COPD: Strategies for Diagnosis and Effective Management
Learning Objectives

• List the critical goals of COPD management

• Outline the recommended therapies for stable and exacerbated COPD

• Identify patients and conditions for which referral is appropriate
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**Target Audience**
Primary care physicians, nurse practitioners, and physician assistants

**Grant Support**
This program is supported by an educational grant from Boehringer Ingelheim and Pfizer Inc.
Planning Committee Disclosures

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Julie White has nothing to disclose.

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Roy C. Blank, MD, is on the speakers’ bureaus for Merck, Pfizer Inc., and Takeda Pharmaceutical Company Ltd.

Dr. Blank does not plan to discuss off-label/investigational uses of products.

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Dennis E. Niewoehner, MD, serves as a consultant for, receives grant support from, and is on the speakers’ bureaus for Boehringer Ingelheim and Pfizer Inc.; and serves as a consultant for Adams Respiratory Therapeutics, Forest Laboratories, and GlaxoSmithKline.

Dr. Niewoehner plans to discuss off-label/investigational uses of formoterol, salmeterol, or tiotropium for managing exacerbations of COPD.
Data from Your Chart Review

Lara Zisblatt, MA
Assistant Director
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Boston, Massachusetts
Participants in the Program

• 205 people registered
• 71 people started the program
• 43 people started their initial chart review
• 16 people completed their initial chart review
• 15 people submitted their action plans and are awaiting their follow-up chart review
Participants Data

- Average confidence level in treating COPD: 6.3

- Treatment:

  27.45% (n=28) of patients with moderate, severe, or very severe COPD with symptoms are NOT on long-acting bronchodilators

  8% (n=9) of patients with moderate, severe, or very severe COPD with symptoms are NOT on any inhaled bronchodilators

  6.8% (n=7) of patients with moderate, severe, or very severe COPD with symptoms are NOT on pharmacotherapy
COPD Project

• Please complete chart reviews as soon as possible
• If you are having trouble completing the chart reviews, please let us know. We can help!
• If you have any questions, please e-mail us at mentorqi@bu.edu
COPD: Management of Stable and Exacerbated Disease

Dennis E. Niewoehner, MD
Professor of Medicine
University of Minnesota
Minneapolis, Minnesota
Treatment of COPD According to Spirometric Stage of Disease

I: Mild
- \( \text{FEV}_1/\text{FVC} < 0.70 \)
- \( \text{FEV}_1 \geq 80\% \text{ predicted} \)

Add long-term oxygen if chronic respiratory failure.
Consider surgical treatments.

II: Moderate
- \( \text{FEV}_1/\text{FVC} < 0.70 \)
- \( 50\% \leq \text{FEV}_1 < 80\% \text{ predicted} \)

Add inhaled glucocorticosteroids if repeated exacerbations.
Add regular treatment with one or more long-acting bronchodilators (when needed).
Add rehabilitation.

III: Severe
- \( \text{FEV}_1/\text{FVC} < 0.70 \)
- \( 30\% \leq \text{FEV}_1 < 50\% \text{ predicted} \)

Add short-acting bronchodilator (when needed).

IV: Very Severe
- \( \text{FEV}_1/\text{FVC} < 0.70 \)
- \( \text{FEV}_1 < 30\% \text{ predicted} \)

Active reduction of risk factor(s); influenza vaccination.
Add regular treatment with one or more long-acting bronchodilators (when needed).
Add rehabilitation.

COPD = chronic obstructive pulmonary disease; \( \text{FEV}_1 = \) forced expiratory volume (in liters) in 1 second; \( \text{FVC} = \) forced vital capacity.
Goals of COPD Management

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

Reduction in Exacerbations: Inhaled Corticosteroids

ICS = inhaled corticosteroids; CI = confidence interval.
Reduction in Exacerbations: Inhaled Long-acting Beta-Agonists*

*Salmeterol

- Mahler 2002
- Brusasco
- Calverley 1
- Celli
- Chapman
- Rennard
- Van Noord
- Mahler 1999
- Boyd
- Subtotal

*Formoterol

- Calverley 2
- Aalbers
- Rossi
- Wadbo
- Dahl
- Szafranski
- Subtotal
- Total

Relative Risk (95% CI) of Exacerbation:

