COPD 2009

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Definition of COPD

COPD is a preventable and treatable disease state that is
- Characterized by airflow limitation that is not fully reversible
- Usually progressive
- Associated with an abnormal inflammatory response of the lungs to noxious particles or gases
- Primarily caused by cigarette smoking
- Related to systemic consequences

Who is the COPD Patient?

Perception

- COPD is a disease of the elderly
- COPD afflicts the working age population
- 50% of COPD patients are younger than age 65
- Patients < 65 accounted for 67% of COPD office visits and 43% of hospitalizations
- COPD is as common as asthma and diabetes in population aged 45-64

Reality

- COPD is on the Rise
- COPD is a disease of men

COPD in Younger Patients

- COPD is on the Rise
- COPD affects the working age population
- 50% of COPD patients are younger than age 65
- Patients < 65 accounted for 67% of COPD office visits and 43% of hospitalizations
- COPD is as common as asthma and diabetes in population aged 45-64
COPD in women is on the rise

- In 2000, women accounted for 63% of all self-reported cases of COPD.¹
- COPD mortality rates for women (1980-2000) have increased by 182%²
- In 2000, COPD hospitalizations for women outnumbered those for men (404,000 vs 322,000).
- Increased morbidity and mortality in women likely reflects increased smoking by women.²

¹Mannino, et al. MMWR 2002;51(suppl 1-16). ²CDC. Facts about Chronic Obstructive Pulmonary Disease. Available at http://www.cdc.gov. Netter illustrations used with permission from Icon Learning Systems, a division of MediMedia USA, Inc. All rights reserved.

Clinical COPD Is Just the Tip of the Iceberg

Prevalence in NHNES III

- Repeated exacerbations and hospitalizations

When to Perform Spirometry:
Diagnosis of COPD (GOLD Guidelines)

- Exposure
- Tobacco
- Occupational Pollution
- Symptoms
- Exercise Impairment
- Dyspnea, Wheezing Cough ± Sputum

Spirometry Measurement in COPD

Spirometry measures maximal volume of air forcibly exhaled from the point of maximal inhalation and the volume of air exhaled during the first second.


Lung Volume Terminology

Normal

COPD

Comparison of Lung Volume Parameters

Effects of Exercise on Hyperinflation

Damaging Cycle of COPD

Adapted from Global Initiative for Chronic Obstructive Lung Disease (GOLD) Executive Summary. Updated 2003. Available at: http://www.goldcopd.com
Damaging Cycle of COPD

COPD
- Expiratory Flow Limitation
- Air Trapping
- Hyperinflation

Dyspnea
Deconditioning
Reduced Exercise Endurance
Inactivity

Poor Health-Related Quality of Life

An abbreviated history of COPD therapy

Symptomatic relief
- Reduce Hyperinflation
- Acute Bronchodilation
- Improve Health Status

What we can do

Effects of Bronchodilators on Clinical Outcomes in Patients With COPD

<table>
<thead>
<tr>
<th>FEV1 Modifier</th>
<th>Lung Volume</th>
<th>Dyspnea</th>
<th>HRQL*</th>
<th>Exercise Tolerance*</th>
<th>Disease Modifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting beta2-agonists</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Long-acting beta2-agonists</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Long-acting anticholinergic</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Although the results from a number of drug studies are not uniform, many of the drugs studied provide these results. N/A = evidence not available.

Adapted from Celli et al. Eur Respir J. 2004;23:932-946.
An abbreviated history of COPD therapy

- Prevent/Treat Exacerbations
- Symptomatic relief
- Improve Health Status
- Reduce Hyperinflation

What we can do

COPD Exacerbations

Defined as an acute change in dyspnea, cough and/or sputum sufficient enough to warrant therapy change

In a 12-month observational study (n=127), 77% of patients reported having at least one exacerbation

The prevention of exacerbations is recognized as a key goal in COPD disease state management

*Based on diary records of symptom-defined and healthcare-defined exacerbations.

