The Asthma COPD Overlap Syndrome

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The “Dutch” Hypothesis

Genetic susceptibility

Environmental Factors
- Allergen
- Infection
- Smoking
- Air Pollution

“Asthma

Chronic Obstructive Pulmonary Disease

“bronchitis [COPD] and asthma are different patterns of the same condition”

The reason why it is difficult to differentiate asthma from COPD

In 1995, the American Thoracic Society stated:

… it may be impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis and emphysema with partially reversible airflow obstruction and bronchial hyperresponsiveness.⁶¹
Overlap: Why is it a problem?

1. It is common
2. Diagnostic uncertainty for doctors; confusion for patients
3. Severe form of CAO: natural history, treatment non-response (ICS and OCS), high resource use
4. Not covered in guidelines / strategy documents
5. Not studied in clinical trials
Suggested names for Asthma COPD Overlap

- Asthma-COPD phenotype
- Mixed asthma-COPD
- Mixed COPD-asthma
- Asthma with fixed airflow obstruction
- COPD with asthmatic component
- Eosinophilic COPD phenotype
- Hyper-reactive COPD phenotype
Coexistence of Asthma & COPD in young, middle-aged & elderly in general population

- Random general population: Gene Environment Interactions in Respiratory Diseases (GEIRD) study
  - Screening questionnaire
  - Doctor diagnosed asthma or COPD

<table>
<thead>
<tr>
<th>Age class (years)</th>
<th>Asthma only % (95% CI)</th>
<th>Asthma + COPD % (95% CI)</th>
<th>COPD only % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 - 44</td>
<td>8.2 (7.5-9.0)</td>
<td>1.6 % (1.3-2.0)</td>
<td>3.3 (2.8-3.8)</td>
</tr>
<tr>
<td>45 - 64</td>
<td>4.9 (4.0-5.9)</td>
<td>16.5%</td>
<td>5.7 (4.7-6.7)</td>
</tr>
<tr>
<td>65 - 84</td>
<td>2.9 (1.8-4.0)</td>
<td>21.7%</td>
<td>13.3 (11.1-15.5)</td>
</tr>
</tbody>
</table>

- Females (RR 1.63)
- More symptomatic: breathless, cough & wheeze
  - More exacerbations
  - More hospitalizations

De Marco R, et al, PLOS ONE 2013; 8:5.e62985
COPDGene Study: COPD with history of Asthma

- Poorer quality of life (SGRQ)
- Higher probability of exacerbation in past year
- More frequent exacerbations
  - OR 3.55 (95% CI: 2.19-5.75)  p<0.001
- More rapid lung function decline
- More refractory to ICS and OCS
- Higher OCS requirement

POPE – COPD Phenotypes

Figure 2. Recruitment of COPD subjects according participating countries (N = 3,745)

<table>
<thead>
<tr>
<th>Country</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serbia</td>
<td>550 (14.7%)</td>
</tr>
<tr>
<td>Poland</td>
<td>477 (12.7%)</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>453 (12.1%)</td>
</tr>
<tr>
<td>Hungary</td>
<td>407 (10.9%)</td>
</tr>
<tr>
<td>Russia</td>
<td>381 (10.2%)</td>
</tr>
<tr>
<td>Slovakia</td>
<td>370 (9.9%)</td>
</tr>
<tr>
<td>Croatia</td>
<td>362 (9.7%)</td>
</tr>
<tr>
<td>Austria</td>
<td>357 (9.5%)</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>311 (8.3%)</td>
</tr>
<tr>
<td>Slovenia</td>
<td>70 (1.9%)</td>
</tr>
<tr>
<td>Latvia</td>
<td>7 (0.2%)</td>
</tr>
</tbody>
</table>

Figure 4. Phenotypes of COPD (N = 3,366)

- ACOS (N = 231): 63.3%
- Non-exacerbator (N = 2,129): 20.4%
- Frequent exacerbator with CB (N = 687): 9.5%
- Frequent exacerbator without CB (N = 319): 6.9%

Population-based categorisation of patients with respiratory symptoms in New Zealand

Wellington Respiratory Survey: >50 years (N= 469) from random general population

Definitions used

**Asthma**
- post b.d $\geq$15% FEV$_1$, or
- PEF variability for 1 week, or
- physician diagnosis plus symptoms or reliever use in last 12 months

