COPD Update 2014

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Director, COPD Center
University of Colorado Health Sciences Center

What is COPD?

• Exposure
• Fixed Airflow Obstruction
• With or Without Symptoms

AJRCCM 163:1256, 2001
What is COPD?

- Symptoms
  - Breathlessness
  - ± Cough
  - ± Chest tightness

Ugly Facts

USA... 2010

- 3rd leading cause of death and disability (behind heart disease, cancer and strokes)
- Affects 16 million people (~ 14 million are undiagnosed)
- $50 billion per year
- 8 million outpatient visits
- 1.5 million ER visits
- 726,000 hospitalizations

Centers for Disease Control (CDC) and Prevention's National Center for Health Statistics (NCHS) report, Dec 10, 2010
What Happens in COPD Lungs?

“Arbol e Pulmones”
NF Voelkel
Small Airways Disease

Normal

COPD
Matthew Bailie  1793
The Morbid Anatomy of the Most Important Parts of the Human Body

Samuel Johnson 1709-1784
• Decreased vascularity in emphysema
COPD is not just a lung disease

- Heart and vascular disease
- Pulmonary Hypertension
- Lung cancer (4-6 fold)
- Osteoporosis
- Poor nutrition/weight loss
- Muscle dysfunction
- Depression
- Cognitive dysfunction

COPD is a disease of the entire body

COPD
Definition & Diagnosis
**Definition of COPD**

**GOLD Guidelines -- 2014**

1) Known risk factor
2) Airflow limitation that is not fully reversible
   - Not dependent on symptoms

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**Fletcher Peto Lung Function Curves**

Fletcher and Peto, 1977
COPD Risk Factors

• Exposures
  – Tobacco smoke
    • Including pipe and cigar smoke, passive smoke, intrauterine exposure (impaired lung development)
  – Occupational dust exposure
    • Mineral dusts: silica, coal, iron and other mineral dusts
    • Organic dusts: sawdust and grain dust

COPD Risk Factors

• Host
  – $\alpha$1-antitrypsin deficiency
  – Socioeconomic status
• HIV Seropositivity
• Childhood infection history
• Gender
Dysfunction/paralysis
Laryngeal neoplasm

Neoplasm
Stenosis
Amyloidosis
Tracheobronchomegally

Neoplasm
Stenosis
Amyloidosis
Bronchiectasis/CF
Sarcoidosis

Asthma
Sarcoidosis
HP, LAM, RB, OB, EG
Diffuse panbronchiolitis

COPD
Grade & Treatment
COPD Classification
GOLD Guidelines

Grade 1 (mild)
FEV₁ ≥ 80%

Grade 2 (moderate)
50% ≤ FEV₁ < 80%

Grade 3 (severe)
30% ≤ FEV₁ < 50%

Grade 4 (very severe)
FEV₁ < 30%

Non-pharmacologic Therapy
Smoking Cessation!!

“The Face of Addiction”
NF Voelkel

Colorado Quit Line  1-800-639-QUIT
Smoking Cessation

• Brief 3-minute period of counseling is effective

But, most effective:
• Structured Counseling + Social Support
• Outside social support
• Nicotine replacement
• Antidepressants (buproprion/nortriptyline)
• Chantix

GOLD Guidelines 2014

Persistent Smokers with Advanced COPD in Colorado

• Persistent Smokers
  – More likely to live alone (?) social isolation
  – Increased symptoms
  – Decreased QOL
  – Less use of inhaled medications
  – Less vaccination for PNA and Influenza
  – Trend toward higher ER visits

Ty Kiser, PharmD
Hypoxemia

Oxygen Therapy for Severe Resting Hypoxemia

- Increases survival > 15h/day
- Improves:
  - Hemodynamics
  - Polycythemia
  - Cognition
  - QOL
  - Healthcare utilization (maybe)
  - Not exercise

GOLD Guidelines  www.goldcopd.com
**Medical Research Council (MRC) Trial**  
*Ann Intern Med 93;391 1980*

- **Objective:** Determine the effect of LTOT on mortality
- **Design:** 87 patients studied over ≥ 3 years  
  Placebo vs. LTOT (~2L) at 15h per day
- **Inclusion Criteria**
  - Resting PaO₂ 40-60 mm Hg
  - Post-bronchodilator FEV₁ < 1.2 L
  - History of CHF with ankle edema
- **Results (LTOT vs Placebo)**
  - Improved survival
  - No improvement in healthcare utilization

