Strategies to Break the Cycle of Severe COPD Exacerbation

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Disclosures

• I have no pertinent financial disclosures
• The opinions and slides in this presentation are my own
Efficacy and Safety of Different Doses of Systemic Corticosteroids in COPD Exacerbation

Xiaofeng Pu, Liang Liu, Binbin Feng, Maolin Wang, Limei Dong, Zhengji Zhang, Qingze Fan, Ying Li and Guojun Wang

Respiratory Care October 2020, respcare.07925. DOI: https://doi.org/10.4187/respcare.07925

http://rc.rcjournal.com/content/early/2020/10/13/respcare.07925.abstract
US COPD Epidemiology

- Prevalent
- Mortality
- $49.0 BILLION
  - COPD Costs
  - Costs attributable to having COPD were $32.1 billion in 2010 with a projected increase to $49.0 billion by 2020.
  - About 0.2% of the US GDP

Figure 4. Age-adjusted death rates for the 10 leading causes of death: United States, 2016 and 2017

- Heart disease
- Cancer
- Unintentional injuries
- Chronic lower respiratory diseases
- Stroke
- Alzheimer disease
- Diabetes
- Influenza and pneumonia
- Kidney disease
- Suicide

1Statistically significant decrease in age-adjusted death rate from 2016 to 2017 (p < 0.05).
2Statistically significant increase in age-adjusted death rate from 2016 to 2017 (p < 0.05).

NOTES: A total of 2,613,503 resident deaths were registered in the United States in 2017. The 10 leading causes accounted for 74.0% of all deaths in the United States in 2017. Causes of death are ranked according to number of deaths. Rankings for 2016 data are not shown. Data table for Figure 4 includes the number of deaths for leading causes. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db328_tables-508.pdf#4.


Acute COPD Exacerbation (AECOPD) Definition

• **GOLD definition:**
  • “Acute worsening of symptoms requiring escalation in treatment, often with corticosteroids and/or antibiotics”

• **Mild**

• **Moderate**

• **Severe**

GOLD Criteria, https://goldcopd.org/
Severe Exacerbation Epidemiology

- In 2006, there were 1,254,703 hospitalizations for COPD exacerbations, with total inpatient costs of $11.9 billion (and $9,545 per hospitalization)

- Contrary to overall in-patient trends within the period 2001–2012, there has been no significant improvement in: the number of hospital discharges, ED visits, and 30-day readmissions.

- Patients who have been admitted to hospital for a severe exacerbation of COPD are at substantial risk for rehospitalization (15–25%)

Exacerbations beget exacerbations

Hazard function of successive hospitalized COPD exacerbations (per 10,000 per day) from the time of their first ever hospitalization for a COPD exacerbation over the follow-up period. For further explanations, see text. Reproduced from Thorax with permission from BMJ Publishing Group, Ltd.88

Persistent Negative Impact:

- Decreased quality of life and functional status.
- Increase in healthcare utilization and cost.
- Increased morbidity and mortality.

Soler-Cataluña JJ, Martínez-García MÁ, Román Sánchez P, et al
Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease
Severity of COPD Exacerbations Matter

1) No exacerbations
2) ED visits
3) Admitted
4) Readmissions

Scope of this Presentation

- Common pitfalls in diagnosis and management of COPD
- Optimal inpatient care of COPD exacerbations
- Strategies to break the cycle of exacerbation
Common scenario

- You are called to the ED to admit a 67-year-old 30 pack year former smoker for COPD exacerbation. The patient complains of increased dyspnea and new, higher volume yellow sputum. Past medical history includes coronary artery disease and osteoporosis. Patient has had 3 outpatient exacerbations in past year, two ED visits, and two admissions for COPD. Outpatient medications include tiotropium handihaler daily, fluticasone 250/salmeterol diskus twice per day, propranolol. No spirometry is available in chart.

- In the ED patient has been given 125 mg of solumedrol, azithromycin 500 mg IV, albuterol via nebulizer, and the patient is on BiPAP at 15/5, 40% FiO2.

- Temperature: 99 F, HR 100, BP 133/75, RR 26, SpO2 99%

- CXR and CT chest performed demonstrating left lower lobe pneumonia with significant centrilobular emphysema, no PE

- Labs: CBC with no peripheral eosinophilia

https://lungdiseasenews.com/2015/04/21/day-tiotropium-respinmat-dose-proven-effective-24-hour-bronchodilator-asthma-patients/
Strategies in Management of Severe AECOPD

• Confirm the Diagnosis of COPD
• Characterize the patient’s COPD
  • Identify phenotype/endotype of COPD
  • Assess for associated comorbidities/confounding causes of dyspnea
• Identify the Exacerbating Cause
• Pharmacotherapy For COPD
  • Role of inhaled corticosteroids
  • Role of systemic corticosteroids
  • Bronchodilators: Medication and Delivery
  • Antibiotics
  • Other medications: Beta blockers, roflumilast, chronic macrolides, Vitamin D
• Respiratory Support
  • Hypercapnic “death spiral”
  • Acute and nocturnal mechanical ventilation
Confirm/Challenge the Diagnosis of COPD

• Is this actually COPD?
  • COPD is both OVER-diagnosed and UNDER-diagnosed

Common Pitfall: [Image: https://www.medicalnewstoday.com/articles/324644.php]
Much of COPD is **under-diagnosed** until it’s advanced
- Early COPD is often asymptomatic
  - FEV1 ~ 60% when symptoms start

What’s the effect?
- Worse quality of life
- Higher mortality rate from diagnosis,
- More exacerbations

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Gender Bias in the Diagnosis of COPD*

Kenneth R. Chapman, MD, FCCP; Donald P. Tashkin, MD, FCCP; and David J. Pye, PhD

Table 1. Percentage of Diagnoses Offered at Each Stage of the Survey Process

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>History and Physical</th>
<th>Spirometry</th>
<th>Oral Steroid Trial</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>COPD</td>
<td>64.6</td>
<td>49.0</td>
<td>76.0</td>
</tr>
<tr>
<td>Asthma</td>
<td>32.3</td>
<td>43.8</td>
<td>21.9</td>
</tr>
<tr>
<td>Other, nonrespiratory</td>
<td>3.1</td>
<td>7.3</td>
<td>2.1</td>
</tr>
</tbody>
</table>
OVER-diagnosis of COPD

• Among 16,177 participants, 919 (5.7%) reported a previous medical diagnosis of COPD.

