating ACO may be equally challenging since its management comes largely from asthma and COPD studies, the relevance of which deserves careful consideration. The current challenge in the management of ACO cases is to identify the “treatable traits” in each patient based on a deep understanding of the critical causal pathways.

This paper is intended to present the various approaches to ACO diagnosis and to evaluate the role of currently existing diagnostic tests to centralize this information as a platform and solid foundation for dedicated research on the ACO patient population which will contribute to the creation of elaborated clinical guidelines.

12. References

Introduction-References:

1) Potsma, D.S, Reddel, HK., ten Hacken, NHT, van den Berge, M. Asthma and chronic obstructive pulmonary diseases-similarities and differences. Clin Chest Med (Mar, 2014).

2) Milne,S. Mannino, D., and Sin, D..Asthma-COPD Overlap and Chronic Airflow Obstruction: Definitions, Management,andUnanswered Questions.The Journal Allergy and Clinical Immunology (Feb,2020)

3) Marsh, S. Travers J. Weatherall ,M. et al. Proportional classifications of COPD phenotypes. Thorax 2008.

4) Weatherall ,M. Travers J, et al. Distinct clinical phenotypes of airways disease defined by cluster analysis. Eur Respir J 2009;34:812-8.

5) Diagnosis of diseases of chronic airflow limitation: asthma COPD and asthma- COPDS overlap syndrome(ACOS). Available from: http://www.goldcopd.org/asthma-copd-overlap.html. (Accessed on May 2021)

6) G, PG. JL, S. The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax 2009;64:728-35.

7) Kauppi, P. Kupiainen, H. Lindqvist ,A. et al. Overlap syndrome of asthma and COPD predicts low quality of life. J Asthma 2011;48:279-85.

8) Andersen H, Lampela P, Nevanlinna A, et al. High hospital burden in overlap syndrome of asthma and COPD. Clin Respir J 2013;7:342-6.

(ForCOPDand Asthma overview)

9) National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051). www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm (Accessed on May 2021).

10) Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. www.ginasthma.org (Accessed on March 2020).

11) British Guideline on the Management of Asthma/(2019). https://www.brit-thoracic.org.uk/guidelines-and-quality-standards/asthma-guideline/ (Accessed on May 2021).

12) S M, Brooks., M A, Weiss. I L, Bernstein. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. Sep;88(3):376-84. doi: 10.1378/chest.88.3.376.

13)J W, Yunginger ., C E, Reed. E J, O'Connell. L J, Melton et al. A community-based study of the epidemiology of asthma. Incidence rates, 1964-1983. Affiliations expan PMID: 1416415 DOI: 10.1164/ajrccm/146.4.888

14)C McCormack,M. , K ,Stoller, , Hollingsworth, H. Overview of pulmonary function testing in adults. May 27, 2020.(Accessed on May 2021).

15) M ,Cloutier . P Baptist,A. , V Blake ,K. et al. 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Mar,2021. .(Accessed on May 2021).

16) Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease: 2020 Report. www.goldcopd.org (Accessed on May 2021).

17) Buist ,S. McBurnie,M. M Vollmer.W, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study.Lacet: doi: 10.1016/S0140-6736(07)61377-4.(Sep 2007).

18) Buist.S . McBurnie.M, Vollmer.W, et al.International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 1;380(9844):806.(Sep 2012).

19) S. Gershon , Warner.L, Cascagnette.P, J Charles. V. Lifetime risk of developing chronic obstructive pulmonary disease: a longitudinal population study.Lancet. PMID: 21907862, DOI: 10.1016/S0140-6736(11)60990-2(Sep 2011).

20) D. Kochanek, Murphy.S, Xu.J, et al.Mortality in the United States, 2016.PMID: 30500322. https://pubmed.ncbi.nlm.nih.gov/30500322/ (Accessed on May 2021).

21) J. Capistrano, van Reyk.D, Hui. C,et al.Evidence of Biomass Smoke Exposure as a Causative Factor for the Development of COPD. Dec 2017. doi: 10.3390/toxics5040036, PMCID: PMC5750564, PMID: 29194400.

