Medical Therapy for COPD

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Patient Presentation

• 55 year old female who smoked 2 packs of cigarettes a day for 35 years
• She has shortness of breath and a productive cough
• She notices wheezing with exertion on occasion
Definition of COPD

• COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

This definition does not use the terms chronic bronchitis and emphysema.

Risk Factors for COPD

- Cigarette smoking is the primary cause of COPD.
- The WHO estimates 1.1 billion smokers worldwide, increasing to 1.6 billion by 2025.
- According to World Health Organization (WHO) estimates, 210 million people have COPD.

Of the six leading causes of death in the United States, only COPD has been increasing steadily since 1970.

Jemal A. et al.  JAMA 2005
**Prognosis – COPD**

- **BODE Index** - A scale consisting of body mass index (BMI), obstruction, dyspnea score and exercise capacity has been shown to help predict survival.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points on BODE Index</th>
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<tbody>
<tr>
<td>FEV1 (%) predicted</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Distance walked in 6 min (meters)</td>
<td>≤300 300-340 350-400 ≤410</td>
</tr>
<tr>
<td>MMRC dyspnea scale*</td>
<td>0-1 2 3 4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0-21 &gt;21</td>
</tr>
</tbody>
</table>

*MMRC dyspnea scale ranges from 0 (none) to 4 (wheeze when dressing or undressing).

<table>
<thead>
<tr>
<th>BODE Index Score</th>
<th>One year mortality</th>
<th>Two year mortality</th>
<th>22 month mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2</td>
<td>7%</td>
<td>8%</td>
<td>19%</td>
</tr>
<tr>
<td>2.1-3</td>
<td>11%</td>
<td>12%</td>
<td>22%</td>
</tr>
<tr>
<td>3.4</td>
<td>21%</td>
<td>24%</td>
<td>40%</td>
</tr>
<tr>
<td>≥4.5</td>
<td>27%</td>
<td>31%</td>
<td>60%</td>
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**Pathogenesis**

- **Noxious particles and gases**
- **Host factors**
- **Lung inflammation**
- **Anti-oxidants**
- **Anti-proteinases**
- **Oxidative stress**
- **Proteinases**
- **Repair mechanisms**

**COPD pathology**
COPD Heterogeneity - Phenotypes

- COPD patients are at increased risk for:
  - Myocardial infarction, angina
  - Osteoporosis
  - Respiratory infection
  - Depression
  - Diabetes
  - Lung cancer

Systemic Effects & Co-Morbidities

- Extrapulmonary effects of COPD:
  - Weight loss
  - Nutritional abnormalities
  - Skeletal muscle dysfunction
Goals of COPD Management

- Smoking cessation – tobacco control
- Relieve symptoms
- Prevent progression
- Improve exercise tolerance
- Prevent/treat complications including exacerbations
- Reduce mortality

Therapy at Each Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Mild</td>
<td>• FEV₁/FVC &lt; 0.70&lt;br&gt;• FEV₁ &lt; 60% predicted&lt;br&gt;Add short-acting bronchodilator (when needed)</td>
</tr>
<tr>
<td>II: Moderate</td>
<td>• FEV₁/FVC &lt; 0.70&lt;br&gt;• FEV₁ &lt; 60% predicted&lt;br&gt;Add regular treatment with one or more long-acting bronchodilators (when needed); Add rehabilitation</td>
</tr>
<tr>
<td>III: Severe</td>
<td>• FEV₁/FVC &lt; 0.70&lt;br&gt;• FEV₁ &lt; 50% predicted&lt;br&gt;Add inhaled glucocorticosteroids if repeated exacerbations&lt;br&gt;Consider surgical treatments</td>
</tr>
</tbody>
</table>
Available Medical Therapy

- Albuterol
- Levalbuterol
- Ipratropium
- Albuterol/Ipratropium
- Inhaled Steroids
- Tiotropium
- Salmeterol
- Formoterol
- Arformoterol
- Salmeterol/fluticasone
- Formoterol/budesonide

None of the existing medications for COPD have been shown to modify the long-term decline in lung function that is the hallmark of this disease.