**Emphysema**
- Macroscopic emphysema on CT, or
- AFO with TLCO/VA <LLN

**Chronic Bronchitis**
- British MRC definition

**COPD**
- FEV$_1$/FVC <0.7
Population-based classification of patients aged 50 years and older

Wellington Respiratory Survey: >50 years (N= 469) from random general population

Axis-aligned proportional rectangles

Overlap of diagnoses 56%

COPD defined as FEV₁/FVC < 0.7

Pathways to Chronic Airflow Obstruction

No asthma
- No allergies
- No family history
- Smoking
  - Risk factors

Clinical features of asthma

Asthma
- Allergies
- Family history
- Smoking
  - +/- risk factors

Asthma
- Allergies
- Family history
- No smoking
  - No risk factors

COPD

??
Unexpected mild emphysema in non-smoking asthma with persistent AFO

72-year-old women non-smoker, lifelong asthma
• Mild centrilobular emphysema, fractured alveolar septae
• Mucin in terminal bronchioles
• Neutrophils predominate

### Inflammatory cells in the lamina propria

<table>
<thead>
<tr>
<th>Cells (cells/mm²)</th>
<th>Fixed airflow obstruction (n=21)</th>
<th>History of COPD (n=11)</th>
<th>History of asthma (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophages</td>
<td>91.3 (47.0–102.0)</td>
<td>99.4 (65.0–105.6)</td>
<td>86.0 (41.0–97.7)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>109.5 (71.0–180.0)</td>
<td>88.5 (43.0–156.0)</td>
<td>157.0 (99.0–183.0)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>30.0 (5.0–57.5)</td>
<td>5.0 (2.3–33.0)</td>
<td>50.0 (10.0–280.0)**</td>
</tr>
<tr>
<td>Mast cells</td>
<td>45.0 (13.5–70.0)</td>
<td>40.0 (18.7–65.0)</td>
<td>53.0 (9.2–120.0)</td>
</tr>
<tr>
<td>CD4⁺</td>
<td>142.0 (65.0–210.0)</td>
<td>109.0 (18.0–138.2)</td>
<td>218.0 (110.7–372.2) *</td>
</tr>
<tr>
<td>CD8⁺</td>
<td>45.0 (25.2–102.0)</td>
<td>72.5 (36.5–145.0)</td>
<td>40.0 (15.2–71.5)</td>
</tr>
<tr>
<td>CD4⁺/CD8⁺</td>
<td>2.0 (0.97–7.75)</td>
<td>1.2 (0.27–3.15)</td>
<td>7.0 (2.0–21.0)</td>
</tr>
</tbody>
</table>

Medians with interquartile range  
Versus COPD patients: *p<0.05, **p<0.01  

Longitudinal asthma cohort: Lung function decline

Mean (±SE) FEV1:FVC

Age (years)

Males

No wheezing ever
Remission
Transient wheezing
Intermittent wheezing
Relapse
Persistent wheezing

Evidence for early-life origins of COPD risk

European Community Respiratory Health study
1993 13 359 20-45 year olds
Follow-up 9 years later on 7738

Risk factors for FEV1 decline
- Maternal asthma
- Paternal asthma
- Childhood asthma
- Maternal smoking
- Childhood respiratory infections

Early childhood disadvantage associated with:
- Lower lung function
- No catch-up
- Faster rate of decline
- Higher risk of COPD

Two Clinical Definitions (phenotype):

1. Asthma with partially reversible airflow obstruction, with or without emphysema or DLco <80% pred.

2. COPD with emphysema accompanied by reversible or partially reversible airflow obstruction, with or without environmental allergies or DLco <80% pred.
Stepwise approach to diagnosis and initial treatment

Chapter 5.

Diagnosis and initial treatment of asthma, COPD and asthma-COPD overlap (ACO)

*www.ginasthma.org & www.goldcopd.org

A joint project of GINA and GOLD
There are no pathognomonic features for asthma, COPD or ACOS.

Phenotypic features / risk factors present the likelihood (probability) of a diagnosis.