• Postbronchodilator spirometry was unobstructed in 569 subjects (61.9%): false positive COPD.
  • 37.7% with “emphysema” or “chronic bronchitis” had no airflow limitation.

• Among the subjects with false positive COPD, 45.7% reported current use of respiratory medication.
What is Chronic Obstructive Pulmonary Disease (COPD)?

Global Initiative for Chronic Obstructive Lung Disease (GOLD) Definition of COPD

“Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.”

Global Initiative for Chronic Obstructive Lung Disease (GOLD) Accessed June 2019 at www.goldcopd.org
What is Chronic Obstructive Pulmonary Disease (COPD)?

- Symptoms
- Respiratory Mechanics (ie, Spirometry/PFT)
- Anatomic Distortion
- Exposure

https://www.patheos.com/blogs/driventoabstraction/2018/07/blind-men-elephant-folklore-
Symptoms

- Chronic dyspnea/shortness of breath
- Cough
  - with or without sputum production
- Weight loss, cachexia
- Emotional stress
- Acute Exacerbations
Why spirometry?

- **Make the diagnosis**
  - And identify potential alternative diagnoses
- Identify rapid decliners, hyperinflated patients, etc.
- Grade degree of obstruction correlated with symptom/exacerbation burden
- Candidacy for certain therapies (endobronchial valves, lung volume reduction surgery)
Spirometry Interpretation

Exhalatory Flow

Inspiratory Flow
Normal vs. Obstruction Spirometry

FEV₁ = Forced exhalatory volume at 1 second
FVC = Forced vital capacity

Obstruction: FEV₁/FVC < 0.7 (or lower than 95% LLN)
Normal Spirometry

**Time Constant** = time to exhale a lung unit = Airway Resistance x Alveolar Compliance

Red = Proximal Airway  
Green = Small Airways
Obstruction: FEV1/FVC <0.7 (or lower than 95% LLN)
Obstructive Lung Disease vs COPD

Asthma
- Bronchiectasis
- Sarcoidosis
- Cystic fibrosis
- Tracheobronchomalacia
- LAM
- PLCH

COPD= chronic obstructive pulmonary disease; LAM=lymphangiomyomatosis; PLCH=pulmonary Langerhans cell histiocytosis (aka eosinophilic granulomatosis)

Slide adapted from presentation by Dr. Michael Schivo
Anatomic Distortion

http://www.medicalook.com/Lung_diseases/Copd.html
Exposures

- Tobacco smoke
- Wildfire smoke
- Indoor pollution/smoke from biomass fuels
- Industrial air pollution
- Infections

Alternative Diseases Misdiagnosed as COPD

- Aspiration pneumonitis/bronchitis
- Obesity hypoventilation syndrome
- Asthma
- Coronary artery disease
- Pulmonary edema/heart failure
- Bacterial pneumonia (important if on inhaled corticosteroids)
- Vocal cord dysfunction
- Bronchiectasis
- Lung Cancer
- Arrhythmia/valvular disease
- Pulmonary embolism
- .......

Any smoking ever + Age >50 + Dyspnea \(\neq\) COPD

Spirometry/PFTs are crucial in tackling this differential
Does this patient have COPD?

- You are called to the ED to admit a 67-year-old 30 pack year former smoker for COPD exacerbation. The patient complains of increased dyspnea and new, higher volume yellow sputum. Past medical history includes coronary artery disease and osteoporosis. Patient has had 3 outpatient exacerbations in past year, two ED visits, and two admissions for COPD. Outpatient medications include tiotropium handihaler daily, fluticasone 250/salmeterol diskus twice per day, propranolol. No spirometry is available in chart.

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Probably.....
Table 1. COPDGene® 2019 Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Symbol</th>
<th># of Disease Features</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Exposure</td>
<td>![Symbol]</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Exposure + CT Abnormal</td>
<td>![Symbol]</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>Exposure + Symptoms</td>
<td>![Symbol]</td>
<td>2</td>
</tr>
<tr>
<td>D</td>
<td>Exposure + Spirometry Abnormal</td>
<td>![Symbol]</td>
<td>2</td>
</tr>
<tr>
<td>E</td>
<td>Exposure + Symptoms + CT Abnormal</td>
<td>![Symbol]</td>
<td>3</td>
</tr>
<tr>
<td>F</td>
<td>Exposure + Spirometry Abnormal + Symptoms</td>
<td>![Symbol]</td>
<td>3</td>
</tr>
<tr>
<td>G</td>
<td>Exposure + Spirometry Abnormal + CT Abnormal</td>
<td>![Symbol]</td>
<td>3</td>
</tr>
<tr>
<td>H</td>
<td>Exposure + Spirometry Abnormal + Symptoms + CT Abnormal</td>
<td>![Symbol]</td>
<td>4</td>
</tr>
</tbody>
</table>
What is the phenotype/endotype of COPD?

In 2010, Han et al. proposed the following definition of COPD Phenotypes:

- “a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, the rate of disease progression, or death)”

Endotype

- A condition defined by a distinct pathobiological mechanism (e.g. emphysema)

Phenotype

- The observable characteristics of an individual resulting from the interaction of its endotype with the environment (e.g. dyspnea)

How many phenotypes?