- Favors LABA
  - Mahler 2002
  - Brusasco
  - Calverley 1
  - Celli
  - Chapman
  - Rennard
  - Van Noord
  - Mahler 1999
  - Boyd
  - Subtotal
- Favors Placebo
  - Calverley 2
  - Aalbers
  - Rossi
  - Wadbo
  - Dahl
  - Szafranski
  - Subtotal
  - Total

0.2 0.5 1 2 5

0.81 (0.73 – 0.90)
0.84 (0.74 – 0.97)
0.82 (0.76 – 0.90)

*Off-label indication.


LABA = long-acting beta-agonists.
VA Tiotropium Trial: Primary Outcomes*

- **≥1 Exacerbation (%):**
  - Placebo: 32.2%
  - Tiotropium: 27.9%
  - *P = .037*

- **≥1 COPD Hospitalization (%):**
  - Placebo: 9.5%
  - Tiotropium: 7.0%
  - *P = .056*

*Off-label indication.
VA = Veterans Administration.
Reduction in Hospitalizations:
Tiotropium vs. Placebo, Ipratropium, or LABA

Reference
Brasasco et al, 2003
Casaburi et al, 2002
Niewoehner et al, 2005

Summary effect—placebo
Vincken et al, 2002
Summary effect—ipratropium
Brasasco et al, 2003
Summary effect—salmeterol

LABA = long-acting beta-agonist.

In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. 
Salmeterol for Stable COPD

FEV\(_1\) = forced expiratory volume in 1 second.

Mean FEV$_1$ Before (24-hour baseline) and After 2 Weeks of Treatment (Day 14)

- **Tiotropium QD + formoterol BID**
- **Tiotropium QD + formoterol QD**
- **Tiotropium QD + placebo BID**
- **24-h baseline**

Tiotropium Plus Formoterol

Patients (%) with exacerbations

\[ P = .006 \]

Arievich, et al. European Respiratory Society Congress; Munich, Germany; September 2-6, 2006.
Tiotropium Plus ICS or LABA

Exacerbations (per Patient-Year)

ICS = inhaled corticosteroids; PBO = placebo; LABA = long-acting beta-agonist.

Fluticasone plus Salmeterol

FEV₁ at baseline and during 24 weeks

$\Delta FEV₁$ (mL)

Time (Weeks)

Placebo

Salmeterol

Fluticasone

Salmeterol + Fluticasone

$P < .05$ for fluticasone/salmeterol vs. salmeterol, fluticasone, and placebo

$P < .05$ for salmeterol and fluticasone vs. placebo

Budesonide plus Formoterol

FEV₁ at baseline and during 12 months

Fluticasone plus Salmeterol

Mean number of exacerbations/year

- Placebo: 1.13
- SALM: 0.97* (25% reduction)
- FP: 0.93* (25% reduction)
- SFC: 0.85** (25% reduction)

*P < .001 vs. placebo; †P = .002 vs. SALM; ‡P = .024 vs. FP.

SALM = salmeterol; FP = fluticasone propionate; SFC = salmeterol plus fluticasone.

Fluticasone plus Salmeterol Mortality in TORCH

TORCH = Towards a Revolution in COPD Health.
Exacerbations — OPTIMAL Trial

Patients (%) with ≥1 exacerbation

- Tiotropium
- Tiotropium + Salmeterol
- Tiotropium + Salmeterol + Fluticasone

Changes in Lung Function Over Time: OPTIMAL Trial

Tio = tiotropium; Salm = salmeterol; Flut = fluticasone.

AECOPD: Definition

- “A sustained worsening of the patient’s [respiratory] condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD”


- Duration 24 hours to 2 weeks

- Exclusion of other causes
  - Pneumonia
  - Congestive heart failure
  - Pulmonary embolism
  - Others

AECOPD = acute exacerbations of chronic obstructive pulmonary disease.
Antibiotics for COPD Exacerbations: Do They Work?

