COPD Exacerbations: Practical Evidence-based Strategies

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American College of Physicians Georgia Chapter Meeting
Pine Mountain, GA, October 24-26, 2014
Disclosure of Financial Relationships

Daniel D. Dressler, MD, MSc, SFHM, FACP

Has disclosed relationships with entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

Co-Editor, Principles and Practice of Hospital Medicine
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Course Director, Southern Hospital Medicine Conference
Course Director, Evidence Based Medicine Precourse
SHM 2014 Annual Meeting

No other financial conflicts of interest to report
COPD Objectives

By the end of this session, participants will be able to:

- Interpret the highest level of medical evidence for management of COPD Exacerbations
- Synthesize literature evidence for the effective management of inpatient exacerbations
- Effectively transition to the outpatient setting
## Description of Levels of Evidence

<table>
<thead>
<tr>
<th>Evidence Category</th>
<th>Sources of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Randomized controlled trials (RCTs). Rich body of data</td>
</tr>
<tr>
<td>B</td>
<td>Randomized controlled trials (RCTs). Limited body of data</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 judgment</td>
</tr>
</tbody>
</table>
Exacerbation of COPD: Definition

- Acute worsening of respiratory symptoms
  - Change in baseline dyspnea, cough, and/or sputum beyond normal day-to-day variations
- Warrants a change in regular medication(s)
- Precipitants (infectious, non-infectious)
- Effects of Exacerbations
  - Negative impact on QOL
  - Increased symptoms and decline in lung function → weeks to recover
  - Significant mortality risk, esp if hospitalized
Exacerbations: Mortality

• Hospitalized
  – Inpatient mortality (non-ICU): 2.5%* (1 in 40)
  – 3-month mortality after hospitalization for exacerbation: 14% (1 in 7)
  – If pCO2>50:
    • 6 month mortality = 33% (1 in 3)
    • 12 month mortality = 43% (nearly 1 in 2)

• ICU
  – 17% in-hospital (1 in 6)
  – 26% in-hospital if intubated* (1 in 4)
  – 45% 1-year mortality (1 in 2)

Work-Up: Evaluate for PRECIPITANTS* of Exacerbation

The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution (Evidence B) GOLD

**INFECTIOUS**
- Tracheobronchitis
  - viral
  - bacterial (H. influenza, S. pneumonia, M. catarrhalis, P. aeruginosa)
  - atypical bacteria (<10%)
- Pneumonia

**NON-INFECTIOUS**
- Medication non-adherence
- Overuse of sedating meds
- Allergy
- CHF or arrhythmias
- Pulmonary Embolism
- Environmental irritants (smoke, smog, workplace irritants)
- Thickening of bronchial secretions
- Trauma/rib fracture/PTX

*Etiology not found in approx 1/3 cases*
DIAGNOSIS

• Exacerbations: CLINICAL Diagnosis

• Spirometry (PFTs and/or Peak Flows)
  – No demonstrated value in setting of COPD exacerbation
  – Useful only in the outpatient diagnosis of stable COPD
  – DIFFERENT for Asthma patients, where spirometry is useful in the setting of stable asthma and asthma exacerbation

• Assess Severity!!
  – Assess symptom response to initial therapy!!
  – ABG, CXR, Sputum GS/Cx
Question #1

Pharmacologic Therapies
Case: Mr. BH

- Mr. BH is a 65 year old portly Southern Gentleman with h/o severe COPD (baseline FEV1 35% predicted) admitted from the ED with 3 days of SOB, increased cough and clear sputum production. + exposure to grandkids with ‘colds’
Case: Mr. BH

• PMH:

1. COPD
   • PFTs: FEV1 35% predicted (FEV1/FVC 60%)
   • baseline pCO2 50

2. CASHD, s/p MI 12/2012
   • Preserved cardiac function (EF 60%)

3. HTN

4. Secondary Pulmonary HTN (mild)
Case: Mr. BH

- Medications on admission:
  - ASA
  - Albuterol MDI prn
  - Carvedilol CR 20mg daily
  - Lisinopril 10mg daily
  - prn SL NTG

