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Review Article

**ASTHMA-COPD OVERLAP SYNDROME (ACOS) - AN UNDER
DIAGNOSED CLINICAL CONDITION AMONG GERIATRICS**Sai Krishna G*¹, Divyanjali P¹, Sumathi K², Komal Krishna T³¹Department of Pharmacy Practice, JSS College of Pharmacy, Mysore, Karnataka, India.²Department of Pharmacy, SIMS College of Pharmacy, Guntur, Andhra Pradesh, India.³Department of Physiotherapy, JSS College of Physiotherapy, Mysore, Karnataka, India.**Abstract:**

Asthma-COPD overlap syndrome (ACOS) is a clinical condition which is characterized by chronic airway inflammation and persistent airflow obstruction with several features usually associated with COPD and asthma respectively. Therefore ACOS is identified by the features that it shares both asthma and COPD. It is crucial to define asthma, COPD and ACOS, as notable clinical entities, since they share common pathologic and functional features. Patients with ACOS have the combined risk factors of smoking and atopy, and are generally younger than patients with COPD and experience acute exacerbations with higher frequency and greater severity than COPD alone. Pharmacotherapeutic considerations require an integrated approach, a consensus international definition of ACOS is needed to design prospective, randomized clinical trials to evaluate specific drug interventions on important outcomes such as lung function, acute exacerbations, quality of life and mortality.

Key words: *Asthma, Chronic obstructive pulmonary disease, ACOS, elderly patients, under diagnosed.***Corresponding Author:****Sai Krishna G,**

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INTRODUCTION: [1]

Asthma and Chronic Obstructive Pulmonary Disease (COPD) are major public health concerns. There are typically characterized as different disease conditions with unique epidemiological features as well as pathophysiological mechanisms. Asthma is an allergic disease that often develops during childhood, although it can also be diagnosed in adult life. It is characterized by airway hyper-responsiveness (AHR) that leads to intermittent and usually reversible airway obstruction, whereas COPD is a chronic respiratory disease that is typically linked to smoking tobacco, usually presents in subjects older than forty years of age, and is characterized by progressive and irreversible airway obstruction. These definitions allow asthma and COPD to be recognized as distinct disease entities. However, this concept needs to be re-evaluated as many epidemiological studies have shown that asthma and COPD may coexist, or at least one condition may evolve into the other creating a condition commonly described as Asthma-COPD Overlap Syndrome. It is a syndrome in which older adults with a significant smoking history have features of asthma in addition to their COPD as it characterized by a functional and pathological overlap between asthma and COPD.

The concurrence of incompletely reversible airflow obstruction (diagnostic feature of COPD) and increased airflow variability (one of the symptom of asthma) is common among elderly population with respiratory symptoms (>65years). People with ACOS have worse outcomes than COPD or Asthma alone. ACOS represents a distinct clinical phenotype with

more frequent exacerbations, hospitalization, worse health-related quality of life, and higher healthcare costs than either disease alone. There is a critical need to better define the management and treatment of this syndrome. [2]

SIGNS AND SYMPTOMS

- Chronic cough or wheezing with or without sputum (early symptom)
- Dyspnoea or exercise intolerance (late symptom)
- Reduction in daily activities of living (physical deconditioning)
- Frequent need for inhaled salbutamol
- Frequent acute exacerbations despite adherence to standard pharmacotherapy
- Labored breathing
- Wheezing
- Coughing, with or without mucus
- Tightness in the chest

Patients with Asthma-COPD overlap syndrome are usually differentiated by increased reversibility of airflow obstruction, increased response to inhaled corticosteroids and bronchial, eosinophilic, systemic inflammation when compared with COPD patients. [3]

RISK FACTORS

Risk factors for coexisting asthma and COPD include ageing, smoking, atopy (e.g. hay fever) and chronic asthma. The coexistence of COPD and asthma in elderly patients are not always due to cigarette smoking. In some people with many years of poor control, persistent airflow limitation may develop as a complication of long-term asthma. [4]

Table 1: Comparison among Asthma, COPD and ACOS [5-8]

