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, categorization as asthma, COPD or the overlap between asthma and COPD (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 (ie., LABA monotherapy), and
  - Patients with COPD receive appropriate symptomatic treatment with bronchodilators or combination therapy, but not inhaled corticosteroids alone (ie., 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
  - Speakers Bureau/Honoraria: Astra Zeneca, Boehringer Ingelheim, Griffins, Pfizer, Purdue, Merck Frosst, Novartis, sanofi, Takeda
  - Consulting Fees: Aerocrine, 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].
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- 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, Griffins, GSK, Merck Frosst, Pfizer, Purdue, Novartis, sanofi, Takeda

GINA REPORT 2014
GOLD REPORT 2014
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 2 puff 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 10 years
- 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.....
Who cares?

- Patients with features of both asthma and COPD experience frequent exacerbations, have poor quality of life, a more rapid decline in lung function and high mortality, and consume a disproportionate amount of healthcare resources.
- The proportion of patients with features of both asthma and COPD is unclear and will have been influenced by the inclusion criteria used. However, prevalence rates between 15 and 55% have been reported.
- Concurrent doctor-diagnosed asthma and COPD has been reported in between 15 and 20% of patients.

Definitions

**Asthma**

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. [GINA 2014]

**COPD**

COPD is a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory responses in the airways and the lungs to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. [GOLD 2014]

**Asthma-COPD overlap syndrome (ACOS)**

Asthma-COPD overlap syndrome (ACOS) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD.

Which one is it?

**ACOS!!**

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

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 &gt;40 years</td>
<td>Usually 40 years, but may have had symptoms as child/kid/adolescent</td>
</tr>
<tr>
<td>Pattern of respiratory symptoms</td>
<td>Symptoms vary over time (day to day, or over longer period), often fleeting, activity, 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 exertional dyspnea are persistent, but variability may be prominent</td>
</tr>
<tr>
<td>Lung function</td>
<td>Current/ worsened variable airflow limitation, e.g. BD reversibility, AHR</td>
<td>FEV1 may be improved by therapy, but post-BD FEV1/FVC &lt; 70% predicted</td>
<td>Airflow limitation not fully reversible, but often with current or historical variability</td>
</tr>
<tr>
<td>Long function between symptoms</td>
<td>May be normal</td>
<td>Persistent airflow limitation</td>
<td>Persistent airflow limitation</td>
</tr>
</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>Past history or family history</td>
<td>Many patients have allergies and a personal history of asthma in childhood and/or family 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>
<tr>
<td>Time course</td>
<td>Often improves spontaneously or with treatment, but may result in fixed airflow limitation</td>
<td>Generally slowly progressive over years despite treatment</td>
<td>Symptoms are partly but significantly reduced by treatment. Progression is usually and treatment needs are high</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>Exacerbations</td>
<td>Exacerbations occur, but risk can be substantially reduced by treatment</td>
<td>Exacerbations can be reduced by treatment. If present, comorbidities could 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>
</tbody>
</table>
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
  - Wheezing 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

How to identify patients with ACOS

Persistent airflow limitation (essential)

PLUS

- The presence of 3 or more features of both asthma and COPD (from table)

The presence of some features may be more important e.g. Childhood asthma, cigarette smoking

The absence of some features is also important e.g. cigarette smoking, reversible airflow obstruction
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

<table>
<thead>
<tr>
<th>Spirometric variable</th>
<th>Asthma</th>
<th>COPD</th>
<th>ACOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal FEV1/FVC</td>
<td>Pre- or post-BD</td>
<td>Compatible with asthma, unaltered by treatment</td>
<td>Not compatible unless other evidence of chronic airflow limitation</td>
</tr>
<tr>
<td>FEV1 &lt;80% predicted</td>
<td>Pre- or post-BD</td>
<td>Compatible with asthma, unaltered by treatment</td>
<td>Compatible with GOLD category A or B</td>
</tr>
<tr>
<td>FEV1 increase in FEV1 &gt;12% and 400mL</td>
<td>Post-BD</td>
<td>High probability of asthma</td>
<td>Common in asthma and COPD</td>
</tr>
<tr>
<td>FEV1 increase in FEV1 &gt;12% and 200mL</td>
<td>Post-BD</td>
<td>Unusual in COPD</td>
<td>Unusual in COPD</td>
</tr>
</tbody>
</table>

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
- Other important strategies for ACOS and COPD
  - Smoking cessation, pulmonary rehabilitation, vaccinations, treatment of comorbidities

- Other therapeutic strategies as for COPD, including smoking cessation, pulmonary rehabilitation, vaccinations, treatment of comorbidities

Step 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></td>
<td>Avoid LABA alone (without ICS)</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></td>
<td>Avoid ICS alone as monotherapy</td>
</tr>
<tr>
<td></td>
<td>Other therapeutic strategies including smoking cessation, pulmonary rehabilitation, vaccinations, treatment of comorbidities</td>
</tr>
<tr>
<td>ACOS, or significant</td>
<td>Start treatment for asthma (low/moderate dose ICS), given the pivotal role of ICS in preventing asthma exacerbations/death</td>
</tr>
<tr>
<td>uncertainty about</td>
<td>Add LABA and/or LAMA, but avoid using LABA without ICS if there are any features of asthma</td>
</tr>
<tr>
<td>diagnosis of COPD</td>
<td>Other therapeutic strategies as for COPD, including smoking cessation, pulmonary rehabilitation, vaccinations, treatment of comorbidities</td>
</tr>
</tbody>
</table>
LABA monotherapy in Asthma?

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.

How do you treat COPD?

• Bronchodilators
• Steroids in which patients

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

Sputum parameter | Baseline | After 4 weeks of treatment with Fluticasone propionate (500 µg twice daily)
--- | --- | ---
Total cell counts | 1.9 (0.8-4.3) | 1.3 (0.3-3.3) |
Neutrophils (%) | 89% (39-95%) | 78% (26-95%) |
Absolute neutrophils (millions/mL) | 1.6 (0.3-4.9) | 1.3 (0.3-2.9) |
Macrophages (%) | 12% (4.0-69%) | 22% (4.0-69%) |
Absolute macrophages (millions/mL) | 0.27 (0.01-1.71) | 0.20 (0.00-2.49) |
Novel treatment?

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

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

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
Investigation | Asthma | COPD
---|---|---
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 (sIgE and/or skin prick tests) | Not essential for diagnosis; increases probability of asthma | Conforms to background prevalence; does not rule out COPD
FENO | Usually normal. Low in current smokers | If high (>50ppb) supports eosinophilic airway inflammation | May be present during exacerbations
Blood eosinophilia | Supports asthma diagnosis | | 
Sputum inflammatory cell analysis | Role in differential diagnosis not established in large populations | | 

**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!

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