
Research Article**Clinical Approach to Asthma COPD Overlap Syndrome****Dr. Pinar Mutlu¹, N.Arzu Mirici²**¹Assistant Professor, Çanakkale 18 Mart University, Faculty of Medicine, Department of Chest Diseases²Professor, Çanakkale 18 Mart University, Faculty of Medicine, Department of Chest Diseases

Abstract: Asthma and chronic obstructive pulmonary disease (COPD) are major public health issues which are associated with high and already increasing prevalence and may cause morbidity, mortality, and socioeconomical costs (1-4). Although asthma and COPD are different entities, the differential diagnosis can be sometimes challenging and it can be impossible in some elderly patients (5). Furthermore, more than 40% of the patients with COPD have reported a history of asthma (6) and asthma is accepted as a risk factor for the development of COPD (7).

It is well-known that, in patients with both COPD and asthma, the disease progresses more rapidly (8), the patients have a worse quality of life-related to the health status, and they have more frequent respiratory system exacerbations (9). In this patient population, there is an increased rate of comorbidities and frequent admissions to health centers, compared to the patients with asthma alone or COPD alone (10-11).

INTRODUCTION

The common epidemiological distribution of asthma and COPD in the overall population has not been clearly defined, yet. One reason for this is that coupling of asthma and COPD is often an exclusion criteria in clinical studies (9,12). Another reason is that the studies related to asthma are often performed in children or young adult population in which the prevalence of COPD is non-significant (13-14) and the studies related to COPD are performed in elderly population in which the prevalence of asthma is low (15).

Therefore, the concept of Asthma-COPD Overlap Syndrome (ACOS) was developed to meet the requirement for defining the common features of both diseases which overlap pathologically and functionally.

DEFINITION AND EPIDEMIOLOGY

ACOS is a syndrome which carries some features of both asthma and COPD and which is characterized by persistent airflow limitation (post-bronchodilator FEV1/FVC<70%) (16). It is still controversial whether ACOS results from asthma acquiring the features of COPD or from the features of asthma in COPD, or whether it manifests itself as ACOS at the beginning. To make the distinction, the available definition of asthma and COPD should be taken into account.

According to the GOLD 2014, new definition of COPD involves fine alterations related to the previous definitions and integrates the findings of recent evidences (17). For instance, the role of exacerbations and comorbidities is, currently, at the forefront of the reversibility concept. Thus, COPD is defined as a diffuse, preventable, and treatable disorder, which is characterized by chronic inflammatory response to harmful particles and gases in the airways and lungs, and the persistent

airflow obstruction is usually progressive; the exacerbations and comorbidities contribute to the disease severity.

On the other hand, in 2014 GINA, asthma was defined as a heterogeneous disease which is often characterized by chronic inflammation of airways (18). Together with variable expiratory airflow limitation, there is a history of respiratory symptoms such as wheezing, dyspnea, chest tightness and cough which change in duration and severity.

Although there are evident similarities between the definitions of asthma and COPD, none of the features are pathognomonic. Therefore, the GINA and GOLD have published a common guideline related to ACOS in 2014 (16). In this guideline, the features of the patients with asthma and COPD are listed separately and it has been stated that the diagnosis of ACOS can be done when same number of features is determined.

The actual prevalence of ACOS is not known. The prevalence of ACOS was found as 13% in COPDGene study (9). These patients have different clinical background with more frequent and severe exacerbations (Odds ratio (OR) 3.55) and giving inhaled corticosteroids to these patients during early period is recommended. Similarly the prevalence of ACOS was found as 12% in PLATINO study also and it has been mentioned that these patients carry the risk of more frequent exacerbations (OR 3.01) (19). In the study of gene environment interactions in respiratory diseases (GEIRD), the ratio of diagnosed asthma-COPD overlap was 1.6% at age 20-44, it was 2.1% at age 45-64 and it was 4.5% at age 65-84. It was found to be more common in females in all age ranges (OR:1.63; 95% CI: 1.15-2.31) (20).