- SH: former town mayor, 60 pack-year Tobacco use, quit 10 years ago, enjoys working on his white convertible Cadillac
Case: Mr. BH

Physical Exam

• VS: BP 150/90, HR 110 (reg), RR 28, T 38.1
• Mild to Mod increased WOB, RR 28, alert.
• Lungs: significant bilat inspiratory and expiratory wheezes
• Ext: 1+ to 2+ edema bilat

Studies

• CXR: Chronic changes, hyperinflation
• ABG:
  – pH 7.32
  – pCO2 59
  – pO2 64 on 2L O2 NC
• Other labs: Cr 1.4, Troponin-I: 0.09
Question #1: Pharmacologic Therapies in COPD Exacerbation

Which pharmacologic therapies are supported by high-level studies (RCTs) demonstrating their benefit in COPD exacerbation to improve outcomes (select all that apply)?

A. Inhaled Bronchodilators
B. Methylxanthine Bronchodilators
C. Oxygen
D. Systemic Steroids
E. Acupuncture, Aromatherapy, Massage*

*According to healingdeva.com !!
The Evidence: Pharmacologic Therapies for COPD Exacerbation

BRONCHODILATOR THERAPIES

Inhaled Bronchodilators

- Short-acting inhaled β2 agonist BDs recommended by guidelines (Evidence A)*
  - Outcomes: Main benefit on symptoms and FEV1
- Some patients benefit from adding a 2nd bronchodilator after maximum dose** of the initial bronchodilator has been reached
- Oral and injected bronchodilators NOT as effective**
- No clinical studies of long-acting inhaled BDs during exacerbation

*American Thoracic Society (ATS), European Respiratory Society (ERS), National Institute for Clinical Excellence (NICE/Thorax), GOLD (Global Initiative for Chronic Obstructive Lung Disease)

Methylxanthine Systemic Bronchodilators

- Meta-analysis summary
- 4 RCTs, 169 total patients
- Evaluation in patients treated in EDs or inpatient for exacerbations of COPD
- Relevant Outcomes:
  - Return to ED, Symptoms, Arrhythmias

## The Evidence: Pharmacologic Therapies for COPD Exacerbation

### BRONCHODILATOR THERAPIES

#### Methylxanthine Bronchodilators: Efficacy

**ED Return Visits within 1 wk**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/W</th>
<th>Control n/W</th>
<th>Odds ratio (95% CI fixed)</th>
<th>Weight %</th>
<th>Odds ratio (95% CI fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salcintfield 1984</td>
<td>6/22</td>
<td>4/30</td>
<td></td>
<td>58.9</td>
<td>2.4 (0.61 to 9.99)</td>
</tr>
<tr>
<td>Wrenn 1981</td>
<td>0/23</td>
<td>1/16</td>
<td></td>
<td>41.1</td>
<td>0.33 (0.01 to 5.75)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>6/45</td>
<td>5/46</td>
<td></td>
<td>100.0</td>
<td>1.53 (0.45 to 5.15)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 1.76$, df=1, P=0.18

Test for overall effect: $z = 0.56$, P=0.5

Favours treatment

**Symptom Scores**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n</th>
<th>Control n</th>
<th>Mean (sd)</th>
<th>Standardised mean difference</th>
<th>Weight</th>
<th>Standardised mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ram 2000</td>
<td>27</td>
<td>23</td>
<td>7.59 (20.04)</td>
<td>-2.89 (20.54)</td>
<td>51.0</td>
<td>0.52 (-0.04 to 1.09)</td>
</tr>
<tr>
<td>Rice 1987</td>
<td>15</td>
<td>13</td>
<td>2.70 (0.88)</td>
<td>5.70 (0.66)</td>
<td>49.0</td>
<td>-3.31 (-4.50 to -2.12)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>42</td>
<td>36</td>
<td></td>
<td></td>
<td>100.0</td>
<td>-1.35 (-5.11 to 2.40)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 32.31$, df=1, P=0.001