22) Centers for Disease Control and Prevention (US); National Center for Chronic Disease Prevention and Health Promotion (US); Office on Smoking and Health (US).A Report of the Surgeon General. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease. Atlanta (GA): Centers for Disease Control and Prevention (US); 2010. ISBN-13: 978-0-16-084078-4. https://www.ncbi.nlm.nih.gov/books/NBK53017/ (Accessed on May 2021).

23) R. Kessler, M.R. Partridge, M. Miravitlles, M. Cazzola, et al.Symptom variability in patients with severe COPD: a pan-European cross-sectional study.Ostinelli

European Respiratory Journal 2011 37: 264-272; DOI: 10.1183/09031936.00051110.

24) R G .Badgett , D J .Tanaka, D K Hunt, M J. Jelley. Can moderate chronic obstructive pulmonary disease be diagnosed by historical and physical findings alone. The American Journal of Medicine

Volume 94, Issue 2, February 1993, Pages 188-196.

25) Pachon.E , Navas.P ,et al.Frequency of Hoover's sign in stable patients with chronic obstructive pulmonary disease.The international Jurnal of clinical practice, May 2006Volume60, Issue5, Pages 514-517.doi: 10.1111/j.1368-5031.2006.00850.x

26) Stephens .M, S Yew.K. Uniformed Services University of the Health Sciences, Bethesda, Maryland. Diagnosis of Chronic Obstructive Pulmonary Disease. Am Fam Physician. 2008 Jul 2008 1;78(1):87-92.

27) Gentryg .S, , GENTRY.B. COPD and Asthma: Differential Diagnosis Sep 2016, American Academy of Family Physician. (2017 Apr) 1;95(7):433-441.

28), A M B .Menezes , P C Hallal, R Perez-Padilla, J R B.Jardim, et al. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America
Eur Respir J, (Sep 2007) 007 Dec;30(6):1180-5. doi: 10.1183/09031936.00083507. Epub 2007 Sep 5.

29) Parks. T , Sellers E, Brice .T , Azithromycin for the Prevention of COPD Exacerbations: The Good, Bad, and Ugly. The American Journal of Medicine, Epub 2015 (Aug 17). PMID: 26291905. DOI: 10.1016/j.amjmed.2015.07.032.

30) Leung.M , Sin.D. Asthma-COPD overlap syndrome: pathogenesis, clinical features, and therapeutic targets. BMJ 2017 Sep 25;358:j3772. doi: 10.1136/bmj.j3772

31) Alshabanat. A, Zafari.Z , Albanyan. O , Dairi .M,et al.Asthma and COPD Overlap Syndrome (ACOS): A Systematic Review and Meta Analysis. 2015 Sep 3;10(9):e0136065. doi: 10.1371/journal.pone.0136065. eCollection 2015.

32) Van Boven. F , Rodríguez. J, Palmer.F , Toledo-Pons. N, et al. Comorbidome, Pattern, and Impact of Asthma-COPD Overlap Syndrome in Real Life.2016 Apr;149(4):1011-20. doi: 10.1016/j.chest.2015.12.002. Epub 2015 Dec 14.

33) Kumbhare.S , Pleasants.R , A Ohar.J , et al Characteristics and Prevalence of Asthma/Chronic Obstructive Pulmonary Disease Overlap in the United States. 2016 Jun;13(6):803-10. doi: 10.1513/AnnalsATS.201508-554OC.

34) Hardin.M , K Silverman.E, Graham Barr.B, Hansel.N,et al.The clinical features of the overlap between COPD and asthma. 2011 Sep 27;12(1):127, doi: 10.1186/1465-9921-12-127.

35) Carlos A Vaz. F , E Murphy.T , O Agogo.G , et al.Asthma-COPD overlap syndrome in the US: a prospective population-based analysis of patient-reported outcomes and health care utilization. Int J Chron Obstruct Pulmon Dis (Feb 2017) doi: 10.2147/COPD.S121223.

36) Venkata.N,Enkata AN. Asthma-COPD overlap: review of diagnosis and management. Current opinion in pulmonary medicine 2019. Curr Opin Pulm Med. doi: 10.1097/MCP.0000000000000649(Mar 2020).