- Miravitlees et al.
  - “no consensus on the number and definition of the different COPD phenotypes, being anywhere from two to 328 million (the estimated number of patients worldwide)”
PERSONALIZED Treatment


https://lungdiseasenews.com/2015/04/21/day-tiotropium-respinat-dose-proven-effective-24-hour-bronchodilator-asthma-patients/


Vitamin D

Endobronchial valves for severe emphysema

Juan C. Herrero, MD, and colleagues B, C, D, E, M. van Rees, B, C, D, E, A. H. van Landeghem, B, C, D, E, and B. van der Meij, B, C, D, E.
PERSONALIZED Treatment

COPD CLINICAL PHENOTYPES/ENDOTYPES
• Frequent exacerbator
• Chronic bronchitis
• High peripheral eosinophils
• Asthma-COPD overlap
• Depression/anxiety
• Pulmonary hypertension
• Cardiac disease
• Alpha-1 Antitrypsin deficiency
• HIV emphysema
• Obstructive Sleep Apnea
• Obesity
• Hyperinflation +/- Giant bullae
• CO2 retainer
• Pulmonary Cachexia
• Active smoker

https://lungdiseasenews.com/2015/04/21/day-tiotropium-respitm-dose-proven-effective-24-hour-bronchodilator-asthma-patients/
Diseases with Higher Prevalence in COPD

- Heart failure
- Coronary artery disease
- Pulmonary vascular disease
- Arrhythmias
- Pulmonary fibrosis
- Peripheral vascular disease
- Hypertension
- Osteoporosis
- Aspiration
- Anxiety and depression
- Lung cancer
- Diabetes
- GERD
- Bronchiectasis
- Obstructive sleep apnea
How can we better phenotype our patient?

• You are called to the ED to admit a 67-year-old 30 pack year former smoker for COPD exacerbation. The patient complains of increased dyspnea and new, higher volume yellow sputum. Past medical history includes coronary artery disease and osteoporosis. Patient has had 3 outpatient exacerbations in past year, two ED visits, and two admissions for COPD. Outpatient medications include tiotropium handihaler daily, fluticasone 250/salmeterol diskus twice per day, propranolol. No spirometry is available in chart.

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What phenotype does this patient have?
  • Frequent exacerbator
  • Endotype:
    • Pauci-immune (low eos)...?inhaled corticosteroids?
Identify the CAUSE of the exacerbation?

• COPD exacerbation is not a manifestation of the underlying disease itself
  • e.g. myocardial infarction: coronary artery disease
• What pushed them over the edge?
Causes of Exacerbation

• Mainly triggered by viral infections
• Infectious tracheitis/bronchitis makes up ~50-60% of severe acute exacerbations
  • The most common bacterial pathogens isolated from sputum and bronchoscopic samples are *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.
  • In patients with more severe disease and/or exacerbations, Gram-negative pathogens, such as *Pseudomonas aeruginosa*, are common.
• Short term exposure to high PM2.5 increases COPD admissions/mortality
• Aspiration is common, especially in very frequent exacerbators
• Remember the non-COPD/non-pulmonary etiologies
What is driving the exacerbation?

• You are called from the ED to admit a 67-year-old 30 pack year former smoker for COPD exacerbation. The patient complains of increased dyspnea and new, higher volume yellow sputum. Past medical history includes coronary artery disease and osteoporosis. Patient has had 3 outpatient exacerbations in past year, two ED visits, and two admissions for COPD. Outpatient medications include tiotropium handihaler daily, fluticasone 250/salmeterol diskus twice per day, propranolol. No spirometry is available in chart.

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Pneumonia, likely bacterial
  o Is this an exacerbation?
Corticosteroids

• Several studies have demonstrated an improvement of several outcomes in AECOPD patients using systemic steroids, including:
  • Length of hospital stay
  • In-hospital oxygen requirement
  • FEV\textsubscript{1}
  • Dyspnea
  • Risk of relapse/treatment failure

• The oral administration is as effective as intravenous administration

• A short duration of treatment is preferred to a long duration
  • A recent meta-analysis suggested that a 5-day course of oral CSs not inferior to those with longer (10- to 14-day) courses
  • Worse outcomes with high dose steroids

• Keep dose modest (~0.5 mg/kg)
  • Beware the lure of solumedrol 125 mg (size of the vial)

ICS in Acute Exacerbations of COPD (AECOPD)

- Early RCTs focused on FEV1 as a primary outcome and enrolled patients with a relatively low exacerbation rate (and hence showed little benefit for ICS)
- More recent RCTs showed ICS + LABA reduced AECOPD by 25-35% when compared to LABA alone

Inhaled corticosteroids in COPD: friend or foe? Alvar Agusti, Leonardo M. Fabbri, Doree Singh, Jørgen Vestbo, Bartolome Celli, Frits M.E. Franssen, Klaus F. Rabe, Alberto Papi
European Respiratory Journal Dec 2018, 52 (6) 1801219; DOI: 10.1183/13993003.01219-2018

Benefits of ICS in COPD:
- Exacerbation rate
- FEV1
- Symptoms

Risks of ICS in COPD:
- Pneumonia in those with:
  - older age
  - lower body mass index (BMI)
  - greater overall fragility
  - receiving higher ICS doses
  - those with blood eosinophils <100

Agusti et al. Summary of ICS/LABA vs. LABA alone on rates of AECOPD

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Agusti et al. Summary of ICS/LABA vs. LABA alone on rates of AECOPD
Blood Eosinophils as Biomarkers

• Analyzed data from three AstraZeneca randomized controlled trials of budesonide-formoterol in patients with COPD with a history of exacerbations and available blood eosinophil counts.

• Patients with any history of asthma were excluded.

