Clinical Phenotypes of COPD

KOUTSOKER ALEXANDRA MD, MSc, Pulmonologist
COPD

- COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

- GOLD 2017
GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2018 REPORT
COPD

Complex and Heterogeneous disease

• COMPLEX: COPD has a number of intrapulmonary and extrapulmonary components whose dynamic interactions along time are not linear.

• HETEROGENEOUS: indicates that not all of these components are present in all individual at any given time point

Agusti A et Thorax 2014
Clinical Phenotype

• A single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death).”

• This more focused definition allows for classification of patients into distinct prognostic and therapeutic subgroups for both clinical and research purposes.
COPD Phenotypes

Disease attributes that describe the diverse symptoms and outcomes of patients:

- Frequent Exacerbations
- Exercise/Activity Intolerance/Hyperinflation
- Chronic Cough and Sputum
- Radiologic: Airway (CL, bronchiectasis), Emphysema
- Asthma COPD Overlap (ACC)
- Symptom Burden
- Comorbidities: Cardiac, Nutritional

COPD

COPD PHENOTYPES

CLINICAL
- Dyspnea
- Frequent Exacerbator
- Low BMI
- Pulmonary Cachexia
- ICS-responsive
- Depression and Anxiety

FUNCTIONAL
- Airflow limitation
- Rapid decliner
- BD-responsiveness
- Hyperresponsiveness
- Hypocapnic
- Poor exercise tolerance
- Hyperinflation
- Low DLCO
- Pulmonary hypertension

RADILOGIC
- Emphysema
- Airways disease

FIGURE 1. Seven chronic obstructive pulmonary disease (COPD) phenotypes that can help individualize care and are defined by their implications for outcomes and day-to-day management.

Subpopulations and phenotyping

Segal, LN, and Martinez, FJ  JACI 2018
Taxonomy of COPD

Segal, LN, and Martinez, FJ JACI 2018
Strongly symptomatic

COPD

- Easily Fatigued
- Frequent Respiratory Infections
- Use of Accessory Muscles to Breathe
- Orthopneic

- Wheezing
- Pursed-Lip Breathing
- Chronic Cough
- Barrel Chest
- Dyspnea
- Prolonged Expiratory Time

- Bronchitis - Increased Sputum

- Cor Pulmonale (Late in Disease)
- Thin in Appearance
Kaplan-Meier curves of 12-month survival after a COPD-related hospitalisation according to level of moderate and vigorous physical activity

Marilyn L. et al. ERJ Open Research 2016
### Frequent Exacerbator

#### Table 3: Initial and annual change in lung function in patients with infrequent and frequent exacerbations

<table>
<thead>
<tr>
<th></th>
<th>Starting value</th>
<th>Annual change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infrequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Exacerbations (reported and unreported)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;2.92 per year</td>
<td>&gt;2.92 per year</td>
</tr>
<tr>
<td></td>
<td>(n=63)</td>
<td>(n=46)</td>
</tr>
<tr>
<td>PEF (l/min)</td>
<td>214</td>
<td>232</td>
</tr>
<tr>
<td></td>
<td>(n=16)</td>
<td>(n=16)</td>
</tr>
<tr>
<td>FEV1 (ml)</td>
<td>893</td>
<td>950</td>
</tr>
</tbody>
</table>

PEF = peak expiratory flow; FEV₁ = forced expiratory volume in 1 second.

*p<0.05, ***p<0.001 annual rates of change between infrequent and frequent exacerbators.

---

**Graph:**

- P<0.05
- **Infrequent Exacerbators**
- **Frequent Exacerbators**

*Donaldson GC et al Thorax 2002*
Frequent Exacerbator

Soler-Cataluna JJ et al Thorax 2005

Piquet J et al ERJ 2013
The bar chart shows the percentage of patients hospitalized for exacerbation in year 1 and with frequent exacerbations across different GOLD stages.

- **GOLD 2 (N=945):**
  - Hospitalized for exacerbation: 7%
  - Frequent exacerbations: 22%

- **GOLD 3 (N=900):**
  - Hospitalized for exacerbation: 18%
  - Frequent exacerbations: 33%

- **GOLD 4 (N=293):**
  - Hospitalized for exacerbation: 33%
  - Frequent exacerbations: 47%
Pink Puffer  Blue Bloater
Boschetto P, Thorax 2006
Papaioannou AI, Respir Med 2010
Pink puffer
- Lower body mass index
- Fewer cardiovascular co-morbidities
- Fewer metabolic co-morbidities
- Less muscle mass
- Hyperinflation
- Low diffusion capacity for CO
- More dyspnoea
- Decreased exercise capacity
- Worse health status
- Lower serum levels of sRAGEs

Blue bloater
- Higher body mass index
- More metabolic co-morbidities
- Cardiac compromise
- OSA-COPD overlap
- Less hyperinflation
- More chronic bronchitis
- Increased exacerbations
- More normal diffusion capacity
- Higher serum levels of inflammatory markers (IL-6 and CRP)
Constellations of comorbidities and theoretical underlying endotypes in COPD.

