COPD: Update and Guidance for Primary Care

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DISCLOSURES

None of the planners or presenters of this session have disclosed any conflict or commercial interest
OBJECTIVES

• Review diagnosis and risk stratification for COPD.
• Discuss multi-morbid syndrome associated with COPD.
• Discuss evidence based treatment for acute exacerbations and stable disease.
65 yo M with dyspnea and cough of acute on chronic duration
Outline

• Background of COPD
• AECOPD
  – Definition/Causes
  – Outcomes of AECOPD
  – Management
    • Oxygen
    • Steroids
    • Antibiotics
    • NIPPV
• Outpatient COPD
  – Management
    • General
    • Oxygen
    • Bronchodilators, Steroids
    • Pulmonary Rehab
    • “Niche” techniques
• Conclusions
Chronic Obstructive Pulmonary Disease (COPD)

GOLD Definition:

COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases and associated with systemic manifestations.

This definition does not use the terms chronic bronchitis and emphysema and excludes asthma (reversible airflow limitation).
The Old World of COPD

- Chronic Bronchitis
- Emphysema
- Asthma

The “old” world view of COPD
Emphysema
Chronic Bronchitis
Asthma

COPD Now

Chronic Bronchitis
Emphysema

COPD fixed, features of CB, emphysema
COPD partially reversible obstruction, features of emphysema, CB

Asthma

Asthma with completely reversible obstruction (FEV₁/FVC ratio > 70% post BD)

Symptoms / features of emphysema, CB with no airflow obstruction
Airflow obstruction from something else (CF, BO etc…)

Chronic Obstructive Pulmonary Disease (COPD)

**Chronic bronchitis**
Defined as the presence of cough and sputum production for at least 3 months in each of 2 consecutive years, (not necessarily associated with airflow limitation).

**Emphysema**
Defined as destruction of the alveoli.

**Increased Mucus Secretion**
**Inflammation of Airways**
Wonderful World of ICD-10

- COPD (J44.0-1,9)
- Emphysema (J43.0-9)
- Chronic bronchitis (J41.0-3)

- At least 40 codes under “Chronic lower respiratory diseases J40-J47”

W56.01XD

Bitten by dolphin, subsequent encounter
Etiology


Figure 1. Chronic obstructive pulmonary disease risk is related to the total burden of inhaled particles.
Epidemiology

• COPD is the fourth leading cause of death
• In the US, estimated to affect 23.6 million adults (13.9%)
  – 10% of these individuals have severe or very severe disease
• COPD Mortality in females has more than doubled over the last 20 years
• COPD is a costly disease
  – Chronic management and exacerbations
  – 50–75% of the costs are for services associated with exacerbations.
• Tobacco smoke is by far the most important risk factor for COPD
  – Prevalence of smoking since 1965 has decreased from 40% to 18%
    BUT 42 million Americans still smoke cigarettes
Death rates for COPD have declined among U.S. men between 1999 and 2006, but death rates in women were unchanged.

US Centers for Disease Control and Prevention, 2002
What is an Acute Exacerbation of COPD?

• Definition: A sustained worsening of a patient’s symptoms from his or her usual state of health that is beyond normal day-to-day variation and is of acute onset.
  – Onset occurring over 1-3 days
Triggers of AE-COPD

Wedzicha, JA, Seemungal T
Lancet 2007
Triggers for AE-COPD

Majority of Triggers for COPD are Infectious: Accounts for up to 70-80%

- Viral: 30%
- Bacterial: 40-50%
- Atypical bacteria: 10-25%
- Air pollution: 5-10%
“Frequent Exacerbators”

Patients with frequent exacerbations

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

>2-3/year

Wedzicha, JA, Seemungal T. Lancet 2007 370:786-796
Quality of Life Dramatically Worse in “Frequent Exacerbators”

70 COPD (Mod-Sev) from London COPD Cohort followed for 1 year

SGRQ Scores: 0 (no disability) to 100 (maximum disability)

