COPD, Asthma, Or Something In Between?

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December 4, 2013
Disclosures

• None
Definitions

• **Asthma**
  “Asthma is a chronic inflammatory disorder of the airways ...causes recurrent episodes of wheezing, breathlessness, chest tightness and coughing ...associated with widespread but variable airflow obstruction that is often **reversible** either spontaneously or with treatment.”

• **COPD**
  “Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is **not** fully reversible”
## Risk Factors for Asthma and COPD

<table>
<thead>
<tr>
<th>Host factors</th>
<th>Asthma</th>
<th>COPD</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Male sex childhood,</td>
<td>Family history of COPD</td>
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<tr>
<td></td>
<td>female sex in adulthood (68)</td>
<td></td>
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<tr>
<td></td>
<td>(Family) history of asthma (71)</td>
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<tr>
<td></td>
<td>Genetic constitution</td>
<td>Family history asthma/atopy (71)</td>
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<tr>
<td></td>
<td>Airway hyperresponsiveness (5)</td>
<td>Genetic constitution</td>
</tr>
<tr>
<td></td>
<td>Atopy (4)</td>
<td>Airway hyperresponsiveness (17, 71)</td>
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<tr>
<td></td>
<td>Low lung function (69)</td>
<td>Low lung function (17)</td>
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<tr>
<td></td>
<td>Overweight (70)</td>
<td></td>
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<tr>
<td>Perinatal factors</td>
<td>Maternal smoking (72)</td>
<td>Maternal smoking (72)</td>
</tr>
<tr>
<td></td>
<td>Maternal diet (11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mode of delivery (73)</td>
<td></td>
</tr>
<tr>
<td>Environmental exposures in childhood</td>
<td>No breastfeeding (10)</td>
<td>Lower respiratory tract infections (13, 71)</td>
</tr>
<tr>
<td></td>
<td>Viral respiratory infections (9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Microbial deprivation (12)</td>
<td></td>
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<tr>
<td></td>
<td>Environmental tobacco smoke exposure (6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Air pollution (74)</td>
<td></td>
</tr>
<tr>
<td>Environmental exposures in adulthood</td>
<td>Occupational exposures (75)</td>
<td>Occupational exposures (13)</td>
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<tr>
<td></td>
<td>Cigarette smoking (7)</td>
<td>Cigarette smoking (71)</td>
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<tr>
<td></td>
<td>Outdoor air pollution (8)</td>
<td>Outdoor air pollution (8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indoor air pollution (13)</td>
</tr>
</tbody>
</table>
ASTHMA

- Allergens
- Ep cells
- Mast cell
- CD4+ cell (Th2)
- Eosinophil

Bronchoconstriction
AHR

COPD

- Cigarette smoke
- Alv macrophage
- Ep cells
- CD8+ cell (Tc1+Tc2)
- Neutrophil

Small airway narrowing
Alveolar destruction

Airflow Obstruction

- Fully Reversible
- NOT Fully Reversible
Does Reversibility Help Distinguish Between Asthma and COPD?
Asthma vs. COPD: Asthma does not Always Reverse

<table>
<thead>
<tr>
<th>% Increase</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum of 200-ml change in FEV₁</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10</td>
<td>58</td>
<td>77</td>
</tr>
<tr>
<td>≥ 15</td>
<td>43</td>
<td>81</td>
</tr>
<tr>
<td>≥ 20</td>
<td>29</td>
<td>87</td>
</tr>
<tr>
<td>No minimum change in FEV₁</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10</td>
<td>63</td>
<td>58</td>
</tr>
<tr>
<td>≥ 15</td>
<td>44</td>
<td>72</td>
</tr>
<tr>
<td>≥ 20</td>
<td>29</td>
<td>84</td>
</tr>
<tr>
<td>Change in FVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10</td>
<td>36</td>
<td>58</td>
</tr>
<tr>
<td>≥ 15</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>≥ 20</td>
<td>11</td>
<td>82</td>
</tr>
</tbody>
</table>

Kesten S and Rebuck AS. *Chest* 1994; 105: 1042-1045
Asthma vs. COPD: COPD often Demonstrates Reversibility

Tashkin DP. Eur Respir J 2008; 31: 742-750
Percent of COPD Patients That Exhibit Reversibility in UPLIFT Trial

