A Riddle, Wrapped in a Mystery: Asthma COPD Overlap
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After completion of the session you should be able to:
1. Identify patients with Asthma COPD overlap
2. Appreciate the difficulties in diagnosing and treating the asthma and COPD overlap.
3. Understand the importance of the underlying inflammatory process when deciding the type of pharmacologic treatment to use in a patient with chronic airway disease.

NO SIGNIFICANT FINANCIAL, GENERAL, OR OBLIGATION INTERESTS TO REPORT

“No great advance has ever been made in science, politics, or religion, without controversy”
(Lyman Beecher, 1828)

For every patient, in the final analysis, you must do a clinical trial of one.”
Eugene D. Robin MD
What am I?

I am free for the taking through all of your life,
Though given but once at birth.
I am less than nothing in weight,
But will fell the strongest of you if held.

Revisiting the Dutch hypothesis

• The Dutch hypothesis (Lumpers) suggested the term Chronic Non Specific Lung Disease
  • Proposed that Asthma and COPD have common origins and clinical expressions and are determined both by endogenous (heredity, age and, sex) and exogenous (environment: allergens, smoking, viruses, and air pollution) factors.
• The British Hypothesis (Splitters) suggested that Asthma and COPD are distinct diseases with different causal mechanisms.
Asthma is a heterogeneous condition characterized by chronic airway inflammation. The inflammation causes an increase in bronchial hyperresponsiveness. In susceptible individuals the inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and cough. The episodes are associated with widespread but variable airflow obstruction that is at least partially reversible, either spontaneously or as the result of treatment.

Which of the following is NOT true regarding the asthma COPD overlap?

- It should be suspected in a smoker with a previous history of asthma
- It should be suspected in a late-onset asthmatic with a previous history of smoking
- It should be suspected in a patient with a FEV1/FVC post-BD<70% with a very positive post-bronchodilator response (>400 ml and 15%)
- It should be suspected in patients with a FEV1<50% and frequent exacerbations
- It should be suspected in a patient with a FEV1/FVC post-BD<70, hayfever and persistent blood eosinophil counts >300 cells/µL

Which of the following is NOT true regarding the asthma COPD overlap?

A. It should be suspected in a smoker with a previous history of asthma
B. It should be suspected in a late-onset asthmatic with a previous history of smoking
C. It should be suspected in a patient with a FEV1/FVC post-BD 400 ml and 19%
D. It should be suspected in patients with a FEV1<50% and frequent exacerbations
E. It should be suspected in a patient with a FEV1/FVC post-BD 300 cells/µL
Asthma COPD Overlap An Enigma

• GINA/GOLD Diagnosis of Diseases of Chronic Airflow Limitation
• The Australian Asthma Management Handbook Guidelines for the Diagnosis and Treatment of COPD
• The Japanese Respiratory Society’s COPD guidelines
• The Spanish COPD consensus
• Consensus guidelines for the Czech Pneumological and Physiological Society

Stepwise approach was recommended through clinical history, physical examination, radiology and potentially screening questionnaires. Next a syndromic approach is recommended where the features of airways disease are assembled and the features that favor asthma and COPD are compared. Three or more features of one disease gives a high likelihood of the correct diagnosis; if there are a similar number of asthma and COPD features, then the overlap of asthma–COPD overlap is more likely. Spirometry is then recommended for confirmation of the diagnosis. If asthma–COPD overlap is confirmed, the initiation of asthma therapy is advised; that is, combination ICS/LABA.

Recommends pooling of features corresponding to asthma and COPD in order to make a diagnosis, followed by a trial of ICS and then the addition of LABA for symptom control.

Suggest the following indices for diagnosis of an asthma component: paroxysmal dyspnea, cough and wheeze that is worse at night and in the early morning, atopy and the presence of peripheral blood and or sputum eosinophilia. These guidelines also recommend the initiation of ICS irrespective of the severity of COPD, together with a LABA or LAMA.

Six major and minor criteria required for a diagnosis of asthma–COPD overlap. They suggest that two major criteria (increase in FEV1 ≥15% and ≥400 mL, eosinophilia in sputum and a history of asthma) or one major and two minor (elevated total IgE, history of atopy and positive bronchodilator response of ≥12% and ≥200 mL) on two or more occasions) are strongly suggestive of the overlap phenotype. Treatment recommendations include ICS with adjustment according to symptoms, lung function and sputum eosinophilia in conjunction with a LABA, and as disease severity increases triple therapy with a LAMA is recommended.