More Rapid Decline of Lung Function in “Frequent Exacerbators”

- 109 Patients with moderate to severe COPD
  - Follow for almost 4 yrs with symptom diary card
  - 767 exacerbations
  - Median 2.53/yr
  - “Frequent exacerbator” >2.92/yr

FEV-1 Difference was 8ml/year

Exacerbation Frequency and MI

![Graph showing the relationship between exacerbations (prescriptions of antibiotics and steroids per year) and myocardial infarction (per 100 patient per year).]
High Mortality Associated with ICU AECOPD

- Non ICU Mortality 4-5%
- 508 Pts admitted for AECOPD
  - 379 of these required NIPPV
- ICU admission and Mortality
  - Hospital mortality 31.8%
  - In NIPPV 36.7% died
  - At 6 years 18.3% were alive
- Predictors of decreased survival
  - Age, QOL and APACHE

Crit Care Med 2006; 34:2317–2324
Management of AECOPD

- Oxygen
- Steroids (A)
- Antibiotics (B)
- NIPPV (A)
Oxygen Therapy In COPD

• “Controlled Oxygen Therapy”.
  – PaO2 > 60 mm Hg or SaO2 > 90%
  – CO2 retention: actual implications of hyperoxia debated
  • O2 depresses ventilatory drive even in normal patients and may have modest increase in PCO2
  • O2 therapy can decrease adaptive hypoxic vasoconstriction and worsen V/Q matching
  • Oxygen therapy masks the progression of hypercapnea
Role of Steroids in AECOPD
Steroids Improved All Measures

- 27 patient with AECOPD
- DB-RCT placebo vs. oral steroid taper
  - (60mg x 3d, 40mg x 3dy...)
  - Table 1: mean age 67.8 yrs, FEV-1 58% 30% current smokers

- Outcomes:
  - More rapid improvement in A-a gradient,
  - PaO2
  - PEF and FEV-1
  - Fewer treatment failures

Significant increase in FEV-1 day 3 and 10

Thompson, et al: AJRCCM 1996;154 402-12
Treatment of AECOPD: Steroids

Lower rates for Treatment failure with Steroids compared to Placebo
8 Week vs. 2 Week: No Benefit but more Pneumonia/Hyperglycemia

Niewneuower NEJM1999;340:1941-7
Steroids Meta-Analysis

• 10 “high quality” RCT’s of 951 Patient
  – Decrease treatment Failure rates w/in 30day
    • OR =.48, NNT=9
  – More Rapid Improvement:
    • FEV-1 (mean improvement 140ml @72hr)
    • PaO2
    • Dyspnea Score
  – NO MORTALITY DIFFERENCES
  – Increased Likelihood of Harm- OR 2.29 NNH=6
    • Hyperglycemia- most common OR 5.48

Prospective RCT from ER, non-inferiority trial

N = 314 with AECOPD

40mg IV methylprednisolone then 40 mg prednisone days 2-5, then 40 mg daily 6-14 or matching placebo

All: Abx x 7 days, ICS/LABA, LAMA, q4-6 bronchodilators

Primary outcome: time to next exacerbation by 6 months

Secondary outcomes: all-cause mortality, ΔFEV1, cumulative glucocorticoid dose, and clinical performance (via questionnaires) assessed at the index exacerbation and during 6 months of follow-up.
Outcomes