Disease	Characteristics	Pathophysiology	First-line Therapy	Add-on Therapy
Asthma	<ul style="list-style-type: none"> • Age > 40 • Non smoker • Women > men • Typical atopy present • Exercise limited in between attacks • Dependence on prednisone • Frequent exacerbations (Hallmark feature) 	<ul style="list-style-type: none"> • Moderate to severe airflow obstruction • FEV1/FVC < 0.70 • FEV1 < 68% • DLCO normal • FeNO > 50ppb • Exacerbations >3/year • Sputum eosinophils present 	<ul style="list-style-type: none"> • ICS • ICS + LABA 	<ul style="list-style-type: none"> • LAMA • LTRA • Theophylline • Omalizumab • Prednisone
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COPD	<ul style="list-style-type: none"> • Age \geq 65 • Past or current smoker • No atopy • Exercise very limited • Oxygen dependence • Exacerbations and exercise intolerance (Hallmark feature) 	<ul style="list-style-type: none"> • Chronic airflow obstruction • FEV1/FVC $<$ 0.70 • FEV1 $<$ 50% • DLCO $<$ 80% • FeNO $<$ 25ppb • Hyperinflation present • Exacerbations $>$2/year • Infrequent nocturnal awakenings 	<ul style="list-style-type: none"> • Bronchodilators • LAMA/LABA/both • Smoking cessation • Pulmonary Rehabilitation 	<ul style="list-style-type: none"> • ICS • Roflumilast • Theophylline
ACOS	<ul style="list-style-type: none"> • Age 40-65 • Past or current smoker • Atopy present • Exercise very limited • Very frequent exacerbations (Hallmark feature) 	<ul style="list-style-type: none"> • Moderate to severe airflow obstruction • FEV1/FVC $<$ 0.70 • FEV1 $<$ 68% • DLCO normal • FeNO $>$ 25-50ppb • Hyperinflation present • Exacerbations $>$ 3-5/year • Frequent nocturnal awakenings 	<ul style="list-style-type: none"> • ICS/LAMA / LABA/all • Smoking cessation • Pulmonary Rehabilitation 	<ul style="list-style-type: none"> • LTRA • Omalizumab • Prednisone • Roflumilast • Theophylline
<p><i>FEV- Forced Expiratory Volume, FVC- Forced Vital Capacity, DLCO- Diffusing Capacity of the lung for Carbon monoxide, FeNO- Fractional exhaled Nitric Oxide, ICS- Inhaled Cortico Steroids, LABA- Long-Acting Beta Agonists, LAMA- Long-Acting Muscarinic Antagonists, LTRA- Leukotriene Receptor Antagonists.</i></p>				

DIAGNOSIS:

To reach a diagnosis, imaging tests such as X-ray, CT scans, or MRI may be necessary. It also need a noninvasive test called spirometry, also known as a pulmonary function test, which aid in measuring lung function. In 2014 the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) released a guideline on ACOS. These guidelines suggest as stepwise approach to diagnosis and treatment. The approach proposed by GINA is simple and practical. [9, 10]

Step-Wise Approach for Diagnosis of ACOS

Step 1: Does the patient have chronic airways disease?

A first step in diagnosing these conditions is to identify patients at risk of, or with significant likelihood of having chronic airways disease, and to exclude other potential causes of respiratory symptoms. This is based on the physical examination, detailed medical history and other investigations.

Step 2. The diagnosis of asthma, COPD and ACOS in an adult patient

Given the extent of overlap between features of asthma and COPD, the approach proposed focuses on the features that are most helpful in distinguishing asthma and COPD.

a. Assemble the features that favor a diagnosis of asthma or COPD

From a careful history which includes age, symptoms (in particular onset and variability, progression, seasonality or periodicity and persistence), past history, social and occupational risk factors including smoking history, previous treatment, diagnosis and response to treatment, the features favoring the diagnostic profile of asthma or of COPD can be assembled.

b. Compare the number of features in account of a diagnosis of COPD or a diagnosis of Asthma

Having three or more characteristic feature of either asthma or COPD useful for the correct diagnosis. However, the absence of any of these characteristic features has less predictive value, and does not rule out the diagnosis of either disease. For example, a history of allergies increases the probability that respiratory symptoms are due to asthma, but is not required for the diagnosis of asthma since non-allergic asthma is a well-recognized asthma phenotype and atopy is common in the general population including in patients who develop COPD in future years. When a patient has similar symptoms of both COPD and Asthma, the diagnosis of ACOS should be considered.

c. Consider the level of certainty over the diagnosis of COPD or Asthma, or whether there

are features of both suggesting ACOS (Asthma-COPD overlapping syndrome)

In the absence of pathognomonic features, clinicians recognize that diagnoses are made on the weight of evidence provided there are no features that clearly make the diagnosis unsupportable. Clinicians are able to provide an estimate of their level of certainty and factor it into their decision to treat. Doing carefully may support in the selection of treatment and where there is significant doubt, it may direct therapy towards the safest treatment option for the condition that should not be left untreated.