37) J Barnes.P, Barnes PJ. Against the Dutch hypothesis: asthma and chronic obstructive pulmonary disease are distinct diseases. Am J Respir Crit Care Med. 2006;174(3):240.

38) Siew. LQC, Wu. SY, Ying, S .Corrigan CJ.
Cigarette smoking increases bronchial mucosal IL-17A expression in asthmatics, which acts in concert with environmental aeroallergens to engender neutrophilic inflammation. Clin Exp Allergy. 2017;47(6):740. Epub 2017(Mar 13).

39) Itabashi. S, S, Fukushima. T, Aikawa,et al. Allergic sensitization in elderly patients with chronic obstructive pulmonary disease. Respiration. 1990;57(6):384.

40) Chanoine.S , Marchal .K, Temam. S, Dumas.O , et al. Incidence of asthma progression towards asthma-COPD overlap in old women.European Respiratory Journal 2018 52: PA1175; DOI: 10.1183/13993003.congress-2018.PA1175

41) Miravitlles.M, Alvarez-Gutierrez.F, Calle.M, Casanova.C,et al. Algorithm for identification of asthma–COPD overlap: consensus between the Spanish COPD and asthma guidelines.

European RespiratoryJournal 2017 49: 1700068; DOI: 10.1183/13993003.00068-2017

42) Miravitlles.M/ Diagnosis of asthma–COPD overlap: the five commandments

European Respiratory Journal 2017 49: 1700506; DOI: 10.1183/13993003.00506-2017

43) Barrecheguren .M, Esquinas .C, Miravitlles M. The asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS): opportunities and challenges.

Curr Opin Pulm Med 2015; 21: 74–79.CrossRefPubMedGoogle Scholar

44) Wurst. KE, Reif .K, Bushnell GA, et al. Understanding asthma-chronic obstructive pulmonary disease overlap syndrome. Respir Med 2016; 110: 1–11.CrossRefPubMedGoogle Schola

45) Coumou.H, Guus. A, Westerhof, Selma B. , et al. Predictors of accelerated decline in lung function in adult-onset asthma. Bel

European Respiratory Journal 2018 51: 1701785; DOI: 10.1183/13993003.01785-2017.

46) Eagan. TM, Brogger. JC, Eide GE, et al. The incidence of adult asthma: a review. Int J Tuberc Lung Dis(Jun 2005); 9: 603–612.

47) Masoli .M, Fabian.D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy (May 2004); 59: 469–478.

48) Melgert. BN, Ray. A, Hylkema MN, et al. Are there reasons why adult asthma is more common in females? Curr Allergy Asthma Rep (May 2007); 7: 143–150.

49) Beuther. DA, Sutherland. ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med (Apr 2007); 175: 661–666.

50) Tommola.M, Ilmarinen.P, Leena E,et al.Differences between asthma–COPD overlap syndrome and adult-onset asthma.

European Respiratory Journal (May 2017) 49: 1602383; DOI: 10.1183/13993003.02383-2016

51) Craven.J:Asthma-COPD Overlap Linked to Occupational Pollutants. MDedge News.(March 2021)

52) Tommola.M, Ilmarinen.P, Leena. E ,et al.Occupational exposures and asthma–COPD overlap in a clinical cohort of adult-onset asthma.ERJ Open Research (October 2019) 5: 00191-2019; DOI: 10.1183/23120541.00191-2019.

53)Hirota T, et al. Genome-wide association study identifies three new susceptibility loci for adult asthma in the Japanese population.(Jul 2011) Nat. Genet. 43, 893–896 .

54) Hardin.M , Cho.M , McDonald.M ,et al. The clinical and genetic features of the COPD asthma overlap syndrome. Eur Respir J 2014 Aug;44(2):341-50. doi: 10.1183/09031936.00216013. Epub 2014 (May 29).

55)Hardin .M, et al. The clinical and genetic features of COPD-asthma overlap syndrome. Eur. Respir. J. 44, 341–350 (Aug 2014).

56)Smolonska. J, et al. Common genes underlying asthma and COPD? Genome-wide analysis on the Dutch hypothesis. Eur. Respir. J. 44, 860–872 (Jun 2014)

57)Ferreira .MA, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. Nat. Genet. 49, 1752–1757 (Dec 2017).

