Chronic Obstructive Pulmonary Disease (COPD)
COPD: Outline

• Definition
• Etiology
• Epidemiology
• Pathophysiology
• Clinical Presentation
• Diagnosis
• Prevention
• Treatment
COPD: Definition

Chronic airflow obstruction due to chronic bronchitis and/or pulmonary emphysema
COPD: Definition

**Chronic** airflow obstruction due to chronic bronchitis and/or pulmonary emphysema
COPD is a chronic disease

• Not acute airflow obstruction
  – Bronchitis/bronchiolitis
  – Asthma attack

• Not (completely) reversible
  – Asthma – reversible airflow obstruction
COPD: Definition

Chronic airflow obstruction due to chronic bronchitis and/or pulmonary emphysema
Airflow Obstruction

- Definition of airflow obstruction
  - $\text{FEV}_1/\text{FVC} < 0.70$
  - aka “obstructive ventilatory defect”

- Alternative definition
  - $\text{FEV}_1/\text{FVC} < “lower limit of normal”$
COPD: Definition

Chronic airflow obstruction due to chronic bronchitis and/or pulmonary emphysema
Chronic Bronchitis

• Definition
  – persistent cough and sputum production for at least three months in at least two consecutive years

• Submucosal gland hyperplasia

• Airway edema

• Mucus plugging and airways fibrosis
Types of Airflow Obstruction

Intraluminal: e.g., Secretions

Intramural: e.g., Edema

Extraluminal: e.g., Loss of radial traction
COPD: Definition

Chronic airflow obstruction due to chronic bronchitis and/or pulmonary emphysema
Pulmonary Emphysema

- Destruction of acinar walls

- Physiologic effects
  - Loss of radial traction on airways
  - Increased lung compliance

- Consequences
  - Hyperinflation
  - Poor lung mechanics
Centrilobular emphysema
- Smoking-related
- Upper lobe predominant

Panlobular emphysema
- alpha-1 antitrypsin deficiency
- Lower lobe (basilar) or diffuse
Causes of Airflow Obstruction

- Upper airway obstruction
- Lower airway obstruction
  - COPD
  - Asthma
  - Bronchiectasis (e.g., cystic fibrosis)
  - Large airway obstruction
    - Tumor, stenosis, foreign body aspiration, et al.
  - Bronchiolitis
  - Pulmonary edema
  - Carcinoid syndrome
COPD: Definition

Chronic airflow obstruction due to chronic bronchitis and/or pulmonary emphysema

(Persistent post-bronchodilator FEV$_1$/FVC < 0.70

not due to diseases other than COPD)
Leading Causes of Death in the US, 2006

- Heart Disease: 800,000
- Cancer: 400,000
- Stroke: 200,000
- COPD: 400,000
- Accidents: 200,000

www.cdc.gov
COPD Is as Prevalent as Many Other Chronic Diseases Treated in Primary Care

Percent Change in Age-Adjusted US Death Rates

Risk Factors for COPD

- Cigarette smoke
- Occupational dust and chemicals
- Environmental tobacco smoke (ETS)
- Indoor and outdoor air pollution
- Genetic variation
Smoking and Lung Function

Anthonisen, JAMA 1994
Lung Function Over Time

Never smoked or not susceptible to smoke

Symptoms
Smoked regularly and susceptible to effects of smoking

Disability

Death

FEV$_1$ (%) Relative to Age 25

Age (years)

Fletcher BMJ 1977

stopped smoking at 45 (mild COPD)
stopped smoking at 65 (severe COPD)
Smoking and COPD risk

Lokke, Thorax 2006
α1-antitrypsin (AAT) Deficiency

• Autosomal co-dominant disorder caused by mutation in the SERPINA1 gene

• Phenotypes classified by migration in isoelectric pH gradient from A to Z (slowest migration)

Laurell and Eriksson - 1963
## AAT alleles

<table>
<thead>
<tr>
<th>Allele Groups</th>
<th>Examples</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>M</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>X (Glu363Lys)</td>
<td></td>
</tr>
<tr>
<td>Deficiency</td>
<td>S (Glu264Val)</td>
<td>Intracellular degradation or accumulation</td>
</tr>
<tr>
<td></td>
<td>Z (Glu342Lys)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$M_{\text{malton}}$ (Phe52del)</td>
<td></td>
</tr>
<tr>
<td>Null</td>
<td>Tyr160X</td>
<td>No mRNA or protein</td>
</tr>
<tr>
<td>Dysfunctional</td>
<td>$M_{\text{mineral springs}}$</td>
<td>Defective inhibition of elastase</td>
</tr>
<tr>
<td></td>
<td>Met358Arg</td>
<td></td>
</tr>
</tbody>
</table>