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alonso 1992</td>
<td>0.67 (0.56–0.80)</td>
</tr>
<tr>
<td>Anthonisen 1987</td>
<td>0.80</td>
</tr>
<tr>
<td>Elmes 1965</td>
<td>0.10</td>
</tr>
<tr>
<td>Jorgensen 1992</td>
<td>0.67</td>
</tr>
<tr>
<td>Pines 1968</td>
<td>0.50</td>
</tr>
<tr>
<td>Pines 1972</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>0.67 (0.56–0.80)</strong></td>
</tr>
</tbody>
</table>

CI = confidence interval.
AECOPD: Etiology

80% infectious
- Bacterial pathogens
  - 40%-50%
- Viral infection
  - 30%-40%
- Atypical bacteria
  - 5%-10%

20% noninfectious
- Environmental factors
- Noncompliance with medications

Antibiotics for COPD Exacerbations: Is One Better than Another?

Recent Guideline Recommendations for Antibiotic Therapy in AECOPD

- ATS/ERS—“May be initiated in patients with altered sputum characteristics”
- CTS—“…antibiotics should only be considered for use in patients with purulent exacerbations”
- ERS—Anthonisen I, Anthonisen II with sputum purulence, severe AECOPD
- GOLD—“Antibiotics are only effective…with worsening dyspnea and cough . . . also have increased sputum volume and purulence”
- NICE—“Antibiotics should be used to treat exacerbations of COPD associated with a history of more purulent sputum”

SCCOPE: Time to First Treatment Failure

Meta-analysis Confirms Benefit of Systemic Steroid Use in AECOPD

- 9 studies with 921 participants
  - Corticosteroids reduced treatment failure
    - OR 0.48 (95% CI, 0.34-0.68)
  - Corticosteroids improved FEV$_1$
    - 5.14% predicted (95% CI, 0.64-9.6)
  - Corticosteroids did not impact mortality
    - OR 0.85 (95% CI, 0.45-1.59)
  - Corticosteroids were associated with increased adverse reactions
    - OR 2.28 (95% CI, 1.56-3.34)

OR = odds ratio.
Guidelines for Management of AECOPD

I. Uncomplicated AECOPD
- Age <65
- FEV$_1$ >50% predicted
- <4 AECOPDs/y
- No comorbidity

II. Complicated AECOPD
- Age >65
- FEV$_1$ <50% predicted
- >4 AECOPDs/y
- Comorbidity
- ABX use in past 3 mo

III. Complicated AECOPD at risk for *Pseudomonas*
- FEV$_1$ <35% predicted
- Recurrent antibiotics
- Recurrent steroid courses
- Bronchiectasis

Macrolide
Ketolide
Doxycycline
Second- or third-generation cephalosporin
Respiratory quinolone

Respiratory quinolone
Amoxicillin/clavulanate

Quinolone with antipseudomonal activity

ABX = antibiotics.
COPD: When to Refer

Roy Blank, MD
Southern Piedmont Primary Care
Monroe, North Carolina
Considerations for COPD Referral

• Moderate to severe COPD
  – Beyond comfort level of treating provider
  – Progressive downhill course despite optimal therapy
    ▪ Rapid deterioration
  – Etiology other than tobacco abuse
    ▪ Alpha-1 antitrypsin deficiency
  – Unacceptable quality of life
  – Cor pulmonale; secondary pulmonary hypertension
  – Hypercapnea
  – Consideration of surgical intervention

COPD = chronic obstructive pulmonary disease.
Surgical Treatments

- Resection of giant bullae
- Lung volume reduction surgery
- Lung transplantation
Resection of Giant Bullae

- Resection of giant bullae
  - Indications
    - Large bulla occupying at least 30% of hemithorax
    - Bulla + pneumothorax
  - Predictive factors for favorable outcome
    - Rapid progressive dyspnea
    - >10% weight loss
    - Normal or slightly reduced FVC
    - FEV$_1$ >40%
    - Normal ABGs
    - Bulla >1/3 hemithorax
    - Absence of cor pulmonale
    - Younger age
    - Vascular crowding around bulla

FVC = forced vital capacity; FEV$_1$ = forced expiratory volume (in liters) over 1 second; ABGs = arterial blood gases.
Resection of Giant Bullae (Cont’d)

