Asthma COPD Overlap Syndrome

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Chair, Respiratory Medicine SIFP, CFPC
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Key points

- A step-wise approach to diagnosis is advised, comprising recognition of the presence of a chronic airflow limitation (the Asthma COPD Overlap Syndrome [ACOS]), confirmation by spirometry and, if necessary, referral for specialized investigations.
- Although initial recognition and treatment of ACOS may be made in primary care, referral for confirmatory investigations is encouraged, as outcomes for ACOS are worse than for asthma or COPD alone.
- Treatment should be selected to ensure that:
  - Patients with features of asthma receive adequate controller therapy including inhaled corticosteroids, but not long-acting bronchodilators alone (e.g., LABA monotherapy), and
  - Patients with COPD receive appropriate symptomatic treatment with bronchodilators or combination therapy, but not inhaled corticosteroids alone (e.g., ICS monotherapy).

OBJECTIVE

- Identify patients who have a disease of chronic airflow limitation.
- Distinguish asthma from COPD and the Asthma-COPD Overlap Syndrome (ACOS)
- Decide on initial treatment and/or need for referral

Faculty/Presenter Disclosure

- Faculty: Alan Kaplan MD CCFP(EM) FCFP
- Chair Family Physician Airways Group of Canada
- Chair of Special Interest Focused Practice, College of Family Physicians in Respiratory Medicine
- Relationships with commercial interests:
  - Grants/Research Support: none
  - Speaking Bureau/Honoraria: Astra Zeneca, Boehringer Ingelheim, Griffils, Pfizer, Purdue, Merck Frosst, Novartis, Sanofi, Takeda
  - Consulting Fees: Aerocrine, GSK, Novartis, Takeda, Purdue, Pfizer
  - Other: Member of Health Canada Section on Allergy and Respiratory Therapeutics
  - Member of Public Health Agency of Canada section on Respiratory Surveillance

Disclosure of Commercial Support

- This program has received financial support from [none]
- This program has received in-kind support from [none] in the form of

Potential for conflict(s) of interest:

- The faculty have received consultancy fees, speakers fees or been involved in research from a number of respiratory organizations
- A) there are no organizations supporting this program
- B) The following companies make respiratory products that we may mention in this talk including: Aerocrine, Astra Zeneca, Boehringer Ingelheim, Griffils, GSK, Merck Frosst, Pfizer, Purdue, Novartis, Sanofi, Takeda.
Mitigating Potential Bias

• I have spoken for a number of companies in the area of respiratory medicine, pain medicine, and other topics
• I do not support or speak for one Pharmaceutical organization or product solely

Case

• 62 year old woman
• Smoked 1/2ppd since age of 22
• Now only the occasional cigarette
• SOBOE, wheezes at night, two ER visits for her Asthma this year needing steroids and antibiotics
• CXR in ER was normal
• XST negative

What does she have?

• She is currently on Salmeterol/Fluticasone 125 MDI 2puff BID
• What is the best treatment for her?
• How should she be assessed?

Results

• She has obstruction
• It has significant reversibility
• It does not reverse to normal
• Is this asthma?
• Is this COPD?
• Is this ACOS?

What if her story was

• 50 year old marathon runner
• Smoked 20 pack years, quit x 10years
• Hx of childhood asthma, allergic rhinitis
• Family history of Asthma
• Three ER visits for asthma and one admission over last two years.
• Spirometry, exactly the same.....
### Usual features of asthma, COPD and ACOS (1)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Asthma</th>
<th>COPD</th>
<th>ACOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Usually childhood but can commence at any age</td>
<td>Usually ≥40 years</td>
<td>Usually ≥40 years</td>
</tr>
<tr>
<td>Pattern of respiratory</td>
<td>Symptoms vary over time, often triggered by exercise, emotions including laughter, dust, or exposure to allergens</td>
<td>Chronic usually continuous symptoms, particularly during exercise, with ‘better’ and ‘worse’ days</td>
<td>Respiratory symptoms including exacerbations are persistent, but variability may be prominent</td>
</tr>
<tr>
<td>Airflow limitation</td>
<td>FEV1 may be improved by therapy, but post-BD FEV1/FVC &lt;0.7 persists</td>
<td>Airflow limitation not fully reversible, but often with current or historical variability</td>
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</tbody>
</table>

