COPD- New Therapies for an Old Disease

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Objectives

- Explain the etiology and pathophysiology of COPD
- Differentiate between the various stages of COPD according to the current GOLD guidelines
- Review the current therapeutic options to treat patients with COPD
- Formulate a stepwise approach to the treatment of a patient with COPD

Guidelines

Global Initiative for Chronic Obstructive Lung Disease (GOLD)

www.goldcopd.org
Old Face of COPD

Impact of COPD
- 12.7 million in US diagnosed in 2011
- Estimated 24 million affected
- Morbidity & Mortality
  - Third most common cause of death in US in 2009
  - 133,965 deaths (2009)
  - 715,000 hospitalizations (2010)
  - Females deaths (70,000) > Males (64,000) in 2009
- 1 DEATH EVERY 4 MINUTES

New Face of COPD
COPD Mortality Rate Increasing


Costs of COPD

- $29.5 billion (direct)
  - Hospital visits
- $8 billion (morbidity)
- $12.4 billion (mortality)

$49.9 BILLION TOTAL COSTS IN 2010

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**Definition of COPD**

Disease 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.

**Risk factors for COPD**

- SMOKING
- Occupation
- Indoor & outdoor pollution
- Genetic
  - Alpha-1-antitrypsin deficiency
- History of severe childhood infections
- Socioeconomic status

**Inflammatory Process in COPD**

Chronic Bronchitis: chronic or excessive mucus secretion most days during a period of at least 3 months for at least 2 consecutive years.

Emphysema: condition of the lung characterized by abnormal, permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls, yet without obvious fibrosis.

COPD Clinical Presentation:
- Chronic bronchitis
  - overweight
  - productive cough
  - increased dyspnea on exertion
  - rales/rhonchi
  - peripheral edema
  - Cyanosis
  - “blue bloater”
- Emphysema
  - thin
  - increased dyspnea at rest
  - tachypnea
  - flushed
  - “pursed-lip” breathing
  - use of accessory muscles to breath
  - “pink puffer”
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Assessment

Severity of Airflow Limitation Based on Post-Bronchodilator FEV₁
(Only for patients with FEV₁/FVC < 0.70)

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<tr>
<th>GOLD</th>
<th>Mild</th>
<th>FEV₁ ≥ 80% predicted</th>
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<tr>
<td>GOLD</td>
<td>Moderate</td>
<td>50% ≤ FEV₁ &lt; 80% predicted</td>
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<td>GOLD</td>
<td>Severe</td>
<td>30% ≤ FEV₁ &lt; 50% predicted</td>
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<tr>
<td>GOLD</td>
<td>Very Severe</td>
<td>FEV₁ &lt; 30% predicted</td>
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Assess symptoms

- COPD assessment test (CAT)
  - [http://catestonline.org/](http://catestonline.org/)
  - 8-item
  - Score ranges 0-40 (change ≥ 2 significant)
- Modified British Medical Research Council (mMRC)
  - [http://copd.about.com/od/copdbasics/a/MMRCDyspnScale.htm](http://copd.about.com/od/copdbasics/a/MMRCDyspnScale.htm)
  - 5-item
  - Grade 0-4 (change ≥ 1 significant)
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Goals of therapy for COPD

- Reduce progression of airflow obstruction
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat exacerbation's
- Reduce mortality

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Non-pharmacologic treatment COPD

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Benefits of smoking cessation

- 20 minutes
  - BP, HR
- 12 hours
  - carbon monoxide level in blood
- 2 weeks-3months
  - circulation & lung function

Accessed 2/14
Benefits of smoking cessation

- 1 year
  - Excess risk of coronary heart disease reduced by 50% compared to those who continue to smoke
- 2-5 years
  - Risk of stroke equal to non-smoker
- 10 years
  - Risk of lung cancer by 50% compared to those who continue to smoke
- 15 years
  - Risk of coronary heart disease similar to non-smoker


COEF Risk and Smoking Cessation

Graph by Boehringer Ingelheim Pharmaceuticals, Inc. which was adapted from Fletcher CM, Peto R: The natural history of chronic airflow obstruction. Brit Med J 1977; 1:1645-1648.