• At eosinophil counts >100, a significant treatment effect was recorded for exacerbation reduction with budesonide-formoterol compared with formoterol alone (rate ratio 0.75, 95% CI 0.57-0.99; \( p_{\text{interaction}} = 0.015 \))
Pharmacotherapy: Who should be treated with an ICS?

**FACTORS TO CONSIDER WHEN INITIATING ICS TREATMENT**

Factors to consider when initiating ICS treatment in combination with one or two long-acting bronchodilators (note the scenario is different when considering ICS withdrawal):

<table>
<thead>
<tr>
<th>STRONG SUPPORT</th>
<th>CONSIDER USE</th>
<th>AGAINST USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• History of hospitalization(s) for exacerbations of COPD#</td>
<td>• 1 moderate exacerbation of COPD per year#</td>
<td>• Repeated pneumonia events</td>
</tr>
<tr>
<td>• ≥ 2 moderate exacerbations of COPD per year#</td>
<td>• Blood eosinophils 100-300 cells/μL</td>
<td>• Blood eosinophils &lt;100 cells/μL</td>
</tr>
<tr>
<td>• Blood eosinophils &gt;300 cells/μL</td>
<td></td>
<td>• History of mycobacterial infection</td>
</tr>
<tr>
<td>• History of, or concomitant, asthma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Don’t Forget!!!

# Despite appropriate long-acting bronchodilator maintenance therapy (see Table 3.4 and Figure 4.3 for recommendations);
* Note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

Reproduced with permission of the © ERS 2019: European Respiratory Journal 52 (6) 1801219; DOI: 10.1183/13993003.01219-2018 Published 13 December 2018

FIGURE 3.1
Treatment of stable COPD

**INITIAL PHARMACOLOGICAL TREATMENT**

- **Group A**: A Bronchodilator
  - mMRC 0-1 CAT < 10

- **Group B**: A Long Acting Bronchodilator (LABA or LAMA)
  - mMRC ≥ 2 CAT ≥ 10

- **Group C**: LAMA

- **Group D**: LAMA or LAMA + LABA* or ICS + LABA**
  - *Consider if highly symptomatic (e.g., CAT > 20)
  - **Consider if eos ≥ 300

- ≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization
- 0 or 1 moderate exacerbations (not leading to hospital admission)

**FIGURE 4.1**
Bronchodilators

- Nebulizers > Metered Dose Inhalers (MDI) > Dry powder inhalers (DPI)?
  - A Canadian meta-analysis found no difference in the effect of bronchodilator delivery by a metered-dose inhaler (MDI) or wet nebulizer based on objective measurements.
  - Cochrane review comparing the effects of nebulizers versus pressurized MDI (pMDI) plus spacer or dry powder inhalers (DPI) found no significant difference in the change in FEV₁ at 1 h after dosing between nebulizers versus pMDI plus spacer.
    - there was a trend for greater improvement in FEV₁ when treating with nebulizers
  - Consider measuring peak inspiratory force.

Don’t forget about the device!

• Types:
  • Metered dose inhaler (MDI, e.g. albuterol)
  • Dry powder inhaler (DPI, e.g. tiotropium or Spiriva handihaler)
  • Slow mist inhaler (SMI, e.g. tiotropium or Spiriva Respimat)
  • Nebulizers (e.g. budesonide)

• Risk factors for insufficient drug delivery
  • Age
  • Cognitive or manual impairment
  • Impaired peak inspiratory force (InDial)
  • Crowded upper airway
  • Patient in the American healthcare system
Bronchodilators

• Short-acting $\beta_2$ agonists (SABA) and short acting anticholinergics (SAMA) have no high-quality evidence from randomized-control trials
  • Furosemide in heart failure
• Continuous helpful pragmatically, but high risk for adverse effects
Antibiotics

• In AECOPD with history of purulent sputum an antibiotic is suggested
• A Cochrane review showed that in severe AECOPD, antibiotics:
  • reduce treatment failures (risk ratio 0.77, 95% CI 0.65 to 0.91: high)
  • ...but not the length of hospital stay or mortality (low grade of evidence)
• In very severe AECOPD:
  • Nouria et al. showed a reduction in:
    • mortality (4% versus 17%, \( p = 0.05 \))
    • deaths in hospital (4% versus 22%, \( p = 0.01 \))
    • need for additional course of antibiotics (6% versus 35%, \( p = 0.0006 \))
• Azithromycin is not magic
  • Not significant evidence for one antibiotic over another (Bactrim, FQ, doxycycline, macrolides have all been studied with no superiority even in some head to head studies)

FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
2. IF NOT:
   ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
   - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   ✓ Place patient in box corresponding to current treatment & follow indications
   ✓ Assess response, adjust and review
   ✓ These recommendations do not depend on the ABCD assessment at diagnosis

**DYSNEA**

- LABA or LAMA
  - LABA + LAMA
    - Consider switching inhaler device or molecules
    - Investigate (and treat) other causes of dyspnea
  - LABA + ICS
    - LABA+LAMA+ICS

**EXACERBATIONS**

- LABA or LAMA
  - LABA + LAMA
    - LABA + LAMA + ICS
      - Roflumilast
        - FEV1 < 50% & chronic bronchitis
      - Azithromycin
        - In former smokers
        - Consider if eos < 100
        - Consider if eos ≥ 100
  - LABA + ICS

* eos = blood eosinophil count (cells/µL)
* Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization
** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS

Don’t Forget!!!
Roflumilast (Brand: Daliresp)

- **Mechanism**: PDE4 inhibitor that decreases inflammation by impairing intracellular cAMP degradation. No bronchodilator effects.
- **Dosing**: Non-efficacious initial dosing to avoid ADE (250 mcg daily), then 500 mcg daily orally
- **Indication**: recurrent exacerbations with FEV$_1$ <50% predicted and chronic bronchitis (best in patients with severe exac. history)
- **ADE**: diarrhea, weight loss (~2-3kg)
- **Effect**: decreases exacerbations (RR ~0.8) in high risk patients
Chronic azithromycin

- **Dosing**: 250 mg daily or 250/500 mg TIW oral azithromycin
- **Indication**: former smokers with recurrent exacerbations
- **ADE**: hearing loss, drug resistance, and QTc prolongation
- **Effect**: decreases exacerbations (RR ~0.8) in high risk patients
  - Less effect in active smokers
  - Only data at 1 year
Vitamin D Deficiency

• Biomarker vs. treatable trait?