Pooling probabilities strengthens diagnosis.
Phenotypic features of asthma and COPD in adults

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<thead>
<tr>
<th>Asthma</th>
<th>Overlap syndromes</th>
<th>COPD</th>
</tr>
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<td>Childhood onset atopic asthma</td>
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<td></td>
</tr>
<tr>
<td>Atopy / allergies / family history</td>
<td></td>
<td></td>
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<td>Occupational asthma</td>
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<td>FEV1 reversibility tests / AHR</td>
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<td>Atopy / allergies / family history</td>
<td>100%</td>
<td>64%</td>
</tr>
<tr>
<td>Occupational asthma</td>
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<tr>
<td>Allergic rhinitis</td>
<td>59%</td>
<td>55%</td>
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| **Overlap syndromes**                         |
| FEV1 reversibility tests >80%                  |

| **COPD**                                      |
| 66%                                           |

Tashkin D, et al, ERJ 2008; 31:742
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<tr>
<td><strong>RRR 1.27</strong></td>
<td><strong>Smoking / 1.70</strong></td>
<td><strong>Alpha 1-AT deficiency / 3.16</strong></td>
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5x higher neutrophils in ACOS
## Usual features of ACOS

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>Age &gt;40 years, but may have symptoms in childhood or early adulthood</td>
</tr>
<tr>
<td><strong>Pattern of respiratory symptoms</strong></td>
<td>Symptoms, including exertional dyspnea, are persistent but variability may be predominant</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td>Airflow limitation is not fully reversible, but often with current or historical variability</td>
</tr>
<tr>
<td><strong>Lung function between symptoms</strong></td>
<td>Persistent airflow limitation</td>
</tr>
<tr>
<td><strong>Past or family history</strong></td>
<td>Frequently a history of doctor-diagnosed asthma (current or previous), allergies and a family history of asthma and/or history of noxious exposures</td>
</tr>
<tr>
<td><strong>Time course</strong></td>
<td>Symptoms are partly but significantly reduced by treatment. Progression is usual and treatment needs are high</td>
</tr>
<tr>
<td><strong>Chest X-ray</strong></td>
<td>May have hyperinflation and other changes of COPD</td>
</tr>
<tr>
<td><strong>Exacerbations</strong></td>
<td>More common than in COPD but are reduced by treatment. Comorbidities can contribute to impairment</td>
</tr>
<tr>
<td><strong>Typical airway inflammation</strong></td>
<td>Eosinophils and/or neutrophils in sputum</td>
</tr>
</tbody>
</table>
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)
ACOS - A description for clinical use

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.
### STEP 2: SYNDROMIC DIAGNOSIS IN ADULTS
(i) Assemble the features for asthma and for COPD that best describe the patient.
(ii) Compare number of features in favour of each diagnosis and select a diagnosis

<table>
<thead>
<tr>
<th>Feature: if present suggests -</th>
<th>ASTHMA</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>□ Before age 20 years</td>
<td>□ After age 40 years</td>
</tr>
<tr>
<td>Pattern of symptoms</td>
<td>□ Variation over minutes, hours or days</td>
<td>□ Persistent despite treatment</td>
</tr>
<tr>
<td></td>
<td>□ Worse during the night or early morning</td>
<td>□ Good and bad days but always daily symptoms and exertional dyspnea</td>
</tr>
<tr>
<td></td>
<td>□ Triggered by exercise, emotions including laughter, dust or exposure to allergens</td>
<td>□ Chronic cough &amp; sputum preceded onset of dyspnea, unrelated to triggers</td>
</tr>
<tr>
<td>Lung function</td>
<td>□ Record of variable airflow limitation (spirometry or peak flow)</td>
<td>□ Record of persistent airflow limitation (FEV/FVC &lt; 0.7 post-BD)</td>
</tr>
<tr>
<td>Lung function between symptoms</td>
<td>□ Normal</td>
<td>□ Abnormal</td>
</tr>
<tr>
<td>Past history or family history</td>
<td>□ Previous doctor diagnosis of asthma</td>
<td>□ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema</td>
</tr>
<tr>
<td></td>
<td>□ Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)</td>
<td>□ Heavy exposure to risk factor: tobacco smoke, biomass fuels</td>
</tr>
<tr>
<td>Time course</td>
<td>□ No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year</td>
<td>□ Symptoms slowly worsening over time (progressive course over years)</td>
</tr>
<tr>
<td></td>
<td>□ May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks</td>
<td>□ Rapid-acting bronchodilator treatment provides only limited relief</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>□ Normal</td>
<td>□ Severe hyperinflation</td>
</tr>
</tbody>
</table>

**NOTE:** These features best distinguish between asthma and COPD. Several positive features (3 or more) for either asthma or COPD suggest that diagnosis. If there are a similar number for both asthma and COPD, consider diagnosis of ACOS.

