Updates on Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Central Texas Society of Health-System Pharmacists Fall Seminar
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The University of Texas Health Science Center at San Antonio

Pharmacist Learning Objectives

1. Describe the initial treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD).
2. Explore recent literature supporting a shorter duration of steroid treatment for acute exacerbations of COPD.
3. Recommend antibiotic therapy based on patient-specific factors for appropriate patients with acute exacerbations.
4. Assess patient risk and symptoms to determine if changes to the COPD maintenance regimen are warranted.

Pharmacy Technician Learning Objectives

1. Discuss the initial treatment of acute exacerbations of COPD.
2. Explain recent evidence supporting a shorter duration of steroid treatment for acute exacerbations of COPD.
3. Identify which patients with an acute exacerbation of COPD should receive antibiotics.
4. Re-evaluate a patient’s maintenance regimen for COPD after an acute exacerbation.

What is an Acute Exacerbation of COPD?

• An acute event characterized by
  – Worsening of respiratory symptoms
  – Beyond normal day-to-day variation
• Leads to a change in medication
• Largest predictor of risk of exacerbations is a history of exacerbations

Financial Disclosures

• No conflicts to disclose

GOLD Guidelines, 2014 Update
www.goldcopd.org
Exacerbations and Decline in Lung Function

FEV₁ % Predicted

Acute exacerbation

Acute exacerbation

FEV₁, forced expiratory volume in 1 second

COPD Is the 3rd Leading Cause of Death in the U.S., 2010

Deaths due to COPD among U.S. Adults, 1999-2007

Deaths, men

Deaths, women

Hospitalizations, men

Hospitalizations, women

Common Causes

Pollution May Lead to Exacerbation

Management
Patient Case

WR is a 62 year-old-male presenting to the emergency room with ↑ shortness of breath, an increase in sputum production, and a change in sputum color over the past 2 days. He has been using albuterol 6 to 8 times daily for the past several days. He had one acute exacerbation of COPD this winter. His grandson recently had the flu.

Medical History: 43-year smoking history
15-year history of COPD, angina, & depression

Current COPD regimen: salmeterol 2 puffs BID
albuterol/ipratropium inhaler 2 puffs QID PRN
metoprolol tartrate 50 mg PO BID

Post bronchodilator PFT: Obtained at last clinic visit 3 months ago
FEV₁ of 1.3 liters (46% of predicted)
FVC of 2.2 liters
FEV₁/FVC ratio of 59%

Clinical Presentation

• Diagnosis based solely on change in symptoms
  – ↑ shortness of breath
  – ↑ sputum production
  – Sputum purulence

• Evaluate
  – Severity of COPD
  – Duration or worsening of symptoms
  – Previous exacerbations
  – Co-morbidities
  – Current treatment regimen

GOLD Guidelines, 2014 Update
www.goldcopd.org

Assessment of Severity

Potential Indications for Hospital Admission
• ↑ intensity of symptoms (ex: new resting dyspnea)
• Severe underlying COPD
• Onset of new physical signs
  • Central cyanosis
  • Peripheral edema
  • Paradoxical chest wall movements & use of accessory muscles
  • Hemodynamic instability
  • Deteriorated mental status
• ↓ response to initial management
• High risk comorbidity or new arrhythmia
• Frequent exacerbations
• Older age
• Insufficient home support


Initial Management

Diagnosis of Acute Exacerbation of COPD

Triage based on Severity

Supplemental Oxygen
Noninvasive Ventilation
Invasive Mechanical Ventilation

Drug Treatment
Bronchodilators
Steroids
Antibiotics
Adjunct Treatments

Re-Evaluation of Home Regimen

Initial Management

• Bronchodilator Therapy
  – Mainstay of treatment
  – ↑ dose or frequency of short-acting bronchodilator
  – Combine short-acting β-agonist and short-acting anticholinergic
  – Use spacers or nebulizers

• Adjunctive Therapy
  – DVT prophylaxis
  – Treatment of associated conditions
  • Example: diuretics for volume overload secondary to heart failure

Description of Levels of Evidence in GOLD Guidelines

<table>
<thead>
<tr>
<th>Evidence Category</th>
<th>Sources of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Randomized controlled trials</td>
</tr>
<tr>
<td></td>
<td>Rich body of data (i.e., several studies with consistent findings)</td>
</tr>
<tr>
<td>B</td>
<td>Randomized controlled trials</td>
</tr>
<tr>
<td></td>
<td>Limited body of data (i.e., fewer or smaller studies, may have inconsistent results)</td>
</tr>
<tr>
<td>C</td>
<td>Nonrandomized trials</td>
</tr>
<tr>
<td></td>
<td>Observational studies</td>
</tr>
<tr>
<td>D</td>
<td>Panel consensus judgement</td>
</tr>
</tbody>
</table>

Initial Management

Diagnosis of Acute Exacerbation of COPD

Triage based on Severity

Supplemental Oxygen

Drug Treatment

Ninvasive Ventilation

Invasive Mechanical Ventilation

Re-Evaluation of Home Regimen

Questions regarding Corticosteroid Use

1. What dose should I use?
2. What route of steroid administration is preferred?
3. How long should I treat with steroids?