Test for overall effect: $z = 0.71$, P=0.5

Favours control
The Evidence: Pharmacologic Therapies for COPD Exacerbation

BRONCHODILATOR THERAPIES

Methylxanthine Bronchodilators: Adverse Effects

Arrhythmias/Palpitations

The Evidence: Pharmacologic Therapies for COPD Exacerbation

**OXYGEN**

- 2014 GOLD Guidelines:
  - “Titrate to improve hypoxemia with a target oxygen saturation of 88-92%.” (no evidence level provided)
  - Flow-controlled systems (e.g. Venturi mask) preferred

- Indicated for hypoxemic patients (PaO2 < 60)

- Monitor closely for signs of hypercarbia and respiratory failure (i.e. ABG 30 – 60 min after initiation of new O2 rx)
What about Steroids…
The Evidence: Pharmacologic Therapies for COPD Exacerbation
SYSTEMIC CORTICOSTEROIDS

- Systemic glucocorticosteroids recommended in hospital management of COPD exacerbations
  - Shorten recovery time, improve lung function (FEV1) and hypoxemia (Evidence A)*
  - Reduce relapse, treatment failure and hospital LOS (Evidence B)*
  - Oral as good as (possibly better than) IV
- 40 mg prednisolone daily \(\times 5\) days is effective and safe (Evidence B)*
- No role for inhaled corticosteroids in acute exacerbation of COPD (no studies to date*)

Association of Corticosteroid Dose and Route of Administration With Risk of Treatment Failure in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

- Retrospective Cohort, ~80,000 patients admitted for acute COPD exacerbation
- Low dose, oral steroids vs high-dose IV steroids
- Outcomes: Treatment Failure, LOS, Cost
- **Low dose, oral steroids:** no worse than, and in some adjusted analyses up to ~10% improved outcomes over high-dose, IV steroids

Short-term vs Conventional Glucocorticoid Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease
The REDUCE Randomized Clinical Trial

Short-course Steroids for Acute Exacerbations of COPD

Methods: Multicenter double blind, RCT (noninferiority), 314 patients COPD, >85% severe or very severe airflow limitation, 92% admitted

D#1: 40mg IV methylprednisolone (all patients)

D#2-5: 40mg oral prednisone (intervention)

D#2-14: 40mg oral prednisone (standard care)

1º Outcome: Time to next COPD exacerbation

2º Outcomes: mortality, need for mechanical ventilation, change FEV$_1$, clinical performance, hospital LOS, cum steroid dose

5-Day vs. 14-Day Systemic Steroids for Acute Exacerbation of COPD

<table>
<thead>
<tr>
<th>Outcome (ITT)</th>
<th>5-day Steroids</th>
<th>14-day Steroids</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-exacerbation at 6 months</td>
<td>36%</td>
<td>37%</td>
<td>0.95 (0.7-1.29)</td>
<td>&gt;&gt;0.05 (p-value for non-inferiority=0.006)</td>
</tr>
<tr>
<td>Deaths</td>
<td>7.7% (n=12)</td>
<td>8.4% (n=13)</td>
<td>0.93</td>
<td>0.87</td>
</tr>
<tr>
<td>Cumulative prednisone dose</td>
<td>200mg</td>
<td>560mg</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median LOS (days)</td>
<td>8</td>
<td>9</td>
<td>1.25</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Outcomes Associated with Corticosteroid Dosage in Critically Ill Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease

What about ICU Patients?

- Prospective cohort 17,239 patients at 473 hospitals admitted to ICU with AECOPD
  
  - 36% received lower dose steroids (≤240mg/day)
  
  - 64% received higher dose steroids (>240mg/day)

- Methods: multivariate analysis and propensity-matched analysis

- Results:
  
  - Lower ICU LOS, Hospital LOS (-0.44 days), cost (-$2559), and fungal infection (3.3% vs. 4.4%). [p<0.01 for each]
  
  - Trend towards lower hospital mortality (OR 0.85, p=0.06)

Which pharmacologic therapies are supported by high-level studies (RCTs) demonstrating their benefit in COPD exacerbation to improve outcomes (select all that apply)?

A. Inhaled Bronchodilators
B. Methylxanthine Bronchodilators
C. Oxygen
D. Systemic Steroids
E. A and D only
F. A, C and D only
G. All of the above
H. None of the above
Question #2

(enough with the easy stuff...)
Case (continued)

Question #2

• Admission orders written…

• …medical or PA/NP student presentation… student reports that she witnessed significant purulent sputum production while interviewing the patient for 90 minutes.