Step 3: Spirometry

Spirometry is required for the assessment of patients with suspected disease of the airways. It should be performed at the initial or a subsequent visit, if possible before and after a trial of treatment. Early confirmation of the diagnosis may avoid unrequired trials of therapy, or delays in initiating other investigations.

Spirometry verify the chronic airflow limitation but is of more limited value in distinguishing between asthma with fixed airflow obstruction, COPD and ACOS Measurement of peak expiratory flow (PEF), even though it is not an alternative to spirometry, if it is performed repeatedly over a period of 1–2 weeks may help to confirm the diagnosis of asthma, but a normal peak expiratory flow does not rule out either asthma or COPD. A high degree of variability in lung function may also be found in ACOS.

After obtaining the results of other investigations and spirometry, the provisional diagnosis from the syndrome based assessment must be reviewed and if necessary it should be revised. Spirometry at a single visit should not be considered for diagnosis, and results must be considered in the relation of the clinical presentation of the patient, and whether treatment has been commenced. long-acting bronchodilators and Inhaled corticosteroids influence results, particularly if a long withhold period is not used prior to performing spirometry. Further investigations might be necessary either to assess or confirm the diagnosis or to assess the response to initial and subsequent treatment.

Step 4: Commence initial therapy

Experience with a differential diagnosis equally balanced between COPD and asthma (i.e. ACOS) the default position should start the treatment accordingly for asthma. This recognizes the vital role of ICS in preventing morbidity and mortality in patients with uncontrolled asthma symptoms, for whom even clearly having ‘mild’ symptoms (when compared to the patients with moderate or severe symptoms of COPD) which might indicate significant risk of a life-threatening attack.

If the syndromic assessment recommends asthma or ACOS, or there is significant uncertainty about the diagnosis of COPD, it is advisable to start treatment as for asthma until further investigations has been performed to confirm or contradict this initial position.

Treatment would include an ICS (in a low or moderate dose, depending on level of symptoms). A long-acting beta 2-agonist (LABA) should also be continued (if already prescribed), or added. It is important that patients should not be treated with a LABA without an ICS (often called LABA monotherapy) if there are features of asthma.

If the syndromic assessment recommends COPD, appropriate symptomatic treatment with bronchodilators or combination therapy should be recommended, but not ICS alone as monotherapy

Step 5: Criteria for specialized investigations (if necessary)

Further diagnostic evaluation and referral for expert opinion is necessary in the following conditions:

- i. Patients with persistent symptoms and/or exacerbations despite treatment.
- ii. Diagnostic uncertainty, especially if an alternative diagnosis e.g. bronchiectasis, bronchiolitis, post-tuberculous scarring, pulmonary fibrosis, pulmonary hypertension, and other causes of respiratory symptoms needs to be excluded.
- iii. Patients with suspected asthma or COPD in whom atypical or additional signs or symptoms e.g. significant weight loss, night sweats, haemoptysis, fever or other structural lung disease suggest an additional pulmonary diagnosis. This should be efficient early referral, without necessarily waiting for a trial of treatment for asthma or COPD.
- iv. When chronic airways disease is suspected but syndromic features of both asthma and COPD are few.
- v. Patients with comorbidities that may interfere with the assessment and management of their airways disease.
- vi. Referral may also be appropriate for problems arising during on-going treatment of asthma, COPD or ACOS, as outlined in the GOLD and GINA strategy reports.

MANAGEMENT OF ASTHMA-COPD OVERLAP SYNDROME [11]

Goals of treatment of ACOS should be to control or reduce symptoms and impairment, and to reduce risks such as acute exacerbations, decline in lung function and adverse effects from medicines. Treatment should be started as for asthma. The Australian Asthma Handbook recommends treatment

with long-term inhaled corticosteroids (ICS) to reduce the risk of asthma flare-ups in addition to a long-acting bronchodilator in patients with coexisting asthma and COPD. Treatment should also include:

- a) Smoking cessation
- b) Pulmonary rehabilitation
- c) Vaccinations (such as flu, pneumonia, and whooping cough)
- d) Allergen avoidance
- e) Treatment of comorbidities
- f) Disease management training
- g) Healthy eating and nutrition education
- h) Oxygen therapy (if necessary) etc.,

Patient education and self-management, within cognitive function, has been shown to reduce hospitalizations for exacerbations and infections.

