Therapeutic Options
Asthma COPD Overlap (ACO)

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I will be discussing off-label use of drugs as no drug is currently approved for ACO
Objectives

Incorporate evidence to delineate therapeutic similarities and differences between asthma, COPD and ACO in clinical scenarios
Consider this patient

56 year-old male with COPD

40 pack-years smoking history; current smoker
Daily cough, wheeze and shortness of breath for the past 5 years
History of childhood asthma
Seasonal allergies spring/fall

FEV₁ 42% predicted
FEV₁/FVC 0.48
What additional testing would you consider?

A. Spirometry with bronchodilator challenge
B. FeNO
C. Blood eosinophil count
D. All of the above
What additional testing would you consider?

A. Spirometry with bronchodilator challenge
B. FeNO
C. Blood eosinophil count
D. All of the above
56 year-old male with COPD

FEV$_1$ improved 410 ml and 16% after bronchodilator. FEV$_1$/FVC 0.62

Blood eosinophil count 350 cells/mm$^3$

FeNO 38 ppb
ACO diagnostic criteria - there are many

Consensus definition from a round table discussion

- Age ≥ 40 years
- ≥ 10 pack-years of smoking or equivalent air pollution exposure
- Post-BD FEV₁/FVC < 0.70 or LLN
- Documented history of asthma before age 40 or BDR > 400 ml in FEV₁

- Documented history of atopy or allergic rhinitis
- BDR FEV₁ ≥ 200 ml and 12% on 2 or more visits
- Blood eosinophil count ≥ 300 ml

ACO = 3 major + at least 1 minor criteria

Spanish guidelines (GesEPOC-GEMA consensus)

≥ 35 years
Smoker (or former smoker) ≥ 10 pk-yr
FEV₁/FVC post BDT < 70%

Current diagnosis of asthma

No

Yes

BDT ≥ 15% and 400 mL, and/or
Blood eosinophilia ≥ 300 cells/µL

Yes

ACO

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What would prescribe to your patient?

A. LAMA
B. LABA/LAMA
C. ICS/LABA
D. ICS/LABA/LAMA
What would prescribe to your patient?

A. LAMA
B. LABA/LAMA
C. ICS/LABA
D. ICS/LABA/LAMA
Management Challenges in ACO

- Lack of consensus in diagnosis/definition
- Heterogeneity – multiple endotypes
- Outcomes vary in studies but typically worse than COPD or Asthma alone
- Exclusion from clinical trials – No evidence to guide Rx
Management principles ACO

- Evaluate
  - Symptoms, exacerbation history, physical function
  - Lung function, BD reversibility
  - Comorbidities and triggers
  - Current smoking
  - Blood eosinophils, FeNO, Atopy

- Goals
  - Symptom management
  - Exacerbation reduction
  - Disease modification
Management approaches in ACO

Universal therapies
- Disease education
- Smoking cessation
- Vaccinations
- Allergen/irritant avoidance
- Comorbidity management
- Oxygen assessment
- Adherence/technique
- Pulmonary rehabilitation
Management approaches in ACO

Questions to ask:

- 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 by 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?
- Type-2 inflammation: Eos, FeNO?

ICS
ICS/LABA
ICS/LABA/LAMA
Advanced Therapies

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Maselli D. et al. CHEST 2019; 155(1):168-177
Management approaches in ACO

Questions to ask:

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 unrelated to triggers?
Documentation of persistent airflow limitation?
Previous doctor’s diagnosis of COPD?
Previous noxious inhalation exposure?
Hyperinflation on chest radiograph?
Absent type-2 inflammation?

Asthma  COPD

LAMA or LABA

LAMA/LABA

ICS/LABA/LAMA

Advanced Therapies

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Maselli D. et al. CHEST 2019; 155(1):168-177
Blood eosinophils in COPD vary over time

Blood eosinophils in COPD are associated with worse survival
ICS/LABA in ACO

- Ontario, CN, population based longitudinal study of 38,266 patients newly prescribed LABA or ICS/LABA therapy
- Median 2.5 years follow-up
- COPD + asthma, > 65 years old
- 28% of population studied
- In COPD + Asthma: ICS/LABA resulted in lower risk of all-cause mortality and COPD hospitalization (HR 0.84)
- COPD w/o Asthma: No benefit

Gershon. JAMA 2014, 312:1114
ICS in COPD – Effect by Eos

- *Post hoc* analysis of two replicate RCTs
- 3177 patients followed over 12 months
- Mod-severe COPD with at least 1 exacerbation in the last year
- ICS vs. ICS/LABA
- Effect size stratified by blood eosinophils
LAMA add-on therapy in ACO

• 472 patients with COPD + asthma
• 12-week randomized, controlled trial
• LAMA added to usual therapy. ICS use required per inclusion criteria
• Percent of patients with COPD exacerbations:
  – Tiotropium: 5.7%
  – ICS only: 10.7%
Omalizumab in ACO
Data from Australian Xolair Registry