Hanania NA et al. Chest 2011;140:1055-1063
Reversibility By COPD Severity

Hanania NA et al.  Chest 2011;140:1055-1063
FEV$_1$ Decline Rates Over 5 Years

Cantoli M et al. JACI 2010;125:830-7
FEV₁ Decline Rates Over 5 Years

Cantoli M et al. JACI 2010;125:830-7
Venn Diagram of Asthma/COPD overlap syndrome
Differences and Similarities

• Reversibility is NOT a key distinguishing factor
• Both asthma and COPD patients can exhibit irreversible, fixed obstructive defects
• Asthma is a risk factor for COPD
• 1 out of 6 patients with COPD is a never smoker
• Does an Asthma + COPD phenotype exist and how do we characterize these patients?
Burden of Concomitant Asthma and COPD in a Medicaid Population

Objectives:

- #1 – To determine whether the health burden is different in adults with diagnoses of asthma and COPD
- #2 – To determine if there in an incremental health-care burden in patients with asthma and COPD compared to those with only one diagnosis

Burden of Concomitant Asthma and COPD in a Medicaid Population

9,131 patients aged 40-64 with COPD and/or Asthma dx in months 1-36, and have complete pharmacy information

COPD dx in months 1-30?

Yes

Asthma dx in months 1-30?

Yes

Asthma/COPD cohort (2604)

COPD cohort, censored at the time of asthma dx (196)

Asthma/COPD cohort (n=2604)

No

Asthma dx in months 30-36? (3455)

Yes

COPD cohort (3259)

No

Asthma/COPD cohort (n=3,455)

No

COPD dx in months 30-36? (3072)

Yes

Asthma cohort, censored at the time of COPD dx (174)

Asthma cohort (n=3,072)

No

Asthma dx in months 30-36? (3455)

Yes

COPD cohort (3259)

No

Asthma/COPD cohort (n=3,455)

No

Asthma cohort, censored at the time of asthma dx (196)

Asthma/COPD cohort (n=2604)

FIGURE 1. Cohort determination. Dx = diagnosis.
Findings

- Patients with co-occurring disease constitute comparable proportions of the population
- Consume more medical resources than either asthma or COPD alone
- Health care cost are 2-6x higher

Limitations

• Retrospective
• Medicaid population: more women, Blacks, lower income
• Lack data on potential confounding factors:
  - disease severity
  - smoking
  - environmental exposures
• Cost estimations serve as proxies

Clinical Features of COPD and Asthma Overlap

- Cross-sectional observational study
- Examined first 2500 subjects in the COPDGene study to assess
  - Smoking
  - BODE
  - SGRQ
  - Exacerbations
  - Chest CT
Exacerbations

Figure 1 Exacerbations: Percentage of frequent and severe exacerbations among subjects with COPD compared to subjects with COPD and asthma. *p < 0.0001 for the difference between COPD and COPD with asthma.
Findings and Limitations

• Subjects with COPD and asthma have distinct, clinically-relevant characteristics
• More likely to be younger, Black, and less smoking history
• Worse health-related QOL
• More likely to have frequent and severe respiratory exacerbations

• Cross-sectional, self-report of physician diagnosed asthma
Asthma/COPD Phenotype?

- Implications for disease management and treatment
- Improved monitoring of prevention of exacerbations in patients with COPD and asthma may improve QOL, potential survival
COPD is a disease of multiple phenotypes
Operational Definition of a COPD 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)”

Defining a Phenotype

Clinical Phenotype Defined By Similar Outcome

Validation of Molecular Marker or Determination of Therapeutic Response in Target Population

Symptomatic, Physiologic, and/or Radiologic Characterization of Phenotype

Biologic or Molecular Characterization of Phenotype

+/− Development of Therapy

Phenotypic Variation in COPD: Emphysema vs. Airways

64 year old man
FEV\textsubscript{1} = 49% predicted

64 year old woman
FEV\textsubscript{1} = 51% predicted
How Does Phenotypic Variation Effect Pharmacotherapy?
**Asthma Pharmacotherapy**

**Intervetin Asthma**

**Step 1**
- **Preferred:** SABA PRN
- **Alternative:** Cromolyn, LTRA, Nedocromil, or Theophylline

**Step 2**
- **Preferred:** Low-dose ICS + LABA
  - OR Medium-dose ICS + LABA
- **Alternative:** Low-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 3**
- **Preferred:** Medium-dose ICS + LABA
- **Alternative:** Consider Omalizumab for patients who have allergies

**Step 4**
- **Preferred:** High-dose ICS + LABA AND
- **Alternative:** Consider Omalizumab for patients who have allergies