• In SPIROMICS cohort of 1609 patients;
  • Each 10-ng/mL decrease in 25-OH-vitamin D was associated with lower baseline lung function (−1.04% predicted; 95% CI, −1.96% to −0.12% predicted; \( P = .03 \)) and increased odds of any exacerbation in the year before enrollment (OR, 1.11; 95% CI, 1.01-1.22; \( P = .04 \))

• Metanalysis by Jolliffe et al.:
  • “Vitamin D supplementation safely and substantially reduced the rate of moderate/severe COPD exacerbations in patients with baseline 25-hydroxyvitamin D levels”

• GOLD guidelines recommend treatment in frequent exacerbators with levels less than 25 nmol/L
Beta Blockers in COPD

- **Beta blockers likely cause a mild decrease in FEV1**

- **Retrospective Data Supporting Benefit of Beta Blockers in COPD**
  - Du *et al.*, 2014, meta-analysis of 15 retrospective of COPD patients → beta-blockers are associated with 38% reduction in AECOPD and 28% decrease in mortality

- **Beta-blockers are underutilized in COPD patients even when clear cardiac indications exist**
  - Lipworth *et al.*, 2016 and van der Woude *et al.*, 2005 → Patients post-MI with COPD are prescribed beta blockers only 20-60% of the time
  - Negative effects on FEV1 and symptoms are minimal, especially in cardio selective beta blockers

- **Potential mechanism of action in COPD?**
  - Reducing systemic inflammation
  - The number of goblet cells and their mucous release
  - Inhibition of neutrophil chemotaxis


Metoprolol for the Prevention of Acute Exacerbations of COPD

## Design

<table>
<thead>
<tr>
<th>BLOCK</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DESIGN</strong></td>
<td>Multicenter (US) RCT</td>
</tr>
<tr>
<td><strong>COHORT</strong></td>
<td>COPD patients (FEV1&lt;80) without indications for BBs (MI, CHF) and at risk for AECOPD (mod or sev AECOPD in past year or home O2)</td>
</tr>
<tr>
<td><strong>INTERVENTION</strong></td>
<td>Dose adjusted Metoprolol</td>
</tr>
<tr>
<td><strong>PRIMARY OUTCOMES</strong></td>
<td>Time to AECOPD</td>
</tr>
</tbody>
</table>


COPD Exacerbations

A Freedom from Exacerbation of COPD

B Freedom from Severe or Very Severe Exacerbation of COPD

Hazard ratio, 1.05 (95% CI, 0.84–1.32)
P=0.66 by log-rank test

Hazard ratio, 1.91 (95% CI, 1.29–2.83)
### Severity of Exacerbations

**Table 2. Rate of Exacerbation of COPD, According to Severity.**

<table>
<thead>
<tr>
<th>Severity of Exacerbation</th>
<th>Metoprolol (N = 268)</th>
<th>Placebo (N = 264)</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events no.</td>
<td>Rate (95% CI) no. of events/person-yr</td>
<td>Events no.</td>
</tr>
<tr>
<td>Any severity</td>
<td>289</td>
<td>1.40 (1.21–1.61)</td>
<td>272</td>
</tr>
<tr>
<td>Mild</td>
<td>163</td>
<td>0.78 (0.65–0.94)</td>
<td>178</td>
</tr>
<tr>
<td>Moderate</td>
<td>34</td>
<td>0.17 (0.11–0.25)</td>
<td>36</td>
</tr>
<tr>
<td>Severe</td>
<td>81</td>
<td>0.40 (0.30–0.52)</td>
<td>55</td>
</tr>
<tr>
<td>Very severe</td>
<td>11</td>
<td>0.05 (0.03–0.10)</td>
<td>3</td>
</tr>
<tr>
<td>Moderate or greater</td>
<td>126</td>
<td>0.62 (0.50–0.77)</td>
<td>94</td>
</tr>
<tr>
<td>Severe or very severe</td>
<td>92</td>
<td>0.45 (0.35–0.58)</td>
<td>58</td>
</tr>
</tbody>
</table>
Results

• **Stopped** early due to inefficacy (and potential harm)
  • Among patients with moderate or severe COPD who did not have an established indication for beta-blocker use, the time until the first COPD exacerbation was similar in the metoprolol group and the placebo group.
  • Hospitalization for exacerbation was more common among the patients treated with metoprolol.
Conclusions

• No role for beta-blockers for the *treatment* of COPD
• This study should not deter the use of beta-blockers in COPD patients with a cardiac indication
  • Consider withholding beta-blockers in patients with very severe COPD at high risk for severe exacerbation
Are the medications for this patient optimized?

• You are called to the ED to admit a 67-year-old 30 pack year former smoker for COPD exacerbation. The patient complains of increased dyspnea and new, higher volume yellow sputum. Past medical history includes coronary artery disease and osteoporosis. Patient has had 3 outpatient exacerbations in past year, two ED visits, and two admissions for COPD. Outpatient medications include tiotropium handihaler daily, fluticasone 250/salmeterol diskus twice per day, propranolol. No spirometry is available in chart.