58) Shrine. N, et al. New genetic signals for lung function highlight pathways and chronic obstructive pulmonary disease associations across multiple ancestries. Nat. Genet. 51, 481–493 (Mar 2019)

59) Pividori .M, Schoettler. N, DL. N, et al. Shared and distinct genetic risk factors for childhood-onset and adult-onset asthma: genome-wide and transcriptome-wide studies. Lancet Respir. Med. 7, 509–522 (Jun 2019).

60) Sakornsakolpat .P, Prokopenko.D , Lamontagne.M et al. Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations. Nat. Genet. 51, 494–505 (Aug 2019)

61) Ferreira.M, Matheson.M , Tang.C , et al. Genome-wide association analysis identifies 11 risk variants associated with the asthma with hay fever phenotype. J. Allergy Clin. Immunol. 133, 1564–1571 (Jun 2014)

62) Zeiger.R , Schatz.M 2, .Li.Q, et al. High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma. J Allergy Clin Immunol Pract 2, 741–750 (Dec 2014)

63) A. Charokopos , Braman , C.A. Powell , G. Mhango , K. Sigel 2, Lung Cancer Risk of Patients with Asthma-Chronic Obstructive Pulmonary Disease Overlap. American Journal of Respiratory and Critical Care Medicine (Aug 2020).

64) Hardin.M, Silverman.K, Barr.R, Hansel.N Hardin .M, Silverman .EK, Barr RG, BJ.M, et al.
The clinical features of the overlap between COPD and asthma. Respir Res (Sep 2011) 27;12(1):127. doi: 10.1186/1465-9921-12-127.

65) Won Bang.D, J. Yang, Eell .Ryoo ,et al. Asthma and risk of non-respiratory tract infection: a population-based case–control study. BMJ Jurnal. Volume 3, Issue 10

66) Juhn YJ, Kita H, Yawn BP, et al. Increased risk of serious pneumococcal disease in patients with asthma. J Allergy Clin Immunol. (Oct 2008);122:719–23.

67) Capili CR, Hettinger A, Rigelman-Hedberg N, et al. Increased risk of pertussis in patients with asthma. J Allergy Clin Immunol.(Apr 2012) DOI: 10.1016/j.jaci.2011.11.020

68) Frey. D, Jacobson .R, Poland. G, Li X, Juhn Y. Assessment of the association between pediatric asthma and Streptococcus pyogenes upper respiratory infection. Allergy Asthma Proc. (Oct 2009).

69) A Bjur.K , L Lynch.R, Fenta.Y, Ha Yoo.K , et al. Assessment of the association between atopic conditions and tympanostomy tube placement in children. Allergy Asthma Proc. (Jun 2012); DOI: 10.2500/aap.2012.33.3529.

70) J Juhn.Y. Risks for infection in patients with asthma (or other atopic conditions): is asthma more than a chronic airway disease?J Allergy Clin Immunol (Aug 2014) doi: 10.1016/j.jaci.2014.04.024.

71)Welch MJ. Inhaled steroids and severe viral infections. Journal of Asthma. J Asthma (Jun 1994) doi: 10.3109/02770909409056768

72) O'Byrne. P, Pedersen.S, Carlsson.L, Radner.F, et al. Risks of Pneumonia in Patients with Asthma Taking Inhaled Corticosteroids. Am J Respir Crit Care Med. (Mar 2011).

73) Hallifax.R, spontaneous pneumothorax. Reference Module in Biomedical Sciences, (2019).

74) Spindelboeck.W,Moser.A: Pneumothorax secondary to chronic obstructive pulmonary disease. Am J Emerg Med (Oct 2012) doi: 10.1016/j.ajem.2011.09.015.

75)Guo.Y, Xie.C XIE.C, R. Robriguez. , .W.R. Factors related to recurrence of spontaneous pneumothorax. Official Journal of Asian pacific society of Respirology. Volum 10, Issue 3,09 (June 2005).