### Usual features of asthma, COPD and ACOS (2)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Asthma</th>
<th>COPD</th>
<th>ACOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbations</td>
<td>Exacerbations occur, but risk can be substantially reduced by treatment</td>
<td>Exacerbations can be reduced by treatment. If present, comorbidities contribute to impairment</td>
<td>Exacerbations may be more common than in COPD but are reduced by treatment. Comorbidities can contribute to impairment</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Usually normal</td>
<td>Severe hyperinflation and other changes of COPD</td>
<td>Similar to COPD</td>
</tr>
<tr>
<td>Time course</td>
<td>Generally slowly progressive over years despite treatment</td>
<td>Symptoms are partly but significantly reduced by treatment. Progression is usual and treatment needs are high</td>
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</tr>
<tr>
<td>Comorbidities</td>
<td>Many patients have allergies and a personal history of asthma</td>
<td>History of exposure to noxious particles or gases (mainly tobacco smoking or biomass fuels)</td>
<td>Frequently a history of doctor-diagnosed asthma (current or previous), allergies, family history of asthma, and/or a history of noxious exposures</td>
</tr>
</tbody>
</table>

### Other names:
- Asthma-COPD phenotype
- Mixed Asthma-COPD
- Mixed COPD-Asthma
- Asthma with fixed airflow limitation
- COPD with asthmatic component
- Eosinophilic COPD phenotype
- Hyper-reactive COPD phenotype
Stepwise approach to diagnosis and initial treatment

For an adult who presents with respiratory symptoms:
1. Does the patient have chronic airways disease?
2. Syndromic diagnosis of asthma, COPD and ACOS
3. Spirometry
4. Commence initial therapy
5. Referral for specialized investigations (if necessary)

Step 1 – Does the patient have chronic airways disease?

- **Clinical history**: consider chronic airways disease if
  - Chronic or recurrent cough, sputum, dyspnea or wheezing, or repeated acute lower respiratory tract infections
  - Previous doctor diagnosis of asthma and/or COPD
  - Previous treatment with inhaled medications
  - History of smoking tobacco and/or other substances
  - Exposure to environmental hazards, e.g. airborne pollutants

- **Physical examination**
  - May be normal
  - Evidence of hyperinflation or respiratory insufficiency
  - Wheeze and/or crackles

  Cough and velcro-like crackles = IPF

- **Radiology** (CXR or CT scan performed for other reasons)
  - May be normal, especially in early stages
  - Hyperinflation, airway wall thickening, hyperlucency, bullae
  - May identify or suggest an alternative or additional diagnosis, e.g. bronchiectasis, tuberculosis, interstitial lung disease, cardiac failure

- **Screening questionnaires**
  - Designed to assist in identification of patients at risk of chronic airways disease
  - May not be generalizable to all countries, practice settings or patients
  - See GINA and GOLD reports for examples

The peripheral eosinophil counts and sputum eosinophil counts were significantly higher, and the reversibility due to a response to the treatment with ICS was better in the COPD with asthma group in the current series. These results suggest that COPD patients with asthmatic symptoms also had features of asthma such as a mixed inflammatory pattern with increased eosinophils. A significant correlation was observed between the increases in FEV1 in response to treatment with ICS and sputum eosinophil counts, thus suggesting that high sputum eosinophil counts might be a good predictor of response to ICS.
Sputum eosinophils predict “COPD with Asthma” and thus response (FEV1 increase) to ICS

Step 3 - Spirometry

- Essential if chronic airways disease is suspected
- Confirms chronic airflow limitation
- More limited value in distinguishing between asthma with fixed airflow limitation, COPD and ACOS
- Measure at the initial visit or subsequent visit
- If possible measure before and after a trial of treatment
- Medications taken before testing may influence results
- Peak expiratory flow (PEF)
  - Not a substitute for spirometry
  - Medications taken before testing may influence results