• Question: Are there other medical therapies we should add to Mr. BH’s regimen (supported by high-level evidence) for this acute exacerbation (select all that apply)?

A. Mucolytics

B. Chest Physiotherapy (Chest PT)

C. Antibiotics

D. Selective Phosphodiesterase-4 inhibitors

E. Sildinafil/Viagra for pulmonary HTN

(...oops, contraindicated with his nitrate therapy)
The Evidence for Mucolytics...
The Evidence: Pharmacologic Therapies for COPD Exacerbation

MUCOLYTIC AGENTS

• 5 RCTs of Mucolytic/Mucokinetic agents in the setting of COPD Exacerbations did NOT demonstrate shortening of disease course, but may improve symptoms*

• However, outpatient use of mucolytics in COPD patients may reduce number of exacerbations…

Mucolytic Agents for Chronic Bronchitis or COPD

**Outcome**
Reduced exac 21% per year (0.5 per year)

No exac during study period
- **Mucolytic:** 41%
- **Placebo:** 56%
- **NNT = 7**

High-Dose N-Acetylcysteine in Stable COPD

The 1-Year, Double-Blind, Randomized, Placebo-Controlled HIACE Study

- Double-blind, RCT, 120 patients
  - Avg age 70 y/o; reasonably severe COPD: avg FEV1 53% predicted, average of 2 exacerbations per year at baseline

- Intervention: NAC 600mg oral bid vs placebo

- Outcomes
  - Reduced exacerbations with NAC (0.96/yr vs. 1.71 per yr, p=0.019) at one year
  - Trend towards more patients exacerbation free at one year (54% vs 38%, p=0.088)
  - Non-significant lower hospital admissions at one year (p=0.196)

What about Pulmonary Toilet?
The Evidence: Therapies for COPD Exacerbation

CHEST PHYSIOTHERAPY

• Mechanical percussion of the chest by PTs or RTs is ineffective (or detrimental)
• No change or decrease in FEV1
• Therefore: NO Pulmonary Toilet!

*Based on 3 RCTs and 1 observational study

The Evidence: Pharmacologic Therapies for COPD Exacerbation

ANTIBIOTICS

• Antibiotics indicated for exacerbation...
  – COPD Exacerbation with 3/3 ‘cardinal symptoms’: increased dyspnea, increased sputum volume, increased sputum purulence (Evidence B)*
  – COPD Exacerbation with 2/3 ‘cardinal symptoms’ that includes increased sputum purulence (Evidence C)*; or requires mechanical ventilation

• Antibiotics indicated for hospitalized exacerbation...?

*GOLD Initiative Guidelines 2014
## Antibiotics for Acute Exacerbation of COPD: Meta-Analysis (2012)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>Antibiotics</th>
<th>Placebo</th>
<th>RR</th>
<th>NNT or NNH</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Failure (non-ICU)</td>
<td>612</td>
<td>42%</td>
<td>52%</td>
<td>0.77</td>
<td>10</td>
<td>0.0002</td>
</tr>
<tr>
<td>Treatment Failure (ICU)</td>
<td>93</td>
<td>11%</td>
<td>57%</td>
<td>0.19</td>
<td>2</td>
<td>0.00002</td>
</tr>
<tr>
<td>Mortality (non-ICU)</td>
<td>531</td>
<td>2.6%</td>
<td>3.5%</td>
<td>1.02</td>
<td>NS</td>
<td>0.98</td>
</tr>
<tr>
<td>Mortality (ICU)</td>
<td>93</td>
<td>4%</td>
<td>22%</td>
<td>1.53</td>
<td>6</td>
<td>0.01</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>1243</td>
<td>11%</td>
<td>7%</td>
<td>1.53</td>
<td>30</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Antibiotic Therapy and Treatment Failure in Patients Hospitalized for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

- Retrospective Cohort

- Compared
  - Antibiotics within 1st 2 days of admission vs.
  - No antibiotics within 1st 2 days of admission