In UC Davis Asthma Network (UCAN) severe asthma clinic, the prevalence of ACOS is half of the severe asthma cases (24.3% vs 52.9%, $p=0.0009$), while the mean age of the patients with asthma is 51.3, it is 72.4 in COPD and 66.7 in ACOS. The ratio of ACOS increases with age (21).

RISK FACTORS AND PATHOGENESIS

The chronic airway diseases such as asthma, COPD and ACOS develop as a result of interaction of genetic and environmental factors. A few possible pathways can cause ACOS development in adults. The first pathway is development of fixed airway limitation and COPD in patients with early-onset asthma together with cigarette smoking habit in time. The second possible pathway is presence of features of COPD and late-onset asthma (eosinophilic asthma and aspirin-sensitive asthma which is observed in adults) in patients with history of life-long cigarette smoking.

Although there are convincing evidences related to the fact that eosinophils play important role in ACOS similar to Th2-high profile asthma, there is no previous study related to the underlying mechanism of inflammation. In several studies, it has been demonstrated that the presence of eosinophil in induced sputum in patients with COPD and ACOS is associated with the response to corticosteroid treatment (22-24). Similar to the inflammatory diseases affecting the bronchial tree such as asthma and COPD, it is expected to find some evidences of Th-1 pattern (such as COPD) and Th-2 pattern (such as asthma) in also ACOS. We hope the studies related to the reliable biological markers of Th1 and Th2 inflammation would provide additional information in future.

ACOS IN GUIDELINES

Specific criteria related to the diagnosis of this special syndrome has been first present in the COPD guideline of Spanish Chest Disease and Chest Surgery Society in 2012 (25). According the Spanish COPD guideline, the diagnosis of ACOS is done with the presence of two major criteria or one major and two minor criteria. Major criteria are strong positive bronchodilator test ($([FEV1]>15\%$ and >400 ml increase), eosinophilia in sputum and history of asthma, minor criteria are high total IgE, history of atopy and positive bronchodilator test ($FEV1>12\%$ and >200 mL increase).

In addition to the Spanish guideline, in the recent Finnish COPD guideline, it is recommended adding FeNO (FENO 50 ppb) higher than 50 pieces per billion as a major criterion and additional peak flow (PEF) as an asthma specific additional minor criterion (26).

In the COPD guideline of Czech Republic, which was published in 2013, the definition of ACOS was done with similar criteria of the Spanish guideline (27).

Up to the present, the most comprehensive guidelines related to the diagnosis and treatment of ACOS are 2014 GINA and GOLD guidelines (17,18).

The features which can support the diagnosis of ACOS according GINA-GOLD are as follows:

- 1) It often begins after age 40 but it can start in childhood and young adult.
- 2) Persistent respiratory symptoms, variability are remarkable.
- 3) Airflow limitation does not recover completely.
- 4) Exposure to irritating agents such as in diagnosed asthma, allergy or COPD.
- 5) Persistent airflow limitation
- 6) The symptoms recover with treatment but the requirement for treatment is always present.
- 7) Exacerbations are more frequent than COPD but decreases with treatment.
- 8) Comorbidities affect the course.
- 9) Chest X-ray is consistent with COPD.
- 10) Eosinophilia in sputum is typical, neutrophilia may be present or absent.

Considering all previous recommended criteria, the recent Spanish Asthma Guideline (GEMA 2015) recommended the doctors to use a diagnostic algorithm in routine clinical practice (28). Furthermore, when compared with the others, this approach consists of oral corticosteroid test with prednisolone for evaluation of reversibility of bronchial obstruction. If $FEV1/FVC$ is below 70% following bronchodilator test, methacholine test and the presence or absence of biological markers to Th2 inflammatory response can be helpful in differentiation of COPD and ACOS.

TREATMENT OF ACOS

The present approach for pharmacotherapy of ACOS is provided by the results obtained from the subpopulations of the asthma or COPD studies. The first option for the patients with ACOS recommended by Spanish guideline (25) is to add inhaler corticosteroid to treatment of COPD as also mentioned in the Finland and Czech guidelines (26,27).