Table 2. Results for the Primary End Point

<table>
<thead>
<tr>
<th>Primary End Point</th>
<th>Event Frequencies, No. (%)</th>
<th>Hazard Ratio (90% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional Treatment (n = 155)</td>
<td>Short-term Treatment (n = 156)</td>
<td></td>
</tr>
<tr>
<td>Reexacerbations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention to treat</td>
<td>57 (36.8)</td>
<td>56 (35.9)</td>
<td>0.95 (0.70-1.29)</td>
</tr>
<tr>
<td>Per protocol</td>
<td>57 (38.3)</td>
<td>54 (36.7)</td>
<td>0.93 (0.68-1.26)</td>
</tr>
<tr>
<td>Subgroup analyses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOLD grade 1 and 2</td>
<td>6 (33.3)</td>
<td>6 (26.1)</td>
<td>0.73 (0.28-1.88)</td>
</tr>
<tr>
<td>3</td>
<td>19 (35.9)</td>
<td>15 (33.3)</td>
<td>0.93 (0.52-1.67)</td>
</tr>
<tr>
<td>4</td>
<td>31 (39.7)</td>
<td>34 (40.5)</td>
<td>0.99 (0.66-1.49)</td>
</tr>
<tr>
<td>Glucocorticoid pretreatment</td>
<td>13 (46.4)</td>
<td>16 (45.7)</td>
<td>0.93 (0.50-1.72)</td>
</tr>
<tr>
<td>Yes</td>
<td>44 (35.8)</td>
<td>40 (33.3)</td>
<td>0.88 (0.61-1.26)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Cumulative prednisone dose, median (IQR), mg\textsuperscript{3,h}

<table>
<thead>
<tr>
<th></th>
<th>Conventional Treatment (n = 155)</th>
<th>Short-term Treatment (n = 156)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean, mg</td>
<td>793</td>
<td>379</td>
<td>&lt;.001f</td>
</tr>
<tr>
<td>Difference in means,</td>
<td>-414 (-521 to -307)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“Steroids for all”

• Steroids for all hospitalized with AECOPD
  – For home management in Patients with FEV-1 <50%

• Prednisone 30-40mg daily, no benefit to longer than 7-14 days duration

• Advantages of Dose or Route unknown
Antibiotics In Acute Exacerbation of COPD
Antibiotics In AECOPD

- DB-RCT Cross over trial of AECOPD with 362 exacerbations in 173 patients over 3.5yrs
  - Doxycycline 200mg BID vs placebo
  - Outcomes prospectively evaluated based on Severity of Exacerbation
    - Type 1- Increase dyspnea, increased sputum volume, and increase sputum purulence
    - Type 2- Any 2 of the Above
    - Type 3- Any one of above

Efficacy of Antibiotics According to Exacerbation Severity


* = P<.05
Treatment Failure/Deterioration According to Severity of Exacerbation

International Guidelines support these findings in their recommendations
Require at least 2/3 symptoms for antibiotic therapy

Cochrane Meta-Analysis

- 11 trials RCT’s including 917 patients
  - Looked at Mortality, Treatment Failure, Sputum Purulence and Complications

Mortality

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Antibiotic Group n/N</th>
<th>Placebo Group n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nouira 2001</td>
<td>4/47</td>
<td>18/46</td>
<td>0.22 [0.08, 0.59]</td>
<td>80.08</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Pines 1968</td>
<td>1/15</td>
<td>3/15</td>
<td>0.33 [0.04, 2.85]</td>
<td>13.20</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Pines 1972</td>
<td>0/89</td>
<td>1/86</td>
<td>0.32 [0.01, 7.80]</td>
<td>6.71</td>
<td></td>
<td>A</td>
</tr>
</tbody>
</table>

Total events: 5 (Antibiotic Group), 22 (Placebo Group)
Test for heterogeneity: \( \chi^2 = 0.16, \text{df} = 2 (P = 0.92), I^2 = 0\%
Test for overall effect: \( Z = 3.21 (P = 0.001)\)

NNT = 8

Ram SF, et al: Cochrane 2006 (2) CD 04403
Treatment Failure and Sputum Production both Improved with Abx

Higher incidence of Diarrhea with Antibiotic Administration.