- 85,000 patients, 413 hospitals

- Significant reduction in treatment failure (RR 0.87)
  - Lower intubation, lower inpatient mortality, lower 30-day readmission for COPD (all differences 0.5-0.9%)
  - Slightly higher C.diff rate (difference 0.1%)

Association Between Antibiotic Treatment and Outcomes in Patients Hospitalized with Acute Exacerbation of COPD Treated with Systemic Steroids

- Retrospective cohort
- 53,900 patients admitted to medical ward for COPD exacerbation
- Outcomes:
  - **In-hospital mortality** 40% lower in antibiotic group (1.0% vs. 1.8%, RR 0.60, p<0.001).
  - **30-day readmission** 13% lower in antibiotic group (RR 0.87, p<0.05)

CHEST 2013; 143(1):82–90
### Which Antibiotic?...not great evidence

**I. Uncomplicated AECOPD**
- Age ≤65 yr
- FEV$_1$ >50% of predicted
- <4 AECOPD/yr
- No comorbidity

*H influenzae*
*S pneumoniae*
*M catarrhalis*
*H parainfluenzae*
*M pneumoniae*
*C pneumoniae*
Viral pathogens

**II. Complicated AECOPD**
- Age >65 yr
- FEV$_1$ <50% of predicted
- >4 AECOPD/yr
- Comorbidity
- Antibiotic use in past 3 mo

Group I plus other gram-negative enteric bacilli
Increased β-lactam resistance

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

*P aeruginosa*

---

**I. Uncomplicated AECOPD**
- Age ≤65 yr
- FEV$_1$ >50% of predicted
- <4 AECOPD/yr
- No comorbidity

Macrolide
Doxycycline
2nd- or 3rd-generation cephalosporin
Respiratory quinolone

**II. Complicated AECOPD**
- Age >65 yr
- FEV$_1$ <50% of predicted
- >4 AECOPD/yr
- Comorbidity
- Antibiotic use in past 3 mo

Respiratory quinolone
Amoxicillin-clavulanate

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

Quinolone with antipseudomonal activity
Phosphodiesterase-4 Inhibitors in Stable COPD

• Drugs: roflumilast (Daliresp) or cilomilast (Ariflo)
  – Oral selective, long-acting inhibitor of PDE-4
  – Antiinflammatory effects
  – NOT EVALUATED in COPD Exacerbations
  – In Chronic Stable COPD:
    • Improves FEV1
    • Improves QOL Score
    • Reduces Exacerbations
    • …but increases mild adverse events and $$

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PDE4</th>
<th>Placebo</th>
<th>NNT/NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 exacerbation</td>
<td>25%</td>
<td>29%</td>
<td>25</td>
</tr>
<tr>
<td>≥1 adverse event</td>
<td>70%</td>
<td>66%</td>
<td>25</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11%</td>
<td>4.1%</td>
<td>15</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.3%</td>
<td>2.3%</td>
<td>17</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5.5%</td>
<td>1.5%</td>
<td>25</td>
</tr>
<tr>
<td>Headache</td>
<td>5.8%</td>
<td>3.8%</td>
<td>50</td>
</tr>
</tbody>
</table>

Bottom Line: Pharmacologic Therapies for Hospitalized with COPD Exacerbation

**YES!**
- Inhaled Bronchodilators
  - Duh! (Evidence A)
- Oxygen
  - Duh! (No Evidence)
- Systemic Steroids (Evidence A)
  - Improves BD response
  - Reduces Hospital LOS
  - Improves time to next exacerbation or rx failure
- Antibiotics
  - MORTALITY benefit for ICU patients. Reduced treatment failure for all inpatients.

**NO!**
- Methylxanthine
  - Note that GOLD does list this medication
- Mucolytic Agents
  - Little valuable evidence for exacerbations
  - Some evidence in chronic COPD for decreasing exacerbations
- Chest PT
- New PDE-4 Inhibitors (for chronic COPD management only)
What other medical therapies improve outcomes in acute exacerbations of COPD?

