COPD--Changing Concepts of Pathogenesis and New Ideas for Old Treatments

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Chronic obstructive pulmonary disease (COPD)

“...a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible.”
Scope of the Problem

• COPD is incredibly common; estimates vary but likely > 6% population
• COPD is the fourth leading cause of death (since 1994). Estimated to be the third leading cause of death by 2020.
• In the US, direct costs of COPD are ~$29 billion and indirect costs are ~ $20 billion.
Normal Airway

Jeffery PK. Thorax 53:129; 1998
Bronchial Surface after Subacute Exposure to Cigarette Smoke

Jeffery PK. Thorax 53:129; 1998
Histopathological Features of COPD

Clinical Features of COPD

• Smoker (usually > 1 pack/day for 20 years)
• Symptoms (begin in the fifth or sixth decade)
  – Cough
    • worse in am
    • sputum
      – generally mucoid and < 60 ml/day
      – purulent during exacerbation
  – Dyspnea
    • insidious in onset
    • worse with exertion
  – Wheezing
Pulmonary Function Tests

• COPD is diagnosed and staged primarily by pulmonary function testing (PFTs).

• Spirometry
  – decreased FEV1
  – decreased FEV1/FVC ratio (<0.7)
  – “coved” appearance to the expiratory limb of a flow-volume loop
Flow Volume Loops

Normal

COPD

Predicted

Actual

Flow

Volume (L)

TLC RV

IC

Flow (L/s)

Volume (L)

1 sec

8 7 6 5 4 3 2

8 7 6 5 4 3 2

-2 -3 -4 -5

-2 -3 -4 -5
Flow Volume Loop During Exercise: obstructive lung disease
Effects of Exercise on Hyperinflation

- VT: Volume of Tissue
- IRV: Inspiratory Reserve Volume
- ERV: Expiratory Reserve Volume
- RV: Residual Volume
- IC: Inspiratory Capacity
- TLC: Total Lung Capacity

**Normal**
- Years - Decades

**Progression**
- Air Trapping at Rest
- Years - Decades

**Static Hyperinflation**
- Rest
- Air Trapping at Rest

**Dynamic Hyperinflation**
- Seconds - Minutes Exercise
- Air Trapping During Exercise
Severe emphysema

Mild emphysema
Decline of FEV\textsubscript{1} with Age and Smoking History

FEV\textsubscript{1} (% of value at age 25)

Age (years)

Never smoked or not susceptible to smoke

- Smoked regularly and susceptible to smoke
- Stopped at 45
- Stopped at 65

Death

Disability

Lungs too big? Make them smaller...
A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema

National Emphysema Treatment Trial Research Group*
D Upper-Lobe Predominance, Low Base-Line Exercise Capacity (N=290)

No. at Risk
Surgery       139 121 93 61 17
Medical therapy 151 120 85 43 13

E Upper-Lobe Predominance, High Base-Line Exercise Capacity (N=419)

No. at Risk
Surgery       206 176 124 82 35
Medical therapy 213 192 149 104 35

F Non–Upper-Lobe Predominance, Low Base-Line Exercise Capacity (N=149)

No. at Risk
Surgery       84 67 52 28 6
Medical therapy 65 55 36 17 5

G Non–Upper-Lobe Predominance, High Base-Line Exercise Capacity (N=220)

No. at Risk
Surgery       109 83 71 43 12
Medical therapy 111 96 69 40 17
FEV$_1$: Prognostic Implications

The BODE Score

Azithromycin for Prevention of Exacerbations of COPD

P<0.001 by log-rank test and Wilcoxon signed-rank test
Why I don’t like this study...
Lung Microbiome

• Conventional wisdom--healthy lungs are sterile
• Culture independent techniques demonstrate a complex bacterial microbiome in the lung.
  – post partum the lung is populated by microbes derived from the mother
  – the most common phyla observed in normal lung are *Bacteroides*, *Firmicutes*, and *Proteobacteria*
  – distinct lung microbiota and altered diversity are observed in lung disease