**Nocturnal Oxygen Treatment Trial (NOTT)**  
*Ann Intern Med 93;391 1980*

- **Objective:** Determine the effect of LTOT on mortality
- **Design:** 203 patients studied over ≥ 1 year  
  Nocturnal vs. Continuous LTOT
- **Inclusion Criteria**
  - Resting PaO₂ ≤ 55 mm Hg
  - PaO₂ ≤ 59 mm Hg plus edema, HCT ≥ 55 or P pulmonale
- **Results (Continuous vs Nocturnal)**
  - Improved survival, QOL and cognition
  - No improvement in exercise
  - Trend toward improved COPD healthcare utilization

Tom Petty
**Isolated Nocturnal Hypoxemia**

- No accepted definition of nocturnal oxygen desaturation in COPD.
- Nocturnal hypoxemia is associated with:
  - *Increased mortality* (Fletcher ARRD 145;1070, 1992 & Chaouat ERJ 14;1002, 1999)
  - *Poor sleep quality by reduced sleep time, increase stage changes and frequent arousals* (Cormick Thorax 41;846, 1986)
- Randomized clinical trials show:
  - No improved mortality
  - Chaouat ERJ 14;1002, 1999
  - Mixed effects on sleep quality
    - Caverley ARRD 126;206, 1982
    - Fleetham ARRD 126;429, 1982

**Isolated Exertional Hypoxemia**

- Definition: Oxygen saturation ≤ 88% with exercise
- Exertional hypoxemia is associated with:
  - Increased Mortality
  - Casanova Chest 134;746, 2008
  - Drummond Chest 134;497, 2008
  - Kawakami Chest 81;182, 1982
  - Takigawa Respir Med 101;561, 2007
- Randomized clinical trials show:
  - Improvement in exercise capacity acutely (at initiation)
  - May improve quality of life short-term (6 weeks)
  - Long-term benefits are unknown
**Oxygen Therapy**

**Indications…**

- $\text{PaO}_2 \leq 55 \text{ mmHg}$
- $\text{SaO}_2 \leq 88$

OR

- $\text{PaO}_2 55 - 60 \text{ mmHg}$
- $\text{SaO}_2 \leq 89$
  - Pulmonary HTN
  - Peripheral edema
  - Polycythemia ($\text{HCT} > 55\%$)

**Rest**

**Exercise**

**Sleep**

- 30-45% desaturate
- $\text{SaO}_2 \leq 93\%$ - Predictive
- $\text{SaO}_2 > 95\%$ - Safe

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**Use of Oxygen Therapy in Colorado**

- **No oxygen therapy**
  - 2% hypoxemic at rest
  - 42% hypoxemic with exertion

- **Oxygen therapy**
  - 8% hypoxemic at rest
  - 58% hypoxemic with exertion

*Jason McCarl MD*
Pulmonary Rehabilitation

- Exercise training
- Nutritional counseling
- Disease education
  - Inhaler use
  - Oxygen
  - End of life

GOLD Guidelines www.goldcopd.com

Positive effects in all stages...

- Improves exercise capacity and QOL
- Reduces:
  - Dyspnea
  - Anxiety and depression
  - Number and length of hospitalization

GOLD Guidelines www.goldcopd.com
**Pulmonary Rehab in Colorado**

A

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<th>Participation (%)</th>
<th>Current Pulm Rehab</th>
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B

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<th>Participation (%)</th>
<th>Past Pulm Rehab</th>
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P=0.06

P=0.01

*Derek Linderman MD*

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**Pharmacologic Therapy**
Management of Stable COPD

- Pharmacotherapy for COPD is used to:
  1. Decrease symptoms (SOB, cough and sputum)
  2. Decrease exacerbations

- Not used to modify the long-term decline in lung function

GOLD Guidelines  www.goldcopd.com

COPD Symptom/Risk Model
**Bronchodilators**

- Decrease symptoms
- Decrease exacerbations
- Increase exercise capacity

...even in the absence of an effect on FEV₁

**Recommendation:**

<table>
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<th>Risk</th>
<th>Treatment</th>
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<tr>
<td>C</td>
<td>Yes-Regular</td>
</tr>
<tr>
<td>D</td>
<td>Yes-Regular</td>
</tr>
</tbody>
</table>

- **Persistent symptoms**
- **Repeated exacerbations**

**Bronchodilators**

- **β₂ Agonists**
  - Albuterol: 200μg QID, 3m 4-6h
  - Salmeterol (Serevent): 50-100μg BID, 25m 12h
  - Formoterol (Foradil): 6-12μg BID, 3m 12h
  - Indacaterol (Arcapta): 75-300μg qD, <5m >24h
  - Vilanterol (TBA): 25μg qD, 15m >24h