A. Oral Mucolytic therapy
B. Chest Physiotherapy (Chest PT)
C. Antibiotics
D. Selective Phosphodiesterase-4 inhibitors
E. All of the above
F. A and C only
G. A and D only
H. B and C only
I. C and D only
Question #3

(enough of the drugs, let's move onto electronics gadgets...)
Question #3: NPPV for COPD Exacerbation

• Will Mr. BH benefit from non-invasive positive pressure ventilation (NPPV)?

• Based on guidelines, which admitted patients with COPD exacerbation should be placed on NPPV?

A. pH ≤ 7.35
B. pCO2 ≥ 45
C. Severe dyspnea or signs of increased work of breathing
D. A and B only
E. A and C only
F. B and C only
G. A, B and C

Reminder—ABG on 2L O2 NC: pH 7.32, pCO2 59, pO2 64
NPPV vs Usual Care

- **Meta-Analysis of RCTs (14)**
  - Concealed allocation, unblinded

- **Patients**
  - COPD with Respiratory Failure
  - Total of **758 patients** studied

- **Outcomes**
  - Mortality (n = 622), Treatment Failure (n = 541), Intubation (n = 758), LOS (n = 546), Surrogate Outcomes (RR, pCO2, pH)

**Averages for Studies**
- Age: 63-76
- Adm pH: 7.26-7.34
- FEV1: 0.68-1.03

### NPPV vs Usual Care—Outcome: Mortality

**RR = 0.52 (95% CI: 0.35, 0.76), NNT = 10**

NPPV vs Usual Care—
Outcome: Treatment Failure

RR 0.48 (95% CI: 0.37, 0.63), NNT = 5

**NPPV vs Usual Care**

**Outcome:** Intubation

RR 0.41 (95%CI: 0.33, 0.53), **NNT = 4**

NPPV vs Usual Care—
Outcome: LOS

<table>
<thead>
<tr>
<th>Study</th>
<th>NPPV N</th>
<th>Mean(SD)</th>
<th>UMC N</th>
<th>Mean(SD)</th>
<th>Weighted Mean Difference (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avdeev 1998</td>
<td>20</td>
<td>26.00 (7.00)</td>
<td>20</td>
<td>34.00 (10.00)</td>
<td>-8.00 [-12.44, -3.56]</td>
<td>7.1</td>
<td>-8.00 [-12.44, -3.56]</td>
</tr>
<tr>
<td>Barbe 1996</td>
<td>10</td>
<td>10.60 (3.24)</td>
<td>10</td>
<td>11.30 (3.90)</td>
<td>-0.70 [-3.84, 2.44]</td>
<td>14.1</td>
<td>-0.70 [-3.84, 2.44]</td>
</tr>
<tr>
<td>Bott 1993</td>
<td>30</td>
<td>10.50 (5.30)</td>
<td>30</td>
<td>11.90 (8.80)</td>
<td>-1.40 [-5.08, 2.28]</td>
<td>10.3</td>
<td>-1.40 [-5.08, 2.28]</td>
</tr>
<tr>
<td>Brochard 1995</td>
<td>43</td>
<td>23.00 (17.00)</td>
<td>42</td>
<td>35.00 (33.00)</td>
<td>-12.00 [-23.20, -0.80]</td>
<td>1.1</td>
<td>-12.00 [-23.20, -0.80]</td>
</tr>
<tr>
<td>Celikol 1998</td>
<td>15</td>
<td>11.70 (3.50)</td>
<td>15</td>
<td>14.60 (4.70)</td>
<td>-2.90 [-5.87, 0.07]</td>
<td>15.8</td>
<td>-2.90 [-5.87, 0.07]</td>
</tr>
<tr>
<td>Dikensoy 2002</td>
<td>17</td>
<td>8.00 (2.10)</td>
<td>17</td>
<td>12.30 (3.30)</td>
<td>-4.30 [-6.16, -2.44]</td>
<td>40.3</td>
<td>-4.30 [-6.16, -2.44]</td>
</tr>
<tr>
<td>Kramer 1995</td>
<td>11</td>
<td>14.00 (10.44)</td>
<td>12</td>
<td>17.30 (9.05)</td>
<td>-2.40 [-10.75, 5.95]</td>
<td>2.0</td>
<td>-2.40 [-10.75, 5.95]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>273</td>
<td>273</td>
<td></td>
<td></td>
<td>3.24 [-4.42, 2.00]</td>
<td>100.0</td>
<td>3.24 [-4.42, 2.00]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=13.34 df=7 p=0.06 I² =47.5%
Test for overall effect z=5.38 p<0.00001