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>Asthma</th>
<th>Some features of asthma</th>
<th>Features of both</th>
<th>Some features of COPD</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONFIDENCE IN DIAGNOSIS</td>
<td>Asthma</td>
<td>Possible asthma</td>
<td>Could be ACOS</td>
<td>Possibly COPD</td>
<td>COPD</td>
</tr>
</tbody>
</table>
Accuracy of Syndromic Diagnosis of COPD (vs asthma) in patients with cough and difficult breathing:
Combining positive & negative features (n=800)

<table>
<thead>
<tr>
<th>Diagnostic feature For COPD</th>
<th>FEATURE PRESENT Adjusted likelihood ratio</th>
<th>FEATURE ABSENT Adjusted likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking &gt;20 P-yrs</td>
<td>1.97 (1.42-2.71)</td>
<td>0.59 (0.46-0.76)</td>
</tr>
<tr>
<td>Symptoms worsen slowly</td>
<td>1.84 (1.40-2.45)</td>
<td>0.54 (0.41-0.73)</td>
</tr>
<tr>
<td>Onset of symptoms &gt;40 yr</td>
<td>1.54 (1.22-0.96)</td>
<td>0.57 (0.42-0.79)</td>
</tr>
<tr>
<td>No previous diagnosis of asthma</td>
<td>4.08 (3.05-5.38)</td>
<td>0.28 (0.22-0.36)</td>
</tr>
<tr>
<td>No day to day variability</td>
<td>1.99 (1.43-2.76)</td>
<td>0.58 (0.46-0.78)</td>
</tr>
<tr>
<td>Male</td>
<td>1.40 (1.02-1.88)</td>
<td>0.72 (0.54-0.98)</td>
</tr>
</tbody>
</table>

Combination of features:

<table>
<thead>
<tr>
<th></th>
<th>Combination of features:</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 features</td>
<td>135.5 (44.8-315.8)</td>
</tr>
<tr>
<td>4 features</td>
<td>10.72</td>
</tr>
<tr>
<td>ROC for 4 features</td>
<td>0.95</td>
</tr>
</tbody>
</table>

### Accuracy of Syndromic Diagnosis of ASTHMA (vs COPD) on history in patients with cough and difficult breathing:
Combining positive & negative features (n=800)

<table>
<thead>
<tr>
<th>Diagnostic feature For ASTHMA</th>
<th>FEATURE PRESENT Adjusted likelihood ratio</th>
<th>FEATURE ABSENT Adjusted likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous diagnosis of asthma</td>
<td>4.03 (3.03-5.18)</td>
<td>0.21 (0.16-0.28)</td>
</tr>
<tr>
<td>Audible wheeze</td>
<td>1.48 (1.08-2.00)</td>
<td>0.72 (0.56-0.94)</td>
</tr>
<tr>
<td>Day to day variability of symptoms</td>
<td>1.73 (1.37-2.22)</td>
<td>0.49 (0.37-0.67)</td>
</tr>
<tr>
<td>No worsening of symptoms over time</td>
<td>2.17 (1.62-2.91)</td>
<td>0.46 (0.35-0.61)</td>
</tr>
<tr>
<td>Smoking &lt;20 p-yrs</td>
<td>1.80 (1.31-2.48)</td>
<td>0.48 (0.36-0.70)</td>
</tr>
<tr>
<td>Female</td>
<td>1.42 (1.05-1.85)</td>
<td>0.70 (0.53-0.95)</td>
</tr>
</tbody>
</table>

**Combination of features:**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>7 features</td>
<td>58.0 (32.2-105.1)</td>
<td>0.01 (0.01-0.20)</td>
</tr>
<tr>
<td>4 features</td>
<td><strong>11.9</strong></td>
<td><strong>0.14</strong></td>
</tr>
<tr>
<td>ROC for 4 features</td>
<td><strong>0.95</strong></td>
<td><strong>0.95</strong></td>
</tr>
</tbody>
</table>

Step 2 – Syndromic diagnosis of asthma, COPD and ACOS

- Assemble the features that, **when present**, most favor a diagnosis of asthma or COPD

- Compare the number of features on each side
  - If the patient has **≥3 features** of either asthma or COPD, there is a strong likelihood that this is the correct diagnosis