Severe asthma vs. ACO (diagnosis of COPD or FEV₁ <80%/ever smokers)

177 participants

Baseline data and at 6 months of anti-IgE therapy

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Omalizumab in ACO
post hoc analysis from Prospero

Hanania NA. et al. JACI 2019
Benralizumab in Eosinophilic COPD

- Phase 2a study of 101 patients
- Mod-severe COPD
- At least 1 acute exacerbation in the previous year
- Sputum eosinophils ≥ 3%
- Placebo vs. benralizumab
- 48 weeks
- No effect overall
- Pre-specified analysis by blood eos

Mepolizumab in Eosinophilic COPD

Two phase 3 trials of mepolizumab vs placebo for 52 weeks
Mod-Severe COPD with h/o exacerbations

<table>
<thead>
<tr>
<th>Blood Eosinophil Count</th>
<th>Mepolizumab Group</th>
<th>Placebo Group</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150 with no historical count ≥300</td>
<td>184/184</td>
<td>190/190</td>
<td>1.23 (0.99–1.51)</td>
</tr>
<tr>
<td>&lt;150 regardless of historical count</td>
<td>236/640</td>
<td>230/645</td>
<td>1.10 (0.91–1.34)</td>
</tr>
<tr>
<td>≥150 to &lt;300</td>
<td>257/456</td>
<td>235/455</td>
<td>0.92 (0.76–1.11)</td>
</tr>
<tr>
<td>≥300 to &lt;500</td>
<td>112/456</td>
<td>110/455</td>
<td>0.75 (0.55–1.00)</td>
</tr>
<tr>
<td>≥500</td>
<td>53/456</td>
<td>67/455</td>
<td>0.72 (0.48–1.09)</td>
</tr>
<tr>
<td>&lt;150 with historical count ≥300</td>
<td>53/456</td>
<td>42/455</td>
<td>0.64 (0.40–1.03)</td>
</tr>
</tbody>
</table>

Mepolizumab Better  Placebo Better

Pavord ID et al. NEJM 2017; 377: 1613
Roflumilast in ACO?

<table>
<thead>
<tr>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reduces airway inflammation</td>
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</tr>
<tr>
<td>2. Reduces bronchoconstriction</td>
<td>2. Improves airway remodeling</td>
</tr>
<tr>
<td>3. Enhances mucociliary clearance</td>
<td>3. Improves pulmonary ventilation function</td>
</tr>
<tr>
<td>4. Improves airway remodeling</td>
<td>4. Reduces oxygen free radical release</td>
</tr>
<tr>
<td>5. Relieves airway hyperresponsiveness</td>
<td>5. Inhibits pulmonary fibrosis</td>
</tr>
</tbody>
</table>

Azithromycin in ACO with exacerbations?

Azithromycin for Prevention of Exacerbations of COPD
Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D., J. Allen D. Cooper, Jr., M.D., Gerard J. Criner, M.D., Jeffrey L. Curtis, M.D., Mark T. Dransfield, M.D., Melan K. Han, M.D., Stephen C. Lazarus, M.D., Barry Make, M.D., Nathaniel Marchetti, M.D., Fernando J. Martinez, M.D., Nancy E. Madinger, M.D., Charlene McEvoy, M.D., M.P.H., Dennis E. Niewoehner, M.D., Janos Porszasz, M.D., Ph.D., Connie S. Price, M.D., John Reilly, M.D., Paul D. Scanlon, M.D., Frank C. Sciruba, M.D., Steven M. Scharf, M.D., Ph.D., George R. Washko, M.D., Prescott G. Woodruff, M.D., M.P.H., and Nicholas R. Anthonisen, M.D., for the COPD Clinical Research Network

Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial
Peter G Gibson, Ian A Yang, John W Upham, Paul N Reynolds, Sandra Hodge, Alan L James, Christine Jenkins, Matthew J Peters, Guy B Marks, Melissa Baraket, Heather Powell, Steven J Taylor, Lex E X Leong, Geraint B Rogers, Jodie L Simpson

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Summary

- The key goals of management of airways disease include identification of specific treatment targets, optimize symptom control and reduce risk for patients.
- Best practices are based on evidence from robust clinical trials.
- Unfortunately, with ACO, we are in an ‘evidence free’ zone as these patients have been systematically excluded from such clinical trials.
- Real life studies focusing on pheno-endo-types of ACO and efficacy of targeted therapies are urgently needed.
Until then…

CHRONIC AIRWAY DISEASES

INITIAL THERAPY
- COPD: LABA or LAMA
  - LABA + LAMA
- ACO: ICS*
  - ICS + LABA
- Asthma: ICS
  - ICS + LABA

ADVANCED THERAPY
- UNCONTROLLED SYMPTOMS
- FREQUENT EXACERBATORS

EVALUATE FOR TREATABLE TRAITS
- Roflumilast**
- Chronic macrolides
- If negative consider
- Elevated IgE levels
  - Peripheral eosinophilia
  - If positive consider
- Monoclonal antibodies#
  - (Anti-IgE, Anti-IL5)
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