LOS Reduction **3.2 days** (95%CI: 2.1 - 4.4 days)

Bottom Line: NPPV in COPD Exacerbation

• Improves respiratory status
  – Improves physiologic variables (pH, PCO₂, RR, breathlessness)
• Reduces Hospital LOS
  – >3 days on average!
• Reduced Intubation Rate
  – NNT 4
• Reduced complications (e.g. VAP)
• Improves mortality!!
  – NNT 10

GOLD Guidelines:
Indications for NPPV (at least one of below)

– Respiratory acidosis
  • pH ≤ 7.35 and/or pCO₂ ≥ 45 mmHg
– Severe dyspnea with signs of resp fatigue or increase WOB

GOLD Evidence Level A (2014)
What if my patient did get intubated? Can I use NPPV for vent weaning?

Noninvasive ventilation as a weaning strategy for mechanical ventilation in adults with respiratory failure: a Cochrane systematic review

- **Meta-analysis, 15 RCTs, 1 quasi-RCT, 994 pts**
  - 100% COPD pts in 9; 75% COPD pts in 3; 20-30% COPD pts in 3 trials; 1 trial excluded COPD

- **Outcomes:** mortality, VAP, LOS, adverse events

**Results:**

**NPPV for Weaning from Ventilator**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NPPV weaning</th>
<th>Invasive weaning</th>
<th>RR</th>
<th>NNT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>12%</td>
<td>23%</td>
<td>0.53</td>
<td>10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VAP</td>
<td>7.4%</td>
<td>30%</td>
<td>0.25</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weaning failure</td>
<td>23%</td>
<td>36%</td>
<td>0.63</td>
<td>8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>3.4%</td>
<td>21.1%</td>
<td>0.19</td>
<td>6</td>
<td>0.001</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>-3.3 days</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital LOS (COPD only)</td>
<td>-6.9 days</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Conclusion:** Reduced mortality, VAP, complications, LOS with NPPV weaning (compared to no NPPV)

**Impact HM:** COPD patients should have strong consideration for NPPV weaning post extubation

Clinical Bottom Line: NPPV in COPD Exacerbation

• Maintain a low threshold to utilize!
• Apply in the ED!!
  – Early intervention likely improves outcomes
• Monitor closely with ABGs (30-60 min after initiation or change in NPPV settings)
• Adjust with assistance from RT
  – Mask type, pressure levels (usual start 10/5)
• Recommendations/Guidelines: pH 7.25-7.35
  – But likely benefit in COPD exacerbation with
    • pH < 7.25 (use cautiously, monitor closely)
• Valuable in post-extubation management (weaning)
Question #3: NPPV for COPD Exacerbation

Based on guidelines, which admitted patients with COPD exacerbation should be placed on NPPV?

A. pH ≤ 7.35
B. pCO2 ≥ 45
C. Severe dyspnea or signs of increased work of breathing
D. A and B only
E. A and C only
F. B and C only
G. A, B and C
Case (continued)

- Mr. BH was placed on NPPV in the ED, started on q2 hour albuterol nebulizer therapy, IV methylprednisolone 30mg bid, doxycycline 100mg bid, and continued on his cardioselective beta-blocker.

- His symptoms improved quickly, and he was able to rapidly wean off of NPPV and repeat ABG on Day 2 revealed pH 7.42, pCO2 38, pO2 69 on 1L NC.
Question #5: Follow Up

• By when should this patient have outpatient follow up after his admission for COPD exacerbation?

A. Within 3 days
B. Within 1 month
C. Within 3 months
D. During his next hospitalization
62,746 patients, retrospective cohort

2/3 had follow up with PCP or pulmonologist within 30 days

Lower likelihood of outpatient f/u: black race, lower SES, older age, prior hospitalization, teaching hospital, larger hospital, nonprofit hospital

30-d f/u associated with significantly lower ED-revisit (HR 0.86) and lower hospital readmission (HR 0.91)

Question #6

Prevention
During Hospitalization
and
At Discharge
Question #6: Prevention During Hospitalization and At Discharge

• What interventions should be instituted by hospitalists (during admission or at discharge), as supported by outcomes in COPD patients?