Guidelines for COPD

Global Initiative for Chronic Obstructive Lung Disease

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

UPDATED 2013
# Classification by Severity:
## GOLD Guidelines

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| 0: At risk | Normal spirometry  
Cough, sputum                                      |
| I: Mild  | FEV₁/FVC <70%  
FEV₁ ≥80% predicted  
With or without chronic symptoms (cough, sputum) |
| II: Moderate | FEV₁/FVC <70%  
50% <FEV₁<80% predicted  
With or without chronic symptoms (cough, sputum) |
| III: Severe | FEV₁/FVC <70%  
30% <FEV₁<50% predicted  
With or without chronic symptoms (cough, sputum) |
| IV: Very Severe | FEV₁/FVC <70%  
FEV₁<30% predicted; or FEV₁<50% predicted plus chronic respiratory failure (PaO₂ <60 mm Hg) or clinical signs of right heart failure |

Global Initiative for Chronic Obstructive Lung Disease  
www.goldcopd.com/
# Combined Assessment of COPD

When assessing risk, choose the **highest** risk according to GOLD grade or exacerbation history. One or more hospitalizations for COPD exacerbations should be considered high risk.

## Patient Characteristic Spirometric Classification Exacerbations per year mMRC CAT

<table>
<thead>
<tr>
<th>Patient</th>
<th>Characteristic</th>
<th>Spirometric Classification</th>
<th>Exacerbations per year</th>
<th>mMRC</th>
<th>CAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low Risk Less Symptoms</td>
<td>GOLD 1-2</td>
<td>≤ 1</td>
<td>0-1</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>B</td>
<td>Low Risk More Symptoms</td>
<td>GOLD 1-2</td>
<td>≤ 1</td>
<td>≥ 2</td>
<td>≥ 10</td>
</tr>
<tr>
<td>C</td>
<td>High Risk Less Symptoms</td>
<td>GOLD 3-4</td>
<td>≥ 2</td>
<td>0-1</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>D</td>
<td>High Risk More Symptoms</td>
<td>GOLD 3-4</td>
<td>≥ 2</td>
<td>≥ 2</td>
<td>≥ 10</td>
</tr>
</tbody>
</table>

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Manage Stable COPD: Goals of Therapy

- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

Reduce symptoms

Reduce risk

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### Therapeutic Options: COPD Medications

<table>
<thead>
<tr>
<th>Category</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta2-agonists</strong></td>
<td></td>
</tr>
<tr>
<td>Short-acting beta2-agonists</td>
<td>(SABA)</td>
</tr>
<tr>
<td>Long-acting beta2-agonists</td>
<td>(LABA)</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td></td>
</tr>
<tr>
<td>Short-acting anticholinergics</td>
<td>(SAMA)</td>
</tr>
<tr>
<td>Long-acting anticholinergics</td>
<td>(LAMA)</td>
</tr>
<tr>
<td><strong>Combination</strong></td>
<td></td>
</tr>
<tr>
<td>Short-acting beta2-agonists +</td>
<td>anticholinergic in one inhaler</td>
</tr>
<tr>
<td><strong>Methylxanthines</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Inhaled corticosteroids</strong></td>
<td>(ICS)</td>
</tr>
<tr>
<td><strong>Combination</strong></td>
<td></td>
</tr>
<tr>
<td>Long-acting beta2-agonists +</td>
<td>corticosteroids in one inhaler</td>
</tr>
<tr>
<td><strong>Systemic corticosteroids</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Phosphodiesterase-4 inhibitors</strong></td>
<td></td>
</tr>
</tbody>
</table>
### Global Strategy for Diagnosis, Management and Prevention of COPD

**Manage Stable COPD: Pharmacologic Therapy**

(Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Recommended First choice</th>
<th>Alternative choice</th>
<th>Other Possible Treatments</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 and LABA</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA or LAMA</td>
<td>LAMA and LABA or LAMA and PDE4-inh. or LABA and PDE4-inh.</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA and/or LAMA</td>
<td>ICS + LABA and LAMA or ICS+LABA and PDE4-inh. or LAMA and LABA or LAMA and PDE4-inh.</td>
<td>Carbocysteine SABA and/or SAMA Theophylline</td>
</tr>
</tbody>
</table>
Prevention of AECOPD

• Smoking cessation
• Pharmacotherapy
  – Bronchodilators: LAMA and LABA
  – Inhaled corticosteroids
  – Combination therapy: ICS + LABA
  – Azithromycin
  – PDE4 inhibition
• Immunizations
  – Influenza, pneumococcal
• Rehabilitation and education
Using inhalers

• Inhaled medications are the cornerstone of asthma and COPD therapy
• Poor technique is reported in up to 94% of patients
• Improper inhaler use leads to poor disease control
• Patient who never receive instruction and those who use more than one type of device make more mistakes
Inhaler instruction

• Helps improve technique and self-efficacy
• Can be effectively taught by anyone who is properly trained
• Is poorly taught by most physicians
• Is more effective as a demonstration than in written form
• Benefits are short lived. Techniques need to be reinforced to be effective long term.
The problem with inhaled therapy...
aer·o·sol
noun: aerosol; plural noun: aerosols
1. a substance enclosed under pressure and able to be released as a fine spray, typically by means of a propellant gas.
CHEMISTRY
a colloidal suspension of particles dispersed in air or gas.
Where do the particles go?