- **Anti-cholinergics**
  - Iprotropium (Atrovent): 40μg QID, 15m 6-8h
  - Tiotropium (Spiriva): 18μg qd, 30m 24h
  - Glycopyrronium (TBA): 44μg qd, 5m 24h
  - Aclidinium (Tudorza Pressair): 400μg BID, 30m 12h
**Tiotropium (Spiriva)**

- Long-acting, anti-cholinergic bronchodilator
- Blocker of M1 & M3 receptors
- **Benefits**
  - Improves lung function (short and long-term)
  - Relieves symptoms
  - Improves exercise performance
  - Reduces exacerbations
  - Improves health status
- **Superior to Ipratropium**
  - Better bronchodilator
  - Better quality of life
  - Decreased exacerbations
- **Superior to long-acting β2-agonists**
  - Better short- and long-term bronchodilator
  - Slightly fewer exacerbations than Serevent

Tashkin DP. Chest 125;249, 2005

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**Salmeterol (Serevent)**

- Long-acting, partial β2 agonist
- **Benefits**
  - Lung function (short and long-term)
  - Relieves symptoms
  - Reduces exacerbations
  - Improves health status
- **Combination with anti-cholinergics**
  - Additive effect with Ipratropium
- **Problems**
  - Possible tachyphylaxis

Tashkin DP. Chest 125;249, 2005
**Formoterol (Foradil)**

- Long-acting, complete β2 agonist
- **Benefits:**
  - Lung function (short and long-term)
  - Relieves symptoms
  - May improve exercise performance
  - Reduces exacerbations
  - Improves health status

- **Combination with anti-cholinergics**
  - Additive effects with Ipratropium
  - Additive effects Tiotropium (*van Noord* ERJ 26;214, 2005)

- **Problems**
  - No reported tachyphylaxis

*Tashkin DP. Chest 125;249, 2005*

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**Inhaled Glucocorticoids**

- Decrease symptoms
- Decrease exacerbations

**Recommendation:**

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- Persistent symptoms
- Repeated exacerbations
Combination Inhalers

- **Fluticasone/Salmeterol (Advair)**
  - DPI and HFA
  - Diskus: 100/50, 250/50 or 500/50mcg one puff BID
  - HFA 45/21, 115/21, 230/21 two puffs BID
- **Budesonide/Formoterol (Symbicort)**
  - HFA only
  - 80/4.5 or 160/4.5mcg two puffs BID
- **Mometasone/Formoterol (Dulera)**
  - HFA only
  - 100/5 or 200/5mcg two puffs BID
- **Fluticasone/Vilanterol (Breo Ellipta)**
  - DPI only
  - 100/25 mcg one puff daily

Clinical Trials
**Uplift Trial**  
*NEJM 359;1543 2008*

- **Objective:** Determine the effects of Spiriva on the long-term decline in lung function
- **Design:** 5993 patients studied over 4 years  
  Spiriva vs Placebo
- **Results**
  - No affect on the rate of FEV₁ decline
  - Improved pre- and post-bronchodilator FEV₁
  - Improved QOL ~ 3 units (SGRQ)
  - Decreased exacerbations (~15%), related hospitalizations (~15%) and respiratory failure (~33%)
  - No increased cardiovascular mortality

**POET-COPD Trial**  
*NEJM 364;1093 2011*

- **Objective:** Determine the effects of Spiriva vs. Serevent on prevention of COPD exacerbations
- **Design:** 7376 patients studied over 1 year  
  Spiriva vs Serevent
- **Results for Spiriva**
  - Increased the time to the first exacerbation (185 vs. 165 d)
  - Reduced the risk for an exacerbation by 17%
  - Increased time to the first severe exacerbation
  - Reduced the annual number of moderate and severe exacerbations
  - No increased mortality
Inspire Trial
AJRCCM 177;19 2008

• Objective: Compare the ability of Spiriva or Advair (500/50) to prevent COPD exacerbations
• Design: 1323 patients studied over 2 years
  Spiriva + Placebo
  Advair + Placebo
• Results
  – No difference in exacerbation rates
  – Spiriva: improved lung function but had a higher withdrawal rate
  – Advair: slightly better QOL, more PNAs, lower mortality (3% vs 6%)

TORCH Trial
NEJM 356;775 2007

• Objective: Determine whether Advair decreases mortality
• Design: 6112 patients studied over 3 years
  Placebo     Serevent   Fluticasone   Advair (500/50)
• Results
  – Mortality: Advair reduced mortality by 2.6% (17.5%) vs Placebo (P=0.052)
  – Placebo (15.2%), Serevent (13.5%), Fluticasone (16%), Advair (12.6%)
  – Advair vs Placebo
    – reduced exacerbations (25%), hospitalizations (17%),
    – increased lung function, QOL and PNAs (6%)
**Clinical Trial Summary**