Route of Steroid Administration

- Prospective evaluation of 210 patients
  - Compared 5 days of prednisolone 60 mg orally (n=103) vs intravenously (n=107)
  - No difference in overall, early, or late treatment failure or length of stay

- Pharmacoepidemiological study of 79,985 patients
  - Groups:
    - High dose (120-800 mg prednisone equivalent), intravenous (n=73,765)
    - Low dose (20-80 mg prednisone equivalent), oral (n=6,220)
  - Propensity-matched analysis:
    - Oral, low dose steroid associated with ↓ risk of treatment failure, length of stay, and cost vs intravenous, high dose steroids
Reduction in the Use of Corticosteroids in Exacerbated COPD

The REDUCE Trial

- Population
  - Mean age 70 years, 60% male, all past or current smokers
  - Predominantly GOLD Grade 3 or 4

- Outcomes
  - Primary: time to next exacerbation within 180 days
  - Secondary: all-cause mortality, change in FEV\textsubscript{1}, cumulative steroid dose, duration of hospital stay, need for mechanical ventilation, glucocorticoid-associated adverse events


Randomized, non-inferior multicenter study (n=314)
Methylprednisolone 40 mg IV on day 1
Prednisone 40 mg PO daily x 5 days (n=157)
Prednisone 40 mg PO daily x 14 days (n=157)

Outcome Comparison

<table>
<thead>
<tr>
<th>Measure</th>
<th>Conventional Treatment (n=155)</th>
<th>Short-Term Treatment (n=156)</th>
<th>Comparison Measure</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to next exacerbation within 180 days</td>
<td>57 (36.8%)</td>
<td>56 (35.9%)</td>
<td>HR: 0.95 (90% CI: 0.70-1.29)</td>
<td>0.006</td>
</tr>
<tr>
<td>Death</td>
<td>13 (8.4%)</td>
<td>12 (7.7%)</td>
<td>HR: 0.93 (95% CI: 0.40-2.20)</td>
<td>0.87</td>
</tr>
<tr>
<td>Need for mechanical ventilation</td>
<td>21 (13.6%)</td>
<td>17 (11.1%)</td>
<td>OR: 0.78 (95% CI: 0.37-1.63)</td>
<td>0.49</td>
</tr>
<tr>
<td>Cumulative prednisone dose (mg)</td>
<td>560 (IQR: 560-773)</td>
<td>200 (IQR: 200-310)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

A dose of 40 mg prednisone per day for 5 days is recommended (Evidence B).


Initial Management

- Diagnosis of Acute Exacerbation of COPD
- Triage based on Severity
  - Supplemental Oxygen
  - Drug Treatment
    - Bronchodilators
    - Steroids
    - Antibiotics
    - Adjunct Treatments
  - Noninvasive Ventilation
  - Invasive Mechanical Ventilation
  - Re-Evaluation of Home Regimen

Common Pathogens

- Common Bacteria
  - H. influenzae
  - S. pneumoniae
  - M. catarrhalis

- Atypical Bacteria
  - 5-10%

- Viruses
  - 30-40%

- Bacteria
  - 40-60%

- In more severe disease:
  - P. aeruginosa
  - Enteric gram negatives
  - Penicillin-resistant S. pneumoniae

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  - Enteric gram negatives
  - Penicillin-resistant S. pneumoniae

Patient Case

Should WR be initiated on antibiotic therapy for treatment of his acute exacerbation of COPD?

a. Yes
b. No

Who Should Receive Antibiotics?