In GINA and GOLD 2014 guidelines, stepped treatment approach is recommended for ACOS. According to this:

- If the differential diagnosis of asthma or COPD cannot be done during the initial syndrome-based assessment of ACOS, the initial treatment should be similar to that of asthma. The reason for this is taking into consideration of the morbidity and even the mortality reduction effect of ICSs in patients with uncontrolled asthma.
- Similarly if the initial assessment suggests ACOS or asthma or if the possibility of COPD is low, again the treatment should be similar to that in asthma. In this situation, the first treatment option should be low-moderate dose ICS according to the severity of symptoms. LABA should be added to this treatment or if the patient has already been using, it should be continued. The point that should be kept in mind is that it is necessary not to give LABA alone, meaning as monotherapy.
- If the syndrome-based initial assessment suggests COPD, the first line treatment should be done as combined treatment with bronchodilators and if necessary with ICSs. Treatment should not be started with ICS alone.

- The treatment of ACOS should consist of other treatment strategies in addition to all these pharmacological treatment. These are; giving up cigarette smoking, pulmonary rehabilitation, vaccines, determination of comorbidities and their treatment and control as mentioned in GINA and GOLD guidelines.
- If persistent symptoms and attacks are present despite the treatment, if there is uncertainty in diagnosis and there is possibility of another diagnosis and if it is necessary to

exclude these, if there are atypical symptoms such as fever, weight loss, night sweating and hemoptysis, and if there are severe comorbidities affecting the treatment, the patients should be transferred to a more advanced center.

In conclusion, there is an unmet need for prospective studies to be able to understand the underlying mechanisms in ACOS. Therefore, we suggest that long-term investigations are necessary for confirmation of diagnostic criteria and for determination of biological markers of the disease.

Table 1. The features of asthma and COPD which can be used in diagnosis of ACOS and the treatment options

Asthma	COPD	
Age of onset	• < 20 years old	• > 40 years old
Characteristics of symptoms	<ul style="list-style-type: none"> • Variation of symptoms within minutes, hours and days • Worsening of symptoms at night and towards morning • Symptoms developing with triggering factors 	<ul style="list-style-type: none"> • Symptoms do not disappear despite the treatment • Fine and bad days might be present however daily symptoms and exercise dyspnea are always present • Chronic cough and unable to expectorate Dyspnea unrelated with the triggering factors Respiratory functions
Respiratory functions	• Variable airway obstruction (with RFT or PEF)	• Persistent airflow limitation (post BD FEV1/FVC < 0.7)
RFT in periods without symptoms	• Normal	• Abnormal
Background and family history	<ul style="list-style-type: none"> • Previous diagnosis of asthma • Family history of asthma and allergy 	<ul style="list-style-type: none"> • Previous diagnosis of COPD, chronic bronchitis or emphysema • Exposure to tobacco or biomass
Course of disease	<ul style="list-style-type: none"> • No worsening in symptoms in time, seasonal or annual variation • Spontaneous remission or remission with treatment, rapid response to BD or response to ICS within weeks 	<ul style="list-style-type: none"> • Slow progression in time • SABA provides partial relief
Chest X-ray	• Radiology is normal	• Severe air trapping

Diagnosis	≥3 features of asthma	Some features of asthma	≥ 3 and same number of features from both diseases	Some features of COPD	≥ 3 features of COPD
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Precise diagnosis	Asthma	Probable asthma	ACOS	Probable ACOS	COPD
Treatment	ICS+LABA (LABA is not used alone) LTRA Tiotropium Omalizumab Theophylline	ICS+LABA (LABA is not used alone)	ICS + LABA and/or LAMA	LABA and/or LAMA ± ICS (ICS is not used alone)	LABA and/or LAMA ± ICS (ICS is not used alone) Roflumilast Theophylline

RFT: Respiratory function test, BD: Bronchodilator, ICS: Inhaled corticosteroid, FEV1: Forced expiratory volume in first second,
SABA: Short-acting beta-2 agonist, LABA: Long-acting beta agonist, LAMA: Long-acting anticholinergic.

Table 1. The features of asthma and COPD which can be used in diagnosis of ACOS and the treatment options

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