Enhancing Patient Diagnosis and Management of COPD:
A Case-Based Review

June 23, 2012
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Educational Partner:
CME Incite, LLC
Session 1: Enhancing Patient Diagnosis and Management of COPD: A Case-Based Review

Learning Objectives

1. Prevent COPD exacerbations by recognizing the clinical factors that put patients at risk by improving early recognition and intervention.
2. Stratify COPD severity and develop individualized treatment plans on the basis of spirometry results.
3. Tailor both initial and maintenance therapies for COPD according to the standards set by evidence-based guidelines.

Faculty

Stephen I. Rennard, MD
Larson Professor of Internal Medicine
Division of Pulmonary, Critical Care, Sleep and Allergy
University of Nebraska Medical Center
Omaha, Nebraska

Stephen Rennard, MD, is Larson Professor of Medicine in the pulmonary and critical care medicine section of the department of pathology and microbiology and the department of genetics, cell biology, and anatomy at the University of Nebraska Medical Center in Omaha. He received an AB with honors in folklore and mythology from Harvard University and an MD with honors from the Baylor College of Medicine in Houston, Texas. He completed internal medicine training at Barnes Hospital, Washington University, in St. Louis, Missouri, and trained in pulmonary diseases at the National Institutes of Health, where he remained for seven years, conducting research in the cell biology of lung disease.

Dr Rennard currently serves on the board of directors of the COPD Foundation and the Alpha-1 Foundation. He is a member of the National Heart Lung Education Program Executive Committee and is the chair of the steering committee for SPIROMICS. He is an external advisor to the Thomas Petty Aspen Lung Conference and the University of California, Davis Pulmonary Training Grant.

Dr Rennard maintains an active program of clinical investigation in COPD and smoking cessation and a program of basic research in the mechanisms of lung tissue repair and remodeling, including the role of stem cells in disease pathogenesis and repair.

Fernando J. Martinez, MD, MS
Professor, Department of Internal Medicine
Director, Pulmonary Diagnostic Services
University of Michigan
Ann Arbor, Michigan

Fernando J. Martinez, MD, MS, is professor of internal medicine, associate chief for clinical research in the division of pulmonary and critical care medicine, director of pulmonary diagnostic services, and co-medical director of lung transplantation at the University of Michigan Health System, Ann Arbor, Michigan. After graduating from the University of Florida School of Medicine, he completed his residency in internal medicine at Beth Israel Hospital and his fellowship in pulmonary medicine at the Boston University Pulmonary Center.

Dr Martinez’s main research interests include chronic obstructive pulmonary disease (COPD), interstitial lung disease, lung transplantation, and lung volume reduction. Currently, he is a member of numerous societies, including the American Thoracic Society, the European Respiratory Society, American College of Chest Physicians, and the Fleischner Society. Previously, he was a member of the American Thoracic Society committees that generated guidelines for the management of COPD, respiratory infections, and cardiopulmonary exercise testing and is the former chair of the Clinical Problems Assembly of the American Thoracic Society. He is currently a member of the GOLD Executive and Science Committees. Dr Martinez sits on a number of editorial boards, including those for the Journal of COPD and American Journal of Respiratory and Critical Care Medicine.
**Faculty Financial Disclosure Statements**

The presenting faculty report the following:

Dr Rennard serves as a speaker for AARC; Almirall; American College of Osteopathic Physicians; Asan Medical Center; American Thoracic Society; California Society of Allergy; CME Incite; COPD Foundation; Creative Educational Concepts; Dey; Duke University; Forest; France Foundation; HSC Medical Education; Information TV; American Lung Association; Novartis (Horsham); Nycomed; Otsuka; PeerVoice; Pfizer; Shaw Science; University of Washington; University of Alabama Birmingham; and VA Sioux Falls. He is a consultant for ABIM; Able Associates; Adelphi Research; Align2Action; Almirall/Prescott; APT Pharma/Britnall; AstraZeneca; American Thoracic Society; Beilenson; Boehringer Ingelheim; Boehringer Ingelheim (ACCP); BoomCom!; Britnall and Nicolini; Capital Research; Chiesi; Clarus Acuity; Common Health; Complete Medical Group; ConsultComplete; COPDForum; DataMonitor; Decision Resources; Dunn Group; Easton Associates; Equinox; Forest; Frankel Group; Fulcrum; Gerson Lehrman; Globe Life Sciences; GlaxoSmithKline; Guidepoint; Health Advances; Hoffmann-La Roche; InforMed; Insyght; KOL Connection; Leerink Swann; M. Pankove; McKinsey; MDRx Financial; MedImmune; Merek; Novartis; Nycomed; Oriel; Osterman; Pearl; Penn Technology; Pennside; Pfizer; PharmaVentures; Pharmaxis; Prescott; PricewaterhouseCoopers; Propagate; Pulmonary Reviews; Pulmatrix; J. Reckner Associates; Recruiting Resource; Roche; Sankyo; Schering; Schlesinger Medical; SciMed; Smith Research; Sudler & Hennessy; Summer Street Research; Talecris; Think Equity; UBC; Uptake Medical; and Vantage Point Management.

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**Education Partner Financial Disclosure Statement**

The content collaborators at CME Incite report the following:

Priya Wanchoo, MBBS, has no financial relationships to disclose.

**Suggested Reading List**


Drug List

- Generic
  - Tiotropium
  - Formoterol
  - Theophylline
  - Albuterol
  - Ipratropium
  - Terbutaline
  - Albuterol/ipratropium
  - Roflumilast
  - Aclidinium bromide
    (Phase III)
  - Azithromycin

- Trade
  - Spiriva
  - Foradil
  - Various
  - N/A
  - Daxas, Daliresp
  - Zithromax

Enhancing Patient Diagnosis and Management of COPD: A Case-Based Review

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Division of Pulmonary, Critical Care, Sleep and Allergy
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Pretest Question
?
To make a definitive diagnosis of COPD, which of the following is the most important factor that would lead you to an accurate diagnosis?

1. An abnormal spirometry test
2. The patient’s history of smoking
3. A chest x-ray that shows flattening of the diaphragm and focal bullae
4. Decreased functional capacity on the 6-minute walk test

Pretest Question
?
A 53-year-old white male presents for his annual visit. Although he quit 10 years ago, he is a previous cigarette smoker with a 20 pack-year history. During the past 12 months, he has had 3 episodes of bronchitis. You perform a spirometry and the results show FEV1/FVC=0.6, and the FEV1 is 67% of predicted. How would you classify his COPD?

1. Mild COPD
2. Moderate COPD
3. Severe COPD
4. Not sure

Pretest Question
?
When a patient progresses from moderate to severe classification of COPD, what would be the most appropriate addition to their current treatment regimen?

1. Theophylline
2. PDE4 inhibitor
3. Short-acting β2-agonist
4. Long-acting β2-agonist
5. None of the above

Pretest Question
?
Which of the following goals can be achieved with current pharmacotherapy?

1. Improved exercise tolerance
2. Partial disease regression
3. Reduction of exacerbations
4. All of the above
5. 1 and 3 only
Case Study 1: Meet Sam

Patient: Sam
- Age: 52
- Race: Caucasian
- Occupation: Accountant
- Marital Status: Married
- Lifestyle: Social smoker but used to smoke a pack a day for 10 years

Relevant Medical History
- Reports having bronchitis a couple of times a year for the past several years. Breathlessness on physical exercise

Current Medications
- Has been treated episodically with antibiotics for his bronchitis

Smoking Cessation Slows Disease Progression: Observational Study

Inflammation in Small Airways at Different Stages of COPD Severity

Mechanisms of Airflow Limitation in COPD

ARS Question

What tests would you order for Sam?
1. Chest x-ray
2. Spirometry
3. Pulse oximetry
4. None, refer to pulmonologist
Assess: Who Has Early-Stage COPD and Who Do You Test?