Smoking cessation products

- Nicotine gum (Nicorette 2,4mg)
- Nicotine patch (Nicoderm 7,14,21mg)
- Nicotine inhaler (Nicotrol inhaler 10mg)
- Nicotine nasal spray (Nicotrol NS 0.5mg)
- Nicotine lozenge (Committ 2mg, 4mg)
- Bupropion SR (Zyban 150mg)
- Varenicline (Chantix 0.5mg, 1mg)
CVS Leads By Example!

- February 5, 2014, CVS announced that it will no longer sell cigarettes and other tobacco products in its stores (7600 store nationwide)


Electronic cigarettes

- Designed to deliver nicotine or other substances via vapor.
- Composed of rechargeable battery-operated heating element, replaceable cartridge, and atomizer.
- Cartridge contains 0-16mg of nicotine
- Diethylene glycol, irritants, genotoxins, animal carcinogens (nitrosamines)

http://www.fda.gov/forconsumers/consumerupdates/ucm225210.htm accessed 2/14
http://www.fda.gov/newsevents/publichealthfocus/ucm252360.htm accessed 2/14

Electronic cigarettes Regulation

- FDA has not evaluated e-cigarettes for safety or effectiveness
  - Limited FDA laboratory studies found significant variation in quality control (see previous slide)
  - Family Smoking Prevention and Tobacco Control Act (TCA) 2009 amended the Federal Food, Drug, and Cosmetic Act (FDCA) to give FDA authority to regulate “tobacco products.”
  - FDA issued warning letters to 5 distributors of violations of the Federal Food, Drug, and Cosmetic Act (FDCA)
  - Between 2008-2010 the FDA detained and/or refused admission of products offered by Sottera, Inc.

http://www.fda.gov/forconsumers/consumerupdates/ucm225210.htm accessed 2/14
http://www.fda.gov/newsevents/publichealthfocus/ucm252360.htm accessed 2/14
Electronic cigarettes Regulation

- In 2010, US Court of Appeals for the DC Circuit, in Sottera, Inc. v. FDA
  - Court determined that the FDA can regulate e-cigarettes and other products as "tobacco products" and are not drugs/devices unless they are marketed for therapeutic purposes
  - FDA filed in 12/2013 to amend the FDCA & TCA regarding other tobacco products that meet the definition of "tobacco products" be subject to FDA regulation

Electronic cigarettes Use amongst Middle & High School Students

Pharmacologic treatment COPD

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<td>ICS-LABA or LAMA</td>
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<td>PDE-4 inhibitor; SABA +/- SAMA; Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS-LABA and/or LAMA</td>
<td>ICS-LAMA; ICS-LABA+LAMA; LAMA + LABA; LAMA + PDE-4 inhibitor</td>
<td>Carbocysteine; SABA +/- SAMA; Theophylline</td>
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**=P<0.05 **=P<0.01
Short-acting Muscarinic Antagonist (SAMA)

- Ipratropium (Atrovent HFA®, Ipratropium 0.02% neb soln)
- Dosage
  - MDI 2 puffs qid
  - Neb soln 500mcg tid-qid
- Adverse effects
  - Dry mouth

Long acting muscarinic antagonist (LAMA)

- Tiotropium bromide (Spiriva Handihaler®)
  - M-3 receptor blocker
  - 1 puff (18mcg) daily
- Adverse effects
  - Dry mouth, URI, pharyngitis, sinusitis
- Do not use in conjunction with SAMA or LAMA

Tiotropium & Mortality

  - Meta-analysis of randomized-controlled trials
    - 5 RCT included
    - RR 1.52 (95% CI, 1.06-2.16) of mortality
**Tiotropium & Mortality**

- Wise RA, et al. NEJM 2013
  - RDBPC Tiotropium Respimat® (2.5, 5mcg) vs Handihaler® (18mcg)
  - n=27,135
  - mean follow-up 2.3 years
  - Risk of Death HR 0.96 (95% CI, 0.84 to 1.09)
  - Non-superior with respect to risk of 1st exacerbation 0.98 (95% CI, 0.87 to 1.14)

