Update in COPD

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Faculty Disclosures

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Personal financial interests in commercial entities that are relevant to my presentation(s) or other faculty roles:

- Genentech, Research Grant (completed), Co-inventor on patent application
- Regulus, Unfunded research collaboration (reagents)
- Pfizer, CTI Strategic Alliance
- MedImmune, Consultant (completed)

Objectives

- Burden of disease:
  - Understand the need for early recognition, prevention, and treatment of COPD
- COPD diagnosis:
  - Importance of spirometry, symptom and exacerbation assessment
- Current treatment options:
  - Review current GOLD guidelines
  - Recent Advances: azithromycin for the prevention of exacerbations
- The Future of COPD:
  - Phenotyping in COPD
COPD: Breadth of the Definition

- Chronic Bronchitis
- Emphysema
- Chronic Airflow limitation

COPD: Preventable and Treatable
GOLD Consensus Report, December 2011

“COPD, a common preventable and treatable disease is characterized by persistent airflow limitation...”

*Airflow limitation is usually progressive and is associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases."

*Exacerbations and comorbidities contribute to the overall severity in individual patients. “

COPD is a Major Public Health Problem

- 16.3 million office visits each year due to COPD
- 672,000 hospitalizations each year for COPD
  - 21% mortality rate at one year after being hospitalized for a COPD exacerbation in a large VA cohort
- COPD is currently the 3rd-leading cause of death in the United States

Total costs for COPD estimated at $49.9 billion in 2007

References:
Percent Change in Age-Adjusted US Death Rates

Occupational or Work-related COPD is also a Major Public Health Problem

- Population Attributable Risk is 15-20%
- Total costs for Occupational COPD estimated at $5 billion annually in the US alone

Recognition of work-relatedness is difficult

- Lack of a standard definition
- No typical pathology (unlike pneumoconioses)
- COPD is multifactorial (concurrent cigarette smoke exposure)
### COPD: General Risk Factors

<table>
<thead>
<tr>
<th>Established</th>
<th>Probable</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>Occupational exposure</td>
<td>Low birth weight</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Occupational exposure</td>
<td>Childhood respiratory infections</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>α-1-Antitrypsin deficiency (genetic abnormality)</td>
<td>Family history</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Air pollution</td>
<td>Atopy</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Alcohol</td>
<td>IgA deficiency</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Poverty</td>
<td>Blood type A</td>
</tr>
</tbody>
</table>


### COPD: Occupational Risk Factors for Chronic Bronchitis

- **Minerals**
  - Coal
  - Vitreous fibers
  - Oil mist
  - Portland cement
  - Silica/silicates

- **Metals**
  - Osmium
  - Vanadium
  - Welding fumes

- **Organic Dust**
  - Cotton
  - Grain
  - Wood

- **Gases**
  - Disocyanate
  - Sulfur dioxide
  - Engine exhaust

- **Smoke**
  - Fires


### COPD: Occupational Risk Factors for Emphysema

- Much harder to measure, data from autopsy studies

- Gold miners
- Silica exposure
- Coal dust

COPD: Occupational Risk Factors for Decline in FEV1

Much harder to specify the cause, Population based studies
- Miscellaneous exposures to dust and gases


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Spirometry Steps For Suspected COPD

<table>
<thead>
<tr>
<th>STEP 1</th>
<th>OAD (COPD or Asthma)</th>
<th>FEV1/FVC</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70%</td>
<td>&gt;70%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
</tr>
<tr>
<td>&gt;80%</td>
</tr>
<tr>
<td>&lt;80%</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Concomitant restrictive component
Disease must be detectable in an early stage:
Lung Function Over Time

- FEV1 (% Relative to Age 25)

Never smoked or not susceptible to smoke
Smoked regularly and susceptible to its effects
Stopped smoking at 45 (Mild COPD)
Stopped smoking at 65 (Severe COPD)

Death
Disability
Symptoms


Underdiagnosis of COPD in the United States

Diagnosed with chronic bronchitis or emphysema
Airflow limitation (GOLD 1 or higher)