- Test patients with:
  - Chronic cough and sputum
  - Exposure to risk factors
  - Even if no dyspnea

- Early stage:
  - Airflow limitation that is **not fully reversible**
  - With or without the presence of symptoms

Assess for COPD: A Common Story

- Cough
  - Intermittent or daily
  - Present throughout day; seldom only nocturnal

- Sputum
  - Any pattern of chronic sputum production

- Dyspnea
  - Progressive and persistent
  - "Increased effort to breathe," "heaviness," "air hunger," or "gasping"
  - Worse on exercise
  - Worse during respiratory infections

- Exposure to risk factors
  - Tobacco smoke
  - Occupational dusts and chemicals
  - Smoke from home cooking and heating fuels

Assess: Physical Examination

- Rarely diagnostic in COPD
- Physical signs of airflow limitation
  - Rarely present until significant impairment of lung function
  - Low sensitivity and specificity

Assess: Spirometry to Diagnose

Why do office spirometry?

- Diagnostic accuracy: 30% of time diagnosis changes
  - COPD
  - Not COPD
  - Heart failure
  - Asthma
  - Restrictive lung disease
  - Normal: Expensive meds discontinued

- Respect: Patients respect physicians who use technology (future of family medicine)
- Patient convenience: You can avoid an unnecessary referral and additional visit
- Diagnostic power: You can connect diagnostic information with rest of clinical encounter
- Financial benefit to practice

ARS Question

In terms of using spirometry in your practice, which is the biggest challenge you face?

1. Limited by availability of the equipment
2. Time constraints
3. Difficulty with interpreting the test
4. Unfamiliar with spirometric classification of COPD severity

Measurements

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Characteristic measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>Forced expired volume in 1 second</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>FEV₁/FVC Ratio</td>
<td>Ratio of the above</td>
</tr>
<tr>
<td>PEFR</td>
<td>Peak expiratory flow rate</td>
</tr>
</tbody>
</table>
Spirometry: Normal and COPD

Assess: Measure Airflow
- Postbronchodilator FEV₁ <80% predicted + FEV₁/FVC <70% confirms the presence of airflow limitation that is not fully reversible

Category Characteristics
I: Mild COPD
- FEV₁ ≥ 80% predicted
II: Moderate COPD
- FEV₁ ≤ 50% predicted
- FEV₁ <80% predicted
III: Severe COPD
- FEV₁ ≥ 30% predicted
- FEV₁ <50% predicted
IV: Very severe COPD
- FEV₁ <30% predicted

Classif ication of Severity of Airflow Limitations COPD (GOLD 2011)

Assess: Medical History in Those With Established Disease
- Exacerbations or hospitalizations?
- Comorbidities that contribute to restriction of activity
- Appropriateness of current medical treatments
- Impact of disease on patient’s life
  - Limitation of activity
  - Missed work and economic impact
  - Effect on family routines
  - Depression or anxiety
  - Dyspnea
- Social and family support
- Possibilities for reducing risk factors, especially smoking


Sam’s Spirometry Results

<table>
<thead>
<tr>
<th></th>
<th>Prebronchodilator</th>
<th>Postbronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>2.02</td>
<td>2.27</td>
</tr>
<tr>
<td>FVC</td>
<td>3.85</td>
<td>4.26</td>
</tr>
<tr>
<td>FEV₁/FVC Ratio</td>
<td>52%</td>
<td>53%</td>
</tr>
</tbody>
</table>
ARS Question

What is Sam’s diagnosis?
1. Asthma
2. COPD
3. Reactive airway disease
4. Bronchitis

Clinical Features Differentiating COPD and Asthma

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker or ex-smoker</td>
<td>Nearly all</td>
<td>Possibly</td>
</tr>
<tr>
<td>Symptoms when aged younger than 35 years</td>
<td>Rare</td>
<td>Often</td>
</tr>
<tr>
<td>Chronic productive cough</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>Persistent and progressive</td>
<td>Variable</td>
</tr>
<tr>
<td>Nighttime waking with SOB and/or wheezing</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Atopic symptoms and seasonal allergies</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Significant diurnal variability</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Favorable response to ICS</td>
<td>Inconsistent</td>
<td>Consistent</td>
</tr>
</tbody>
</table>