• In the ED patient has been given 125 mg of solumedrol, azithromycin 500 mg IV, albuterol via nebulizer, and the patient is on BiPAP at 15/5, 40% FiO₂.
  • Temperature: 99 F, HR 100, BP 133/75, RR 26, SpO₂ 99%
  • CXR and CT chest performed demonstrating left lower lobe pneumonia with significant centrilobular emphysema, no PE
  • Labs: CBC with no peripheral eosinophilia

  - Selective BB
  - ICS likely not indicated
  - Should consider azithromycin/daliresp
  - Vit D testing?
Supplemental Oxygen Therapy

- **GOLD** recommends titrating supplemental oxygen therapy to achieve a target saturation of 88%–92%.

- **MYTH**: Excessive oxygen in COPD leads to hypoventilation.

- **FACT**: Uncontrolled oxygen administration in acute exacerbation of severe COPD has a limited effect on minute ventilation and thus does not explain the total increase in PaCO2.

---

**Figure 1. Effect of minute ventilation during oxygen-induced hypercapnia.** During 15 minutes of high oxygen administration, an initial decrease in minute ventilation, which recovers substantially, is seen in patients with acute exacerbation of chronic obstructive pulmonary disease. However, the oxygen-induced hypercapnia does not recover. CO₂, carbon dioxide; Vₑ, minute ventilation. Based on data of Aubier and colleagues [4].
Hypoxic vasoconstriction

- Two factors predominantly lead to worsening hypercapnia in COPD
  - Haldane effect
  - V/Q mismatch due to hypoxic vasoconstriction

Abdo and Heunks *Critical Care* 2012, 16:323
http://ccforum.com/content/16/5/323

Non-Invasive Positive Pressure Ventilation (NIPPV)

- **NIPPV**
  - Decreases RR and work of breathing
  - Reduced mortality and intubation compared when oxygen alone
  - Preferred over high flow nasal canula, although the latter does improve hypercapnia and work of breathing

- **Tips for “Not Tolerating BIPAP”**
  - Mask fit
  - Increase EPAP/CPAP
  - Decreasing inspiratory pressure (more does not equal better)
Non-Invasive Positive Pressure Ventilation (NIPPV)

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- **Tips for “Not Tolerating BIPAP”**
  - Mask fit
  - Increase EPAP/CPAP
  - Decreasing inspiratory pressure (more does not equal better)
Non-Invasive Positive Pressure Ventilation (NIPPV)

- High EPAP/IPAP to overcome hyperinflation
- IPAP still necessary often when patients near failure
Pulmonary Rehabilitation

• Pulmonary rehabilitation (PR) is a comprehensive non-pharmacological treatment
  • Monitored exercise
  • ~Occupational Therapy for Dyspnea (pursed lip breathing, pant breathing, etc.)
  • In depth RT evaluation (DME, O2 qualification/titration)
  • Education
  • Community
• PR has optimal benefit in COPD patients both during and immediately after AECOPD
• Reduces readmission, AECOPD, increases QOL/functional status

**ONLY** 48.8% of Medicare patients had annual flu vaccine

- Existing data suggests clear benefit reducing lower respiratory tract infections requiring moderate AECOPD and mortality
  - Poole *et al.* 2010 Cochrane review:
    - “It appears, from the limited number of studies performed, that inactivated vaccine reduces exacerbations in COPD patients.”

- Flu vaccination is an ATS 1b recommendation
Effectiveness of Influenza Vaccination on Hospitalizations and Risk Factors for Severe Outcomes in Hospitalized Patients With COPD

- Influenza-positive patients experienced higher crude mortality (9.7% vs 7.9%; $P = .047$) and critical illness (17.2% vs 12.1%; $P < .001$) compared with influenza-negative patients.
- 38% reduction in influenza-related hospitalizations in vaccinated vs unvaccinated individuals.

**Conclusions:**
- Exacerbations secondary to influenza have higher mortality and critical illness.
- Vaccination reduces influenza-related hospitalization.
Recommendations for our patient

• Likely COPD, but need to arrange PFTs/spirometry (even inpatient)
• Screen for cause of exacerbation (including aspiration)
• Prednisone 0.5 mg/kg instead of 125 methylprednisone
• BiPAP: increase EPAP, consider evaluating for nocturnal MV on follow up
• Judicious lorazepam a reasonable idea to avoid hypercapnia spiral
• Decrease Fio2 to goal saturation 88-92%
• STOP inhaled corticosteroids
• Consider alternative inhaler device
• Start chronic azithromycin or roflumilast
• Ok to use betablocker, but consider selective BB
• Influenza vaccine
• Pulmonary rehabilitation referral
• Move beyond the thinking of COPD as a single disease
Take Home Points:

• Phenotype for personalized care

CLINICAL PHENOTYPES
• Frequent exacerbator
• Chronic bronchitis
• Asthma-COPD overlap
• Depression/anxiety
• Pulmonary hypertension
• Cardiac disease
• Alpha-1 Antitrypsin deficiency
• HIV emphysema
• Obstructive Sleep Apnea
• Obesity
• Hyperinflation
• Giant bullae
• CO2 retainer
• Cachexia
• Active smoker
• ...............
Take Home Points:

• Identify the exacerbating cause/contributors

Exacerbation cause
• Bacterial or viral infection
• Aspiration
• Pulmonary embolism
• Heart failure
• Coronary disease
• Asthma overlap
Take Home Points:

• Hospital admission is a symptom of failed outpatient therapy:
  • Start measures to prevent recidivism immediately and aggressively prior to and at discharge
  • Appropriate bronchodilators/ICS if indicated
  • Chronic Azithromycin
  • Roflumilast (dailresp)
  • Mucolytics
  • Smoking cessation
  • Vaccinations
  • Pulmonary rehabilitation
  • ?Vitamin D?
  • ?beta blockers?
  • Comorbidities identified and optimized
  • Social determinants of health
COPD takes a team

- ROAD RT team (for patients admitted with AECOPD)
- Comprehensive COPD Clinic
- Pulmonary rehabilitation
- COPD Foundation (www.COPDfoundation.org)
  - COPD Pocket Tool for Providers and Patients
  - Great educational resource on inhaler technique
AE + COPD

