GOLD Objectives

- Increase awareness of COPD among health professionals, health authorities, and the general public
- Improve diagnosis, management and prevention of COPD
- Stimulate research in COPD

http://www.goldcopd.org

Definition of COPD

- COPD is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients.
- Its pulmonary component is characterized by 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.
- Advanced COPD is associated with gas exchange abnormalities and, in severe cases, respiratory failure that can progress to cor pulmonale.

Burden of COPD: Mortality

- COPD is a leading cause of mortality worldwide and projected to increase in the next several decades.
- COPD mortality trends generally track several decades behind smoking trends.
- In the US and Canada, COPD mortality for both men and women have been increasing.
- In the US in 2000, the number of COPD deaths was greater among women than men.

Risk Factors for COPD

- Genes
- Exposure to particles
- Tobacco smoke
- Occupational dusts
- Indoor air pollution from heating and cooking with biomass in poorly ventilated dwellings
- Outdoor air pollution
- Lung growth and development
- Oxidative stress
- Gender
- Age
- Respiratory infections
- Socioeconomic status
- Nutrition
- Comorbidities

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Pathophysiology of COPD

- Increased mucus production and reduced mucociliary clearance - cough and sputum production - increased airways resistance
- Loss of elastic recoil - airway collapse
- Increase smooth muscle tone
- Pulmonary hyperinflation/air trapping
- Gas exchange abnormalities - hypoxemia ± hypercapnia due to V/Q mismatch

Changes in Large Airways* of COPD Patients

Changes in Lung Parenchyma of COPD Patients

Changes in Pulmonary Arteries of COPD Patients

Concept of Protease-Anti-protease Imbalance in COPD
How does loss of elastic fibers in the lung lead to abnormalities in the mechanics of breathing and gas exchange?
In Emphysema, the EPP is Downstream during Expiration, Leading to Airway Closure.

Major Clinical Subtypes of COPD
- Emphysema
- Chronic bronchitis
- COPD with airway hyperreactivity

Overlap Between COPD and Asthma

Differential Diagnosis: COPD and Asthma

**COPD**
- Onset in mid-life
- Symptoms slowly progressive
- Long smoking history
- Dyspnea during exercise
- Largely irreversible airflow limitation

**ASTHMA**
- Onset early in life (often childhood)
- Symptoms vary from day to day
- Symptoms at night/early morning
- Allergy, rhinitis, and/or eczema also present
- Family history of asthma
- Largely reversible airflow limitation

α₁-Antitrypsin (AAT) Deficiency
- Enzyme prevents loss of lung elastic fibers
- Deficiency causes pan-lobular emphysema
- Over 75 allelic variants of AAT: Homozygous PIZZ variant: 15-30% of normal AAT levels (PiMM)
- Earlier development of COPD
  - Airflow obstruction in early 40s
  - Accelerated by 10 to 15 years
  - Occurs in 1:5000
- Z allele – 3-5% population

α₁-Antitrypsin (AAT) Deficiency
- Progressive dyspnea in young patients
- Accounts for 60% of emphysema cases <40 yrs
- 2% of all cases of COPD
- Pneumothorax, respiratory failure, cirrhosis
- Treatment
  - Stop smoking
  - Avoid pollution/dust
  - Weekly replacement therapy
  - ?Aerosol recombinant AAT
  - ??Gene therapy
Symptoms of COPD
- Cough, often productive
- Slowly progressive dyspnea
- A subset of patients with COPD have wheezing
- History of exacerbations, especially in the winter months

Signs of COPD
- Prolongs expiratory phase, distant breath sounds
- A subset of patients have wheezing
- Hyperinflation/barrel chest; decreased chest wall expansion
- In severe COPD, signs of pulmonary hypertension (e.g., loud P2) and right heart failure (e.g., peripheral edema)

Diagnosing COPD
- Spirometry (with and without bronchodilators to assess reversibility airway obstruction)
- CXR: Hyperinflation, bullae
- ECG (e.g., right heart strain, RVH)
- ABG (in selected patients): hypoxemia +/- hypercapnea
- Screen for α1-Antitrypsin deficiency if age < 45 or +FHx

Differential Diagnosis of COPD
- COPD
  Onset in mid-life, progressive symptoms, long history of smoking, exertional dyspnea, irreversible airflow limitation, productive sputum production in chronic bronchitis subtype
- Asthma
  Often, but not always, early age of onset, daily variation in symptoms, nighttime/early AM symptoms, family history, atopic history, largely reversible airflow limitation
- Bronchiectasis
  Large volume of purulent sputum, frequent bacterial infections, coarse râles, clubbing, bronchial dilation and wall thickening on CXR and Chest CT