## AAT genotypes and emphysema risk

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Prevalence</th>
<th>A1AT Serum Concentration</th>
<th>Risk of Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>91%</td>
<td>150-350 mg/dL</td>
<td>Background</td>
</tr>
<tr>
<td>MS</td>
<td>6%</td>
<td>110-340 mg/dL</td>
<td>Background</td>
</tr>
<tr>
<td>MZ</td>
<td>3%</td>
<td>90-210 mg/dL</td>
<td>Background</td>
</tr>
<tr>
<td>SS</td>
<td>0.1%</td>
<td>100-200 mg/dL</td>
<td>Background</td>
</tr>
<tr>
<td>SZ</td>
<td>0.1%</td>
<td>75-120 mg/dL</td>
<td>20-50%</td>
</tr>
<tr>
<td>ZZ</td>
<td>0.02%</td>
<td>20-45 mg/dL</td>
<td>80-100%</td>
</tr>
</tbody>
</table>

**α1-antitrypsin Deficiency (AAT)**

- 2% of COPD pts have severe A1AD
  - 59,000 Americans
  - Only 10,000 are receiving replacement therapy
- AAT inhibits neutrophil elastase
- Panlobular emphysema
- Younger pts with **basilar** emphysema
- Can also cause liver disease
- Treatment
  - Intravenous pooled plasma α1-antitrypsin
  - May slow the decline in lung function
Matrix metalloproteinase-12 and COPD risk

Hunninghake, *NEJM* 2009
Respiratory System Mechanics

Gas Exchange

Ventilation

Vascular Changes

Causes of Disease

Structural Change

Functional Change

- Physical examination
- Radiographic examination
- Histological examination
Lung Compliance is Increased in Pulmonary Emphysema
Comparison of Lung Volume Parameters

Volume

Normal

COPD

TLC
IRV
ERV
RV

FRC

IC

V_T

V_T
Airway Resistance is determined by Airway Caliber

Intraluminal: e.g., Secretions

Intramural: e.g., Edema

Extraluminal: e.g., Loss of radial traction
Dynamic Airway Compression during Forced Expiration
Gas exchange in COPD

• Mild hypoxemia is common
• Severe hypoxemia is rare
• Mechanisms of hypoxemia
  – Increased V/Q mismatch (MAJOR)
  – Alveolar hypoventilation (minor)
• Shunt and diffusion abnormalities do NOT contribute to hypoxemia in COPD
Abnormal Ventilation in COPD

• Increased dead space ventilation
  – Emphysematous regions are poorly perfused
  – Increased work of breathing

• Alveolar hypoventilation
  – Common (but not universal) in advanced disease
  – Worsens during severe “exacerbations” (acute deterioration often in the setting of acute bronchitis)
Clinical Presentation of COPD

• Millions have early, asymptomatic COPD

• Common symptoms
  – Cough with sputum production (chronic bronchitis)
  – Exertional dyspnea
  – Muscular wasting

• During an exacerbation
  – Change in sputum quantity, color, or consistency
  – Wheezing
  – Increased dyspnea
Physical Exam in COPD

• Early disease = normal exam

• Common findings
  – Increased anteroposterior chest diameter
    • “Barrel chest”
  – Bilaterally diminished breath sounds
  – Muscular wasting

• During an exacerbation
  – Wheezing
  – Rhonchi
  – Cyanosis
COPD VS NORMAL: PA
COPD VS NORMAL: LATERAL
COPD VS NORMAL: CT
Diagnosing COPD

• Clinical presentation
• Airflow obstruction without reversibility
• Exclusion of alternative causes
  – Asthma
  – Bronchiecetasis (e.g., cystic fibrosis)
  – Congestive heart failure
  – Tuberculosis
  – Other causes of airflow obstruction
Spirometry is the BEST test for diagnosis and staging of COPD