Ram SF, et al: Cochrane 2006 (2) CD 04403
Current Abx Guidelines

- Administer in Patients with
  - Type 1 exacerbation (increase Dyspnea, increase Sputum volume and increase sputum purulence)
    - Type 2 Exacerbations - unclear
  - Severe Exacerbations requiring NIPPV
  - Should Cover Most Likely Organisms
    - *Strept Pneumoniae*
    - *H Influenza*
    - *Moraxella Catarrhalis*
    - Prior known microbes
    - *Pseudomonas aeruginosa* in more severe obstruction

www.goldcopd.com
Role of Non-Invasive Positive Pressure Ventilation (NIPPV) in COPD Exacerbation
How We Breath!

Pressure Gradient Drives Flow Both In and Out

Diaphragm Generates Negative Pleural Pressure

Normal Airways I:E--1:3

Inspiration

Exhalation

Recoil of Lung And Chest Wall
The Normal Lung on Exhalation

- Elastic recoil
- Radial traction from surrounding parenchyma
- Cartilage rings
Asthma and Chronic Bronchitis

- Radial traction from surrounding parenchyma
- Elastic recoil
- Airways Inflammation
- Respiratory secretions
- Cartilage rings
Emphysema with Pursed Lip breathing or NIPPV

Elastic recoil

IMPAIRED Radial traction from surrounding parenchyma

Airways Inflammation

Respiratory secretions

Parenchymal destruction

Cartilage rings

Pursed lip breathing

PEEP

+ 20

+ 20

+ 20

+ 20
NIPPV in AECOPD

- RCT of NIPPV vs usual care, 85 patients w/ AECOPD (screened 275)
  - Inclusion (≥2 of 3): RR>30, PO2 <45, or pH<7.35 on room air
  - Excluded other than COPD, DNR/DNI
- PSV 20 cmH₂O and NO PEEP
- Outcomes:
  - Intubation/death/LOS/Physiologic Parameters at 1 hr.
  - Strict criteria for intubation

Lower Mortality and Hospital LOS with NIPPV

- At 1hr on NIPPV vs. Control (all P<.05)
  - Decrease PCO2 and RR,
  - Increased pH and PaO2

<table>
<thead>
<tr>
<th></th>
<th>Intubation (%)</th>
<th>LOS (Days)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>25</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>NIPPV</td>
<td>74</td>
<td>41</td>
<td>29</td>
</tr>
</tbody>
</table>

* = P<.05

NIPPV RCT’s for COPD

- Cochrane Review- COPD to prevent
  - 14 RCT with 758 patients
    - Mortality: NNT 10
    - Intubation: NNT 4
    - Decrease PaCO2 and LOS (3.24 day)

RAM SF Cochrane Review 2004 (#) CD 004104
Adverse Effects of NIPPV

- Mask Leaks
- Inability to tolerate mask
- Facial Breakdown- 
  - 10-15% poorly documented
- Gastric Distension
- Eye irritation
- Dryness to Upper Airway/ Rhinitis
- Enteral access for nutrition and medications
NIPPV is Not a Vacation Destination

- 77% do well with NIPPV
- Predictors of Poor Outcome
  - GCC <11 at outset
  - Elevated RR, APACHE II or Resp Acidosis At 2Hr

Must Give up on NIPPV at Some Point

Patient Selection Essential

- Ventilatory failure
- Hypoxemic but usually FiO2<50%*
- Resp distress prior to failure

• Exclusion
- Recent Facial or Gastroesophageal Surgery, Craniofacial Trauma
- Copious Secretions
- Expected duration >2-3 days*
- Hemodynamic Instability
- Uncooperative/ Not Alert
- Poor bulbar function
- Extreme Obesity*
Readmissions

• Medicare data suggest 20.2% of COPD exacerbation patients are readmitted by 30 days.