- Retrospective cohort study of 84,621 patients
  - Early antibiotic treatment (within 2 days) associated with:
    - ↓ need for mechanical ventilation, inpatient mortality, readmission for an acute exacerbation
    - ↑ readmission with C. difficile

- 2012 Cochrane Review
  - High quality data to support mortality reduction in severe COPD exacerbations
  - Benefit controversial in mild to moderate exacerbations

Antibiotics should be given to patients who:

- Have all 3 cardinal symptoms (Evidence B)
- Have 2 cardinal symptoms and one is sputum purulence (Evidence C)
- Require invasive or non-invasive mechanical ventilation (Evidence B)

Use of Procalcitonin

- Single center, randomized controlled trial (n=208)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Procalcitonin-guided treatment (n=102)</th>
<th>Standard antibiotic therapy (n=106)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic prescription</td>
<td>Procalcitonin: 40%</td>
<td>Standard: 72%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antibiotic exposure</td>
<td>RR 0.56 (95% CI 0.43 – 0.73)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- No difference
  - Background therapy of AECOPD
  - Clinical outcome, FEV\(_1\) improvement at 14 days or 6 months
  - Exacerbation rate, rehospitalization rate, or mean time to next exacerbation


Stability Parameters for Discharge

- Able to use long-acting bronchodilators with or without inhaled corticosteroids
- Use of short-acting bronchodilators no more than every 4 hours
- Ambulatory (if was previously able)
- Able to eat and sleep without frequent dyspnea
- Clinically stable for 12-24 hours
- Arterial blood gases stable for 12-24 hours
- Patient, family, and physician are confident that the patient can manage successfully at home
- Follow-up and home arrangements in place

Initial Management

Diagnosis of Acute Exacerbation of COPD

Triage based on Severity

Supplemental Oxygen

Drug Treatment

- Bronchodilators
- Steroids
- Antibiotics
- Adjunct Treatments

Re-Evaluation of Home Regimen

Goals of Treatment of Stable COPD

**REDUCE SYMPTOMS**
- Relieve symptoms
- Improve exercise tolerance
- Improve health status

**REDUCE RISK**
- Prevent disease progression
- Prevent & treat exacerbations
- Reduce mortality

Classification of Severity of Airflow Limitation in COPD

<table>
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<tr>
<th>Stage</th>
<th>Characteristics (POST-bronchodilator)</th>
<th>In patients with FEV(_1)/FVC &lt; 70%:</th>
</tr>
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<tbody>
<tr>
<td>GOLD 1: Mild</td>
<td>FEV(_1) ≥80% predicted</td>
<td></td>
</tr>
<tr>
<td>GOLD 2: Moderate</td>
<td>FEV(_1) 50-79% predicted</td>
<td></td>
</tr>
<tr>
<td>GOLD 3: Severe</td>
<td>FEV(_1) 30-49% predicted</td>
<td></td>
</tr>
<tr>
<td>GOLD 4: Very Severe</td>
<td>FEV(_1) &lt;30% predicted</td>
<td></td>
</tr>
</tbody>
</table>

MAINTENANCE THERAPY

Goals of Treatment of Stable COPD

- Relieve symptoms
- Improve exercise tolerance
- Improve health status

- Prevent disease progression
- Prevent & treat exacerbations
- Reduce mortality

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<td>GOLD 4: Very Severe</td>
<td>FEV(_1) &lt;30% predicted</td>
<td></td>
</tr>
</tbody>
</table>
COPD Assessment Test (1 of 2)

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I never cough</td>
<td>0</td>
</tr>
<tr>
<td>I have no phlegm (mucus) in my chest at all</td>
<td>0</td>
</tr>
<tr>
<td>My chest does not feel tight at all</td>
<td>0</td>
</tr>
<tr>
<td>When I walk up a hill or one flight of stairs I am not breathless</td>
<td>0</td>
</tr>
</tbody>
</table>

COPD Assessment Test (2 of 2)

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am not limited doing any activities at home</td>
<td>0</td>
</tr>
<tr>
<td>I am confident leaving my home despite my lung condition</td>
<td>0</td>
</tr>
<tr>
<td>I sleep soundly</td>
<td>0</td>
</tr>
<tr>
<td>I have lots of energy</td>
<td>0</td>
</tr>
</tbody>
</table>

The Modified Medical Research Council (MMRC) Dyspnea Questionnaire

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I get breathless only with strenuous exercise</td>
<td>0</td>
</tr>
<tr>
<td>I get short of breath when hurrying on the level or walking up a hill</td>
<td>1</td>
</tr>
<tr>
<td>I walk slower than people of the same age and do on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level</td>
<td>2</td>
</tr>
<tr>
<td>I stop for breath after walking about 100 meters or after 5 minutes on the level</td>
<td>3</td>
</tr>
<tr>
<td>I am too breathless to leave the house, or I am breathless when dressing or undressing</td>
<td>4</td>
</tr>
</tbody>
</table>