The Czech guideline defined major and minor criteria for the diagnosis of asthma–COPD overlap: Major criteria included (a) strong bronchodilator test (BDT) positivity (FEV1 >15% and >400 mL), (b) bronchoconstrictor test (BCT) positivity, (c) FeNO ≥45–50 ppb and/or ↑eosinophils (sputum) ≥3%, (d) history of asthma. Minor criteria included (a) mild BDT positivity (FEV1 > 12% and > 200 mL), (b) ↑ total IgE, (c) history of atopy and definite COPD diagnosis. The COPD+asthma phenotype can be confirmed by the presence of two major criteria or one major plus two minor criteria.

Why the Controversy over Defining ACO?

• The definitions assume that patients that have features of both asthma and COPD represent a homogenous group
• Each disease has a different mechanism and probably is composed of multiple endotypes with diverse disease manifestations
• The definitions lack assignment of how much weight each disease has on the clinical manifestations and outcomes
• The definitions are sensitive but lack specificity
• Most clinical trials of asthma and of COPD have excluded patients with overlapping features, which limits our understanding of patients who have characteristics of both diseases
Complex multifactorial Heterogeneous Syndrome rather than simple disease entities

**Phenotypes:** Observable characteristics often with no direct relationship to disease process.

**Endotypes:** Biological mechanisms that underlie a distinct disease entity present within a phenotype.

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**Asthma Phenotypes and Endotypes**

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**After asthma: airways diseases need a new name and a revolution**

Asthma remains a frightening diagnosis with an unclear progress and outcome. The estimated global burden of asthma has substantially increased in recent years, leading to difficulties in understanding the disease. Asthma is a chronic disease characterized by inflamed and hyper-reactive airways, leading to symptoms such as wheezing, shortness of breath, chest tightness, and coughing, especially at night or early in the morning.

Shared Subgroups between Asthma and COPD

Asthma COPD Overlap (ACO) Phenotypes/Endotypes

Asthma and COPD converge in older patients.

Diagnosis and initial treatment of asthma, COPD and asthma-COPD overlap (ACO)
A joint project of GINA and GOLD

GINA Global Strategy for Asthma Management and Prevention
GOLD Global Strategy for Diagnosis, Management and Prevention of COPD
Phenotypic Characteristics That May Help The Clinician Decide If Asthma or COPD Carry More Weight In ACO

**More Consistent With Asthma**
- Onset of symptoms before the age of 20 y
- Variation of symptoms over time
- Worsening of symptoms during the night or early morning
- Symptoms triggered exposure to allergens, dust, exercise
- Documentation of variable airflow limitation
- Previous doctor’s diagnosis of asthma
- Family history of asthma and allergy
- Normal chest radiograph

**More Consistent With COPD**
- Onset of symptoms after the age of 40 y
- Persistence of symptoms despite treatment
- Good and bad days, but always some degree of symptoms
- Chronic cough and sputum production unrelated to triggers
- Documentation of persistent airflow limitation
- Previous doctor’s diagnosis of COPD
- Previous exposure to noxious particles or gases such as tobacco smoke or biomass fuels
- Hyperinflation on chest radiograph
GINA GOLD Definition of Asthma COPD Overlap

**Spanish Respiratory Society’s algorithm for the identification of patients with ACO**

(a) Wagener and colleagues found that the best cut-off point for blood eosinophils was 270 cells/μl to detect sputum eosinophilia (AUC: 89%) in patients with ACO.

(b) Patients with moderate-to-severe COPD and blood eosinophil counts of ≥300 cells/μl have shown an increased risk of exacerbations in a recent study, which was prospectively validated in the ECLIPSE study.

(c) It has been found that COPD patients with blood eosinophil levels ≥300 cells/μl achieved a greater reduction in exacerbations following ICS treatment compared with bronchodilators.

ACO’s specific inflammatory characteristics remain largely unknown (if they really do exist).
The five commandments of ACO diagnosis

1) A patient with asthma may develop non-fully reversible airflow obstruction but this is not COPD, not even ACO; it is obstructive asthma.

2) A patient with asthma who smokes may also develop non-fully reversible airflow obstruction, which differs from obstructive asthma and from “pure” COPD. This is the most frequent type of patient with ACO.

3) Some patients who smoke and develop COPD may have a genetic Th2 background (even in the absence of a previous history of asthma) and can be identified by high eosinophil counts in peripheral blood. These individuals could be included under the umbrella term of ACO.

4) A patient with COPD and a positive bronchodilator test (>200 mL and >12% FEV1 change) has reversible COPD but is not an asthmatic, or even ACO.

5) A patient with COPD and a very positive bronchodilator test (>400 mL FEV1 change) is more likely to have some features of asthma and could also be classified as ACO.

Prevalence of Asthma COPD Overlap (ACO)

- The reported prevalence of ACO increases with age and ranges between 1.6% and 4.5% in general population studies and up to 27% and 33% among asthma and COPD populations, respectively.