• Half of readmissions were related to respiratory illness (27% overall were COPD)

Readmission Prevention Measures

• Data is conflicting on efficacy
  – Pulmonary rehab (<3 weeks)
  – Early follow-up with pulmonology
  – Education
  – Visiting nurse care
Acute Exacerbation: Summary

• AECOPD
  – Frequent exacerbations
    • Decrease QOL, More Rapid decline in Lung Function, Increased RR MI and CVA
  – Management
    • Oxygen
    • Steroids for all
    • Antibiotics for most
    • NIPPV - time limited trial
  – Prevention is essential
  – Readmission prevention remains challenging
Outpatient COPD - Goals

COPD management plan includes four components:

(1) assess and monitor disease,
(2) reduce risk factors,
(3) manage stable COPD,
(4) manage exacerbations.

1. Relieve symptoms
2. Prevent disease progression
3. Improve exercise tolerance
4. Improve health status
5. Prevent and treat complications
6. Prevent and treat exacerbations
7. Reduce mortality
Outpatient COPD - Diagnosis

Consider COPD, and perform spirometry, if any of these indicators are present in an individual. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is needed to establish a diagnosis of COPD.

<table>
<thead>
<tr>
<th>Dyspnea that is</th>
<th>Progressive (worsens over time)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Usually worse with exercise</td>
</tr>
<tr>
<td></td>
<td>Persistent (present every day)</td>
</tr>
<tr>
<td></td>
<td>Described by the patient as an “increased effort to breathe,” “heaviness,” “air hunger,” or “gasping”</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>May be intermittent and may be unproductive</td>
</tr>
<tr>
<td>Chronic sputum production</td>
<td>Any pattern of chronic sputum production may indicate COPD</td>
</tr>
<tr>
<td>History of exposure to risk factors, especially,</td>
<td>Tobacco smoke</td>
</tr>
<tr>
<td></td>
<td>Occupational dusts and chemicals</td>
</tr>
<tr>
<td></td>
<td>Smoke from home cooking and heating fuels</td>
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</tbody>
</table>

AECOPD patients often don’t have confirmatory PFT’s


553 Patient with “COPD”

- 69% with PFTs
- 31% without PFTs

789 Patient with CHF

- 78% with Echo
- 22% without Echo

ICD -9 Review of admitting diagnosis then looked at studies over last 8 years.
Symptoms and PFT’s worsen with AECOPD

Median Recovery Time For PFTs was 7 days

PFT’s Around an Exacerbation to Aide in Documentation of Disease and severity

Severity by Spirometry

I: Mild
- FEV$_1$/FVC < 0.70
- FEV$_1$ ≥ 80% predicted

II: Moderate
- FEV$_1$/FVC < 0.70
- 50% ≤ FEV$_1$ < 80% predicted

III: Severe
- FEV$_1$/FVC < 0.70
- 30% ≤ FEV$_1$ < 50% predicted

IV: Very Severe
- FEV$_1$/FVC < 0.70
- FEV$_1$ < 30% predicted or FEV$_1$ < 50% predicted plus chronic respiratory failure

BODE index

<table>
<thead>
<tr>
<th>B - (BMI &lt;21)</th>
<th>O - (Obstruction: 0-3 points)</th>
<th>D - (Dyspnea: 0-3 points)</th>
<th>E - (Exercise capacity on 6MWD: 0-3 points)</th>
</tr>
</thead>
<tbody>
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<table>
<thead>
<tr>
<th></th>
<th>4 year survival</th>
</tr>
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<tbody>
<tr>
<td>0-2</td>
<td>80%</td>
</tr>
<tr>
<td>3-4</td>
<td>67%</td>
</tr>
<tr>
<td>5-6</td>
<td>57%</td>
</tr>
<tr>
<td>7-10</td>
<td>18%</td>
</tr>
</tbody>
</table>

Comorbidities of carcinomas (HR 2-6), and anxiety in woman (HR ~14) worsen prognosis

2. On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.

3. I stop for breath after walking about 100 yards or after a few minutes on level ground.

4. I am too breathless to leave the house or I am breathless when dressing.
General Measures

• Multi-morbid management (CVD, DM2, OSA, cancers, psychiatric, etc.)
• LDCT lung cancer screening
• Pneumococcal and influenza vaccines
• Smoking cessation
• Supplemental O2 (>15h/d) for SpO2>88%
Bronchodilators/Inhaled steroids: General Caveats

Goal is symptom relief and exacerbation prevention.