Patient Classification

<table>
<thead>
<tr>
<th>RISK</th>
<th>GOLD Classification of Airflow Limitation</th>
<th>Symptom</th>
<th>Breathing</th>
<th>Exacerbation History</th>
<th>Exacerbation History in last 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW RISK</td>
<td>(C) High-Risk, Less Symptoms</td>
<td>CAT &lt; 10</td>
<td>mMRC 0-1</td>
<td>1</td>
<td>1 or ≥ 2 leading to hospital admission</td>
</tr>
<tr>
<td>HIGH RISK</td>
<td>(D) High-Risk, More Symptoms</td>
<td>CAT ≥ 10</td>
<td>mMRC ≥ 2</td>
<td>0</td>
<td>2 or ≥ 1 leading to hospital admission</td>
</tr>
</tbody>
</table>

Patient Case

What changes, if any, should be made to WR’s maintenance regimen for his COPD?

- a. Add theophylline
- b. Change salmeterol to combination salmeterol + fluticasone
- c. Add roflumilast
- d. Add aclidinium

Treatment Options

<table>
<thead>
<tr>
<th>Long-Acting Beta Agonists</th>
<th>Long-Acting Anticholinergics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formoterol</td>
<td>Tiotropium</td>
</tr>
<tr>
<td>Arformoterol</td>
<td></td>
</tr>
<tr>
<td>Indacaterol</td>
<td></td>
</tr>
<tr>
<td>Salmeterol</td>
<td></td>
</tr>
<tr>
<td>Glocaterol</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhaled Corticosteroids</th>
<th>Combination Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide</td>
<td>Vilanterol + Umeclidinium</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>Mometasone + Formoterol</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Fluticasone + Salmeterol</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Fluticasone + vilanterol</td>
</tr>
<tr>
<td>Mometasone</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methyikanthines</th>
<th>Phosphodiesterase-4 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>Roflumilast</td>
</tr>
</tbody>
</table>
Initial Pharmacologic Management of COPD

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Recommended 1st Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>A  Low Risk, Less Symptoms</td>
<td>SA-ACh PRN or SABA PRN</td>
</tr>
<tr>
<td>B  Low Risk, More Symptoms</td>
<td>LA-ACh or LABA</td>
</tr>
<tr>
<td>C  High Risk, Less Symptoms</td>
<td>ICS + LABA or LA-ACh</td>
</tr>
<tr>
<td>D  High Risk, More Symptoms</td>
<td>ICS + LABA and/or LA-ACh</td>
</tr>
<tr>
<td>Other Possible Treatments</td>
<td>Other Possible Treatments</td>
</tr>
</tbody>
</table>

SA: short-acting; LA: long-acting; ACh: anticholinergic; ICS: inhaled corticosteroid

Patient Case

WR is a 62 year-old male presenting to the emergency room with ↑ shortness of breath, an increase in sputum production, and a change in sputum color over the past 2 days. He has been using albuterol 6 to 8 times daily for the past several days. He had one acute exacerbation of COPD this winter. His grandson recently had the flu.

Medical History: 43-year smoking history, 15-year history of COPD, angina, & depression

Current COPD regimen: salmeterol 2 puffs BID, albuterol/ipratropium inhaler 2 puffs QID PRN

Post-bronchodilator PFT: Obtained at last clinic visit 3 months ago

FEV₁ of 1.3 liters (46% of predicted)
FVC of 2.2 liters
FEV₁/FVC ratio of 59%

Other Possible Treatments

Roflumilast
Theophylline

Combination Therapy

Retrospective, population-based, longitudinal cohort study (n=11,872)

New users of LABA + ICS (n=8712)
New users of LABAs alone (n=3160)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LABAs alone (n=3160)</th>
<th>LABA + ICS (n=8712)</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death and COPD hospitalisation</td>
<td>1179 deaths (37.3%)</td>
<td>1214 deaths (36.4%)</td>
<td>0.92 (95% CI 0.88-0.96)</td>
</tr>
<tr>
<td>Death and COPD hospitalisation in patients with asthma</td>
<td>1174 deaths (36.4%)</td>
<td>1214 deaths (36.4%)</td>
<td>0.92 (95% CI 0.88-0.96)</td>
</tr>
<tr>
<td>Death and COPD hospitalisation in patients not on LA-ACh</td>
<td>733 (66.4%)</td>
<td>1695 (59.5%)</td>
<td>0.79 (95% CI 0.73-0.86)</td>
</tr>
</tbody>
</table>

Withdrawal of Inhaled Glucocorticoids

The WISDOM Trial

Multicenter, randomized, double blind, active control non-inferiority study (n=2485)
6 week run in: tiotropium + salmeterol + fluticasone