The Majority of Healthcare Costs for Managing COPD Are Associated With Exacerbations

In 2005, there were approximately 721,000 hospitalizations due to COPD

- Average costs (2001 data) for a COPD-related:
  - Emergency Department Visit—$571
  - Hospitalization ranged from $5,997 (standard hospitalization) to $36,743 (ICU plus intubation)

50%-75% of all COPD costs are for services associated with exacerbations

Outcomes of AECOPD

- In ICU patients: Hospital mortality – 20%-24%
- In hospitalized patients: Hospital mortality – 2.5%-10%
- In ER patients: Relapse (repeat ER visit) – 22%-32%
- In outpatients: Treatment failure rate – 13%-33%

Health Status Changes Following an Exacerbation

- SGRQ Score

Prevention of Acute Exacerbations in COPD

COPD Exacerbations
Preventative Measures

Long acting bronchodilators
Inhaled corticosteroids
Phosphodiesterase inhibitors
Mucolytics/Antioxidants
Immunizations-influenza vaccine pneumococcal vaccine
OM-85(Broncho-vaxim)
Macrolides
Case management
Lung Volume Reduction Surgery

Prevention of COPD Exacerbations:
Pneumococcal and Influenza Vaccination

Relative Risk (95% CI) of Exacerbation


Prevention of AECOPD
Additive Drug Effects

Favors Active Treatment  Favors Placebo

TRISTAN LABA ICS Comb
Calverley LABA ICS Comb
Mahler LABA ICS Comb
Szafranski LABA ICS Comb
Summary LABA ICS Comb

0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0

Adapted from Sin et al. JAMA. 2003;290:2301-2312.

Prevention of COPD Exacerbations:
Influenza Vaccination


COPD Exacerbations
Preventative Measures

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COPD Exacerbations
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Case management
Lung Volume Reduction Surgery
Management of Acute Exacerbations in COPD

**Bronchodilators in Acute Exacerbations of COPD**
- Initiate or increase dose of short-acting inhaled beta₂-agonists (e.g., albuterol)
- Add anticholinergic (e.g., ipratropium) if no prompt response
- Role of methylxanthines (aminophylline, theophylline) is controversial: some benefits as third-line drug, but side effects and drug interactions
- Delivery method (nebulization or metered dose) can be individualized

Systemic Corticosteroids in Acute Exacerbations of COPD

- Corticosteroids shorten recovery time, help restore lung function
- Add to bronchodilators if baseline FEV₁ is <50% predicted
- Dosage, length of treatment, administration, and setting have varied widely
- 2-week course as beneficial as 8-week course
- 5-day course not as beneficial as 10-day course
- GOLD-recommended regimen: 30-40 mg prednisolone for 10-14 days
- Common side effect: hyperglycemia (mostly in patients with type 2 diabetes)

AECOPD: Etiology of AECOPD

- 80% Infectious
- 20% Noninfectious
  - Bacterial pathogens
    - 40%-50%
  - Viral infection
    - 30%-40%
  - Atypical bacteria
    - 5%-10%
- Environmental factors
- Noncompliance with medications

COPD Exacerbations: Antibiotic Therapy

- Elmes et al, 1957
- Berry et al, 1960
- Faar et al, 1962
- Elmes et al, 1965
- Petersen et al, 1967
- Pines et al, 1972
- Nicotra et al, 1982
- Anthonisen et al, 1987
- Jorgensen et al, 1992

Antibiotics in Acute Exacerbations

- Beneficial in patients with 2 or more symptoms: worsening dyspnea, increased sputum volume, increased sputum purulence
- Patients with severe exacerbations and/or severe underlying COPD are most likely to benefit
- Traditional regimen: 3-14 days of tetracycline, amoxicillin, or trimethoprim-sulfamethoxazole
- Choice of agent should reflect local patterns of antibiotic sensitivity among S pneumoniae, H influenzae, and M catarrhalis
- Exacerbations have been linked to new strains of these organisms

**Effects Size**

- Overall
  - Favors Placebo
  - Favors Antibiotic


NPPV in Acute Exacerbations of COPD

- Tight-fitting mask with bilevel positive airway pressure
- Early-care alternative to endotracheal tube or tracheostomy
- Physiologic improvements: increases pH, reduces PaCO₂
- Symptomatic improvements: reduces severity of breathlessness
- Decreases intubation rate, mortality rate, and hospital length of stay
- NPPV: now a standard of care in acute exacerbations…but still controversial in severe stable COPD
- Unresolved issues: efficacy in “real-world” settings, costs, ideal patients

NIH/NHLBI. Global Initiative for Chronic Obstructive Lung Disease (“GOLD”), Updated 2003.