Differential Diagnosis of COPD, cont’d
- Congestive heart failure (CHF)
  History of heart disease, orthopnea, paroxysmal nocturnal dyspnea, fine râles, CXR appearance (cardiomegaly, interstitial or alveolar edema), restrictive pattern on pulmonary function tests (PFTs)
- Bronchiolitis
  Onset in younger age/non-smokers, history of rheumatic diseases or fume exposure, diffuse panbronchiolitis associated with sinusitis, chest CT appearance
- Interstitial lung disease
  Adult-onset, often associated with rheumatic diseases, environmental exposure, restrictive pattern on PFTs, CXR and chest CT appearance
- Tuberculosis
  Constitutional symptoms, fever, +PPD, leukocytosis, apical/cavitary infiltrates

Question: Why perform spirometry?

Answer: Not everyone with lung disease has asthma or COPD!
Spirometry: Normal and Patients with COPD

Radiology of COPD

Motivational Medicine for Smokers

Radiology of Other Obstructive Lung Diseases

Bronchiectasis

Bronchiolitis

GOLD Staging for COPD Severity

<table>
<thead>
<tr>
<th>Stage</th>
<th>Severity</th>
<th>FEV₁/FVC*</th>
<th>FEV₁ (% predicted)*</th>
<th>Symptoms/Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mild</td>
<td>≤0.7</td>
<td>≥80</td>
<td>With or without symptoms</td>
</tr>
<tr>
<td>II</td>
<td>Moderate</td>
<td>≤0.7</td>
<td>50-80</td>
<td>With or without symptoms</td>
</tr>
<tr>
<td>III</td>
<td>Severe</td>
<td>≤0.7</td>
<td>30-50</td>
<td>With or without symptoms</td>
</tr>
<tr>
<td>IV</td>
<td>Very severe</td>
<td>≤0.7</td>
<td>&lt;30</td>
<td>without respiratory failure or RHF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30-50</td>
<td>plus presence of respiratory failure or RHF</td>
</tr>
</tbody>
</table>

*Post-bronchodilators
RHF = right heart failure (cor pulmonale)
COPD and Co-Morbidities

COPD patients are at increased risk for:

- Coronary artery disease
- Osteoporosis
- Respiratory infection
- Depression
- Diabetes
- Lung cancer
- Sleep apnea

Management of Stable COPD: Reduce Risk Factors

- One out of two long-term smokers will die of a smoking-related cause.
- Reduction of total personal exposure to tobacco smoke, occupational dusts and chemicals, and indoor and outdoor air pollutants are important goals to prevent the onset and progression of COPD.
- Smoking cessation is the single most effective intervention in most people to reduce the risk of developing COPD and stop its progression.

Management of Stable COPD: Smoking Cessation

- Pharmacotherapy is successful in assisting long-term smoking cessation. Options include: nicotine replacement therapy (NRT), bupropion (Zyban, Wellbutrin) and Varenicline (Chantix).
- The order of efficacy of pharmacotherapy for smoking cessation is: varenicline > bupropion > NRT. However, most studies report only modest (<20%) long-term quit rates.

Bronchodilators and COPD

Inhalation treatment vs. placebo

<table>
<thead>
<tr>
<th>Inhalation treatment</th>
<th>RR (95% CI)</th>
<th>RR</th>
<th>n*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipratropium</td>
<td>0.95 (0.78-1.15)</td>
<td>0.60</td>
<td>4</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>0.84 (0.78-0.90)</td>
<td>&lt;0.001</td>
<td>4</td>
</tr>
<tr>
<td>LABA</td>
<td>0.87 (0.82-0.93)</td>
<td>&lt;0.001</td>
<td>17</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>0.85 (0.75-0.96)</td>
<td>0.01</td>
<td>8</td>
</tr>
<tr>
<td>Combined LABA/ corticosteroids</td>
<td>0.77 (0.58-1.01)</td>
<td>0.06</td>
<td>4</td>
</tr>
</tbody>
</table>