Spirometric response does not predict clinical response.

Targeting the dynamic hyperinflation is likely part of why long-acting agents are so useful.

HFA via spacer has same bio-availability as a nebulizer.

Small increased risk of pneumonia with ICS, but had signal toward improved survival in >mod COPD with frequent exacerbations.
TORCH

• Prospective 4 arm RCT (placebo, salmeterol, fluticasone, sal/flutic combination)
• Patients: >10 p-y, age 40-80, FEV1/FVC <= 0.7, FEV1 <60%
• N = 6184 patients randomized
• Primary outcomes: survival by 3 yrs
• Secondary outcomes: exacerbation rates, symptoms (SGRQ), lung function
• Patients followed every 12 weeks

### TORCH

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Combination</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>15.2%</td>
<td>12.6%</td>
<td>ARR 2.6%, HR 0.825, ( p=0.052 )</td>
</tr>
<tr>
<td>Exacerbations</td>
<td>1.13/yr</td>
<td>0.85/yr</td>
<td>Rate ratio: 0.75, ( p&lt;0.001 )</td>
</tr>
<tr>
<td>( \Delta \text{FEV1} )</td>
<td>-0.062L</td>
<td>+0.029L</td>
<td>0.092L (0.075-0.108), ( p&lt;0.001 )</td>
</tr>
<tr>
<td>SGRQ</td>
<td>+0.2</td>
<td>-3</td>
<td>-3.1 (-4.1—2.1), ( p&lt;0.001 )</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12.3%</td>
<td>19.6%</td>
<td>( p&lt;0.001 )</td>
</tr>
</tbody>
</table>

**Combination > fluticasone or salmeterol > placebo**

UPLIFT

• Prospective DB-RCT of tiotropium vs placebo over 4 years
• Patients: >10 p- y, >=age 40, FEV1/FVC <= 0.7, FEV1 <70%
• N = 5993 patients randomized
• Primary outcomes: yearly decline in FEV1
• Secondary outcomes: exacerbations, SGRQ, mortality, etc.

<table>
<thead>
<tr>
<th></th>
<th>placebo</th>
<th>tiotropium</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yearly decline in FEV1</td>
<td>32mL</td>
<td>27mL</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Exacerbations per pt-yr</td>
<td>0.85 +/- 0.02</td>
<td>0.73 +/- 0.02</td>
<td>HR 0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95%CI (0.81-0.91)</td>
</tr>
<tr>
<td>SGRQ</td>
<td></td>
<td></td>
<td>2.7 (2-3.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>16.5%</td>
<td>14.9%</td>
<td>HR 0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95%CI (0.79-1.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.09</td>
</tr>
</tbody>
</table>

LABA vs tio

• Prospective DB-RCT of tiotropium vs salmeterol over 1 year
• Patients: >10 p-y, >=age 40, FEV1/FVC <= 0.7, FEV1 <70% and at least 1 exacerbation in past year
• N = 7376 patients randomized
• Primary outcomes: time to first exacerbation
• Secondary outcomes: number of exacerbations, SGRQ, mortality, adverse events, etc.

### LABA vs tiotropium

<table>
<thead>
<tr>
<th></th>
<th>Salmeterol</th>
<th>Tiotropium</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to 1st exacerbation</strong></td>
<td>145 days</td>
<td>187 days</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td></td>
<td></td>
<td>(0.77-0.90)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Exacerbation per 100p-y</strong></td>
<td>0.72</td>
<td>0.64</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Rate ratio</strong></td>
<td></td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Serious adverse event</strong></td>
<td>16.5%</td>
<td>14.7%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>2.1%</td>
<td>1.7%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Roflumilast

- Prospective DB-RCT of roflumilast vs placebo over 1 year (2 studies in different sites)

- Patients: >20 p-y, >=age 40, FEV1/FVC <= 0.7, FEV1 <50% and at least 1 exacerbation in past year and had chronic productive cough

- N = 3901 patients randomized
- ICS withheld

- Primary outcomes: Δpre-FEV1, and rate of exacerbations
- Secondary outcomes: Δpost-FEV1, time to all-cause mortality, health utilization, adverse events, etc.