76) Michael A. Grippi. Fishman's Pulmonary Diseases and Disorders, 5e, chapter 29: Approach to the Patient with Respiratory Symptoms(Jun 2015).

77) 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. https://ginasthma.org/wp-content/uploads/2019/11/GINA-GOLD-2017-overlap-pocket-guide-wms-2017-ACO.pdf (Accessed May 2021).

78) Van Tho.N, Yun Park.H , Nakano D. Kocakava. Asthma COPD overlap syndrum (ACOS). Marmara Medical Jurnal. (Apr 2016).

78) Badgett .RG, Tanaka. DJ, DK.H, et al. Can moderate chronic obstructive pulmonary disease be diagnosed by historical and physical findings alone? Am J Med. (Feb 1993); DOI: 10.1016/0002-9343(93)90182-o

79) Lemyze.M , Bart.F. Hoover sign. CMAJ. (Feb 2011) DOI: 10.1503/cmaj.092092

80) Zimmermann .B, Mikolich.M J, G Ho Jr. Olecranon bursitis in patients with chronic obstructive pulmonary disease. Am J Med. (Sep;1996). doi: 10.1016/s0002-9343(96)80140-9

81) Khalil.Z, Snen.H, Hana.B, Hana.M et al. Spirometric and clinical profiles in asthma copd overlap. European Respiratory Journal 2019 . DOI: 10.1183/13993003

82) Marron.R, Vega Sanchez.M. Images in COPD:Asthma-COPD Overlap Syndrome. hronic Obstr Pulm Dis. Chronic Obstr Pulm Dis vl.6(2); 2019

(Apr 2019). doi: http://doi.org/10.15326/jcopdf.6.2.2018.0169

83) Cosentino.J, Zhao.H , Hardin.M, Hersh.C, et al. Analysis of asthma-chronic obstructive pulmonary disease overlap syndrome defined on the basis of bronchodilator response and degree of emphysema. Ann Am Thoracic Soc.(Sep 2016); doi: HTTPS://DOI.ORG/10.1513/ANNALSATS.201511-761OC.

84) Corlateanu.A, Covantev.S, . Mathioudakis.A, Botnaru.V,et al. Asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS): current evidence and future research directions. (May 2017) doi: HTTPS://DOI.ORG/10.1186/S40749-017-0025-X

85) Gao .Y, Zhai. X, Li .K, et al. Asthma COPD overlap syndrome on CT densitometry: a distinct phenotype from COPD. COPD. (Aug 2015). doi: HTTPS://DOI.ORG/10.3109/15412555.2015.1102874

86) Kobayashi.S, Hanagama.M, Yamanda.S, Ishida.M,et al. Inflammatory biomarkers in asthma-COPD overlap syndrome. Int J Chron Obstruct Pulmon Dis (2016);11:2117-23.

87) Vedel-Krogh. S, Nielsen. SF, Lange .P, Vestbo. J, et al. Blood eosinophils and exacerbations in chronic obstructive pulmonary disease. The Copenhagen General Population Study. Am J Respir Crit Care Med (Sep 2016).

88) MacDonald. MI, Osadnik .CR, Bulfin .L, Hamza .K,et al. Low and high blood eosinophil counts as biomarkers in hospitalized acute exacerbations of COPD. Chest 2019;156:92-100. (Accessed by May 2021).

89) Hirai. K, Shirai .T, Suzuki. M, Akamatsu. et al. A clustering approach to identify and characterize the asthma and chronic obstructive pulmonary disease overlap phenotype. Clin Exp Allergy (Jun 2017)

90) Barnes.N, Sharma.R, Lettis.S , Calverley.P . Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. Eur Respir J (May 2016).

91) Calverley.P, Pauwels.R, Vestbo.J, Jones.P, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet(Feb 2003).

92) A Wedzicha.J, Banerj.D , Chapman.K, , et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. N Engl J Med (May 2016).

93) Chen.F , Huang.X, Li Liu.Y, Lin.G,et al. Importance of fractional exhaled nitric oxide in the differentiation of asthma-COPD overlap syndrome, asthma, and COPD. Int J Chron Obstruct Pulmon Dis.(Sep 2016).

94) Barker AF. Bronchiectasis. New England Journal of Medicine (May 2002).