**Step 5**
- **Preferred:** High-dose ICS + LABA + oral corticosteroid AND

**Step 6**
- **Step up if needed**
  - (first, check adherence, environmental control, and comorbid conditions)
  - **Assess control**
  - **Step down if possible**
    - (and asthma is well controlled at least 3 months)

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**Quick-Relief Medication for All Patients**

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

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*Guidelines for the Diagnosis and Management of Asthma (EPR-3) 2007. NIH, NHLBI. August 2007.*
Tiotropium Bromide Step Up Therapy in Uncontrolled Asthma

Peters SP et al. NEJM 2010;363:1715-26
Tiotropium Relieves Static Hyperinflation in COPD

Effects of Long-acting Bronchodilators on Exacerbations

Number of Exacerbations per Patient Year

- Placebo: 1.49
- Salmeterol: 1.23
- Tiotropium: 1.07

N = 1207

P = 0.025

28% decrease
TORCH: Effects of Treatment on Exacerbations – Relation With Baseline FEV$_1$

![Graph showing the rate of moderate/severe exacerbations across different FEV$_1$ levels with Placebo, SAL, FP, and SFC treatment groups.](image-url)
PDE4 Inhibitors in COPD

- CD8+ T-cell
- Macrophage
- Neutrophil
- Airway smooth muscle cells
- Epithelial cells
- Capillary
- NANC nerves
- Sensory nerves
- Fibroblasts

NANC = Nonadrenergic and Noncholinergic
Roflumilast Reduced Exacerbations in Patients With COPD Associated With Chronic Bronchitis

Pooled post hoc analysis of patients with chronic bronchitis

All patients
Δ = -26.2%
(CI -38;-11)
P=0.0010

ICS: yes
Δ = -30.2%
(CI -44;-13)
P=0.0012

ICS: no
Δ = -15.5%
(CI -39;17)
P=0.3103
Roflumilast Improved Lung Function When Added to First-line Maintenance Treatment

Change in Pre-bronchodilator FEV₁

Mean Change in FEV₁ (L)

- Yellow: Tiotropium + Roflumilast (n=371)
- Gray: Tiotropium + Placebo (n=372)

Weeks

80 ml
PDE4 Inhibitors Included as a New Class of Treatment in 2010 GOLD Guidelines

Roflumilast Information:

“In patients with Stage III: Severe COPD or Stage IV: Very Severe COPD and a history of exacerbations and chronic bronchitis, the phosphodiesterase 4 inhibitor, roflumilast, reduces exacerbations treated with oral glucocorticosteroids. These effects are also seen when roflumilast is added to long-acting bronchodilators.”
Impact of Exacerbations in COPD

Patients With Frequent Exacerbations

- Faster Decline in Lung Function
- Greater Airway Inflammation
- Poorer Quality of Life
- Higher Mortality
Pulmonary Function May Recover Slowly After an Exacerbation

Daily Median PEFR as % Baseline

Exacerbation

Days

N=91
Exacerbator Phenotype

• ECLIPSE helps promote the stability of the exacerbator phenotype
• Greatest FEV$_1$ decline with frequent exacerbations

↑ Susceptibility to viral infection due to defects in innate immune response

Chronic inflammation
Oxidative stress
Epithelial injury
↑ Susceptibility to viral infections

Chronic bacterial infections

Exacerbator phenotype
Azithromycin in Prevention of AECOPD

P<0.001 by log-rank test and Wilcoxon signed-rank test
Pulmonary Rehabilitation

- Improves dyspnea
- ? If improves HRQOL is asthma/COPD overlap
Smoking Cessation

• To reduce lung function decline
• Decrease risk of irreversible airflow obstruction
What is the Specialized Treatment for an Asthma/COPD subtype?
Recommended Therapy

• Acknowledgment of COPD in addition to asthma
• LABA and LAMA for exacerbation prevention
• Consideration for roflumilast or azithromycin if on usual therapy and frequent exacerbations
• Treatment of allergies if indicated
• Vaccinations
• Co-morbidity assessment (CAD, CHF, PH, Depression, physical deconditioning, tobacco, allergy, sinus disease)
• COPD symptom assessment
Conclusions

• Several COPD pathogenic hypotheses include asthma and/or shared risk factors
• Reversibility does not reliably distinguish between asthma and COPD
• Asthma/COPD phenotype has higher health care utilization and cost
• Asthma/COPD phenotype has worse health related QOL
• Asthma/COPD phenotype more likely to have frequent and severe exacerbations
• Future studies are needed to assess best therapies, better define asthma/copd overlap syndrome