- > 5 µ impaction
- 1-5 µ sedimentation
- < 1 µ like gas
Pattern of Aerosol Deposition: comparison of delivery devices
Evaluation of MDI teaching: questionnaire (n=30)

- Inhaler instruction: 87%
- Cleans inhaler: 43%
- Frequency of inhaler: 33%
- Knows correct dose: 47%
- Knows name of inhaler: 52%
- Identifies empty inhaler: 47%
- Uses more than 1 inhaler: 43%
- Order of inhalers: 52%
Evaluation of MDI teaching: vitalograph demonstration (n=30)

- Shakes inhaler before actuation: 83%
- Inhaler actuation: 53%
- Delivery: 47%
- Breath hold: 73%
- Wait time between puffs: 40%
# Inhaler Instructions

Ask your healthcare provider how to use these correctly

<table>
<thead>
<tr>
<th>Inhaler Name (Use the inhalers that are checked)</th>
<th>Metered dose</th>
<th>Dry Powder</th>
<th>Capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol (Proventil HFA®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium (Atrovent HFA®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide/ Formoterol (Symbicort®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mometasone (Asmanex®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formoterol (Foradil®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiotropium (Spiriva®)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th># of Puffs</th>
<th>Times Per Day</th>
<th>As Needed</th>
<th>Times Per Day</th>
<th>Primary Action</th>
<th>Times Per Day</th>
<th>Times Per Day</th>
<th>2 Times Per Day</th>
<th>1 Time Per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Beta-2 agonist)</td>
<td></td>
<td>(Inhaled Steroid/Beta-2 agonist)</td>
<td>(Beta-2 agonist)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Opens large airways</td>
<td></td>
<td>Decreases airway swelling and opens large airways</td>
<td>Opens large airways</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Short acting</td>
<td></td>
<td>Long acting</td>
<td>Long acting</td>
<td></td>
</tr>
</tbody>
</table>

| Important Points to Remember | Use as rescue for shortness of breath or wheezing. Works within minutes. May make you feel jittery*. | Use even if you don’t think you need it. Works within 30 minutes*. Not a rescue for asthma attacks. | Use even if you don’t think you need it. After removing from foil package, write the date on the inhaler and discard after 90 days. Rinse mouth after use. Not a rescue for asthma attacks. | Use even if you don’t think you need it. After removing from foil package, write the date on the inhaler and discard after 45 days. Rinse mouth after use. Not a rescue for asthma attacks. | Use even if you think you don’t need it. Refrigerate unopened capsule packages. Can store at room temperature for 4 months. Not a rescue for asthma attacks. | Use even if you think you don’t need it. Not a rescue for asthma attacks. |

*Prime inhaler with two sprays before very first use and if not used in over 3 days.

Rev. 11/11

Refer to back for instructions on how to use each type of inhaler.

PhE Approved 2/2012
Hurdles to inhaler education

- Consistency
- Repetition
- Adaptibility
  - For each patient
  - As inhalers change
- Who will teach?
Possible Solution?

https://vimeo.com/140420509
The Dyspnea Spiral in COPD

dyspnea → deconditioning → inactivity → dyspnea → deconditioning → inactivity → DISABILITY
Pulmonary Rehabilitation Program Components

- Education
- Respiratory care instruction
- Psychosocial support
- Exercise training
Long-term Effects of PR Plus Maintenance

• Improvement in
  – Dyspnea
  – Exercise capacity
  – Rate of decline of FEV$_1$
  – Severity of disease by BODE index
  – Success rate of smoking cessation
  – Survival, number of respiratory deaths

• Effects are sustained up to 3 years
Summary: COPD Management

- Diagnose
- Reduce risk
- Reduce symptoms
- Reduce complications

Education

- Spirometry
- Smoking cessation
- Pharmacotherapy
- Pulmonary rehabilitation
- Immunize
- Prevent exacerbations
- Consider oxygen