Clinical Features COPD Asthma

Smoker or ex-smoker
Symptoms when aged younger than 35 years
Chronic productive cough
Breathlessness
Nighttime waking with SOB and/or wheezing
Atopic symptoms and seasonal allergies
Significant diurnal variability
Favorable response to ICS

Differential Diagnosis (Aside From Asthma)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Signs/Symptoms</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>Fine basilar crackles</td>
<td>CXR, PFTs, echo</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Large volumes purulent sputum, repeated infections</td>
<td>CT scan, PFTs</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Onset at any age</td>
<td>CXR, sweat test, genetic testing</td>
</tr>
<tr>
<td>Bronchiolitis obliterans</td>
<td>Onset earlier age, nonsmokers, Hx RA, fume exposure</td>
<td>CT scan</td>
</tr>
<tr>
<td>Diffuse panbronchiolitis</td>
<td>Mostly male and nonsmokers, chronic sinusitis in almost all</td>
<td>CXR, HRCT</td>
</tr>
</tbody>
</table>

COPD: Systemic Consequences/Comorbidities*

- Physical deconditioning
- Exercise intolerance
- Skeletal muscle dysfunction
- Osteoporosis
- Atherosclerotic cardiovascular disease
- Metabolic syndrome
- Anemia
- Anxiety and depression
- Lung cancer

*Mechanistic factors: Systemic inflammation and physical inactivity

Lung Volumes: Air-Trapping and Hyperinflation in COPD


Operating Lung Volumes at Rest and During Exercise

Normal Predose COPD Postdose

Global Strategy for Diagnosis, Management, and Prevention of COPD Diagnosis and Assessment: Key Points

- A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease
- Spirometry is required to make the diagnosis; the presence of a postbronchodilator FEV₁/FVC <0.70 confirms the presence of persistent airflow limitation and thus of COPD

Sam’s Diagnosis: COPD

- FEV₁/FVC ratio is low
- FVC and FEV₁ were partially reversible with a beta agonist, but are still substantially reduced from normal and the ratio is <0.70
- Spirometry results, in conjunction with Sam’s signs, symptoms, and history, suggest that COPD is the correct diagnosis

Goals for Treatment of Stable COPD

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

Treatment Strategies and Reducing the Risk of Exacerbation

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Ann Arbor, Michigan

Case Study 2: Meet George

<table>
<thead>
<tr>
<th>Patient: George</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: 62</td>
</tr>
<tr>
<td>Race: African American</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed with COPD 5 years ago</td>
</tr>
<tr>
<td>Previously smoked about 20 cigarettes a day but cut down to 10 after his last exacerbation. Can't quit</td>
</tr>
<tr>
<td>HT and hypercholesterolemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presenting Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening dyspnea, cough, purulent sputum over the past 3 days</td>
</tr>
<tr>
<td>Auscultation of the chest reveals scattered expiratory wheeze</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium</td>
</tr>
<tr>
<td>Albuterol PRN</td>
</tr>
</tbody>
</table>

Initial Treatment Considerations

- Encouragement of smoking cessation
- Individual pharmacologic therapy recommendation based on severity, drug availability, and patient response
- Influenza and pneumococcal vaccination offered to every patient
- Patients who get short of breath easily should be offered rehabilitation, as it can:
  - Improve symptoms
  - Increase quality of life
  - Enhance physical and emotional participation in everyday activities
Therapeutic Options for COPD: Formulations and Duration of Action