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**Long acting muscarinic antagonist (LAMA)**

- Aclidinium (Tudorza pressair®)
  - M-3 receptor blocker
  - 1 puff (400mcg) twice daily
  - Adverse effects
    - Headache, pharyngitis, sinusitis
  - Do not use in conjunction with SAMA or LAMA

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**Beta-2 agonist in COPD**

- Short-acting beta-2 agonist (SABA)
  - Albuterol 2-4 puffs (MDI+spacer)q4-6hrs prn or 2.5-5mg(nebulizer)q4-6hrs prn
- Long-acting beta-2 agonist (LABA)
  - Salmeterol (Serevent Diskus®) 1 puff BID
  - Formoterol (Foradil Aerolizer®) 12mcg puff BID; (Perforomist®) 20mcg neb BID
  - Aformoterol (Brovana®) 15mcg neb BID
  - Indacaterol (Arcapta neohaler®) 75mcg dpi once daily
Combination Inhalers

- **SABA + SAMA**

<table>
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<tr>
<th>Medication</th>
<th>Device</th>
<th>Dose</th>
<th>Frequency</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combivent® Respimat® (albuterol/ipratropium)</td>
<td>MDI</td>
<td>100 mcg/20 mcg</td>
<td>1 INH QID</td>
<td>$$$$$$</td>
</tr>
<tr>
<td>Duales™ (albuterol/ipratropium)</td>
<td>NEB</td>
<td>1.5 mcg/1.5 mcg</td>
<td>3 INH</td>
<td>$$$$$$</td>
</tr>
</tbody>
</table>

- **LABA + LAMA**

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<th>Device</th>
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<th>Frequency</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anoro® Ellipta® (umeclidinium/vilanterol)</td>
<td>DPI</td>
<td>62.5 mcg/mg</td>
<td>1 INH daily</td>
<td>??</td>
</tr>
</tbody>
</table>

- **LABA + ICS**

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<th>Device</th>
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<th>Frequency</th>
<th>Cost</th>
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<tbody>
<tr>
<td>Advair® Diskus® (fluticasone/salmeterol)</td>
<td>DPI</td>
<td>250/50, 500/50 mcg</td>
<td>1 INH BID</td>
<td>$$ – $$$</td>
</tr>
<tr>
<td>Symbicort® (budesonide/formoterol)</td>
<td>MDI</td>
<td>160/4.5 mcg</td>
<td>2 INH</td>
<td>$$$</td>
</tr>
<tr>
<td>Breo® Ellipta® (fluticasone furoate/vilanterol)</td>
<td>DPI</td>
<td>100/25 mcg</td>
<td>1 INH daily</td>
<td>$$</td>
</tr>
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**Breo Ellipta®**  
(fluticasone furoate/vilanterol)

- Fluticasone furoate/vilanterol 100/25 mcg once daily
- Adverse effects
  - Nasopharyngitis, URTI, Headache, Oral candidiasis
- Drug interactions
  - CYP 3A4 inhibitors (ketoconazole) increase effects
  - Hepatic impairment (moderate-severe )
  - No dose adjustment but 3X exposure to FF

**Anoro Ellipta®**  
(umeclidinium/vilanterol)

- Umeclidinium/vilanterol 62.5/25 mcg once daily (approved 12/18/13)
- Adverse effects
  - Pharyngitis, sinusitis, LRTI, diarrhea, constipation, extremity pain, muscle spasm, neck & chest pain
- Additive interaction with other anticholinergics
- Drug interactions
  - CYP 3A4 inhibitors (ketoconazole) increase effects
Calverley PM, et al. NEJM 2007

- Double-blind, randomized, placebo controlled, multi-center study
- N=6184
- 2 week run-in
- 3 year treatment period (all taken twice daily)
  - Placebo
  - 50mcg SALM
  - 500mcg FP (high dose)
  - 500mcg FP (high dose)+ SALM 50mcg

Results (FP/SALM vs placebo)