**Potfalls**
1. Dry delivery devices
2. Excessive prednisone/steroids
3. Inhaler cost/education and cycling
4. Missed/incorrect diagnosis
5. Avoid gas
6. Death spiral of hypercapnia/hypoxemia
7. Following O2 drop to tackle severity/progress
8. Inappropriate LOS use/PEA
9. Missed vaccinations

**Myths**
1. O2 therapy is a new drug
2. "Anxiety" = hypercapnia
3. O2 symptom = mortality
4. "Magic" anti-asthma medications

**Strategies**
1. Identify the precipitant; treat accordingly
2. Initiate therapies to prevent future exacerbations (steroids, antibiotics)
3. Assume COPD, is the correct diagnosis!
4. Phenotype the COPD
5. Mechanical ventilation
6. CEP or anesthetic crinkle

**RESOURCES**
- Triage for AE/COPD evaluation
- GOLD
- EHR data, phase for AE/COPD note
COPD Paradigm

CLINICAL PHENOTYPES

• Frequent exacerbator
• Chronic bronchitis
• Asthma - COPD overlap
• Depression/anxiety
• Pulmonary hypertension
• Cardiac disease
• Alpha-1 Antitrypsin deficiency
• HIV emphysema
• Obstructive Sleep Apnea
• Obesity
• Hyperinflation
• Giant bullae
• CO2 retention
• Cachexia
• Active smoker

https://lungdiseasenews.com/2015/04/21/day-tiotropium-respinmat-dose-proven-effective-24-hour-bronchodilator-asthma-patients/
COPD Phenotypes

- Frequent exacerbator
- Chronic bronchitis
- Asthma - COPD overlap
- Depression/anxiety
- Pulmonary hypertension
- Cardiac disease
- Alpha-1 Antitrypsin deficiency
- HIV emphysema
- Obstructive Sleep Apnea
- Obesity
- Hyperinflation
- Giant bullae
- CO2 retention
- Cachexia
- Active smoker

Chronic Bronchitis

Emphysema

COPD
COPD Phenotypes

**Chronic Bronchitis**
- Frequent exacerbations
- Bronchiectasis
- Asthma overlap
- Active smokers

**Emphysema**
- Alpha1 ATD
- HIV
- Environmental factors
- Giant bullae
COPD Phenotypes

**Clinical Phenotypes**
- Frequent exacerbator
- Chronic bronchitis
- Asthma
- COPD overlap
  - Depression/anxiety
  - Pulmonary hypertension
  - Cardiac disease
  - Alpha-1 Antitrypsin deficiency
  - HIV emphysema
- Obstructive Sleep Apnea
- Obesity
- Hyperinflation
- Giant bullae
- CO₂ retention
- Cachexia
- Active smoker

**Overlapping Dx:**
- Asthma (ACOS)
- CAD
- Heart failure
- Pulm Htn
- Depression
- Pulmonary fibrosis

**Mimics:**
- Obesity
- Hypoventilation
- Aspiration
- Bronchiectasis
INPATIENT COPD EXACERBATION CONSULTATION AND DISCHARGE FOLLOW-UP

U.S. Department of Veterans Affairs

PULMONARY NURSE

Assists in Pulm Clinic Follow Up

“Meet and Greet” and Education during hospitalization

IP Pulmonary Evaluation
(Outlined in COPD note)

AECOPD Admission

WARD
Housestaff/
Attendings
Huddle/NP/RN/Hospi
talist/RT Identifies
Potential High Risk
“Missed Case”
ICU team once patient on floor

IP & O/P Treatment Rec’s

Telephone F/u
By Pulmonary RN

Alert Pulm RN (and
PCP) via co-signer on
note

OUTPATIENT RESOURCES

RTC order placed
with specific
pulmonary or PCP
disposition delineated by
PCCM

OUTPATIENT PULM DISPO

ASSIGNED PRIMARY
CASE

Inpatient MSA

CC PCP to IP Note
regardless of dispo. OK
to refer back to PCP if
no escalation
necessary

Urgent Pulmonary
If Non-urgent full

PCCM=pulmonary critical care medicine
HBPC=home based primary care
HIH=hospital in home
AECOPD=acute exacerbation of COPD
O/P= Outpatient
IP= Inpatient
MSA=medical support assistant (i.e., clerk)

Additional CONSULT INFO
1. Diagnostics (e.g. PFTs, TTE, IgE, RAST)
2. DME recs (e.g. BIPAP)
3. Exacerbating causes
4. Comorbid evaluation
5. Initiation of advanced therapies
6. Medication recommendations

RTC= Respiratory Therapy Coordinator
PFTs=Pulmonary Function Tests
TTE=Transthoracic Echocardiogram
IgE=Immunoglobulin E
RAST=Radiall Alergy Skin Test
PCCM=Pulmonary Critical Care Medicine
HBPC=Home Based Primary Care
HIH=Hospital In Home
AECOPD=Acute Exacerbation of COPD
O/P=Outpatient
IP=Inpatient
MSA=Medical Support Assistant (i.e., clerk)
Influenza-positive patients experienced higher crude mortality (9.7% vs 7.9%; \( P = .047\)) and critical illness (17.2% vs 12.1%; \( P < .001\)) compared with influenza-negative patients.