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Inhaled</th>
<th>Nebulizer Solution</th>
<th>Oral</th>
<th>Duration of Action, Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>β₂-agonists</td>
<td>Short-acting</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Long-acting</td>
<td>X</td>
<td>X</td>
<td>(transdermal)</td>
</tr>
<tr>
<td>Combination short-acting β₂-agonists plus anticholinergic in 1 inhaler</td>
<td>Short-acting</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>Long-acting</td>
<td>X</td>
<td>X</td>
<td>Up to 24</td>
</tr>
<tr>
<td>Combination long-acting β₂-agonists plus anticholinergic in 1 inhaler</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphodiesterase-4 inhibitors</td>
<td>X</td>
<td>24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Smoking Cessation Modalities for Patients With COPD

- Nicotine replacement therapy
  - Transdermal system
  - Gum
  - Lozenge
  - Inhaler
  - Nasal spray
- Bupropion
- Varenicline

Continuous Abstinence Weeks 9-12 in COPD, Cardiovascular Disease, and Phase 3 Trials

Varenicline: Most Common Adverse Events

From 12-Week, Fixed-Dose, Placebo-Controlled Studies

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Varenicline 0.5 mg BID, % (n=129)</th>
<th>Varenicline 1.0 mg BID, % (n=221)</th>
<th>Placebo, % (n=805)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>16</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Insomnia*</td>
<td>19</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>9</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

*Includes preferred terms: Insomnia/initial, insomnia/middle, insomnia/early morning awakening. Adverse events listed occurred >5% and twice the rate seen in placebo-treated patients.

Varenicline Warning

- Psychiatric symptoms
  - Agitation
  - Depressed mood
  - Suicidal ideation
  - Suicidal behavior

- Warning: Patients should be monitored, and they and their families and caregivers should be alerted to monitor for these symptoms
- Advise patients and caregivers that the patient should stop taking varenicline and contact a healthcare provider immediately if agitation, depressed mood, or changes in behavior that are not typical for the patient are observed or if the patient develops suicidal ideation or suicidal behavior (May 2008)
- July 1, 2009: FDA has required the manufacturers of the smoking cessation aid varenicline ... to add new boxed warnings and develop patient Medication Guides highlighting the risk of serious neuropsychiatric symptoms in patients using these products
- July 2011: FDA issued new information: varenicline may increase the risk of certain cardiovascular adverse events in patients with cardiovascular disease

Bronchodilators: Mechanisms of Action

- Anti-cholinergic
- β-agonist
- Theophylline
- cAMP
- AMP
- Smooth muscle cell
**Bronchodilators**

**β₂-Agonists**

- Short acting
  - Fenoterol
  - Salbutamol (albuterol)
  - Terbutaline
- Long acting (LABA)
  - Formoterol
  - Salmeterol

**Anticholinergic Bronchodilators**

- Mode of action
  - Cholinergic tone is only reversible component of COPD
  - Normal airways have small degree of vagal cholinergic tone
- Short acting
  - Ipratropium bromide
- Long acting (LAMA)
  - Tiotropium
  - Indacaterol
  - Aclidinium (currently under FDA review)

**Bronchodilators: Combos and Methylxanthines**

- Combination β₂-agonists plus anticholinergic in 1 inhaler
  - Fenoterol/Ipratropium
  - Salbutamol/Ipratropium
- Methylxanthines
  - Aminophylline (slow-release preparations)
  - Theophylline (slow-release preparations)
  - Level 8-12 mcg/mL

**Effect Tiotropium on Dynamic Hyperinflation**

![Graph showing effect of Tiotropium on dynamic hyperinflation](image)

**UPLIFT: Frequency of Exacerbations Compared With Control**

<table>
<thead>
<tr>
<th>Tiotropium (Mean SE)</th>
<th>Control Mean (SE)</th>
<th>Rate Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.73 (0.02)</td>
<td>0.84 (0.02)</td>
<td>0.86</td>
<td>0.81-0.91</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

14% reduction in number of exacerbations

**Aclidinium Twice Daily Improves FEV₁ and Health Status**

![Graph showing improvement in FEV₁ and health status](image)
Fluticasone Propionate/Salmeterol 250/50 Decreases Moderate to Severe COPD Exacerbations in 1-Year Comparative Study