- Consider the level of certainty around the diagnosis
  - Diagnoses are made on the weight of evidence
  - The absence of any of these typical features does not rule out either diagnosis, e.g. absence of atopy does not rule out asthma

  - **When a patient has a similar number of features of both asthma and COPD, consider the diagnosis of ACOS**
### Box 5-2a. Usual features of asthma, COPD and asthma-COPD overlap

<table>
<thead>
<tr>
<th>Feature</th>
<th>Asthma</th>
<th>COPD</th>
<th>Asthma-COPD overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>Usually childhood onset but can commence at any age.</td>
<td>Usually &gt; 40 years of age</td>
<td>Usually age ≥40 years, but may have had symptoms in childhood or early adulthood</td>
</tr>
<tr>
<td><strong>Pattern of respiratory symptoms</strong></td>
<td>Symptoms may vary over time (day to day, or over longer periods), often limiting 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><strong>Lung function</strong></td>
<td>Current and/or historical variable airflow limitation, e.g. BD reversibility, AHR</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>
</tr>
<tr>
<td><strong>Lung function between symptoms</strong></td>
<td>May be normal between symptoms</td>
<td>Persistent airflow limitation</td>
<td>Persistent airflow limitation</td>
</tr>
<tr>
<td><strong>Past history or family history</strong></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 and gases (mainly tobacco smoking and biomass fuels)</td>
<td>Frequently a history of doctor-diagnosed asthma (current or previous), allergies and a family history of asthma, and/or a history of noxious exposures</td>
</tr>
<tr>
<td><strong>Time course</strong></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 usual and treatment needs are high</td>
</tr>
<tr>
<td><strong>Chest X-ray</strong></td>
<td>Usually normal</td>
<td>Severe hyperinflation &amp; other changes of COPD</td>
<td>Similar to COPD</td>
</tr>
<tr>
<td><strong>Exacerbations</strong></td>
<td>Exacerbations occur, but the risk of exacerbations can be considerably 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><strong>Airway inflammation</strong></td>
<td>Eosinophils and/or neutrophils</td>
<td>Neutrophils ± eosinophils in sputum, lymphocytes in airways, may have systemic inflammation</td>
<td>Eosinophils and/or neutrophils in sputum.</td>
</tr>
</tbody>
</table>

### Box 5-2b. Features that if present favor asthma or COPD

<table>
<thead>
<tr>
<th>Feature</th>
<th>More likely to be asthma if several of...*</th>
<th>More likely to be COPD if several of...*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early age</strong></td>
<td>Onset before age 20 years</td>
<td>Onset after age 40 years</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Variation in symptoms over minutes, hours or days</td>
<td>Good and bad days but always daily symptoms and exertional dyspnea</td>
</tr>
<tr>
<td></td>
<td>Symptoms worse during the night or early morning</td>
<td>Chronic cough and sputum preceded onset of dyspnea, unrelated to triggers</td>
</tr>
<tr>
<td></td>
<td>Symptoms triggered by exercise, emotions including laughter, dust or exposure to allergens</td>
<td>Record of variable airflow limitation (spirometry, peak flow)</td>
</tr>
<tr>
<td></td>
<td>Respiratory symptoms</td>
<td>Record of persistent airflow limitation (post-bronchodilator FEV₁/FVC &lt; 0.7)</td>
</tr>
<tr>
<td></td>
<td>Lung function normal between symptoms</td>
<td>Lung function abnormal between symptoms</td>
</tr>
<tr>
<td></td>
<td>Previous doctor diagnosis of asthma</td>
<td>Previous doctor diagnosis of COPD, chronic bronchitis or emphysema</td>
</tr>
<tr>
<td></td>
<td>Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)</td>
<td>Heavy exposure to a risk factor: tobacco smoke, biomass fuels</td>
</tr>
<tr>
<td></td>
<td>No worsening of symptoms over time. Symptoms vary either seasonally, or from year to year</td>
<td>Symptoms slowly worsening over time (progressive course over years)</td>
</tr>
<tr>
<td></td>
<td>May improve spontaneously or have an immediate response to BD or to ICS over weeks</td>
<td>Rapid-acting bronchodilator treatment provides only limited relief.</td>
</tr>
</tbody>
</table>