95) V. Poletti, G. Casoni, M. Chilosi, M. Zompatori. Diffuse panbronchiolitis. European Respiratory Journal. vol. 28 no.(Jun 2006) DOI: 10.1183/09031936.06.00131805.

96) Murgu.S, Egressy.K, Laxmanan.B, Doblare.G et al. Central Airway Obstruction-Benign Strictures, Tracheobronchomalacia, and Malignancy-related Obstruction. Recent advances in chest medicen-volume 150, Issue 2, P426-441, (Aug 2016).

97) 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. https://ginasthma.org/wp-content/uploads/2019/11/GINA-GOLD-2017- overlap-pocket-guide-wms-2017-ACO.pdf (Accessed on May 2021).

98) Pascoe S, Barnes N, Brusselle G, Compton C, Criner GJ et al. Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial. Lancet Respir Med. (Sep 2019).

99) Bafadhel. M, Peterson. S, De Blas. MA, Calverley. PM et al.Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials.Lancet Respir Med. (Jun 2018).

100) Lazarus .SC, Chinchilli .VM, Rollings. NJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. Am J Respir Crit Care Med.(Apr 2007).

101) Gershon.A , CampitellI.M, Croxford.R , Stanbrook.M., et al. Combination long-acting bagonists and inhaled corticosteroids compared with long-acting b-agonists alone in older adults with chronic obstructive pulmonary disease. JAMA. (Sep 2014).

102)Welte .T, Miravitlles. M, Hernandez .P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med.(Oct 2009).

103) Lipson.D, Barnhart .B, Brealey.N. Brooks,et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med. (Apr 2018).

104) Khanna.D, J F Lin.C, Furst.D Goldin.J, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from twomulticentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med. (Oct 2020).

105) Castro .M, Corren .J, Pavord .ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med (Jun 2018).

106) Ortega.H, Liu.M, Pavord.I , Brusselle.G, FitzGerald.J, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. (Sep 2014) DOI: 10.1056/NEJMoa1403290

107) Bleecker.E FitzGerald.J, Chanez.P, Papi.A, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting b2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet (Oct 2019)

108) FitzGerald .JM, Bleecker .ER, Nair .P, et al. Benralizumab, an antiinterleukin-5 receptor a monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet.(Oct 2016)

109) Hanania.N, Alpan.O, Hamilos.L, Condemi.J, et al. Omalizumab in severe allergic asthma
inadequately controlled with standard therapy: a randomized trial. Ann Intern Med.(May 2011).

110) Bel. EH, Wenzel. SE, Thompson. PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med.(Sep 2014).

111) Nair.P, Wenzel.S, Rabe.K, Bourdin., et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med.(May 2017).

112) Rabe. KF, Nair. P, Brusselle. G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med.(Jun 2018).

113) Hanania. NA, Chipps. BE, Griffin. NM, Yoo. et al. TB. Omalizumab effectiveness in asthma-COPD overlap: Post hoc analysis of PROSPERO. J Allergy Clin Immunol. (Apr 2019).

114) Maltby.S, Gibson.P, Powell.H, McDonald.D . Omalizumab Treatment Response in a Population With Severe Allergic Asthma and Overlapping COPD. Chest. (Jun 2017).

115) FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an antiinterleukin-5 receptor a monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA):
randomised, double-blind, placebo-controlled phase 3 trial. Lancet. (Jun 2016

116) Brightling.C, Bleecker.R, Panettieri Jr.R Brightling. CE, et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised double-blind, placebo-controlled, phase 2a study. Lancet Respir Med. (Sep 2014)

117) Kau AL.A, Korenblat .P,.Anti-interleukin 4 and 13 for asthma treatment in the era of endotype.Curr Opin Allergy Clin Immunol. (Dec 2014)

118) Rabe. KF, Nair .P, Brusselle. G, Maspero. JF, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma (Jun 2018).

119) X. Zhao , F Q. Yu , X J. Huang , B Y. Xu , Y L Li , et al. Azithromycin influences airway remodeling in
asthma via the PI3K/Akt/MTOR/HIF-1a/VEGF pathway. J Biol Regul Homeost Agents. (Sep 2018).