The Argument for Selective Screening

Martinez, et al., COPD, 2008;5:85. "COPD Screener"
Symptoms in COPD

- Expiratory Flow Limitation
- Breathlessness
- Deconditioning
- Inactivity
- Reduced exercise capacity
- Poor Quality of Life

Exacerbation Frequency Increases With Disease Severity

Exacerbations Per Year

<table>
<thead>
<tr>
<th>% Predicted FEV₁</th>
<th>0</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80%</td>
<td>1.6</td>
<td>1.8</td>
<td>2.0</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>40%-59%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results based on a cross-sectional observational study of ambulatory COPD patients in Spain. General practitioners (N=201) between October 1994 and May 1995 completed a questionnaire on COPD characteristics of 1001 patients. Exacerbation was defined as an increase in dyspnea, sputum volume, and/or sputum purulence.


Frequency of Exacerbations Is Associated With a Decline in Lung Function

Exacerbations Per Year

<table>
<thead>
<tr>
<th>FEV₁, mL/year</th>
<th>&lt;1.5</th>
<th>&gt;1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>-25.3*</td>
<td>-46.1</td>
<td></td>
</tr>
</tbody>
</table>

Results based on a secondary analysis of 32 patients who recorded daily FEV₁. The median rate of exacerbations seen at clinic was 1.5 per patient per year.

Patients With Frequent Exacerbations Had Significantly Worse Quality of Life

- Mean Difference: -15.1* (0-2 Exacerbations vs. 3-8 Exacerbations)
- Mean Difference: -21.9*
- Mean Difference: -12.2*
- Mean Difference: -14.1*

*P<0.002

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Treatment of Occupational COPD

Prevention

- Primary (reduce exposure to irritants)
  - Elimination
  - Engineering controls
  - Administrative controls
  - Personal protective equipment
- Secondary (screening with questionnaires and spirometry)
- "Tertiary" (the therapeutic options that will be indicated on the subsequent slides)
Treatment of COPD in General
GOLD 2011 Consensus Statement

- Goal of the Combined COPD Assessment is to stratify subjects based on:
  - Risk for exacerbations, hospitalizations and death
  - Symptoms
- Metrics used to stratify:
  - FEV1% predicted
  - Exacerbation history
- Symptoms using either the modified Medical Research Council (mMRC) dyspnea score or the COPD Assessment Test (CAT) score

Classification of Airflow Limitation

<table>
<thead>
<tr>
<th>Classification</th>
<th>FEV1 Predicted Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD I Mild</td>
<td>≥ 80%</td>
</tr>
<tr>
<td>GOLD II Moderate</td>
<td>50% ≤ FEV1 &lt; 80%</td>
</tr>
<tr>
<td>GOLD III Severe</td>
<td>30% ≤ FEV1 &lt; 50%</td>
</tr>
<tr>
<td>GOLD IV Very Severe</td>
<td>FEV1 &lt; 30%</td>
</tr>
</tbody>
</table>

Modified Medical Research Council Questionnaire for Assessing Breathlessness

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>I only get breathless with strenuous exercise</td>
</tr>
<tr>
<td>1</td>
<td>I get short of breath when hurrying or walking up a slight hill</td>
</tr>
<tr>
<td>2</td>
<td>I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking at my own pace on the level</td>
</tr>
<tr>
<td>3</td>
<td>I stop for breath after walking about 100 m or after a few minutes on the level</td>
</tr>
<tr>
<td>4</td>
<td>I am too breathless to leave the house or I am breathless when dressing or undressing</td>
</tr>
</tbody>
</table>
CAT: COPD Assessment Test


GOLD 2011 Consensus Statement

FEV₁ and Risk for Exacerbations, Hospitalization and Death

Combined placebo data from TORCH, Uplift and ECLIPSE

2011 GOLD Consensus Report www.goldcopd.com
Relationship between FEV1 and Quality of Life

Achievable Outcomes of Therapy in COPD

- Bronchodilators are effective in improving airflow and lung volume
- Symptomatic patients with appropriate treatment can expect
  - Relief of dyspnea
  - Improvement of exercise tolerance
  - Improvement of quality of life
  - Decrease in exacerbations