<table>
<thead>
<tr>
<th>Stage</th>
<th>FEV$_1$/FVC</th>
<th>FEV$_1$</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Mild</td>
<td>&lt; 0.70</td>
<td>≥80% predicted</td>
<td></td>
</tr>
<tr>
<td>II: Moderate</td>
<td>&lt; 0.70</td>
<td>50 to 79%</td>
<td></td>
</tr>
<tr>
<td>III: Severe</td>
<td>&lt; 0.70</td>
<td>30 to 49%</td>
<td>PaO$_2$ ≥ 60 mm Hg, and PaCO$_2$ ≤ 50 mm Hg</td>
</tr>
<tr>
<td>IV: Very Severe</td>
<td>&lt; 0.70</td>
<td>30 to 49%</td>
<td>PaO$_2$ &lt; 60 mm Hg or PaCO$_2$ &gt; 50 mm Hg</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.70</td>
<td>&lt;30%</td>
<td></td>
</tr>
</tbody>
</table>
Management by COPD stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>FEV₁</th>
<th>Consider</th>
</tr>
</thead>
</table>
| I: Mild       | >80%  | • Risk factor reduction  
|               |       | • Influenza/pneumococcal vaccination  
|               |       | • Short-acting inhaled β2 agonists                                         |
| II: Moderate  | 50 to 79% | • Long-acting inhaled bronchodilators  
|               |       | • Pulmonary rehabilitation                                                  |
| III: Severe   | 30 to 49% | • Inhaled corticosteroids (if wheezing or repeated exacerbations)    |
| IV: Very Severe| <30%* | • Long-term oxygen therapy  
|               |       | • Surgical therapy                                                           |
| **ASK** | Identify smokers at every visit |
| **ADVISE** | Strongly urge all users to quit |
| **ASSESS** | Determine willingness to quit |
| **ASSIST** | Aid the patient in quitting |
| **ARRANGE** | Schedule follow-up contact |
Pharmacologic therapies for tobacco cessation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usage</th>
<th>6-month abstinence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine replacement</td>
<td></td>
<td>All about 25%</td>
</tr>
<tr>
<td>Nicotine polacrilex (gum)</td>
<td>2-4mg piece every 1-2 hrs x 8-12 weeks</td>
<td></td>
</tr>
<tr>
<td>Nicotine lozenges</td>
<td>1-2mg every hour</td>
<td></td>
</tr>
<tr>
<td>Nasal nicotine spray</td>
<td>0.5 mg inh each nostril hourly x 3-6 months</td>
<td></td>
</tr>
<tr>
<td>Nicotine inhaler</td>
<td>6-16 cartridges/day x 3-6 months</td>
<td></td>
</tr>
<tr>
<td>Transdermal nicotine (patch)</td>
<td>16-24hrs/day x 8 weeks</td>
<td></td>
</tr>
<tr>
<td>Oral medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion sustained release</td>
<td>150mg for 3 days, then 300mg daily x up to 6 months</td>
<td>24%</td>
</tr>
<tr>
<td>Varenicline</td>
<td>See next slide</td>
<td>33%</td>
</tr>
</tbody>
</table>
Varenicline

• Orally-available partial agonist at the α4β2 subunit of the nicotinic acetylcholine receptor

• Effects
  – Stimulates nicotinic receptor (reduces withdrawal)
  – Block nicotine from binding (reduces reward)

• Increases the odds of quitting three-fold (33% 6-month quit rate)

• Use:
  – 0.5mg daily x 3 days, then 0.5 mg BID for 4 days, then 1mg BID for 11 more weeks.
  – Quit smoking 1 weeks after initiating varenicline
  – Successful quitters at 12 weeks should continue for 12 more weeks

• Side effects: nausea, insomnia, abnormal dreams

• Concerns: ?suicidal thoughts, aggressive/erratic behavior
Suggested approach to smoking cessation

• Use the 5 A’s
• Dual approach
  – Counseling
  – Pharmacologic therapy
    • Varenicline most effective
    • May be combined with nicotine replacement
• Tailor therapy to the individual
  – Comorbidities
  – Preferences
### Selected Inhaled Medications for COPD