*Syndromic diagnosis of airways disease: how to use Box 5-2b*

Shaded columns list features that, when present, best identify patients with typical asthma and COPD. For a patient, count the number of check boxes in each column. If three or more boxes are checked for either asthma or COPD, the patient is likely to have that disease. If there are similar numbers of checked boxes in each column, the diagnosis of ACO should be considered. See Step 2 for more details.
## Step 3 - Spirometry

<table>
<thead>
<tr>
<th>Spirometric variable</th>
<th>Asthma</th>
<th>COPD</th>
<th>ACOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal FEV₁/FVC pre- or post-BD</td>
<td>Compatible with asthma</td>
<td>Not compatible with diagnosis (GOLD)</td>
<td>Not compatible unless other evidence of chronic airflow limitation</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>
<td>Usual in ACOS</td>
</tr>
<tr>
<td>FEV₁ =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>
<td>Compatible with mild ACOS</td>
</tr>
<tr>
<td>FEV₁ &lt;80% predicted</td>
<td>Compatible with asthma.</td>
<td>Indicates severity of airflow limitation and risk of exacerbations and mortality</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 (reversible airflow limitation)</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>
<td>Common in ACOS, and more likely when FEV₁ is low</td>
</tr>
<tr>
<td>Post-BD increase in FEV₁ &gt;12% and 400mL from baseline</td>
<td>High probability of asthma</td>
<td>Unusual in COPD. Consider ACOS</td>
<td>Compatible with diagnosis of ACOS</td>
</tr>
</tbody>
</table>

*GINA 2018, Box 5-3*
Step 4 Initial Therapy

If asthma $\rightarrow$ treat asthma, avoid LABA monotherapy

If COPD $\rightarrow$ LABA/LAMA +/- ICS

If ACO (equal balance of features)
- ICS low/medium dose and use asthma step up treatment approach
Step 4 PLUS

two or more controllers + as-needed inhaled reliever

- LAMA
- Roflumilast (PDE4-inhibitor)
- Theophylline
- Omalizumab? Bronchial thermoplasty??
STEP 1  DIAGNOSE CHRONIC AIRWAYS DISEASE
Do symptoms suggest chronic airways disease?

- Yes
- No  
  Consider other diseases first

STEP 2  SYNDROMIC DIAGNOSIS IN ADULTS
(i) Assemble the features for asthma and for COPD that best describe the patient.
(ii) Compare number of features in favour of each diagnosis and select a diagnosis

<table>
<thead>
<tr>
<th>Feature: if present suggests -</th>
<th>ASTHMA</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Before age 20 years</td>
<td>After age 40 years</td>
</tr>
<tr>
<td>Pattern of symptoms</td>
<td>Variation over minutes, hours or days</td>
<td>Persistent despite treatment</td>
</tr>
<tr>
<td></td>
<td>Worse during the night or early morning</td>
<td>Good and bad days but always daily symptoms and exertional dyspnea</td>
</tr>
<tr>
<td>Lung function</td>
<td>Triggers by exercise, emotions including laughter, dust or exposure to allergens</td>
<td>Chronic cough &amp; sputum preceded onset of dyspnea, unrelated to triggers to allergens</td>
</tr>
<tr>
<td>Lung function between symptoms</td>
<td>Record of variable airflow limitation (spirometry or peak flow)</td>
<td>Record of persistent airflow limitation (FEV₁/FVC &lt; 0.7 post-BD)</td>
</tr>
<tr>
<td>Past history or family history</td>
<td>Previous doctor diagnosis of asthma</td>
<td>Previous doctor diagnosis of COPD, chronic bronchitis or emphysema</td>
</tr>
<tr>
<td></td>
<td>Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)</td>
<td>Heavy exposure to risk factor: tobacco smoke, biomass fuels</td>
</tr>
<tr>
<td>Time course</td>
<td>No worsening of symptoms over time, variation in symptoms either seasonally, or from year to year</td>
<td>Symptoms slowly worsening over time (progressive course over years)</td>
</tr>
<tr>
<td>Cough</td>
<td>May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks</td>
<td>Rapid-acting bronchodilator treatment provides only limited relief</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Normal</td>
<td>Severe hyperinflation</td>
</tr>
</tbody>
</table>

NOTE: • These features best distinguish between asthma and COPD. • Several positive features (3 or more) for either asthma or COPD suggest that diagnosis. • If there are a similar number for both asthma and COPD, consider diagnosis of ACOS