Moderate exacerbation: Worsening of COPD symptoms requiring both a change in normal treatment (increased dose of prescribed medication or addition of new drugs, eg, oral steroids, antibiotics) AND medical assistance

Severe exacerbation: Worsening of COPD symptoms requiring hospital or emergency room treatment

Fluticasone Propionate/Salmeterol 250/50 Decreases Moderate to Severe COPD Exacerbations in 1-Year Comparative Study

TORCH: COPD-Related Deaths

Fluticasone Propionate/Salmeterol 250/50

Exacerbation Rates (per Year)

30.5% reduction

SAL 50: salmeterol 50 mcg; FSC 250/50: fluticasone 250 mcg+salmeterol 50 mcg


Once-Daily Indacaterol Improves Trough FEV₁ and Health Status Compared With Placebo

PDE4 Inhibitors Target Inflammatory and Immunocompetent Cells

GOLD Guidelines Updated 2011

Phosphodiesterase-4 inhibitors

- In patients with stage III severe COPD or stage IV very severe COPD (FEV₁<30% of predicted) and a history of exacerbation and chronic bronchitis, the phosphodiesterase-4 inhibitor roflumilast reduces exacerbations treated with oral glucocorticoids
- These effects are also seen with roflumilast when added to long-acting bronchodilators; there are no comparison studies with inhaled glucocorticoids

Effect of Roflumilast in COPD: 1-Year Trials

Pre- and Postbronchodilator FEV₁ Improves With Roflumilast Therapy

Δ = 55 mL (CI: 41-69)
P < 0.0001

Δ = 48 mL (CI: 35-62)
P < 0.0001

Daily Azithromycin Decreases AECOPD

Time to First AECOPD

Log-rank P<0.001

HR: 0.73 (95% CI: 0.63-0.84; P<0.0001)

Combined Assessment of COPD

<table>
<thead>
<tr>
<th>Patient</th>
<th>Characteristics</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, fewer 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>≥2</td>
<td>0/1</td>
<td>≥10</td>
</tr>
<tr>
<td>C</td>
<td>High risk, fewer 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>0/1</td>
<td>≥10</td>
</tr>
</tbody>
</table>

CAT=COPD Assessment Test
mMRC=Modified Medical Research Council Dyspnea Scale

COPD Assessment: A New Model

Pharmacological Therapy of Stable COPD: GOLD 2011

GOLD spirometric classification
mMRC 0-1 mMRC >2
Increasing Risk

Patient is now in 1 of 4 categories:
A: Fewer symptoms, lower risk
B: More symptoms, lower risk
C: Fewer symptoms, higher risk
D: More symptoms, higher risk

Global Strategy for Diagnosis, Management, and Prevention of COPD
Manage Stable COPD: Pharmacologic Therapy
Improved COPD Survival on Long-Term Oxygen Treatment (LTOT)

- 1218 severe COPD patients
- Rehabilitation
- Assess
  - CT distribution
  - Exercise performance
- Randomize
- Surgery
- Medical management
- Reevaluate: 6 months, yearly
- Assess
  - Survival
  - Exercise

Volume Reduction Surgery in Chronic Obstructive Pulmonary Disease: NETT Trial

- Upper Lobe Disease and Poor Exercise Function
- Medical therapy
- Surgery

Adverse Effects of β₂-Agonist Bronchodilators

- Tachycardia
- Palpitations
- Premature ventricular contractions
- Tremors
- Sleep disturbances
- Hypokalemia

Adverse Effects of Anticholinergic Bronchodilators

- Dry mouth
- Urinary retention
- Glaucoma (intraocular administration)

Adverse Effects of Inhaled Glucocorticoids

- Dysphonia
- Thrush
- Local irritation
- Systemic effects
  - Skin bruising
  - Bone density
  - Cataracts
- Pneumonia

Adverse Effects of Roflumilast in Clinical Studies

- Adverse effects associated with roflumilast therapy typically mild to moderate
- Occurred mainly within first weeks of therapy and mostly resolved on continued treatment
- Rare neuropsychiatric events