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence of ACO %</th>
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<tbody>
<tr>
<td>2000</td>
<td>1.6</td>
</tr>
<tr>
<td>2005</td>
<td>4.5</td>
</tr>
<tr>
<td>2010</td>
<td>27</td>
</tr>
<tr>
<td>2015</td>
<td>33</td>
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Eur Respir J 2019; 155(1): 168-177
Pathophysiology: Asthma COPD Overlap

### Distinguishing Features
- Predominant Inflammatory cell type(s): Neutrophil (COPD) vs. Eosinophil (Asthma)
- CD8+ (COPD) vs. CD4+ (Asthma) cells
- ILC2 cells (Asthma)
- Cytokine profiles: Th17 vs. Th2/Th17 (COPD) vs. Th2/Th17 (Asthma)
- Airway smooth muscle cell hypertrophy and proliferation
- Epithelial squamous metaplasia/hyperplasia (COPD)
- Neutrophils (Asthma) vs. "Fixed" airflow obstruction (COPD)
- Reduced diffusing capacity (COPD)
- Airways' vascular capillary bed destruction
- Vascular remodeling
- Centralization and bronchiocentric disease (COPD)
- Post-respiratory (COPD) vs. Good response (Asthma) to corticosteroids
- Exposures: aeroallergens (Asthma) vs. smoke (COPD)

### Areas of Overlap
- Mixed Inflammation: Neutrophils, Eosinophils, Macrophages
- Cytokine profiles: Th1/Th2/Th17
- Airway smooth muscle cell proliferation
- Epithelial goblet cell metaplasia/hyperplasia
- Airway hyperresponsiveness (AHR)
- Bronchodilator responsiveness
- "Fixed" airflow obstruction (COPD, some Severe Asthma)
- Impaired mucus clearance
- Hyperinflation and Air-trapping

References:
- Barnes PJ AJRCCM 1996
- Carr, Zeki, et al AJRCCM 2010
Whether ACO emerges after gradual shifts in airway remodeling and inflammation in a patient with COPD, as the result of noxious exposures in a patient with asthma, or even as a de novo disease with its own pathology is yet to be determined!

ACO Remains an Enigma

What about Prognosis?

• Compared with their counterparts with asthma or COPD alone, patients with ACO have significantly worse respiratory symptoms, poorer quality of life, and increased risk of exacerbations and hospital admissions.

Hypothetical Course of Lung Function
Long term Prognosis of Asthma, COPD and ACO in the Copenhagen City Heart Study

Respiratory Mortality in the Copenhagen City Heart Study: Asthma, COPD and ACO (early vs late onset)

All Cause Mortality in the Copenhagen City Heart Study: Asthma, COPD and ACO (early vs late onset)
Hospital Admissions for Asthma or COPD Exacerbations

Hospital Admissions for Pneumonia in the Copenhagen Heart Study: Asthma, COPD, ACO (early vs late onset)

What would you prescribe to a 60-year-old female with a history of childhood asthma, allergies, cigarette smoking (45 pack-years), and COPD. Referred for unremitting exertional dyspnea • ACT test - 10/25 (poorly controlled) • FEV/FVC ratio - 0.50; FEV1 - 40% predicted • No exacerbations or hospitalizations

A. LAMA
B. LABA/LAMA
C. LABA/ICS
D. LABA/LAMA/ICS
"One size fits all" vs Personalized Approach
Evaluate these features in each individual

**General** – physical function, socioeconomic, psychologic, comorbidities

**Phenotype:**
- Current cigarette smoking
- Respiratory symptoms – mMRC, ACT, CAT
- Exacerbation history – and hospitalizations
- Lung function – spirometry, bronchodilator response
- Allergies, triggers

**Endotype** – Eosinophil count, FeNO

Therapeutic approaches for ACO

- **Universal management**
  - Disease education
  - Smoking cessation
  - Vaccinations
  - Allergen/irritant avoidance
  - Oxygen assessment
  - Comorbidity management
  - Adherence to therapy
- **Symptom reduction**
  - Asthma centric approach
  - COPD centric
  - Exacerbation reduction
  - Disease-modifying

Treatment of Obstructive Airway Disease

<table>
<thead>
<tr>
<th>COPD</th>
<th>ACO</th>
<th>Asthma</th>
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**Treatment of Obstructive Airway Disease**

COPD   
ACO   
Asthma

http://gicowhina.org/
Assessment of COPD Severity

- Spirometry confirmed diagnosis
- Assessment of airflow limitation
- Assessment of symptoms and risk of exacerbations