Pharmacological management

Medications used for the treatment of ACOS include those recommended in guidelines for asthma and COPD. Short-acting beta-agonists (SABAs) (salbutamol, terbutaline) are used for immediate relief of symptoms of asthma and COPD, on an 'as needed' basis. The use of short-acting muscarinic antagonists (SAMAs) or anticholinergic bronchodilator such as ipratropium (Atrovent Metered Aerosol) is primarily used for quick relief of COPD symptoms. [11]

a) Inhaled corticosteroids

Inhaled corticosteroids are very effective anti-inflammatory drugs in the management of asthma and are indicated as combination therapy in COPD when FEV1 <50% predicted and patient has had 2 or more exacerbations in the previous 12 months).

Inhaled corticosteroids in order of increasing potency include, Beclomethasone, Budesonide, Ciclesonide, Fluticasone propionate, Fluticasone furoate. Inhaled corticosteroids can be delivered in combination with long-acting beta2-agonists (LABAs) and/or long-acting muscarinic antagonists (LAMAs).

b) LABAs

LABAs significantly reduce asthma exacerbations, and are the preferred add-on drug to low-dose ICS in the treatment of asthma. LABAs include salmeterol, indacaterol, eformoterol, olodaterol and vilanterol.

It is important to note that LABAs without an inhaled corticosteroid should not be prescribed in patients with ACOS. Combination inhaled corticosteroid/long-acting beta-2 agonist (LABA) in a single inhaler include:

- Budesonide/eformoterol
- Fluticasone propionate/salmeterol
- Fluticasone propionate/eformoterol
- Fluticasone furoate/vilanterol etc.

c) LAMAs

LAMAs are considered first-line therapy for the management of COPD. Recent evidence has also suggested a role in the treatment of asthma. They generally take long to have an effect than LABA bronchodilators. These medications significantly reduce the risk of acute COPD exacerbations, improve exercise tolerance and effectively control symptoms such as dyspnoea.

Long-acting muscarinic antagonist (anticholinergic) agents include tiotropium and newer agents like aclidinium, glycopyrronium and umeclidinium. These newer agents are as effective as tiotropium.

d) LABA/LAMA (Double therapy)

New combination products containing a LABA and LAMA include, Indacaterol/glycopyrronium (110/50), Vilanterol/umeclidinium.

e) ICS, LAMA and LABA (Triple therapy)

In patients who have frequent exacerbations (2 or more in previous 12 months) and have a FEV1 less than 50% predicted may benefit from all three classes of medicines or 'triple therapy': ICS, LAMA and LABA.

f) Other therapies

In more severe cases of ACOS, theophylline or roflumilast may be added. Omalizumab, a IgE selective humanized monoclonal Antibody, is indicated for the management of Moderate-severe allergic asthma in adults. The benefit in COPD and ACOS has not been tested.

Patients with features of asthma should be prescribed adequate therapy to control the condition including inhaled corticosteroids, but not long-acting bronchodilators alone. Patients with COPD should receive appropriate symptomatic treatment with bronchodilators or combination therapy, but not inhaled corticosteroids as monotherapy. Many patients will require triple therapy with inhaled corticosteroids, long-acting beta2-agonists and long-acting muscarinic antagonists, as well as short-acting bronchodilators as relievers. The greater choice of medications and devices provides new fixed dose combinations with once or twice daily dosing. The selection of therapy should consider ease of use, efficiency and patient preferences.

DISCUSSION:

There are many disease conditions which are common but under diagnosed in our daily life. This includes diseases as familiar as Tired All The Time Syndrome (Chronic Fatigue Syndrome), Beauty Parlour Syndrome, Fat Wallet Syndrome, Male Breast Cancer, Selfie syndrome and many more are of

increased concern and clinicians must be made aware of these diseases for better diagnosis and management. There is a deficit of medical and scientific knowledge related to these diseases. Physicians, researchers and healthcare professionals were unaware of the under diagnosed diseases and until very recently there was no real research concerning issues related to the field. [12-18]

CONCLUSION:

ACOS can be managed in primary care with the help of clinical pharmacist being an integral part of supporting and educating the patients. These patients require on-going education in relation to inhaler technique, adherence to medication regimes, non-pharmacological interventions such as vaccinations, breathing exercises and self-management. As ACOS patients likely to have poor outcomes when compare to patients with either COPD or asthma alone, it is essential that they are adequately treated and assessed using the new guidance from GINA & GOLD. As with any chronic condition, clinical pharmacists are in a privileged position to assist patients attain and obtain an optimal quality of life.

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