Risk factors for incidence and progress

- Genes
- Lung function at adolescence and adulthood
- Exposure to other pollutants
- Infections
- Amount of cigarettes
- Physical inactivity

Escalation of treatment

- Consider emphysema intervention
- Consider non-invasive ventilation

- Smoking cessation
- Physical activity
- Vaccination
- Bronchodilatation
- Diagnosis and treatment of comorbidities
- Pulmonary rehabilitation

Clinical phenotypes of severe COPD

- Oxygen
- Palliative care

- Consider inhaled corticosteroids
- Consider roflumilast
- Consider macrolides
Lung Volume Reduction Surgery / Bronchoscopic Lung Volume Reduction

- Lung Volume Reduction Surgery (LVRS)
  Upper lobe predominant Emphysema

\[
P = 0.005  \\
RR = 0.47  \\
\]

\[
\text{Months since randomization}  \\
\]

\[
P = 0.005  \\
\text{RR} = 0.47  \\
\]

Medical
Surgical
40%

National Emphysema Treatment Trial, NEJM 2003

Sciurba FC et al. N Engl J Med
COPD and Comorbidities

Prevalence of comorbidities

- Hypertension
- Anxiety
- BPH
- Sarcopenia
- Osteopenia
- PH
- Heart failure
- Osteoporosis
- Diabetes
- Cataract
- Underweight
- Substance abuse
- Atrial fibrillation
- Erectile dysfunction
- Amyotrophy
- GERD
- Degenerative joint disease
- Prostate cancer
- Depression
- Lung cancer
- CVA
- Hypothyroidism
- Breast cancer
- Pulmonary fibrosis
- Chronic kidney disease
- DVT

Prevalence %

0 5 10 15 20 25 30 35 40 45 50

- Hypertension
- Anxiety
- BPH
- Sarcopenia
- Osteopenia
- PH
- Heart failure
- Osteoporosis
- Diabetes
- Cataract
- Underweight
- Substance abuse
- Atrial fibrillation
- Erectile dysfunction
- Amyotrophy
- GERD
- Degenerative joint disease
- Prostate cancer
- Depression
- Lung cancer
- CVA
- Hypothyroidism
- Breast cancer
- Pulmonary fibrosis
- Chronic kidney disease
- DVT
The arrow represents the odds ratio (OR) for reporting worse self-rate health status among COPD patients with each condition from participants in NHANES 2001-2008.

*Adapted with permission from COPD journal* 

Putcha N et al, COPD 2013
Impact of COPD and comorbidities on mortality.

Smith MC, Wrobel JP. Int J COPD 2014
Asthma – COPD Overlap (ACO)
### 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 2018]

### COPD

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. [GOLD 2018]

### Asthma-COPD overlap [not a definition, but a description for clinical use]

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

This is not a definition, but a description for clinical use, as asthma-COPD overlap includes several different clinical phenotypes and there are likely to be several different underlying mechanisms.
### STEP 2: SYNDROMIC DIAGNOSIS IN ADULTS

1. Assemble the features for asthma and for COPD that best describe the patient.
2. Compare number of features in favour of each diagnosis and select a diagnosis.

<table>
<thead>
<tr>
<th>Features: if present suggest -</th>
<th><strong>ASTHMA</strong></th>
<th><strong>COPD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>Before age 20 years</td>
<td>After age 40 years</td>
</tr>
<tr>
<td><strong>Pattern of symptoms</strong></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><strong>Lung function</strong></td>
<td>Record of variable airflow limitation (spirometry or peak flow)</td>
<td>Record of persistent airflow limitation (FEV$_1$/FVC &lt; 0.7 post-BD)</td>
</tr>
<tr>
<td><strong>Lung function between symptoms</strong></td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td><strong>Past history or family history</strong></td>
<td>Previous doctor diagnosis of asthma, Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)</td>
<td>Previous doctor diagnosis of COPD, chronic bronchitis or emphysema, Heavy exposure to risk factor: tobacco smoke, biomass fuels</td>
</tr>
<tr>
<td><strong>Time course</strong></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), Rapid-acting bronchodilator treatment provides only limited relief</td>
</tr>
<tr>
<td></td>
<td>May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Chest X-ray</strong></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 ACO.