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>Asthma</th>
<th>Some features of asthma</th>
<th>Features of both</th>
<th>Some features of COPD</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONFIDENCE IN DIAGNOSIS</td>
<td>Asthma</td>
<td>Possible asthma</td>
<td>Could be ACOS</td>
<td>Possibly COPD</td>
<td>COPD</td>
</tr>
</tbody>
</table>

STEP 3  PERFORM SPIROMETRY
Marked reversible airflow limitation (pre-post bronchodilator) or other proof of variable airflow limitation

FEV₁/FVC < 0.7 post-BD

STEP 4  INITIAL TREATMENT*

Asthma drugs No LABA monotherapy  
ICS and consider LABA +/or LAMA  
COPD drugs COPD drugs

*Consult GINA and GOLD documents for recommended treatments.

STEP 5  SPECIALISED INVESTIGATIONS or REFER IF:

- Persistent symptoms and/or exacerbations despite treatment.
- Diagnostic uncertainty (e.g. suspected pulmonary hypertension, cardiovascular diseases and other causes of respiratory symptoms).
- Suspected asthma or COPD with atypical or additional symptoms or signs (e.g. haemoptysis, weight loss, night sweats, fever, signs of bronchiectasis or other structural lung disease).
- Few features of either asthma or COPD.
- Comorbidities present.
- Reasons for referral for either diagnosis as outlined in the GINA and GOLD strategy reports.
### Specialized investigations

<table>
<thead>
<tr>
<th>Lung function tests</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLCO</td>
<td>Normal (or slightly elevated).</td>
<td>Often reduced.</td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td>Normal between exacerbations</td>
<td>May be chronically abnormal between exacerbations in more severe forms of COPD</td>
</tr>
<tr>
<td>Airway hyperresponsiveness (AHR)</td>
<td>Not useful on its own in distinguishing asthma from COPD, but higher levels of AHR favor asthma</td>
<td></td>
</tr>
</tbody>
</table>

### Imaging

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>High resolution CT Scan</td>
<td>Usually normal but air trapping and increased bronchial wall thickness may be observed.</td>
<td>Low attenuation areas denoting either air trapping or emphysematous change can be quantitated; bronchial wall thickening and features of pulmonary hypertension may be seen.</td>
</tr>
</tbody>
</table>

### Inflammatory biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test for atopy (specific IgE and/or skin prick tests)</td>
<td>Modestly increases probability of asthma; not essential for diagnosis</td>
<td>Conforms to background prevalence; does not rule out COPD</td>
</tr>
<tr>
<td>FENO</td>
<td>A high level (&gt;50 ppb) in non-smokers is associated with eosinophilic airway inflammation</td>
<td>Usually normal. Low in current smokers.</td>
</tr>
<tr>
<td>Blood eosinophilia</td>
<td>Supports diagnosis of eosinophilic airway inflammation</td>
<td>May be present in COPD including during exacerbations</td>
</tr>
<tr>
<td>Sputum inflammatory cell analysis</td>
<td>Role in differential diagnosis is not established in large populations</td>
<td></td>
</tr>
</tbody>
</table>

DLCO: diffusing capacity of the lungs for carbon monoxide; FENO: fractional concentration of exhaled nitric oxide; IgE: immunoglobulin E
Asthma, COPD and Asthma COPD Overlap Syndrome
Perspectives

1. A problem of definitions
2. Asthma and COPD may coexist and share risk factors
3. An approach to diagnosis & initial treatment
   • GINA/GOLD (2018)
4. Future research:
   ➢ Phenotyping & mechanisms of disease
   ➢ Clinical trials of treatment
Conclusion

• We must treat patients by personalizing therapy on the basis of these treatable traits present in each subject.
Conclusion

ACOS

Various Definitions

13%-55% all COPD patients
50% individuals over 60
25% of severe asthma patients
Conclusion

**Treatment**

- In General

  - COPD
  - Asthma
  - ACOS

  - LAMA +/- LABA/ICS
  - ICS
  - ICS +

  Therapy may better directed if based on phenotype than severity.
Conclusion

Take Home Points

- Clinically an overlap appears apparent
- Different phenotypes driven by various endotypes of diseases
- Now more scientific evidence
- ICS treatment can lead to clinical and spirometric improvement and decrease in exacerbations if based on eosinophilic inflammation
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