120) Pu. Y, Liu. Y, Liao. S, Miao S, Zhou L, Wan L. Azithromycin ameliorates OVAinduced airway remodeling in Balb/c mice via suppression of epithelial-tomesenchymal transition. Int Immunopharmacol. (May 2018).

121) Baines .KJ, . Wright.T, . Gibson.P, Powell.H . Azithromycin treatment modifies airway and blood gene expression networks in
neutrophilic COPD. ERJ Open Res. (Oct 2018).

122) Metz .G, Kraft M. Effects of atypical infections with Mycoplasma and Chlamydia on asthma. Immunol Allergy Clin North Am.(Nov 2010).

123) Maselli.D, Medina.J, Brooks.E, Coalson.J, et al. The immunopathologic effects of Mycoplasma pneumoniae and community-acquired respiratory distress syndrome toxin: a primate model. Am J Respir Cell Mol Biol(Feb. 2018). DOI: 10.1165/rcmb.2017-0006OC.

124) Komiya .K, Ohta .S, Arima .K, et al. Clarithromycin attenuates IL-13-induced periostin production in human lung fibroblasts. Respir Res. 2017;18:37.

125) Gibson.P, Yang.I, Upham.J, Reynolds.P, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet.(Aug 2017).

126) Taylor.S, Leong.L, Mobegi.F, Choo.F , et al. Long-term azithromycin reduces Haemophilus influenzae and increases antibiotic resistance in severe asthma. Am J Respir Crit Care Med. (Aug 2019).

127)Walters .JA, Tang. JN, Poole .P, Wood-Baker. R. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. Cochrane Database Syst Rev. (Jun 2017).

128) Mulpuru.S, Li.L, Lingyun. Ye 2, Hatchette.T, Andrew.M, et al. Effectiveness of influenza vaccination on hospitalizations and risk factors for severe outcomes in hospitalized patients with
COPD. Chest. (Jan 2019).

129) Spruit .MA, Singh .SJ, Garvey .C, ZuWallack .R,et al. Force on Pulmonary Rehabilitation An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013(Oct 2013).

130) Spruit .MA, Singh. SJ, Garvey C, et al. An official American Thoracic Society/ European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188:e13ee64

Care Med 2013. Oct;188(8):e13-e64. 10.1164/rccm.201309-1634ST

131) Cheriamane D, Joshi V, Agarwal K, Purohit G et al. he effect of 6 week pulmonary rehabilitation in COPD-a randomized control study. Am J Respir Crit Care Med (Oct 2013). doi: 10.1164/rccm.201309-1634ST.

132) Troosters .T, Vilaro. J, Rabinovich R, Casas. A, et al. Physiological responses to the 6-min walk test in patients with chronic obstructive pulmonary disease. Eur Respir J 2002. (Sep;2020)

133) Araújo .D, Padrão. E, Morais-Almeida .M, et al. Asthma-chronic obstructive pulmonary disease overlap syndrome - Literature review and contributions towards a Portuguese consensus. Rev Port Pneumol (Apr 2017).

134) Gosselink .R. Controlled breathing and dyspnea in patients with chronic obstructive pulmonary disease (COPD). J Rehabil Res Dev 2003. (Sep 2003).

135) Dechman .G, Wilson .CR. Evidence underlying breathing retraining in people with stable chronic obstructive pulmonary disease*Physical Therapy*, Volume 84, Issue 12, 1 December 2004, Pages 1189–1197, https://doi.org/10.1093/ptj/84.12.1189. (Accessed on May 2021).

136) Elkhateeb .NB, Elhadidi AA, Masood HH, Pulmonary rehabilitation in chronic obstructive pulmonary disease. Egypt J Chest Dis Tuberc(Jun 2015).

137) Sahin. H, Naz. I, Varol .Y, Aksel. N,et al. COPD patients with severe diffusion defect in carbon monoxide diffusing capacity predict a better outcome for pulmonary rehabilitation. Rev Port Pneumol (Apr 2006).