- Spiriva and Serevent both decrease symptoms
- Spiriva decreases AECOPDs better than Serevent
- Advair and Spiriva both decrease AECOPDs equally
- Advair may give a survival advantage

**Inhaled Therapy**

- **Risk Group**
  - **A**
    - Short-acting bronchodilators prn
  - **B**
    - LAA + Albuterol prn
  - **C**
    - LAA + LABA
  - **D**
    - LAA + LABA + ICS
**MACRO Trial**

*NEJM 365;689 2011*

- **Objective:** Determine whether Azithromycin decreases COPD exacerbations
- **Design:** 1142 patients studied over 1 year
  Azithromycin (250mg per day) versus Placebo
- **Results**
  - **Time to first exacerbation:** 266 days vs. 174 days (P<0.001)
  - **Exacerbations per year:** 1.48 vs. 1.83 (P=0.001)
  - **QOL:** improved 2.8 units (P=0.004)
  - **Increased hearing loss:** 25% vs. 20% (P=0.04)

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**Additional Therapies**

- **Phosphodiesterase-4 inh (Roflumilast/Daliresp)**
  - Increases FEV₁ by ~50ml
  - Very small increase QOL
  - No effect on symptoms
  - Decreases COPD exacerbations (OR = 0.78)

- **Statins**
  - No effect on exacerbations
**Vaccinations**

- **Seasonal Flu**
  - Reduces serious illness and death by 50%
  
  *NEJM 331:778, 1994*

- **H1N1 Flu**

- **Pneumococcal vaccination before and after age 65**
  - Reduces disseminated pneumococcal infections in COPD patients by 35%
  
  *JAMA 270:1826, 1993*

  - Decreases CAP in patients with FEV₁ < 40%

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**COPD Exacerbations**
Systemic Steroids

• Decreases treatment failure by 46%
  – Effect not modified by route of administration
  – Lower dose PO equivalent to high dose IV
  – Efficacious in both inpatient and outpatient settings
• Reduces LOS by 1.4 days
• Increased risk of hyperglycemia and myopathy


Treatment length for severe AECOPDs (REDUCE Trial)

JAMA 309;2223, 2013

• Objective: Compare the outcomes of patients treated with 40mg prednisone for 5 days versus 14 days
• Design: Non-inferiority RCT of 314 patients
  • Primary outcome: Time to next AECOPD
• Results:
  – Overall - no difference in time to next AECOPD
  – Decreased hospital days in 5 day group
  – 11-13.6% required mechanical ventilation (? Type)
Antibiotics

- **Hospital**
  - Decreases risk of treatment failure by 13 - 66%
  - Reduces mortality by 78%
  - No effect on length of stay

- **Outpatient**
  - No clear effect on reducing treatment failure


Role of antibiotics in the treatment of COPD exacerbations (inpatient)

*JAMA 303;2035 2010*

- **Objective**: Compare the outcomes of patients treated with antibiotics in the first 2 hospital days
- **Design**: Observational study of 84,621 patients in 2006
  - ICU patients excluded
  - Primary outcome was treatment failure

- **Results**:
  - Overall – antibiotic-treated patients had decreased mechanical ventilation, mortality and lower readmission.
  - Propensity-matched analysis: Lower treatment failure in antibiotic-treated patients.
Non-invasive Ventilation

- Reduced need for endotracheal intubation by 65%
  - Increased efficacy as pH decreases
- Decreased mortality by 55%
- Shortened LOS by 2 days

Summary

• SPIROMETRY
• PULMONARY REHABILITATION
• OXYGEN
• MAXIMIZE BRONCHDILATORS

• THINK ABOUT PALLIATIVE CARE

Lung Volume Reduction Surgery
**National Emphysema Treatment Trial (NETT)**

**Group 1**
- ↑ Survival
- ↑ Exercise
- ↑ Quality of Life

**Group 2**
- ↑ Exercise
- ↑ Quality of Life

**Group 3**
- ↑ Quality of Life

*NEJM 348:2059, 2003*
**National Emphysema Treatment Trial (NETT)**

*Group 4*

*Survival*

*LVRS is not for everyone & it’s not a cure!!!*

*NEJM 348:2059, 2003*

*NEJM 345:1075, 2001*

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**Who can get LVRS?**
Who can get LVRS?

• Use less than 6 liters of oxygen
• Less than 75 years old
• No major medical problems
• Willing to undergo an extensive evaluation
• Willing to undergo intensive pulmonary rehabilitation