### Adverse Reactions Reported by ≥2% of Patients Taking Roflumilast

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Roflumilast 2 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>420 (9.5)</td>
<td>113 (2.7)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>331 (7.5)</td>
<td>89 (2.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>209 (4.7)</td>
<td>60 (1.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>195 (4.4)</td>
<td>87 (2.1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>142 (3.2)</td>
<td>92 (2.2)</td>
</tr>
<tr>
<td>Influenza</td>
<td>124 (2.8)</td>
<td>112 (2.7)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>105 (2.4)</td>
<td>41 (1.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>92 (2.1)</td>
<td>45 (1.1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>91 (2.1)</td>
<td>15 (0.4)</td>
</tr>
</tbody>
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**Roflumilast Warning**

- Psychiatric symptoms
  - Insomnia
  - Anxiety
  - Depressed mood
  - Suicidal ideation
- **Warning:** Patients should be monitored, and they and their families and caregivers should be alerted to monitor for these symptoms
- Advise patients and caregivers that the patient should stop taking roflumilast and contact a healthcare provider immediately if emergence or worsening of following symptoms: insomnia, anxiety, depression, suicidal thoughts, or other mood changes
- Weight loss
  - Patients should be monitored; if unexplained or clinically significant weight loss occurs, weight loss should be evaluated and discontinuation of roflumilast considered

**Azithromycin Study Hearing Changes**

<table>
<thead>
<tr>
<th></th>
<th>Azithro (dB)</th>
<th>Placebo (dB)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>95% CI</td>
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</tr>
<tr>
<td>Start to 3rd month</td>
<td>-0.7</td>
<td>-1.0 to -0.3</td>
<td>-0.0</td>
</tr>
<tr>
<td>Start to 12th month</td>
<td>-1.2</td>
<td>-1.6 to -0.8</td>
<td>-0.9</td>
</tr>
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</table>

**Azithromycin Study Microbiology**

<table>
<thead>
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<th>Participants With Selected Respiratory Pathogens (%)</th>
<th>Azithro</th>
<th>Placebo</th>
<th>P</th>
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<tr>
<td>On Enrollment</td>
<td>14%</td>
<td>10%</td>
<td>0.01</td>
</tr>
<tr>
<td>During Study</td>
<td>14%</td>
<td>10%</td>
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**FDA Review of Azithromycin As of 5/21/2012**

“A small increase in cardiovascular deaths, and in the risk of death from any cause, in persons treated with a 5-day course of azithromycin compared to persons treated with amoxicillin, ciprofloxacin, or no drug. FDA is reviewing the results from this study and will communicate any new information on azithromycin and this study or the potential risk of QT interval prolongation after the agency has completed its review.”

**Clinical Course of COPD**

- **Exacerbations**
  - COPD
    - Expiratory flow limitation
    - Air trapping
    - Hyperinflation
  - Breathlessness
    - Deconditioning
    - Quality of life
    - Inactivity
  - Reduced exercise capacity
- Disability
- Disease Progression
- Death

**Defining Exacerbations in Patients With COPD**

- **GOLD guidelines**
  - Change in the patient's baseline dyspnea, cough, and/or sputum beyond normal day-to-day variation
  - Acute in onset
  - May warrant a change in regular medication
- **ATS/ERS guidelines**
  - Increased symptoms requiring change in usual medications
  - Mild exacerbations (normally managed at home by the patient)
  - Moderate exacerbation (requiring consultation with PCP)
  - Severe exacerbation (needing hospitalization)
Impact of Exacerbations in COPD

Patients with frequent exacerbations

- Faster decline in lung function
- Greater airway inflammation
- Poorer quality of life
- Higher mortality


