Updates in Chronic Obstructive Pulmonary Disease
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Disclosures
• MedImmune – 2009
• Spiration - 2011

COPD - Definition
"Airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases."
- From the Executive Summary of the Global Initiative for Chronic Obstructive Pulmonary Disease (www.goldcopd.org)

Risk Factors for COPD

"What are my chances of getting COPD?"
• Approximately 30-40% of smokers develop COPD
  – Estimated 24 million in US have COPD
• Almost 1/6 people with COPD did not smoke
  – Second hand tobacco smoke
  – Environmental exposure
    • Dust/Particulate
    – Genetic factors

Histopathologic Features of COPD
BOLD Study – Burden of Obstructive Lung Disease

COPD Projected to be the Third-Leading Cause of Death by 2020

Clinical Features of COPD
- Usually presents in 5th decade of life
- Cough
  - Variably productive of sputum, clear to white
  - Worse in the morning
- Dyspnea
  - Insidious in onset
  - Activities abandoned to avoid sensation
- Weight loss or anorexia
- Muscle weakness
- Depression and anxiety

COPD - Diagnosis
Abnormal spirometry (FEV₁ and FVC less than expected)
Degree of abnormality is used to classify patient’s into disease stages (and guide clinical care)
- Mild
- Moderate
- Severe
- Very Severe

COPD Risk and Smoking Cessation
Predictors of rate of decline in lung function:
- Current Smoking: -21+/− 3.8 cc/year (P<0.001)
- Emphysema on CT: -13+/− 4.2 cc/year (P<0.001)


Mortality rates at 14.5 years by cause and smoking status

Surgeon General Recommendations
- Five first-line pharmacotherapies that reliably increase long-term smoking abstinence rates were identified:
  - Sustained-release bupropion
  - Nicotine gum
  - Nicotine inhaler
  - Nicotine nasal spray
  - Nicotine patch
- Newest therapy: varenicline
  - Chantix®

http://www.surgeongeneral.gov/tobacco/

Smoking Cessation
- Saves Lung Function
- Saves Lives
- Pharmacologic Options
- Patient Counseling
  - Even a brief (3 min) period of counseling to urge a smoker to quit results in smoking cessation rates of 5 to 10%


Therapy for Established Disease
- Steroids (inhaled and systemic)
- Beta agonists (Indacaterol)
- Anticholinergic therapy
- Roflumilast
- Oxygen
- Lung volume reduction / Lung transplantation
Inhaled Therapy

- Long and short acting medications
  - Beta agonists, Anticholinergics, Corticosteroids
- Goals of inhaled therapy
  - Palliation of symptoms
  - Prevention of exacerbations
  - Reduction in mortality

Towards a Revolution in COPD Health

- 6112 Subjects with COPD randomized to
  - Placebo
  - Salmeterol 50 ug BID
  - Salmeterol/fluticasone 50ug/500ug BID
  - Fluticasone 500ug BID
- Followed for 3 years
  - All cause mortality
  - Exacerbation frequency
  - Side effects

Salmeterol/Fluticasone Interim Summary

1. Salmeterol and Fluticasone use reduces risk of exacerbations
2. Use of either medication alone (or in combination) does not appear to reduce rate of decline in lung function
3. No definitive evidence that combined therapy saves lives (trend)

Tiotropium

- Long acting anticholinergic
- Maximum bronchodilation in 3 hours
- More selective than ipratropium
- Q 24 hour dosing
- Dry powder inhaler
Tiotropium Interim Summary

1. Tiotropium reduces risk of exacerbation
2. Tiotropium use improves symptoms
3. Tiotropium use does not appear to alter the rate of decline in lung function
4. Tiotropium use does not appear to reduce the COPD related risk of death

Salmeterol/Fluticasone vs Tiotropium for Exacerbations

- 1323 subjects with COPD
  - Randomized to
    - Tiotropium 18ug qd
    - Salmeterol/Fluticasone 50/500ug bid
- Outcomes
  - No difference in exacerbation rate (1.32 vs 1.28 respectively) P=0.66
  - Health status superior in Salmeterol / Fluticasone cohort
  - More pneumonias in those subjects taking combined therapy P=0.008

Am J Respir Crit Care Med Vol 177, pp 19-26, 2008

Roflumilast: Phosphodiesterase-4 Inhibitor

- Anti-inflammatory
- Improves lung function
- May reduce exacerbations
- Additive effect to LABA and LAMA on lung function
- Side effects: Nausea, diarrhea, weight loss, headache.

Lancet 2009;374:695.