Pharmacotherapy for COPD is used to decrease symptoms and/or complications.
## Stage I COPD

- Patients with few symptoms may be managed with short-acting bronchodilators
- Bronchodilators improve hyperinflation at rest and during exercise
  - 676 patients with increased total lung capacity (TLC)
  - Significant fall in TLC, RV, FRC and rise in IC following SABA in 76% of moderate and 62% of severe group
  - FEV1 improvement in only 33% of severe hyperinflation and 26% of moderate

*Newton et al. Response of lung volumes to inhaled salbutamol in a large population of patients with severe hyperinflation. Chest 2002;121:10042-1050.*

## Stage II COPD

- Addition of long-acting bronchodilator when dyspnea is not relieved or with increasing use of short-acting bronchodilator
- No specific recommendation on which long-acting bronchodilator to start
- Consideration for pulmonary rehabilitation
Long-acting Beta Agonists

- Beta-2 adrenergic receptor agonists relax airway smooth muscle cells
- First phase of maintenance therapy for COPD
  - Improve symptoms
  - Improve spirometry and inspiratory capacity
  - Improve frequency of exacerbations
  - Improved quality of life
- LABA use is more effective and convenient than treatment with short-acting bronchodilators

Tiotropium

- Anticholinergic bronchodilator with long duration and once daily dosing
  - Decreases number of exacerbations
  - Improves quality of life
  - Improves airflow and FVC
  - Improves dyspnea

Stage III COPD

- Addition of inhaled corticosteroids
  - Reduction in number of exacerbations
  - Improvements in dyspnea
  - Improvements in health status
  - Should not be used as sole therapy
  - Concern that studies show increased incidence of pneumonia in inhaled steroid-treated groups
  - (18.3% steroid vs 12.3% placebo in TORCH trial)


Combination Therapy

- TORCH trial
  - 6,112 patients in 4 groups
  - Placebo, salmeterol, fluticasone, and salmeterol/fluticasone
  - 2.6% absolute reduction of risk of death but p=0.052
  - Reduced exacerbations (NNT=4), improved quality of life, and reduced rate of decline of FEV1

Triple Combination Therapy

- **Tiotropium and Salmeterol/Fluticasone**
  - 2-year INSPIRE study randomized 1,323 patients with mean baseline FEV1 39% predicted
  - Found no difference in exacerbation rate
  - Although a greater proportion of patients receiving salmeterol-fluticasone had pneumonia (8 vs. 4%), this group had lower all-cause mortality (3 vs. 6%, p = .03).


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### Table: Combination Therapies and Primary Efficacy Outcome(s)

<table>
<thead>
<tr>
<th>Combination</th>
<th>Primary Efficacy Outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipratropium and albuterol lump.1-3</td>
<td>Significant improvement in FEV1/lung function and decreased exacerbations compared to either ipratropium or albuterol monotherapy</td>
</tr>
<tr>
<td>Tiotropium and formoterol1</td>
<td>Significant improvement in FEV1/lung function compared to tiotropium alone</td>
</tr>
<tr>
<td>Fluticasone and salmeterol (TORCH trial)5</td>
<td>Reduced all-cause mortality by 17.5% over 3 years compared to either fluticasone or salmeterol monotherapy</td>
</tr>
<tr>
<td>Formoterol and budesonide4</td>
<td>Significant improvement in FEV1/lung function and decreased symptoms compared to either formoterol or budesonide monotherapy</td>
</tr>
<tr>
<td>Tiotropium plus fluticasone and salmeterol7</td>
<td>Did not statistically influence rates of exacerbation compared to tiotropium alone</td>
</tr>
<tr>
<td>Tiotropium plus budesonide and formoterol8</td>
<td>Significantly increased FEV1/lung function compared to tiotropium alone</td>
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Treatment Concerns

• Ipratropium
  ✓ Controversy over increased cardiovascular mortality in patients treated with ipratropium in clinical trials

• Tiotropium
  ✓ No safety issues in UPLIFT trial
  ✓ Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from trials.
  ✓ The most commonly reported adverse drug reaction was dry mouth.

Medical Investigations

• Many ongoing investigations to improve and develop new long-acting bronchodilators

• Indacaterol
  ✓ Recent investigations show this once daily β2-agonist was well tolerated
  ✓ Sustained 24-hour bronchodilation with rapid onset for patients with moderate to severe chronic obstructive pulmonary disease (COPD).
  ✓ Several studies have shown improvements in FEV1 and symptoms
  ✓ Not yet approved by FDA, requiring more dosing studies.
Medical Investigations

- Statins
    - Non-statin users annual decline FEV1 was 23.9 ml
    - Statin users annual decline FEV1 was 10.9 ml
- Selective PDE-4 inhibitors
  - Potential anti-inflammatory action
  - Mixed results with no significant effect in reducing exacerbations or improving quality of life in trials
  - Use limited by side effects
  - Not FDA approved


Other Medical Therapies

- Antioxidant agents
  - No effect of n-acetylcysteine on frequency of exacerbations, except in patients not treated with inhaled glucocorticosteroids
- Mucolytic agents and Antitussives
  - Not recommended in stable COPD
- Theophylline
  - Remains useful in very limited situations
**Vaccinations**

- In COPD patients, influenza vaccines can reduce serious illness (high degree of evidence to support).
- Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older and for COPD patients younger than age 65 with an FEV1 < 40% predicted (less evidence to support but still warranted).