38% reduction in influenza-related hospitalizations in vaccinated vs unvaccinated individuals

**Conclusions:**

- Exacerbations secondary to influenza have higher mortality and critical illness
- Vaccination reduces influenza-related hospitalization

---

**TABLE 1** Risk Factors for Influenza-Related Hospitalizations Among Adult Patients With COPD and Known Vaccination Status Who Were Hospitalized Between 2011 and 2015 Influenza Seasons

<table>
<thead>
<tr>
<th>Variable</th>
<th>Influenza Positive (n = 1406)</th>
<th>Influenza Negative (n = 2,708)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age categories</td>
<td></td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>16-49 y</td>
<td>41 (2.8%)</td>
<td>57 (2.1%)</td>
<td></td>
</tr>
<tr>
<td>50-64 y</td>
<td>309 (20.7%)</td>
<td>513 (18.9%)</td>
<td></td>
</tr>
<tr>
<td>65-75 y</td>
<td>383 (25.7%)</td>
<td>848 (31.3%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 75 y</td>
<td>757 (50.8%)</td>
<td>1,290 (47.6%)</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>771 (51.7%)</td>
<td>1,360 (50.2%)</td>
<td>.36</td>
</tr>
<tr>
<td>Aboriginal ethnicity(^a)</td>
<td>23 (1.5%)</td>
<td>32 (1.2%)</td>
<td>.31</td>
</tr>
<tr>
<td>Current smoker(^b)</td>
<td>501 (34.4%)</td>
<td>723 (27.2%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>769 (51.6%)</td>
<td>1,528 (56.4%)</td>
<td>.003</td>
</tr>
<tr>
<td>Diabetes</td>
<td>361 (25.6%)</td>
<td>710 (26.2%)</td>
<td>.63</td>
</tr>
<tr>
<td>Renal or liver disease</td>
<td>249 (16.7%)</td>
<td>469 (17.3%)</td>
<td>.22</td>
</tr>
<tr>
<td>Cancer</td>
<td>257 (19.9%)</td>
<td>578 (21.3%)</td>
<td>.28</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>9 (0.6%)</td>
<td>15 (0.6%)</td>
<td>.84</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>67 (4.5%)</td>
<td>99 (3.7%)</td>
<td>.18</td>
</tr>
<tr>
<td>Long-term care resident</td>
<td>117 (9.2%)</td>
<td>189 (7.0%)</td>
<td>.01</td>
</tr>
<tr>
<td>Assisted living</td>
<td>172 (11.5%)</td>
<td>230 (8.5%)</td>
<td>.001</td>
</tr>
<tr>
<td>Oxygen use at home(^c)</td>
<td>151 (10.1%)</td>
<td>556 (20.5%)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Prior physician or ED visit for current illness</td>
<td>490 (32.9%)</td>
<td>669 (24.7%)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Influenza vaccination(^d)</td>
<td>878 (58.9%)</td>
<td>1,912 (70.6%)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>&gt;4 Medications at admission</td>
<td>1,203 (80.7%)</td>
<td>2,320 (85.7%)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

\(^a\)Aboriginal ethnicity not known in 42 of 1,490 case subjects and in 53 of 2,708 control subjects.

\(^b\)Smoking status unknown in 32 of 1,490 case subjects and 40 of 2,708 control subjects.

\(^c\)Oxygen use at home unknown in 1 of 1,490 case subjects and 1 of 2,708 control subjects.

\(^d\)Indicates trivalent influenza vaccine given in influenza season during which patient was admitted to the hospital.
C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations

Christopher C. Butler, F.Med.Sci., David Gillespie, Ph.D., Patrick White, M.D., Janine Bates, M.Phil., Rachel Lowe, Ph.D., Emma Thomas-Jones, Ph.D., Mandy Wootton, Ph.D., Kerenza Hood, Ph.D., Rhiannon Phillips, Ph.D., Hasse Melbye, Ph.D., Carl Llor, Ph.D., Jochen W.L. Cals, M.D., Ph.D., Gurudutt Naik, M.B., M.S., M.P.H., Nigel Kirby, M.A., Micaela Gal, D.Phil., Evgenia Riga, M.Sc., and Nick A. Francis, Ph.D.

Background

• The evidence supporting antibiotics in the treatment of moderate COPD exacerbations is mixed, despite many AECOPD events being caused by infection

• Unwarranted use of antibiotics drives antimicrobial resistance, may negatively affect the microbiome, and distracts from potentially more effective interventions.
  • More than 80% of AECOPD patients receive antibiotic prescriptions in the United States and in Europe

• Recommendations for antibiotic prescribing in primary care practice are generally based on clinical features alone
  • i.e., the Anthonisen criteria: increased sputum volume, increased dyspnea, change in sputum color)

Question:
Can testing for C-reactive protein (CRP) lower antibiotic prescribing without compromising clinical outcomes?

The Role of CRP

<table>
<thead>
<tr>
<th><strong>Butler et al. CRP for Exacerbations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DESIGN</strong></td>
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<tr>
<td><strong>COHORT</strong></td>
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<tr>
<td><strong>INTERVENTION</strong></td>
</tr>
<tr>
<td><strong>DEVICE</strong></td>
</tr>
<tr>
<td><strong>PRIMARY OUTCOMES</strong></td>
</tr>
</tbody>
</table>
The Role of CRP

- Between-group differences in the scores on the Clinical COPD Questionnaire during follow-up were smaller than the published minimal clinically important difference of 0.4.

- The proportion of patients receiving antibiotics was significantly lower in the CRP group than in the usual-care group (57% vs. 77%).
  - Differences only seen if Anthonisen 2 or more

- Not a clinically significant difference in symptom scores

- No higher risk of hospital admission

**Figure 2.** Differential Effect of the Interventions on the Use of Antibiotics during the First 4 Weeks.  
Shown is the predicted probability of antibiotic use for acute exacerbations of COPD during the first 4 weeks according to the number of Anthonisen criteria present. The Anthonisen criteria include increased dyspnea, increased sputum volume, and increased sputum purulence. I bars denote 95% confidence intervals. 

---

The Role of CRP

**Conclusion:**
- POC CRP can help reduce the prescription and usage rates of antibiotics in AECOPD without negatively affecting patient health

**Limitations:**
- Need *point-of-care* CRP measurement