Oxygen Therapy in COPD

- Demonstrated efficacy in patients with:
  - pO2 < 55 mm Hg (sat 88% or less)
  - Evidence of cor pulmonale, polycythemia or RVH

Tiep BL, Clinics in Chest Medicine 1990; Vol II 83: 597
Non-Pharmacologic Therapy

- Pulmonary Rehabilitation
- Lung Volume Reduction Surgery
  - NETT trial shows benefit for selected patients with emphysema.
- Lung Transplantation
  - ~450 transplants for COPD annually
  - Approx 33% of total transplants

Acute Exacerbations of COPD

Associated with
1. Impaired quality of life
2. More rapid decline in lung function
3. Higher health care expense
4. Higher mortality

Am J Respir Crit Care Med 2001;164:208-234.

Pathogenesis of Acute Exacerbations

Inflammatory condition
- Increased airway irritation/inflammation
- Increased mucus production and edema
- Increased resistance to airflow

Causes
- Infectious (bacterial/viral) – 80%
- Air pollution/noxious exposure
- Cardiac/Thromboembolic disease

Exacerbations: Who is at risk?

<table>
<thead>
<tr>
<th>% of Patients</th>
<th>GOLD 2 N=945</th>
<th>GOLD 3 N=900</th>
<th>GOLD 4 N=293</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized in past year</td>
<td>7</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>Frequent AECOPD</td>
<td>22</td>
<td>33</td>
<td>47</td>
</tr>
</tbody>
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Prevention of AECOPD

<table>
<thead>
<tr>
<th>Rate of AECOPD</th>
<th>No Treatment</th>
<th>Long-term beta agonists or anticholinergics</th>
<th>Long-term inhaled corticosteroids</th>
<th>Long-term inhaled antibiotics, anticholinergics, and beta agonists</th>
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How to reconcile the results?

- The increased risk of death did not persist after the course of azithromycin
- Azithromycin is proarrhythmic
- MACRO did not have similar cardiac signal
  - Smaller cohort but much longer treatment
- MACRO screened by EKG

Steroids and AECOPD?

Double blinded RPCT of systemic steroids in AECOPD (n=271)
- Placebo (n=111)
- Glucocorticoids for 2 weeks (n=80)
- Glucocorticoids for 8 weeks (n=80)
Stereoids: IV methylprednisolone 125mg q6hrs x 72 hours followed by 2 or 8 week taper of prednisone 60mg

Endpoints:
1. Hospital LOS
2. Improvement in lung function

NEJM 1999;340:1941-47
Outcomes

Average hospital LOS
- Placebo group: 9.7 days
- Combined steroid group: 8.5 days

Lung function
- FEV₁ improved faster in steroid treated subjects (seen as early as 24 hours)
- No difference in FEV₁ at 2 weeks post enrollment

Steroids: How much?

“The optimal starting dose of corticosteroids is not known…but should not exceed 2 weeks of therapy”

Typical dose:
- 80mg methylprednisolone q8 hrs x 48-72 hours
- Prednisone 40-60mg qd for remaining 2 weeks

Interim Summary

- Antibiotics – Yes
  - Typically fluoroquinolone, amoxicillin/clavunate
  - In presence of bronchiectasis – strongly consider ciprofloxacin (pseudomonas)
- Steroids – Yes
  - 2 week course
  - IV methylprednisolone changing to prednisone with clinical improvement
- Search for other causes:
  - Lack of improvement in 48 to 72 hours
    - Thromboembolic disease/ pulmonary vascular disease
    - Cardiac disease

“What is my risk of getting lung cancer?”

Risk of Lung Cancer

Summary

- Smoking prevention/cessation should be cornerstone of health policy
- Pharmacotherapy, including inhaled corticosteroids, may affect rate of decline in lung function
- Most pharmacotherapy reduces exacerbation risk by 20-25%.
- Pulmonary Rehabilitation is an underused modality.

National Lung Screening Trial (NLST)

- 53,000 current and former smokers, 2 modes of screening
  - Chest X-Ray
    - 442 lung cancer deaths
  - CT scan of the chest
    - 354 lung cancer deaths
- 20% reduction in mortality

Note: NLST (funded by NCI) was approx $ 200 M
http://www.cancer.gov/newscenter/pressreleases/NLSTResultsRelease
The following therapies reduce the risk of acute exacerbations of COPD

A. Inhaled short acting bronchodilators
B. Tiotropium
C. Salmeterol
D. Inhaled corticosteroids
E. Antibiotics
F. Oxygen
G. All of the above
H. B, C, and D

A 65 year old female (FEV₁ 60%) is currently using short acting bronchodilators with persistent sx, what would be the next medication to add? She had 2 episodes of bronchitis requiring antibiotics last winter.

A. Tiotropium once a day
B. Salmeterol twice a day
C. Inhaled corticosteroids
D. Combined salmeterol/corticosteroids
E. None of the above