Use of Short-Acting Bronchodilators in the Treatment of Exacerbations

- Short-acting bronchodilators are a critical component of overall care for patients with exacerbations
- Clinical trial results indicate no significant difference between the effectiveness of short-acting β-agonists and short-acting anticholinergic agents
- Combination therapy is safe, but there is no convincing evidence that it is superior to either agent alone
- There is no difference in the efficacy of short-acting bronchodilator therapy delivered by a nebulizer vs a metered-dose inhaler with a spacer
- Administration of a short-acting β-agonist during an exacerbation does not appear to have adverse cardiovascular effects

Systemic Steroids Reduce AECOPD Treatment Failure

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<tr>
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<th>Placebo Group</th>
<th>Relative Risk, Fixed (95% CI)</th>
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<tr>
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Antibiotics Reduce Risk of AECOPD Treatment Failure

- Antibiotics reduce the risk of AECOPD treatment failure.
- The pooled summary relative risk is 0.54 (95% CI: 0.41-0.71).
- The chi-square for heterogeneity is 15.46, df=5, P=0.009, I^2=67.7%.
- The overall effect is z=4.27, P=0.00002.

Pulmonary Rehabilitation

- Pulmonary rehabilitation is an efficacious and cost-effective intervention for improving functional performance and quality of life, and decreasing health care utilization among patients with COPD
- Programs are underutilized
  - Estimates suggest that fewer than 2% of patients with COPD have participated in pulmonary rehabilitation
  - Many factors, including health system, physician, and patient-related, contribute to underutilization
- Components of pulmonary rehabilitation
  - Exercise/physical activity training
  - Psychosocial support
**Prevent Exacerbations: Key Takeaways**

- Smoking cessation, influenza, and pneumococcal vaccine and knowledge of current therapy can reduce the number of exacerbations and hospitalizations.

**Case Study 2: Meet George**

**Patient: George**
- Age: 62
- Race: African American

**Medical History**
- Diagnosed with COPD 5 years ago
- Previously smoked about 20 cigarettes a day but cut down to 10 after his last exacerbation. Can’t quit
- HT and hypercholesterolemia

**Presenting Problem**
- Worsening dyspnea, cough, purulent sputum over the past 3 days
- Auscultation of the chest reveals scattered expiratory wheeze

**Current Medications**
- Tiotropium
- Albuterol PRN

Are you confident in treating this patient’s exacerbation?

**Summary**

- Spirometry is a useful tool in suspected cases of COPD
- FEV₁/FVC <70%, ≥80% FEV₁, predicted considered mild COPD
  - FEV₁ <30%, considered very severe COPD
- The benefits/goals of pharmacotherapy are to improve exercise tolerance and reduce exacerbations
- Treatment strategies adjust to the stage of the disease
  - Mild disease: Avoid risk factors and add short-acting bronchodilator when needed
  - Moderate disease: Same as mild but add long-acting bronchodilator when needed
  - Severe disease: Add a glucocorticoid

**Posttest Question**

To make a definitive diagnosis of COPD, which of the following is the most important factor that would lead you to an accurate diagnosis?

1. An abnormal spirometry test
2. The patient’s history of smoking
3. A chest x-ray that shows flattening of the diaphragm and focal bullae
4. Decreased functional capacity on the 6-minute walk test

**Posttest Question**

A 53-year-old white male presents for his annual visit. Although he quit 10 years ago, he is a previous cigarette smoker with a 20 pack-year history. During the past 12 months, he has had 3 episodes of bronchitis. You perform a spirometry and the results show FEV₁/FVC=0.6, and the FEV₁ is 67% of predicted. How would you classify his COPD?

1. Mild COPD
2. Moderate COPD
3. Severe COPD
4. Not sure

**Posttest Question**

When a patient progresses from moderate to severe classification of COPD, what would be the most appropriate addition to their current treatment regimen?

1. Theophylline
2. PDE4 inhibitor
3. Short-acting β₂-agonist
4. Long-acting β₂-agonist
5. None of the above
Posttest Question
Which of the following goals can be achieved with current pharmacotherapy?

1. Improved exercise tolerance
2. Partial disease regression
3. Reduction of exacerbations
4. All of the above
5. 1 and 3 only

Questions & Answers