### DIAGNOSIS

<table>
<thead>
<tr>
<th>CONFIDENCE IN 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>Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could be ACO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possibly COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Asthma - Copd Overlap**

<table>
<thead>
<tr>
<th>Characteristics of irreversible asthma and COPD groups (derived from ref 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Final Diagnosis</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age at onset of chronic cough (year)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age at onset of exercise intolerance/dyspnea (year)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>History of allergic rhinitis</td>
</tr>
<tr>
<td>Hypertrophy of nasal turbinates upon examination</td>
</tr>
<tr>
<td>KCO (% predicted)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Change in FEV1 following ICS/LABA therapy (mL)</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Several studies have documented the specificity of DLCO in diagnosing COPD.*

**Fabbri LM** Am J Respir Crit Care Med. 2003, **Magnussen H**, Clin Exp Allergy 1998, **Goedhart DM** COPD. 2006
Asthma – Copd Overlap

Qualitative CT scan changes in asthma and COPD (compiled by the authors)

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide branching and thinning of blood vessels</td>
<td>May be present</td>
<td>Common</td>
</tr>
<tr>
<td>Centrilobular or paraseptal emphysema</td>
<td>Occasionally described (0%–10%); usually limited</td>
<td>Common and usually diffuse</td>
</tr>
<tr>
<td>Panlobular emphysema</td>
<td>Never described</td>
<td>Common (more in α-antitrypsin deficiency than in smoker’s COPD)</td>
</tr>
<tr>
<td>Bullas</td>
<td>Rare/aneudotal reports; usually single</td>
<td>Common</td>
</tr>
</tbody>
</table>

Feisal A Al-Kassimi Int J Chron Obstruct Pulmon Dis. 2013

.......... A greater extent of HRCT scan abnormalities was found in COPD than in severe and mild asthmatics..

Vignola et al. Eur Respir J 2004
Differences and similarities between asthma and COPD

<table>
<thead>
<tr>
<th></th>
<th>Eosinophilic COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Frequent exacerbator phenotype</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Reversible airway obstruction</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Similarities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_{H2}$-high phenotype</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Eosinophilic inflammation</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Steroid responsiveness</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Anti–IL-5/anti-IGE responsiveness</td>
<td>??</td>
<td>+++</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
<th>Neutrophilic asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td>+</td>
<td>-/++</td>
</tr>
<tr>
<td>Frequent exacerbator phenotype</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Irreversible airway obstruction</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Similarities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_{H2}$-low phenotype</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Neutrophilic inflammation</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Steroid resistance</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Eosinophils &lt;2%</td>
<td>Eosinophils ≥2%</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td></td>
<td>FP</td>
<td>Placebo</td>
</tr>
<tr>
<td>Patients n</td>
<td>240</td>
<td>216</td>
</tr>
<tr>
<td>Baseline FEV₁ (mean±se) L</td>
<td>1.46±0.487</td>
<td>1.39±0.469</td>
</tr>
<tr>
<td>Adjusted rate of decline in FEV₁ (mean±se) mL-year⁻¹</td>
<td>-54.2±4.8</td>
<td>-51.3±5.3</td>
</tr>
<tr>
<td>Slope: FP versus placebo (mean±se) (95% CI)</td>
<td>-2.9±7.2 [-17.0-11.3], p=0.688</td>
<td>33.9±11.3 [11.5-56.2], p=0.001</td>
</tr>
</tbody>
</table>

Random coefficients model for each eosinophil subgroup separately, with fixed effects of age, sex, baseline post-bronchodilator FEV₁, treatment group and time, and random subject effects. # using baseline post-bronchodilator FEV₁ as a covariate.

---

**Eo<2%**

**Eo≥2%**

**FP versus placebo=3.8 mL-year⁻¹, p=0.016**

**FP versus placebo=37.7 mL-year⁻¹, p=0.001**

*Barnes NC et al ERJ 2016*
P4 Medicine

- **Personalized**: based on the personal genome data
- **Predictive**: the analysis of these personal data will allow accurate risk predictions for several diseases
- **Preventive**: from that prediction, preventive measures, either in the form of regular screening and/or specific interventions, could be implemented
- **Participatory**: because the participation of the individual is essential for all of the above, for instance, when lifestyle changes are advised or when compliance with chronic treatments are needed.

Augusti A et al AJRCCM 2011
Conclusions

• The most important COPD phenotypes:
  – Strongly symptomatic with low exercise capacity.
  – Frequent exacerbator
  – "Historical" phenotypes (Pink Puffer-Blue bloater)
  – COPD–comorbidities
  – ACO & Eosinophilic & Reversibility

• Understanding of phenotypes sets the basis for the understanding of the underlying endotyping mechanisms.
“An Expert is a person who has made all the mistakes that can be made in a very narrow field”.

Niels Bohr (Copenhagen, Denmark, 1885-1962).
ΕΥΧΑΡΙΣΤΩ