## Roflumilast

<table>
<thead>
<tr>
<th></th>
<th>placebo</th>
<th>roflumilast</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δpre-FEV1 (mL)</td>
<td>-9</td>
<td>40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Δpost-FEV1 (mL)</td>
<td>-4</td>
<td>50</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Moderate or severe exacerbation per p-y</td>
<td>1.37</td>
<td>1.14</td>
<td>RR 0.83, 95%CI (0.75-0.92)</td>
</tr>
<tr>
<td>Median time to first exacerbation</td>
<td>71 days</td>
<td>80 days</td>
<td>HR 0.89, 95%CI (0.80-0.98)</td>
</tr>
<tr>
<td>Median time to second exacerbation</td>
<td>148 days</td>
<td>177 days</td>
<td>HR 0.79, 95%CI (0.69-0.91)</td>
</tr>
<tr>
<td>Time to mortality</td>
<td>211.7 days</td>
<td>206.1 days</td>
<td>P=0.54</td>
</tr>
</tbody>
</table>

Chronic Azithromycin

- Prospective DB-RCT of azithromycin vs placebo for 1 year
- Patients: >40 yo, FEV1/FVC $\leq 0.7$, FEV1 $<50\%$, ever had hospital visit for AECOPD, and on O2 or had systemic steroids in past year.
- Primary outcome: time to first exacerbation
- Secondary outcomes: QOL, nasopharyngeal microbiology, study drug adherence
- N = 1142 randomized

### Chronic Azithromycin

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Azithromycin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to first exacerbation</td>
<td>174 d</td>
<td>266 d</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Exacerbation rate</td>
<td>1.83 per pt/yr</td>
<td>1.48 per pt/yr</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>Mortality</td>
<td>4%</td>
<td>3%</td>
<td>P = 0.87</td>
</tr>
<tr>
<td>Measurable hearing decrement</td>
<td>20%</td>
<td>25%</td>
<td>P = 0.04</td>
</tr>
<tr>
<td>Acquisition of macrolide resistance*</td>
<td>41%</td>
<td>81%</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Pulmonary Hypertension in COPD

- PH is common (≈90% in GOLD IV have mPAP > 20 mmHg)

- PH is risk factor for mortality with 5yr survival ≈36% if mPAP >25 mmHg

Pulmonary Hypertension
Group III: Hypoxemic Lung Disease

- Between 10% and 30% of heart failure admissions in the US are the result of cor pulmonale with the most common cause in the United States being COPD, in 1 study accounting for 84% of cases.
- PH severity is generally mild to moderate if Group III alone

Clinical Trials: COPD related PH

ETRA
• Bosentan
  – Worse oxygenation
  – No improvement in exercise capacity
    • Stolz ERJ 2008

PDE5 Inhibitor
• Acute Sildenafil
  – Worse gas exchange
  – Improved hemodynamics
    • Blanco AJRCCM 2010

• 12 week Tadalafil RCT
  – No improvement in 6MWD or QOL
    • Goudie Lancet Resp Med 2014

To date smoking cessation and supplemental O2 therapy are only effective therapies
Consider PDE4i and/or chronic macrolide

Active reduction of risk factor(s); influenza vaccination
*Add short-acting bronchodilator (when needed)*

*Add regular treatment with one or more long-acting bronchodilators (when needed); Add rehabilitation*

Add inhaled glucocorticosteroids if repeated exacerbations

Consider PDE4i

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

Consider PDE4i and/or chronic macrolide

Risk

GOLD Classification of Airflow Limitation

Symptoms (mMRC or CAT score)

- mMRC 0-1 CAT < 10
- mMRC ≥ 2 CAT ≥ 10

Risk Exacerbation history

- ≥ 2
- 1
- 0

(A)  (B)  (C)  (D)
Pulmonary Rehab

“Pulmonary rehabilitation is an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health-care costs through stabilizing or reversing systemic manifestations of the disease.”