Step 4 – Commence initial therapy

- Initial choices based on syndromic assessment and spirometry
  - If features are consistent with asthma, treat as asthma
  - If features are consistent with COPD, treat as COPD
  - If syndromic assessment suggests ACOS, or there is significant uncertainty about the diagnosis of COPD, start treatment as for asthma pending further investigation
  - Consider both efficacy and safety
    - If any features of asthma, do not prescribe LABA without ICS
    - If any features of COPD, give symptomatic treatment with bronchodilators of combination therapy, but not ICS alone
    - If ACOS, give ICS and consider LABA and/or LAMA
    - Smoking cessation, pulmonary rehabilitation, vaccinations, treatment of comorbidities

Syndromic assessment

<table>
<thead>
<tr>
<th>Asthma</th>
<th>COPD</th>
<th>ACOS</th>
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<tbody>
<tr>
<td>Normal FEV1/FVC</td>
<td>Compatible with asthma</td>
<td>Not compatible with COPD (GOLD)</td>
</tr>
<tr>
<td>Post-BD FEV1/FVC &lt;0.7</td>
<td>Indicates airflow limitation, may improve</td>
<td>Required for diagnosis by GOLD criteria</td>
</tr>
<tr>
<td>FEV1 &gt;80% predicted</td>
<td>Compatible with asthma (good control, or interval between symptoms)</td>
<td>Compatible with GOLD category A or B if post-BD FEV1/FVC &lt;0.7</td>
</tr>
<tr>
<td>FEV1 &lt;80% predicted</td>
<td>A risk factor for exacerbations</td>
<td>Indicates severity of airflow limitation and risk of exacerbations and mortality</td>
</tr>
<tr>
<td>Post-BD increase in FEV1 &gt;12% and 200mL from baseline (measurable reversibility)</td>
<td>Usual at some time in course of asthma; not always present</td>
<td>Common in COPD and more likely when FEV1 is low, but consider ACOS</td>
</tr>
<tr>
<td>Post-BD increase in FEV1 &gt;12% and 400mL from baseline (marked reversibility)</td>
<td>High probability of asthma</td>
<td>Consider ACOS</td>
</tr>
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</table>

Steps 4 - Commence initial therapy

<table>
<thead>
<tr>
<th>Syndromic assessment</th>
<th>Initial treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Start treatment for asthma, usually low-dose ICS and as-needed SABA (see GINA report)</td>
</tr>
<tr>
<td>COPD</td>
<td>Start treatment as for COPD, with as-needed SABA, and regular LABA and/or LAMA if needed (see GOLD report)</td>
</tr>
<tr>
<td>ACOS, or significant uncertainty about diagnosis of COPD</td>
<td>Start treatment for asthma (low/moderate dose ICS), given the pivotal role of ICS in preventing asthma exacerbations/death</td>
</tr>
</tbody>
</table>

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NACI: Asthma 2014

- Children 2 to 18 years of age with asthma should receive PNEU-C-13 as appropriate for their age group and an additional dose of PNEU-P-23 at least 8 weeks after the last dose of PNEU-C-13.
- Adults with asthma should receive one dose of PNEU-P-23.
- At this time further booster doses of PNEU-C-13 or PNEU-P-23 are not recommended.

LABA monotherapy in Asthma?

Anti-inflammatory Action of The ICS Fluticasone: does not work in COPD!

- Fluticasone showed no anti-inflammatory action in stable COPD in an analysis of induced sputum
  - No clinical benefit in terms of lung function or symptom scores
  - No change in induced sputum inflammatory cells, percentage neutrophils, and IL-8 levels

<table>
<thead>
<tr>
<th>Sputum parameter</th>
<th>Baseline</th>
<th>After 4 weeks of treatment with fluticasone propionate (500 µg twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cell counts</td>
<td>1.9 (0.6-4.3)</td>
<td>1.4 (0.3-3.3)</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>80% (30-95%)</td>
<td>76% (28-95%)</td>
</tr>
<tr>
<td>Absolute neutrophils (mL/L)</td>
<td>1.6 (0.3-3.9)</td>
<td>1.3 (0.3-2.9)</td>
</tr>
<tr>
<td>Macrophages (%)</td>
<td>10% (4-40%)</td>
<td>22% (4-60%)</td>
</tr>
<tr>
<td>Absolute macrophages (mL/L)</td>
<td>0.27 (0.15-1.71)</td>
<td>0.23 (0.03-2.34)</td>
</tr>
</tbody>
</table>


Sputum eosinophilia and response to budesonide in COPD: does work in COPD with eosinophilia (ACOS?)