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Drug</th>
<th>Trade Names</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting β2-agonist (SABA)</strong></td>
<td>Albuterol</td>
<td>Ventolin</td>
</tr>
<tr>
<td></td>
<td>Terbutaline</td>
<td>Brethine</td>
</tr>
<tr>
<td></td>
<td>Pirbuterol</td>
<td>Maxair</td>
</tr>
<tr>
<td></td>
<td>Levalbuterol</td>
<td>Xopenex</td>
</tr>
<tr>
<td><strong>Long-acting β2-agonist (LABA)</strong></td>
<td>Formoterol</td>
<td>Foradil</td>
</tr>
<tr>
<td></td>
<td>Arformoterol</td>
<td>Brovana</td>
</tr>
<tr>
<td></td>
<td>Salmeterol</td>
<td>Serevent</td>
</tr>
<tr>
<td><strong>Anticholinergic</strong></td>
<td>Ipratropium (short-acting)</td>
<td>Atrovent</td>
</tr>
<tr>
<td></td>
<td>Tiotropium (long-acting)</td>
<td>Spiriva</td>
</tr>
<tr>
<td><strong>SABA/Anticholinergic</strong></td>
<td>Fenoterol/Ipratropium</td>
<td>Duovent</td>
</tr>
<tr>
<td></td>
<td>Albuterol/Ipratropium</td>
<td>Combivent</td>
</tr>
<tr>
<td><strong>Glucocorticoid</strong></td>
<td>Becolmethasone</td>
<td>Beclovent, Vanceril</td>
</tr>
<tr>
<td></td>
<td>Budesonide</td>
<td>Pulmicort</td>
</tr>
<tr>
<td></td>
<td>Fluticasone</td>
<td>Flovent</td>
</tr>
<tr>
<td></td>
<td>Flunisolide</td>
<td>AeroBid</td>
</tr>
<tr>
<td></td>
<td>Mometasone</td>
<td>Asmanex</td>
</tr>
<tr>
<td></td>
<td>Triamcinalone</td>
<td>Azmacort</td>
</tr>
<tr>
<td><strong>LABA/Glucocorticoid</strong></td>
<td>Formoterol/Budesonide</td>
<td>Symbicort</td>
</tr>
<tr>
<td></td>
<td>Salmeterol/Fluticasone</td>
<td>Advair</td>
</tr>
</tbody>
</table>

*Do not memorize this Table. It is provided for future reference, only.*
TORCH study: LABAs and ICS improve lung function in COPD

Calverley, NEJM 2007
# Relative risk of COPD exacerbation: Inhalational treatment vs. placebo

<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</td>
<td>0.95 (0.78-1.15)</td>
<td></td>
<td>0.60</td>
<td>4</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>0.84 (0.78-0.90)</td>
<td></td>
<td>&lt;0.001</td>
<td>4</td>
</tr>
<tr>
<td>LABA</td>
<td>0.87 (0.82-0.93)</td>
<td></td>
<td>&lt;0.001</td>
<td>17</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>0.85 (0.75-0.96)</td>
<td></td>
<td>0.01</td>
<td>8</td>
</tr>
<tr>
<td>Combined LABA/corticosteroids</td>
<td>0.77 (0.58-1.01)</td>
<td></td>
<td>0.06</td>
<td>4</td>
</tr>
</tbody>
</table>

Key: Ipratropium, short acting anticholinergic  
Tiotropium, long-acting anticholinergic  
LABA, long-acting β-agonist

TORCH study: Reduced mortality with combination therapy?

Calverley, NEJM 2007
Side effects of inhaled medications

- **β2-agonists**
  - Tremor
  - Tachycardiac
  - Hypokalemia
  - Hypoglycemia (rare)
  - LABA: Increased risk of asthma mortality?

- **Anti-cholinergics**
  - Dry mouth
  - Cardiovascular events? (conflicting evidence)

- **Inhaled glucocorticoids**
  - Oropharyngeal thrush (gargle & rinse to prevent)
  - Cataracts
  - Osteoporosis
  - Increased risk of pneumonia in COPD pts?
Surgical therapy for COPD

• Lung Volume Reduction Surgery (LVRS)
  – Resection of the upper 25% of both lungs
  – Improves lung compliance, symptoms, and outcomes

• Lung transplantation
  – Replacement of one or both lungs with lungs from a deceased donor
  – 50% mortality at 5 years

• Selected candidates only!!