Improved outcomes:
Dyspnea
Health related quality of life
Reduced hospital days and healthcare utilization
Increase strength and muscle mass

Concord Hospital Pulmonary Rehab - COPD

• Medicare Guidelines:

  – FEV/FVC <0.7 and FEV1<80% pred.
  – Diagnosis of COPD and/or presence of respiratory failure or cor pulmonale
Program Overview

• Patient Education
  – Basic lung function
  – Breathing re-training
  – Energy conservation
  – Medication and Oxygen Therapy Utilization

• Physical Training and Guidance for Maintenance
Concord Hospital Pulmonary Rehab

- January 2013-July 2014
- 181 patients discharged
- 126 patients (69%) COPD-emphysema
- Mean age 67 (SD 11), range 26-94
- 36% had more than 6 visits and f/u data available
Outcomes

• Dyspnea (MMRC)

• Quality of Life (CRQ)

• Depression (PHQ9)

• 6MWD (ft)
## Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Pre (+/-SD)</th>
<th>Post (+/-SD)</th>
<th>Δ</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMRC</td>
<td>1.9 (1.2)</td>
<td>1.3 (0.83)</td>
<td>-0.63</td>
<td>0.0005</td>
</tr>
<tr>
<td>CRQ-dyspnea</td>
<td>16.3 (5.5)</td>
<td>23.1 (6.0)</td>
<td>6.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRQ-emotional</td>
<td>32.3 (8.0)</td>
<td>38.3 (7.5)</td>
<td>5.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRQ-FTG</td>
<td>14.1 (4.7)</td>
<td>19.0 (4.5)</td>
<td>4.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PHQ9</td>
<td>5.3 (4.8)</td>
<td>3.5 (3.9)</td>
<td>-1.9</td>
<td>0.0014</td>
</tr>
<tr>
<td>6MWD (ft)</td>
<td>1079 (367)</td>
<td>1254 (347)</td>
<td>175</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Surgical Therapy

Lung volume reduction (LVR) surgery for selected patients with upper lobe predominant emphysema and low exercise capacity for whom there may be survival benefit (despite ~8% 90-day mortality in surgically treated patients).

Lung transplant benefit has to be balanced against current median estimated post-transplant survival of ~5 years.

Bronchoscopic LVR

• Minimally invasive approach to decrease hyperinflation and dead space ventilation of diseased lung units
Bronchoscopic LVR

- Techniques attempted: endobronchial valves, coils, endobronchial foam, steam application

- Trials are mixed with modest positive and negative results. Patient selection methods are being developed.

Lancet 2015; 386: 1066–73
Endobronchial coils
Pulmonary Referral*

- Supplemental O2 needed or chronic hypercarbia is present
- Frequent exacerbator (2-3+/yr)
- History of ICU admission
- Pulmonary Hypertension/cor pulmonale

- Young age or minimal smoking history
- Dyspnea out of proportion to spirometry
- Persistent symptoms despite attempt at first line therapy

* No published references, just my own rationale.
Summary

• COPD is bad for patients and part of a multi-morbid patient phenotype
• Exacerbations are best avoided and their frequency helps guide therapy intensity
• Oxygen supplementation and smoking cessation are the only things with known survival benefit
• Pulmonary rehab can help your patient be better with the lungs they have.
Have a good day. (we have work to do.)

McMullan DM and Cohen AG. NEJM: 2006; 354;4