Inhalation treatment vs. active control

<table>
<thead>
<tr>
<th>Inhalation treatment</th>
<th>RR (95% CI)</th>
<th>RR</th>
<th>n*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium vs. Ipratropium</td>
<td>0.77 (0.62-0.95)</td>
<td>0.01</td>
<td>4</td>
</tr>
<tr>
<td>Tiotropium vs. Tiotropium/LABA</td>
<td>0.97 (0.82-1.15)</td>
<td>0.71</td>
<td>1</td>
</tr>
<tr>
<td>Tiotropium vs. Tiotropium/LABA/corticosteroids</td>
<td>1.05 (0.87-1.25)</td>
<td>0.82</td>
<td>1</td>
</tr>
<tr>
<td>LABA vs. Ipratropium</td>
<td>0.89 (0.72-1.10)</td>
<td>0.29</td>
<td>4</td>
</tr>
<tr>
<td>LABA vs. Tiotropium</td>
<td>1.11 (0.93-1.33)</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>LABA vs. corticosteroids</td>
<td>1.06 (0.84-1.34)</td>
<td>0.64</td>
<td>4</td>
</tr>
<tr>
<td>LABA/corticosteroids vs. LABA</td>
<td>0.88 (0.75-1.04)</td>
<td>0.14</td>
<td>8</td>
</tr>
<tr>
<td>LABA/corticosteroids vs. corticosteroids</td>
<td>0.96 (0.80-1.15)</td>
<td>0.51</td>
<td>4</td>
</tr>
<tr>
<td>LABA/corticosteroids vs. Tiotropium</td>
<td>1.19 (1.02-1.38)</td>
<td>0.03</td>
<td>1</td>
</tr>
<tr>
<td>LABA/LABA vs. SABA</td>
<td>0.65 (0.45-0.95)</td>
<td>0.04</td>
<td>2</td>
</tr>
<tr>
<td>SABA vs. Ipratropium</td>
<td>0.58 (0.36-0.94)</td>
<td>0.03</td>
<td>1</td>
</tr>
</tbody>
</table>
Relative risk of mortality in COPD patients: Effect of inhalational treatments

<table>
<thead>
<tr>
<th>Inhalation treatment</th>
<th>RR (95% CI)</th>
<th>RR</th>
<th>P</th>
<th>n*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipratropium vs. placebo</td>
<td>1.20 (0.81-1.78)</td>
<td>0.35</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Tiotropium vs. placebo</td>
<td>0.94 (0.60-1.47)</td>
<td>0.78</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>LABA vs. placebo</td>
<td>0.91 (0.77-1.08)</td>
<td>0.28</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids vs. placebo</td>
<td>1.00 (0.86-1.16)</td>
<td>1.00</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>LABA/corticosteroids vs. placebo</td>
<td>0.82 (0.69-0.98)</td>
<td>0.03</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>LABA/corticosteroids vs. LABA</td>
<td>0.82 (0.52-1.38)</td>
<td>0.38</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>LABA/corticosteroids vs. corticosteroids</td>
<td>0.79 (0.67-0.94)</td>
<td>0.01</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>LABA/corticosteroids vs. Tiotropium</td>
<td>0.48 (0.27-0.85)</td>
<td>0.01</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Key: Ipratropium, short acting anticholinergic

*RR: Relative Risk, CI: Confidence Interval

Inhalation treatment Medications

- Ipratropium, short-acting anticholinergic
- Tiotropium, long-acting anticholinergic
- LABA, long-acting β-agonist
- Corticosteroids
- LABA/corticosteroids

Modified from: Wilt et al., Annals Internal Med. 147:639, 2007

Bronchodilators

- Bronchodilator medications are central to the symptomatic management of COPD. They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations.
- The principal bronchodilator treatments are anticholinergics, β2-agonists, and methylxanthines used singly or in combination.
- Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators.

Management of Stable COPD: Bronchodilators

Management of Stable COPD: Bronchodilators cont’d

- Ipratropium alone is ineffective in decreasing the incidence of acute exacerbations. However, an ipratropium/SABA combination is effective.
- Tiotropium is more effective than ipratropium in decreasing the incidence of acute exacerbations.
- Tiotropium, LABAs and corticosteroids are equally effective as monotherapy to prevent acute exacerbations. However, combination therapy with two or more of LABAs, anti-cholinergics, and corticosteroids is generally more effective than monotherapy.