Continuation of triple therapy (n=1243)
Controlled, stepwise reduction of fluticasone over 12 weeks (n=1242)

• Population
  - Mean age 63.8 years, 82.5% men
  - 61.2% GOLD 3 and 38.1% GOLD 4 airflow limitation

• Outcomes
  - Primary: time to 1st moderate or severe COPD exacerbation
  - Secondary: time to 2nd exacerbation, number of moderate or severe COPD exacerbations, and change from baseline lung function
Withdrawal of Inhaled Glucocorticoids
The WISDOM Trial

Moderate or Severe COPD Exacerbations

Change from Baseline in Trough FEV1

- Hazards ratio: 1.08 (95% CI: 1.04-1.13)
- p=0.03 by Wald’s chi-square test

Daily Fluticasone Dose in Withdow Group

- Reduced to 200 mcg
- Reduced to 80 mcg
- IC withdrawal
- IC continuation

Estimated Probability

Weeks to Event

- ICS withdrawal
- ICS continuation

The Role of Chronic Antibiotics for Prevention of Acute Exacerbations

Azithromycin for Prevention of COPD Exacerbations

- Study Design
  - Randomized, placebo controlled trial of 1142 patients for 1 year
  - Azithromycin 250 mg PO daily vs placebo

- Population
  - Mean age 65 years, 59% male
  - 75% GOLD 3 or 4

- Outcomes
  - Median time to 1st exacerbation
    - Azithromycin (n=570) 266 days (95% CI 227-313)
    - Placebo (n=572) 174 days (95% CI 143-215)
    - <0.001
  - Exacerbation rate per patient year
    - Azithromycin 1.48
    - Placebo 1.83
    - 0.83 (95% CI 0.72-0.95)
    - 0.01
  - Macrolide resistance in patients not colonized at baseline
    - Azithromycin 81%
    - Placebo 41%
    - <0.001

The use of antibiotics, other than treating infectious exacerbations of COPD and other bacterial infections, is currently NOT indicated (Evidence B).

Potential Candidates for Long-Term Azithromycin

- Proposed Criteria for Selecting Candidates for Azithromycin Prophylaxis
  - History of COPD with ≥2 acute exacerbations in the previous year
  - Compliance with current drug regimen and proper use of inhaler
  - Pulse <100 beats per minute
  - Corrected QT interval of <450 msec on electrocardiography
  - Aminotransferase levels <3 times the upper limit of normal range
  - No use of drugs known to cause QT prolongation
  - No decrement in hearing on formal audiography
  - No allergy to macrolides
  - No decrement in hearing on formal audiography
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  - No allergy to macrolides

Simvastatin and Prevention of Acute Exacerbations

- Study Design
  - Prospective, multicenter, randomized, placebo-controlled trial (n=877)
  - Simvastatin 40 mg PO daily (n=430)
  - Placebo (n=447)

- Population
  - Mean age 62.2 years, 44% women, mean FEV1 41.6% predicted
  - Excluded patients already on statins or with an indication for a statin

- Outcomes
  - Primary: annual exacerbation rate (number of exacerbations per person-year)
  - Secondary: time to first exacerbation & severity of exacerbations

Simvastatin and Prevention of Acute Exacerbations

- Effect of Simvastatin on Time to First Acute Exacerbation
  - Annual exacerbation rate per person-year: 1.36±1.61 on simvastatin vs 1.39±1.73 on placebo (p=0.54)
Patient Case

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Use of Beta-Blockers in Patients with COPD

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<tr>
<th>Study</th>
<th>Sample</th>
<th>Results Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutten FH, et al.</td>
<td>2230</td>
<td>32% relative reduction in mortality (only with cardio-selective agents)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29% relative reduction in exacerbations of COPD (with both selective and non-selective agents)</td>
</tr>
<tr>
<td>Short PM, et al.</td>
<td>5977</td>
<td>88% of agents used were cardio-selective</td>
</tr>
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<td>22% mortality reduction with beta-blocker use over 4 years</td>
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<tr>
<td>Quint JK, et al.</td>
<td>1063</td>
<td>50% relative reduction in mortality during hospital admission for myocardial infarction</td>
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Use of Beta-Blockers in Patients with COPD

- Smoking cessation
- Assess inhaler technique
- Education on role on maintenance regimen
- Assess vaccination status
  - S. pneumoniae
  - Influenza

Assess Before Discharge

- Smoking cessation
- Assess inhaler technique
- Education on role on maintenance regimen
- Assess vaccination status
  - S. pneumoniae
  - Influenza

Updates on Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Questions?