An abbreviated history of COPD therapy

- Prevent/Treat Exacerbations
- Symptomatic relief
- Reduce Hyperinflation
- Acute Bronchodilation
- Improve Health Status
- Reduce Mortality
- Preserve Pulmonary Function

What we can do
What we must do

Lung Function Over Time

- Never smoked or not susceptible to smoke
- Stopped smoking at 45 (mild COPD)
- Stopped smoking at 65 (severe COPD)
- Symptoms
- Smoked regularly and susceptible to effects of smoking
- Disability
- Death

Adapted from Fletcher et al. BMJ. 1977;1:1645-1648 (B).

Oxygen reduces mortality in COPD patients with resting hypoxemia

Cumulative Survival (%)

Months

COT = continuous oxygen therapy; NOT = nocturnal oxygen therapy; MRC controls = no oxygen therapy; MRC = domiciliary oxygen therapy.
Lung volume reduction surgery is appropriate in subgroups of COPD

- **All Patients**
  - N = 1218
- **High Risk Patients**
  - LVRS
  - N = 140
  - Upper Lobe / Low Exercise
    - N = 290
    - Upper Lobe / High Exercise
      - N = 419
    - Non Upper Lobe / Low Exercise
      - N = 149
    - Non Upper Lobe / High Exercise
      - N = 220

- **Non High Risk Patients**
  - LVRS
  - N = 1078
  - Upper Lobe / Low Exercise
    - N = 290
    - Upper Lobe / High Exercise
      - N = 419
    - Non Upper Lobe / Low Exercise
      - N = 149
    - Non Upper Lobe / High Exercise
      - N = 220

Mortality

- **Upper Lobe / Low Exercise**
  - Medical
    - P = 0.01
    - RR = 0.57
  - LVRS
    - P₂₅ = 0.003

TorCH: All-cause mortality at 3 years

- Probability of death (%)
  - 0
  - 2
  - 4
  - 6
  - 8
  - 10
  - 12
  - 14
  - 16
  - 18
- Time to death (weeks)
  - 0
  - 12
  - 24
  - 36
  - 48
  - 60
  - 72
  - 84
  - 96
  - 108
  - 120
  - 132
  - 144
  - 156

**Alpha one Replacement Therapy Product Comparison**

- CSL Behring Zemaira 60 mg/kg/week IV 100 ml > 0.70 Yes† 2004
- Talecris Prolastin 60 mg/kg/week IV 200 ml > 0.35 Yes 1987
- Baxter Aralast 60 mg/kg/week IV 250 ml > 0.55 No 2003

* Minimum release specific activity. Actual specific activities for all drugs are much higher.
†† Limited and not promoted

**COPD: The Importance of Co-morbidities**

**What Do COPD Patients Die From?**

- **Mild COPD**
  - GOLD Stage I
- **Moderate COPD**
  - GOLD Stage II
- **Severe COPD**
  - GOLD Stage III

[Graph showing distribution of causes of death in COPD patients.]


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**Overall causes of death in TORCH as adjudicated by the Clinical Endpoint Committee**

- **Unknown**
- **Other**
- **Respiratory**
- **Cardiac**
- **Cancer**

Total Number of Co-Morbidities

- **Total Number of Co-Morbidities**
  - 1-5
  - 6-10
  - 11-15
  - 16-20
  - 20-25

[Bar chart showing distribution of co-morbidities.]


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**COPD and Co-morbidities**

- Arthritic Pains: 70%
- GERD: 63%
- Sinus Disease: 58%
- Heart Disease: 54%
- Hypertension: 52%
- Hyperlipidemia: 51%
- Depression: 38%
- Cataract: 32%
- Osteoporosis: 30%
- Sleep apnea: 20%
- Diabetes: 18%

[Graph showing degree of dyspnea grouped by number of co-morbidities.]