Changes in post-bronchodilator FEV1 in patients with or without sputum eosinophilia

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Budesonide</th>
<th>Prednisone</th>
</tr>
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<tbody>
<tr>
<td>FEV1 (L)</td>
<td>-0.05</td>
<td>0.05</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*p<0.05 within group (sputum eosinophilia) vs placebo
#p<0.05 between groups

Leigh et al. ERJ 2006;27:964-971
What about Asthma: CTS Asthma Continuum

2012 Asthma Management Continuum

Dribble, 5 years above asthma, and AHI

Inhaled Corticosteroid (ICS)

- Optimal for those with moderate persistent symptoms
- 25-50 mcg inhaler
- 100-200 mcg MDI

Step 5 – Refer for specialized investigations if needed

Step 5 – Refer for specialized investigations if needed

Investigation | Asthma | COPD
--- | --- | ---
Lung function tests | | |
DLCO | Normal or slightly elevated | Often reduced
Arterial blood gases | Normal between exacerbations | In severe COPD, may be abnormal between exacerbations
Airway hyperresponsiveness | Not useful on its own in distinguishing asthma and COPD. High levels favor asthma
Imaging | | |
High resolution CT scan | Usually normal; may show air trapping and increased airway wall thickness | Air trapping or emphysema; may show bronchial wall thickening and features of pulmonary hypertension
Inflammatory biomarkers | | |
Tests for atopy (e.g., FEV1 and/or skin prick tests) | Not essential for diagnosis; increase probability of asthma | Conforms to background prevalence, does not rule out COPD
CRP | If High (100 mg/L) supports eosinophilic airway inflammation | Usually normal, low in current smokers
Blood eosinophilia | Supports asthma diagnosis | May be present during exacerbations
Sputum inflammatory cell analysis | Rare in differential diagnosis not established in large populations

Phosphodiesterase-4 inhibitors for the treatment of COPD-specific inflammation

- 38 Patients
- FEV1, 61% predicted
- 4 Weeks treatment
- 500 µg roflumilast
- Lung function improvement 70 mls

Novel treatment?

- Roflumilast treats both neutrophilic and eosinophilic inflammation
- Once daily pill, 500 µg po daily
- GI side effects
- Weight loss

Step 5 – Refer for specialized investigations if needed

Refer for expert advice and extra investigations if patient has:
- Persistent symptoms and/or exacerbations despite treatment
- Diagnostic uncertainty, especially if alternative diagnosis (e.g. TB, cardiovascular disease) needs to be excluded
- Suspected airways disease with atypical or additional symptoms or signs (e.g. hemoptysis, weight loss, night sweats, fever, chronic purulent sputum). Do not wait for a treatment trial before referring
- Suspected chronic airways disease but few features of asthma, COPD or ACOS
- Comorbidities that may interfere with their management
- Issues arising during on-going management of asthma, COPD or ACOS

Maybe you do not have to be fancy???

Blood Eosinophilia in COPD
What would an ACOS action plan look like?

- **Green zone:**
  - LABA/ICS
  - Beta 2 prn

- **Yellow zone:**
  - Prednisone
  - +/- Antibiotic
  - Add second LABD like a LAMA

- **Red Zone:**
  - ER and Beta-2 on way
  - Prednisone if available

**Summary**

- Asthma and COPD Overlap: This is a source of confusion still!
- Treat what is obvious
- No isolated bronchodilators for Asthma
- No isolated ICS for COPD
- Still need the basics (vaccination, smoking cessation, healthy lifestyle, even pulmonary rehabilitation!)
- Five steps to try to work out the optimal therapy
- Step six, review efficacy of what you have done!

**GOOD ADVICE:** WHEN YOU ARE IN DEEP TROUBLE, LOOK STRAIGHT AHEAD.

KEEP YOUR MOUTH SHUT & SAY NOTHING.