Mild
- GOLD 1
- mMRC 2
- CAT < 10
- FEV1 % predicted > 80%

Moderate
- GOLD 2
- mMRC 3
- CAT 10-20
- FEV1 % predicted 50-79%

Severe
- GOLD 3
- mMRC 4
- CAT > 20
- FEV1 % predicted < 50%

Very severe
- GOLD 4
- mMRC 5
- CAT > 30
- FEV1 % predicted < 30%
Long Acting Beta2 Agonists (LABA)
- Salmeterol
- Formoterol
- Indacaterol
- Olodaterol
- Vilanterol

Long-acting muscarinic antagonists (LAMA)
- Tiotropium
- Umeclidinium
- Aclidinium
- Glycopyrrolate
- Revefenacin

Short-Acting Beta2 Agonists (SABA)
- Albuterol
- Levalbuterol

Phosphodiesterase type 4 inhibitors (PDE-4)
- Roflumilast
- Clomilast

Inhaled Corticosteroids (ICS)
- Fluticasone
- Budesonide
- Mometasone
- Beclomethasone
- Ciclesonide
- Flunisolide

Short-Acting Muscarinic Antagonists (SAMA)
- Ipratropium

Other controller options
- Other reliever option

PREFERRED RELIEVER to prevent exacerbations and control symptoms
- STEP 2: Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS formoterol
- STEP 3: Low dose ICS and LABA
- STEP 4: Medium dose ICS and LABA
- STEP 5: High dose ICS, add-on tiotropium, or add-on LTRA

Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA is taken

Medium dose ICS, or low dose ICS+LTRA

High dose ICS, add-on tiotropium, or add-on LTRA

Consider adding low dose OCS, but consider side effects

As-needed low dose ICS formoterol

As-needed short-acting β2-agonist (SABA)

Confirmation of diagnosis if necessary

Symptom control & modifiable risk factors (including lung function)

Comorbidities

Inhaler technique & adherence

Patient goals

Treatment of modifiable risk factors & comorbidities

Non-pharmacological strategies

Education & skills training

Asthma medications

Step 2: Daily low dose ICS or as-needed low dose ICS formoterol

Step 3: Low dose ICS and LABA

Step 4: Medium dose ICS and LABA

Step 5: High dose ICS, add-on tiotropium, or add-on LTRA

Confirmation of diagnosis if necessary

Symptom control & modifiable risk factors (including lung function)

Comorbidities

Inhaler technique & adherence

Patient goals

Treatment of modifiable risk factors & comorbidities

Non-pharmacological strategies

Education & skills training

Asthma medications
Approach to Treatment of Asthma COPD Overlap

- Confirm Diagnosis
- Assess adherence and triggers
- Identify and treat comorbidities
- Assess adherence and triggers
- Identify and treat comorbidities
- Control Symptoms
- Limiting Symptoms
- Infectious exacerbation
- Non Infectious exacerbation
- Rehabilitation

Therapeutic Option of Asthma COPD Overlap

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ACOS w/o eosinophilia</th>
<th>ACOS w/ eosinophilia</th>
<th>ACOS w/ exacerbations</th>
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<tbody>
<tr>
<td>LAMA and/or LABA</td>
<td>+++</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>ICS</td>
<td>?</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Leukotriene Inhib</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Roflumilast, azithromycin</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Biologics</td>
<td>-</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Vaccination</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Comorbidity Rx</td>
<td>+++</td>
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<td>+++</td>
</tr>
<tr>
<td>Pulmonary rehab</td>
<td>+++</td>
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In the Era of Precision Medicine:

ACO: A Riddle Wrapped in Mystery

- ACO affects about a quarter of patients with COPD and almost a third of patients who previously had asthma.
- Compared with their counterparts with asthma or COPD alone, patients with ACO have significantly worse respiratory symptoms, poorer quality of life, and increased risk of exacerbations and hospital admissions.
- Whether this condition emerges after gradual shifts in airway remodeling and inflammation in a patient with COPD, as the result of noxious exposures in a patient with asthma, or even as a de-novo disease with its own pathology is yet to be determined.
- Treatments for asthma or COPD that target eosinophilic, neutrophilic, or paucigranulocytic airway inflammation may be a helpful approach to these patients until further clinical trials can be performed.
- One pragmatic way to account for the heterogeneity of ACO is to adopt a strategy of defining specific and measurable therapeutic objectives for every single patient and identifying the traits that can be treated to achieve those objectives.
- More studies are needed in order to clarify several important issues with regard to ACO, such as the molecular pathways and underlying mechanisms, the identification of possible specific biomarkers for diagnosis and targeted treatment, the prognosis and, finally, the optimal therapeutic interventions.
Always remember that disease can be understood in scientific terms but illness is a human event...