Degree of Dyspnea grouped by # of Co-Morbidities

[Bar chart showing degree of dyspnea grouped by number of co-morbidities.]

 households (N=1,003) [Patient Org (N=2,012) ]
COPD: A Systemic Disease

The Importance of Inflammation

COPD: The Role of Inflammation

Ongoing Lung Inflammation
Systemic Inflammation
End Organ Damage

COPD vs Asthma

COPD vs Asthma: Definitions

COPD
A preventable and treatable disease characterized by airflow limitation that is not fully reversible
Airflow limitation is usually progressive and may be associated with an abnormal inflammatory response of the lungs to noxious particles or gases

Asthma
A chronic inflammatory disorder of the airways with an associated increase in airway hyperresponsiveness
Recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning
Usually associated with widespread but variable airflow obstruction often reversible either spontaneously or with treatment


Asthma vs COPD

History

Asthma
Atopy
Sensitizing agents
Family History
Childhood or young adult onset
Intermittent wheeze/symptoms

COPD
Smoking history
Noxious agents
Later onset
Progressive symptoms

Inflammatory Markers

Asthma
Cells- eosinophils, + macrophages, mast cells
CD4 T-lymphocytes
Meditators: histamine, IL-4, IL-5, IL-13
Effects all airways, little fibrosis, epithelial shedding

COPD
Cells- neutrophils, lymphocytes, +++ macrophages
CD8 T-lymphocytes
Meditators-LTB4, IL-8, TNF-alpha
Effects-peripheral airways, lung destruction, fibrosis and squamous metaplasia
**Asthma vs COPD**

**Physiologic Responses**

<table>
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<tr>
<th>Asthma</th>
<th>COPD</th>
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<tr>
<td>Reversible</td>
<td>Partially reversible</td>
</tr>
<tr>
<td>Bronchodilator response: BA&gt;AC</td>
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</tr>
<tr>
<td>Steroid responsive</td>
<td>+/- Steroid effect</td>
</tr>
<tr>
<td>+/- Dynamic hyperinflation with exacerbations</td>
<td>Progressive static and dynamic hyperinflation</td>
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<tr>
<td>Normal DLCO</td>
<td>Reduced DLCO in emphysema</td>
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**Asthma**
- Reversible
- Bronchodilator response: BA>AC
- Steroid responsive
- +/- Dynamic hyperinflation with exacerbations
- Normal DLCO

**COPD**
- Partially reversible
- Bronchodilator response: AC>BA
- +/- Steroid effect
- Progressive static and dynamic hyperinflation
- Reduced DLCO in emphysema

**Therapy**

**Asthma**
- ICS - first line therapy
- Smoking asthmatics less responsive
- Add bronchodilators - Beta agonists
- Leukotriene modifiers
- +/- Theophyllines

**COPD**
- Bronchodilators - first line therapy
- Add ICS if recurrent exacerbations
- Leukotriene modifiers
- +/- Theophyllines

**Clinical Overlap Between COPD and Asthma**

- COPD: Smoking history, Progressive dyspnea, productive cough, Bronchodilator response: AC>BA, Neutrophilic inflammation
- Asthma: Early and/or family history, Intermittent wheezing, hay fever, atopy, Bronchodilator response: BA>AC, Eosinophilic inflammation

**COPD Misdiagnosis Is Common in Women**

- Hypothetical male patient with COPD symptoms
  - Diagnosed as COPD by 42% of physicians

- Hypothetical female patient with COPD symptoms
  - Diagnosed as COPD by 32% of physicians

- COPD symptoms in women were most commonly misdiagnosed as asthma

42%

32%

**COPDGENE**

- 6000 with COPD
- 4500 current or former smokers without COPD
- 30% African Americans
- CT scans, spirometry pre and post, genetic studies

Minimally Invasive Lung Volume Reduction
Bronchoscopic Valves

Emphasys Endobronchial Valve™

Valve Design
- Self-expanding retainer
  - stabilizes device in airway
- Flexible seals
  - conform to bronchial wall
  - prevent air leak around valve
- One-way valve
  - blocks inspiration
  - allows mucus clearance

Spiration intra-bronchial valve

EBV Procedure Overview

Minimally Invasive Lung Volume Reduction
Bronchoscopic Stent Placements
COPD 2009

Treatable and Preventable
Together We Can Make a Difference