138) Ferreira. G, Feuerman .M, Spiegler. P. Results of an 8-week, outpatient pulmonary rehabilitation program on patients with and without chronic obstructive pulmonary disease. J Cardiopulm Rehabil (Feb 2006).

139) InformedHealth.org. Allergies to animals: Allergen-specific immunotherapy (desensitization) in the treatment of allergies.(Accessed on May 2021).

140) Bafadhel.M , Mckenna.S , Agbetile.J , Fairs.A, et al.Aspergillus fumigatus during stable state and exacerbations of COPD. Eur Respir J (Jun 2014). doi: 10.1183/09031936.00162912.

141) J Vincent.M , Bernstein.J , Basketter.D, LaKind.J,et al. Chemical-induced asthma and the role of clinical, toxicological, exposure and epidemiological research in regulatory and hazard characterization approaches.Regul Toxicol Pharmacol. (Nov 2017) doi: 10.1016/j.yrtph.2017.08.018.

142) Grieger .JA, Wood .LG, Clifton .VL. Improving asthma during pregnancy with dietary antioxidants: the current evidence. Nutrients (Aug 2013).

143) Li.Q, J Baines .K, Gibson .P, G Wood.L . Changes in Expression of Genes Regulating Airway Inflammation Following a High-Fat Mixed Meal in Asthmatics. *Nutrients*. (Jan 2016).

144) Dias. CB, Wood .LG, Garg. ML. Effects of dietary saturated and n-6 polyunsaturated fatty acids on the incorporation of long-chain n-3 polyunsaturated fatty acids into blood lipids. Eur J Clin Nutr (Jul 2016).

145) Gotshall .RW, Mickleborough. TD. Cordain L: Salt intake, asthma, and exercise-induced bronchoconstriction: a review. *Phys Sportsmed*. (Nov 2010).

146) Lieberoth.S, Backer.V, Kyvik.K, Skadhauge.L, et al. Intake of alcohol and risk of adult-onset asthma. Respir Med.(Feb 2012).

147) Tabak .C., Smit H.A., Heederik D., Ocke .M.C., Kromhout .D. Diet and chronic obstructive pulmonary disease: Independent beneficial effects of fruits, whole grains, and alcohol (the MORGEN study) Clin. Exp. Allergy.(May 2001). doi: 10.1046/j.1365-2222.2001.01064.x.

148) Miedema.I, , Feskens.E, Heederik.D, Kromhout.D. Dietary determinants of long-term incidence of chronic nonspecific lung diseases. The Zutphen Study. Am. J. , Volume 138, Issue 1, 1 July 1993, Pages 37–45. https://doi.org/10.1093/oxfordjournals.aje.a116775.

149) Micha.R, Wallace.S, Mozaffarian.D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: A systematic review and meta-analysis. Circulation(Jun 2010). doi: 10.1161/CIRCULATIONAHA.109.924977.

150)4Gronberg A.M., Slinde F., Engstrom C.P., Hulthen .L., et al. Dietary problems in patients with severe chronic obstructive pulmonary disease. J Hum Nutr Diet (Dec 2005). DOI: 10.1111/j.1365-277X.2005.00649.x

151) Aguilar.M, Martin-Lujan.F, 2,3,4 Flores-Mateo.G, Arija-Val.V,., Dietary patterns are associated with lung function among Spanish smokers without respiratory disease (Nov 2016)

doi: 10.1186/s12890-016-0326-x.

13. Acknowledgments

I wish to express my deep gratitude to my mentor, Prof. Dr. Sanja Popović-Grle, for her great professional support and mentoring and for being the one who sowed the seeds in my heart for my passion for internal medicine and especially to the pulmonology field.

I would also like to thank the University of Zagreb, School of Medicine in Croatia for giving me the gift of having the ability to swear the Hippocratic Oath.

As a religious person, I feel obligated to thank God that has guided me throughout my life via the path that enabled me to finish my medical studies.

Lastly, I would like to pay my special regards to my dear parents who treated me with great devotion when I was an asthmatic patient myself and allowed me to fulfill my dream and acquire an academic education that I hope I will be able to use in the future to help any patient who seeks my aid.

This paper is lovingly dedicated to all chronic lung disease patients and their families, who are facing many daily challenges due to their illness.