Bronchodilators in Use in the US in 2008*

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Drug</th>
<th>Trade Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABA</td>
<td>Albuterol</td>
<td>Ventolin</td>
</tr>
<tr>
<td></td>
<td>Ipratropium</td>
<td>Atrovent</td>
</tr>
<tr>
<td>LABA</td>
<td>Fenoterol</td>
<td>Foradil</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>Ipratropium</td>
<td>Atrovent</td>
</tr>
<tr>
<td>SABA/Anticholinergic</td>
<td>Fenoterol/Ipratropium</td>
<td>Atrovent/Combivent</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>Beclomethasone</td>
<td>Budecort, Vanceril</td>
</tr>
<tr>
<td></td>
<td>Budesonide</td>
<td>Pulmicort</td>
</tr>
<tr>
<td></td>
<td>Fluticasone</td>
<td>Flonase</td>
</tr>
<tr>
<td></td>
<td>Flunisolide</td>
<td>Aerolab</td>
</tr>
<tr>
<td></td>
<td>Mometasone</td>
<td>Asmanex</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone</td>
<td>Triamcinolone</td>
</tr>
<tr>
<td>LABA/Glucocorticoid</td>
<td>Fluticasone/Budesonide</td>
<td>Synalar, Advair</td>
</tr>
</tbody>
</table>

*For use and reference in Table. It is provided for future reference only

Management of Stable COPD: Vaccines

- In COPD patients, influenza vaccines can reduce serious illness.
- Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older and for COPD patients younger than age 65 with an FEV1 < 40% predicted.
Management of Stable COPD:
Other Pharmacologic Treatments

- **Antibiotics**: Only used to treat infectious exacerbations of COPD
- **Antioxidant agents**: No effect of n-Acetylcysteine on frequency of exacerbations, except in patients not treated with inhaled glucocorticosteroids
- **Mucolytic agents, Antitussives, Vasodilators**: Not recommended in stable COPD

Management of Stable COPD:
Non-Pharmacologic Treatments

- **Rehabilitation**: All COPD patients benefit from exercise training programs, with improved exercise tolerance and symptoms of dyspnea and fatigue.
- **Oxygen Therapy**: The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival.

Why do Patients with COPD Experience Exercise Limitation?

Dynamic changes in lung volumes during exercise in normal lungs and COPD. Tidal volume ($V_T$) is able to expand, since IC remains constant. In COPD, increases in EELV force $V_T$ closer to the total lung capacity (TLC) and IC is reduced even at rest. Dynamic hyperinflation further increases EELV and reduces IC as minute ventilation increases. $V_T$ is unable to expand and patients cannot achieve high minute ventilation. From: Ferguson, Proc. Am. Thor. Soc. 3:176, 2006.

How Does Pulmonary Rehabilitation Work?

Effect of a high-intensity cycle ergometer exercise training program in a representative patient with COPD. Time courses shown are before ( ) and after ( ) a series of 45-min training sessions, three times a week for 7 wk. IC = Inspiratory Capacity. The increase in IC (TLC minus end expiratory lung volume) reflects decreased air trapping.

Management of Stable COPD:
Surgery

- **Lung volume reduction surgery**: To relieve bullae-induced “trapped lung.” Beneficial in selected patients, especially those with predominantly upper lobe emphysema with low exercise capacity.
- **Bronchoscopic lung volume reduction surgery and airway bypass stenting**: Bronoscopic placement of drug-eluting stents (left) or one-way valves (right) to relieve air trapping.
An exacerbation of COPD is defined as:

"An event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD."

The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution, but the cause of about one-third of severe exacerbations cannot be identified.

- The most common bacterial pathogens associated with acute exacerbations of COPD are: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.
- Patients experiencing COPD exacerbations with clinical signs of airway infection (e.g., increased sputum purulence) may benefit from antibiotics targeting suspected pathogens.

Inhaled bronchodilators (particularly inhaled β₂-agonists with or without anticholinergics) and oral glucocorticoids are effective treatments for exacerbations of COPD.

Noninvasive mechanical ventilation in exacerbations improves respiratory acidosis, increases pH, decreases the need for endotracheal intubation, and reduces PaCO₂, respiratory rate, severity of breathlessness, the length of hospital stay, and mortality.

**BiPAP, a Means of Delivering Non-invasive Positive Pressure Ventilation**

BiPAP = Bi-level positive airway pressure. BiPAP allows for different levels of positive airway pressure during inspiration and expiration. BiPAP decreases the work of breathing and improves alveolar ventilation while resting the respiratory musculature. The improvement in gas exchange with BiPAP occurs because of an increase in V̇ₐ and alveolar ventilation. Externally applied expiratory pressure (positive end-expiratory pressure, or PEEP) decreases the work of breathing by partially overcoming air trapping-reduced "auto-PEEP," which is frequently present in these patients.

**GOLD Website Address**

http://www.goldcopd.org