- Resection of giant bullae
  - Preoperative evaluation
    - CXR; CT chest
    - Measurement of lung volumes by body plethysmography and helium dilution techniques
    - Measurement of diffusion capacity
    - Echocardiogram

CXR = chest x-ray; CT = computed tomography.
Lung Volume Reduction Surgery

- Lung volume reduction surgery
  - Proposed as palliative treatment for severe emphysema
  - Surgical technique that reduces lung volumes by multiple wedge resections
  - Mechanism of benefit is not known for certain
  - Other techniques under investigation
    - Bronchoscopic lung volume reduction
      - Airway occlusion with fibrin-based glue
      - Endobronchial one-way valves
• Lung volume reduction surgery
  – Patient selection
    ▪ Preoperative nonpredictors
      ➢ FEV$_1$, RV, TLC, DLCO, PaO$_2$, PaCO$_2$
    ▪ Predictors of benefit
      ➢ Upper lobe heterogeneous pattern of emphysema on thoracic CT scan
      ➢ Upper lobe pattern of heterogeneous emphysema on perfusion lung scan

RV = residual volume; TLC = total lung capacity; DLCO = diffusing lung capacity for carbon monoxide; PaO$_2$ = partial pressure of oxygen in arterial blood; PaCO$_2$ = partial pressure of carbon dioxide in arterial blood.

Lung Volume Reduction Surgery (Cont’d)

• Lung volume reduction surgery
  – National Emphysema Treatment Trial (NETT)
    ▪ Randomized medical vs. surgical therapy
    ▪ N = 1,218
    ▪ Severe emphysema
    ▪ 6 months of mandatory pulmonary rehabilitation followed by randomization
    ▪ Results published early due to data safety monitoring board concerns of excess mortality in the high-risk group

Lung Volume Reduction Surgery (Cont’d)

- Lung volume reduction surgery
  - National Emphysema Treatment Trial (NETT)
    - High risk; stopped randomization
      - FEV$_1$ <20% predicted
      - DLCO <20% predicted
      - Homogeneous changes on chest CT
    - Additional subsets
      - Upper lobe predominant and high exercise capacity
        » Symptomatic benefit without mortality benefit
      - Upper lobe predominant and low exercise capacity; <40th percentile
        » 47% RRR short-term mortality
        » 57% RRR long-term mortality
        » Improved exercise capacity and health-related quality of life

RRR = relative risk reduction.
• **Appropriate age**
  - **Upper age limits**
    - Heart-lung transplant: Age 55
    - Single lung transplant: Age 65
    - Bilateral lung transplant: Age 60

• **Clinical and physiologically severe disease**

• **Ineffective medical therapy**

• **Limited life expectancy due to lung disease**

• Acceptable nutritional status; 80%-120% ideal body weight; BMI <30

• Satisfactory psychosocial profile and support system

• Adequate financial coverage
American Thoracic Society
Transplantation Guidelines (Cont’d)

- **Contraindications to transplant**
  - Uncontrolled pulmonary or extrapulmonary infection
  - Malignancy in past 2 years
  - Significant CAD or CHF
  - Significant chest wall/spinal deformity
  - Active tobacco smoking
  - Drug or alcohol dependency
  - Medical noncompliance
  - HIV infection
  - Active hepatitis B or C infection
  - Absence of a consistent or reliable social support system

Guidelines for timing referral for lung transplant for COPD and alpha-1 antitrypsin deficiency include:

- BODE index >5
- Postbronchodilator FEV$_1$ <25% predicted
- Resting PaO$_2$ <55-60 mmHg
- DLCO <20% predicted
- Hypercapnia
- Secondary pulmonary hypertension
- Accelerated decline in FEV$_1$

BODE = body mass index (B), percentage of predicted FEV$_1$ (O), dyspnea (D), and the 6-min walk distance (E).

BODE Index

- Use calculator for COPD survival prediction
  - BMI
  - $\text{FEV}_1$
  - 6-minute walk distance
  - Dyspnea scale

BMI = body mass index.
COPD Referral: Potential Patients

• Patients who
  – Have worsening clinical course
  – Have impaired quality of life
  – Are surgical candidates
Discussion/Questions