**GOLD 2007 Treatment Overview**

<table>
<thead>
<tr>
<th>GOLD Stage</th>
<th>I Mild</th>
<th>II Moderate</th>
<th>III Severe</th>
<th>IV Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active reduction of risk factors: influenza vaccine Add short-acting bronchodilators when needed Add regular Rx with &gt;1 long-acting bronchodilator when needed Add rehabilitation Add inhaled corticosteroids (ICS) if repeated exacerbations Add O₂ if chronic respiratory failure.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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**GOLD 2011 Treatment Overview**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>First Choice</th>
<th>Second Choice</th>
<th>Alternative Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SAMA PRN or SABA PRN</td>
<td>LAMA or LABA or SABA and SAMA</td>
<td>Theophylline</td>
</tr>
<tr>
<td>B</td>
<td>LAMA or LABA</td>
<td>LAMA &amp; LABA</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA or LAMA</td>
<td>LAMA &amp; LABA</td>
<td>PDE4 inhibitor SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA or LAMA</td>
<td>ICS &amp; LAMA or ICS &amp; LABA &amp; LAMA or ICS &amp; LABA &amp; PDE4 inhibitor or LAMA &amp; LABA or LAMA &amp; PDE4 inhibitor</td>
<td>Carbocysteine SABA and/or SAMA Theophylline</td>
</tr>
</tbody>
</table>

**For Whom is this Appropriate?**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>First Choice</th>
<th>Second Choice</th>
<th>For Whom is this Appropriate?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SAMA PRN or SABA PRN</td>
<td>LAMA or LABA or SABA and SAMA</td>
<td>Not short of breath on the level &lt; 2 exacerbations in prior year FEV1&gt;50%</td>
</tr>
<tr>
<td>B</td>
<td>LAMA or LABA</td>
<td>LAMA &amp; LABA</td>
<td>Short of breath on the level &lt; 2 exacerbations in prior year FEV1&gt;50%</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA or LAMA</td>
<td>LAMA &amp; LABA</td>
<td>Not short of breath on the level &gt; 2 or more Exacerbations in FEV1&lt;50%</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA or LAMA</td>
<td>ICS &amp; LAMA or ICS &amp; LABA &amp; LAMA or ICS &amp; LABA &amp; PDE4 inhibitor or LAMA &amp; LABA or LAMA &amp; PDE4 inhibitor</td>
<td>Short of breath on the level &gt; 2 or more Exacerbations in FEV1&lt;50%</td>
</tr>
</tbody>
</table>
New therapeutic options
the MACRO Study

The NEW ENGLAND JOURNAL of MEDICINE

Azithromycin for Prevention of Exacerbations of COPD
Michael K. Han, M.D.; Stephen C. Lazazzera, M.D.; Barry Male, M.D.; Nathaniel Manesh, M.D.;
Fernando J. Martinez, M.D.; Nancy E. Maldonado, M.D.; Charlotte M. E. M.L; M.D.; M.P.H.;
Dennis E. Newburger, M.D.; Janos Vacar, Ph.D.; R. Conte; J. Pizzo, M.D.; John R. Bley, M.D.;
Paul D. Stanfield, M.D.; Frank C. Storace, M.D.; Steven M. Schleif, M.D., Ph.D.; George F. Walke, M.D.;
Frederic C. Woodall, M.D., M.P.H.; and Nicholas R. Ambrosino, M.D. for the COPD Clinical Research Network.

Time to First exacerbation
Effect of azithromycin

- Median = 174 days
- Median = 266 days
- HR = 0.73 (0.63, 0.84), P < 0.001

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Future Directions

"Emphysema Predominant"  "Airway Disease Predominant"

Han, et al. Radiology 2011;261(1):274
Summary

- Occupational COPD represents a significant societal burden but is difficult to diagnose in any given patient
- Treatment includes prevention strategies and the usual COPD therapies
- GOLD guidelines for COPD assessment and therapy have been significantly revised in 2011
- Better distinction of the type of COPD any specific patient has is coming... "phenotyping"