**Antibiotics**

- Only used to treat infectious exacerbations of COPD.
- Macrolides - new data that may decrease exacerbations
  - Randomized, double-blind, placebo-controlled study of erythromycin (250 mg BID) over 12 months.
  - Ratio for exacerbations for macrolide-treated patients compared with placebo-treated patients was 0.648 (95% confidence interval: 0.489, 0.859; P=0.003).
  - Patients also had shorter duration exacerbations compared with placebo.

Oral Corticosteroids

- Chronic treatment with systemic glucocorticosteroids should be avoided because of an unfavorable benefit-to-risk ratio.
- If necessary, use the lowest possible dose to attain benefit.
- Consider screening for bone loss.

COPD: Non-pharmacological Management

Philip Diaz MD
Professor of Internal Medicine
Co-Director COPD Program
You are seeing a 58 y.o. patient with COPD who has progressive dyspnea on exertion. She has a 50 pack year tobacco history, but quit 3 years ago. Her spirometry shows an FEV1/FVC of 50%, and an FEV1 55% of predicted. She is symptomatic despite regular use of a salmeterol inhaler and a prn albuterol inhaler.

Which of the following interventions is likely to provide the greatest improvement in her shortness of breath?

A. Adding inhaled ipratropium.
B. Adding Theophylline.
C. Discontinuation of salmeterol and replacement with tiotoprium.
D. Replacement of salmeterol with salmeterol/fluticasone.
E. Pulmonary rehabilitation.
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C. Discontinuation of salmeterol and replacement with tiotropium.
D. Replacement of salmeterol with salmeterol/fluticasone.
E. Pulmonary rehabilitation.

Am J Respir Crit Care Med 1999
What is pulmonary rehabilitation?

- Multidisciplinary, exercise based program
- Directed at patients with chronic respiratory disease with dyspnea on exertion
- Goal: reduce symptoms, optimize functional status and reduce health care
- Addresses systemic manifestations of disease

Systemic inflammation in COPD

- Chronic inflammation occurs in COPD lungs
- “Spillover” of inflammatory molecules into systemic circulation
- Systemic inflammation responsible for COPD related co-morbidities

Sinden and Stockley, Thorax 2010
Skeletal Muscle Dysfunction and COPD

- Deconditioning
- Systemic inflammation
- Malnutrition
- Hypoxemia

↑ DYSPNEA

↑ pCO₂

↑ Lactic acid

Earlier onset anaerobic metabolism

↓ Mitochondrial oxidative enzymes

↓ Capillary density

Deconditioning

Hyperinflation/air-flow obstruction

Increased load and decreased efficiency of respiratory muscles

Increased lactate production during exercise

Dyspnea on exertion

Decreased oxidative capacity of skeletal muscle enzymes

Anxiety/Depression

Intervention with pulmonary rehab
Pulmonary Rehab: Main Components

- Lower extremity endurance training
- Upper extremity strength and endurance training
- Inspiratory muscle training
- Breathing retraining
- Education
- Psychosocial counseling
Lower Extremity Endurance Training

![Image of people exercising]

**FIGURE 3.** Shortness of breath measured by effect size of each trial. *p* values for test of heterogeneity.

J Gen Intern Med 2003; 18:213-221
Effects of Pulmonary Rehab at 1 Year

<table>
<thead>
<tr>
<th></th>
<th>Control Rehab</th>
<th>P value</th>
<th>Pulmonary Rehab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths (n)</td>
<td>12</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalized (n)</td>
<td>41</td>
<td>40</td>
<td>NS</td>
</tr>
<tr>
<td>Admissions/pt</td>
<td>2.2</td>
<td>1.7</td>
<td>.048</td>
</tr>
<tr>
<td>Hospital days (n)</td>
<td>21.0</td>
<td>10.4</td>
<td>.022</td>
</tr>
</tbody>
</table>

Griffiths et al; Lancet 2000;355:362-368

Pulmonary Rehabilitation for COPD: Summary

- Consider for all patients with dyspnea on exertion despite regular inhaler use
- Exercise based: ~3 times/week for 8-12 weeks
- Main benefits:
  - Alleviation of dyspnea
  - Improved exercise tolerance
Presentation Outline