A. Tobacco Cessation Counseling

B. Pneumonia Vaccine (if not previously received) and Influenza Vaccine (if not received this season)

C. VTE Prophylaxis

D. Augment Home Medication Regimen

E. All of the above
Prevention: Augmentation of Home Medication Regimen

• Systematic Review of RCTs and Meta-Analyses
• Published November 2007
• Outcomes:
  ➢ Mortality Reduction
  ➢ Exacerbation Reduction
Summary of Inhaled Therapies for Prevention: Augmentation of Home Medication Regimen—

OUTCOME: Exacerbations

Outpatient Inhaled Therapies that Reduce Exacerbations vs. Placebo (statistically significant)

YES!!

- Tiotropium (p<0.001)  RR = 0.84, NNT = 15
- LABA (p<0.001)        RR = 0.76, NNT = 13
- Corticosteroids (p=0.01)  RR = 0.87, NNT = 22
- Combined LABA and corticosteroid (p=0.06) RR = 0.83, NNT = 16

No!!

- Ipratropium

Bottom Line: Hospitalist Prevention Efforts for COPD Exacerbation

- Tobacco Cessation Counseling
- Pneumonia Vaccine and Influenza Vaccine
- VTE Prophylaxis during hospital stay
- Augment Home Medication Regimen
  - LABA + Corticosteroid inhalers
  - Long-acting Anticholinergics
  - Mucolytic agents
  - PDE-4 inhibitors
  - Azithromycin
    - Efficacy on decreasing COPD exacerbations
    - Possibly unfavorable benefit/risk balance in many
Case

- Mr. DH recovers from his exacerbation, but his resting O2 Sat is 89%.
- Repeat ABG at resolution of exacerbation reveals pO2 57.
- Q: Will Mr. BH benefit from and qualify for home oxygen therapy?
Question #6

Home O2
Who Benefits from and qualifies for Home Oxygen Therapy?

- **Evidence for Benefit**
  - Supplemental O2 for ≥15 hours/day to maintain pO2 > 60*
  - Reduced death** in patients with
    - Mean FEV1 < 30% &
    - PaO2 ≤ 55

- **Medicare Criteria**

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Medicare Coverage Criteria:  
Home Oxygen Therapy

**Group I Coverage**

- **PaO2 ≤ 55 or SaO2 ≤ 88%**
  - At Rest
  - During Sleep
    - OR ↓ PaO2 > 10mmHg or ↓ SaO2 5% associated with symptoms or signs of hypoxemia*
  - During Activity

**Group II Coverage**

- **PaO2 56-59mmHg or SaO2 89% +**
  - Any of the following*:
    - Dependent Edema
    - Pulmonary HTN or Cor Pulmonale
    - Erythrocythemia
      - Hct > 56%
  - Requires re-testing between 61 and 90 days
COPD Exacerbations Final Summary

• Pharmacologic Therapies
  - Bronchodilators
    - Inhaled—YES!
    - Oral/IV—No!
  - Steroids—YES!
    - 5-day course, low dose!
  - Antibiotics—YES!

• Other Therapies
  - Oxygen—YES!
  - NPPV—ABSOLUTELY YES!!!
  - Mucolytics—Maybe?
  - Chest PT—NO!!

• Prevention (Inpatient)
  - Smoking Cessation Counseling—YES!!
  - Vaccines
    - Pneumovax—YES!
    - Influenza Vaccine—YES!
  - VTE Prophylaxis—YES!!

• Prevention (Home Regimen)
  - LABA + Corticosteroid inhalers
  - Long-acting Anticholinergics
  - Mucolytic agents
  - PDE-4 inhibitors
  - Azithromycin (maybe for select pts)

• Home O2: Medicare Criteria
COPD Exacerbations: Practical Evidence-based Strategies

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American College of Physicians Georgia Chapter Meeting
Pine Mountain, GA, October 24-26, 2014