- Risk of death (HR=0.825, 95% CI=0.681 to 1.002; p=0.052)
- Rate of moderate/severe exacerbation (HR=0.75 95% CI=0.69 to 0.81 p<0.001)
  - NNT=4
- Rate of severe exacerbation requiring hospital (HR=0.83 95% CI=0.71 to 0.98 p<0.03)
- Requirement systemic steroid (HR=0.57 95% CI=0.51 to 0.64 p<0.001)
- FEV1 difference 0.092 (p<0.002)
- SGRQ change in score -3.1 (-4.1 to -2.1 p<0.001)

Results (FP/SALM vs SALM)

- Risk of death (HR=0.932, 95% CI=0.765 to 1.134; p=0.48)
- Rate of moderate/severe exacerbation (HR=0.88 95% CI=0.81 to 0.95 p<0.001)
- Rate of severe exacerbation requiring hospital (HR=1.02 95% CI=1.02 to 1.20 p=0.79)
- Requirement systemic steroid (HR=0.71 95% CI=0.63 to 0.79 p<0.001)
- FEV1 difference 0.050 (p<0.001)
- SGRQ change in score -2.2 (-3.1 to -1.2 p<0.001)
ICS + LABA in COPD

<table>
<thead>
<tr>
<th>Study</th>
<th>FEV₁</th>
<th>Dyspnea</th>
<th>QOL</th>
<th>Exacerbation Rate</th>
</tr>
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<tr>
<td>Calverley 2007 FP/SALM vs SALM</td>
<td>↑</td>
<td>n/a</td>
<td>Improved</td>
<td>↑</td>
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<tr>
<td>Calverley 2003 FP/SALM vs SALM</td>
<td>↑</td>
<td>Improved</td>
<td>Improved</td>
<td>↑</td>
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<tr>
<td>Mahler 2002 FP/SALM vs SALM</td>
<td>–</td>
<td>Improved</td>
<td>–</td>
<td>n/a</td>
</tr>
<tr>
<td>Hanania 2003 FP/SALM vs SALM</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>n/a</td>
</tr>
<tr>
<td>Szafranski 2003 BUD/FORM vs FORM</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>↓</td>
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PDE-4 inhibitor

- Roflumilast (Daliresp®)
  - GOLD 3 & 4
  - 500mg tab once daily
  - Adverse effects
    - GI (diarrhea, wt loss, nausea)
    - Headache, dizziness, insomnia
  - Drug interactions
    - CYP 3A4 inhibitors (cimetidine) increase effects
    - CYP 3A4 inducers (rifampin) decrease effects

Inhaled corticosteroids in COPD

- Inhaled steroids may be useful in
  - GOLD 3 & Stage 4
  - ↑ exacerbations
  - ↑ symptoms, lung function, & QOL
  - ↑ risk of pneumonia
- Combination therapy with LABA is more effective than individual agents

Oral corticosteroids in COPD

- Leuppi JD, et al. JAMA 2013
  - Treatment
    - 40mg po daily X 5 days vs 14 days
  - Primary Endpoint
    - Time to next exacerbation in 6 months
  - Results
    - HR 0.95 (90% CI, 0.70 to 1.29)

Antibiotics in COPD

- Patients experiencing COPD exacerbations with clinical signs of airway infection (i.e. increased dyspnea, sputum volume & purulence) may benefit from antibiotic treatment
  - Organisms: Strep pneumoniae, H. influenza
  - Start appropriate antibiotic and continue for 5-10 days

Expectorants / Mucolytics

- Generally NOT useful
    - n=120; 50-80 yrs; GOLD 1-4
    - NAC 600mg po BID vs placebo X 1 yr
    - FEF 25-75% (p=0.37)
    - exacerbation rate 0.75 (p<0.019)
    - n=1006; age 66+/8.7 yrs; GOLD 2-3
    - NAC 600mg po BID vs placebo X 1 yr
    - exacerbation rate 0.78

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Non-pharmacologic treatment COPD

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**Vaccinations in COPD**

- Annual seasonal & H1N1 influenza
- Pneumococcal vaccination
  - 1 before age 65 & 1 after age 65


**On the horizon**

- Aclidinium/formoterol
- Mometasone/formoterol (Dulera®)
- Vilanterol
- Glycopyrolate
- Glycopyrolate/indacaterol
- Olodaterol