- Pulmonary rehabilitation
- Supplemental oxygen
- Surgical options

Your patient with COPD, hospitalized with an acute exacerbation is ready for discharge. At rest on room air his O2 saturation is 94%. Walking around the nurses station several times he is not short of breath, but his O2 sat drops to 86%. As part of his discharge you should:

1. Recommend supplemental oxygen 2 liters/min 24 hours a day
2. Recommend supplemental oxygen 2 liters/min with exertion
3. Recommend supplemental oxygen 2 liters/min with exertion and while sleeping
4. Do not recommend supplemental oxygen; recheck oxygen saturation in the office in 2-4 weeks
Your patient with COPD, hospitalized with an acute exacerbation is ready for discharge. At rest on room air his O2 saturation is 94%. Walking around the nurses station several times he is not short of breath, but his O2 sat drops to 86%. As part of his discharge you should:

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Supplemental O2 in the US

- ~ 1 million users
- ~ 2 billion dollars/year
- Cost increasing by 12-13%
- ~ 75% of Medicare’s outpatient costs for COPD
Rationale for supplemental oxygen in COPD

- Nocturnal Oxygen Therapy Trial (*Annals Internal Medicine 1980*)
  - COPD patients with severe resting hypoxemia
    - pO2 ≤ 55 mmHg
    - pO2 ≤ 59 mmHg
      - With polycythemia, edema or P pulmonale
  - Randomized to nocturnal oxygen vs 24 hour continuous oxygen

*Annals Internal Medicine 1980: Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease*
Criteria for Insurance Reimbursement for Supplemental Oxygen

- Patients with severe resting hypoxemia
  - \( pO2 \leq 55 \text{ mmHg} \) or \( O2 \text{ sat} \leq 88\% \)
  - \( pO2 \leq 59 \text{ mmHg} \)
    - With polycythemia, edema or \( P \) pulmonale
- Oxygen desaturation \( \leq 88\% \) with exertion or while sleeping
  - Use of oxygen under these conditions not evidence based and of unclear benefit

Long Term Oxygen Treatment Trial (LOTT)

- Multicenter study funded by NIH and CMS
- Patients randomized to supplemental O2 or no O2
- Outcomes tracked: mortality, hospitalizations, quality of life
- Eligibility
  - COPD
  - Age > 40
  - Resting O2 sat 89-93\% or
  - O2 sat 80 – 89\% with exertion
Supplemental O2 for COPD recommendations:

- Prescribe 24/day for patients with:
  - Severe resting hypoxemia
    - pO2 < 55 mmHg or O2 sat < 88%
    - pO2 < 59 mmHg
      - With polycythemia, edema or P pulmonale
- Discuss as a treatment option in symptomatic patients without severe resting hypoxemia
  - Oxygen desaturation ≤ 88% with exertion or while sleeping
    - Consider as a therapeutic trial to address exertional dyspnea or daytime fatigue

Presentation Outline

- Pulmonary rehabilitation
- Supplemental oxygen
- Surgical options
Your 64 y.o. emphysema patient with severe obstruction (FEV1 = 36% of predicted) and hyperinflation (residual volume = 240% of predicted) has dyspnea with minimal exertion despite maximal medical management, including supplemental oxygen and a course of pulmonary rehabilitation. He is asking for a referral for possible surgical management of his emphysema. Which would be the most appropriate procedure to consider?

1. Placed of bronchial valves endoscopically
2. Lung volume reduction surgery
3. Lung transplantation
COPD: “Surgical” Options

- Endoscopic placement of bronchial valves
  ✓ Slight improvement in symptoms, but increased exacerbation rate (Sciurba NEJM 2010)

- Lung volume reduction surgery
  ✓ Improved symptoms, exercise tolerance and survival in carefully selected patients
  ✓ Best candidates: upper lobe predominant emphysema

- Lung Transplant
  ✓ Consider for very advanced patients (FEV1 <25% of predicted, elevated pCO2, pulmonary hypertension)

Lung reduction Surgery and Emphysema

Emphysematous upper lung zones

Protocol: Median sternotomy or bilateral video-assisted thoracoscopic. Target areas identified by CT scan and perfusion scan. ~30% of each lung removed by a stapling technique.

More normal lower lung zones

COPD and non-pharmacologic management: take home points

- Consider pulmonary rehabilitation for all COPD patients with dyspnea on exertion
- The scientific basis for supplemental oxygen therapy in COPD is strongest for patients with severe rest hypoxemia
- Surgical options may be appropriate for selected patients with advanced disease