COPD 2009

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Overview
Exacerbations
The Importance of Co-morbidities
COPD vs Asthma
What’s New
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?

COPD is a disease of the elderly

**COPD in Younger Patients is on the Rise**

<table>
<thead>
<tr>
<th>Perception</th>
<th>Reality</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD affects the working age population</td>
<td></td>
</tr>
<tr>
<td>~ 50% of COPD patients are younger than age 65</td>
<td></td>
</tr>
<tr>
<td>Patients &lt; 65 accounted for 67% of COPD office visits and 43% of hospitalizations</td>
<td></td>
</tr>
</tbody>
</table>
| COPD is as common as asthma and diabetes in population aged 45-64 | | 1


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**Who is the COPD Patient?**

<table>
<thead>
<tr>
<th>Perception</th>
<th>Reality</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD is a disease of men</td>
<td></td>
</tr>
</tbody>
</table>


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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%\(^1\)
- In 2000, COPD hospitalizations for women outnumbered those for men\(^2\) (404,000 vs 322,000)
- Increased morbidity and mortality in women likely reflects increased smoking by women\(^2\)

\(^1\)Mannino, et al. MMWR. 2002;51(6 suppl):1-16. \(^2\)CDC. 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.

COPD Is as Prevalent as Many Other Chronic Diseases Treated in Primary Care

Per 1000 Person-years

\[ \begin{array}{c|c|c|c|c}
    & COPD & Diabetes* & CVD & HTN & Obesity \\
    \hline
    24 & 18.2 & 64.4 & 50 & 59 \\
\end{array} \]

Clinical COPD Is Just the Tip of the Iceberg

- 2 million, severe disease*
- 10 million diagnosed
- 4.3 million treated
- 30 million suffer from COPD
- SUBCLINICAL COPD
- ??? Millions at risk from smoking


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Prevalence in NHNES III

*Figure 1. Prevalence of Physiological HTN and COPD*

- Hypertension
- COPD

Celli et al ATS 2004
Figure 2. Prevalence of Patient-Reported HTN and COPD

Celli et al ATS 2004

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

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

Total lung capacity
Inspiratory reserve volume
Inspiratory capacity
Tidal volume
Expiratory reserve volume
Vital capacity
Functional residual capacity
Residual volume
Comparison of Lung Volume Parameters

Effects of Exercise on Hyperinflation
COPD

↓

Expiratory Flow Limitation
Air Trapping
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

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

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

What we can do

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

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staging</td>
<td>I Mild</td>
<td>II Moderate</td>
<td>III Severe</td>
<td>IV Very Severe</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>&lt;70%</td>
<td>&lt;70%</td>
<td>&lt;70%</td>
<td>&lt;70%</td>
</tr>
<tr>
<td>FEV₁</td>
<td>≥80%</td>
<td>50%≤ FEV₁</td>
<td>30%≤ FEV₁</td>
<td>&lt;30% or FEV₁&lt; 50% plus chronic respiratory failure</td>
</tr>
</tbody>
</table>

Avoidance of risk factor(s); influenza vaccination

Add short-acting bronchodilators* when needed

Add regular Rx with ≥1 long-acting bronchodilator.*
Add rehabilitation
Add ICS if repeated exacerbations†
Consider O₂ and surgery

*Anticholinergics or β-agonists; †not FDA-approved for exacerbations; off-label use.


Effects of Bronchodilators on Clinical Outcomes in Patients With COPD

<table>
<thead>
<tr>
<th>Agent</th>
<th>FEV₁</th>
<th>Lung Volume</th>
<th>Dyspnea</th>
<th>HRQOL*</th>
<th>Exercise Tolerance*</th>
<th>Disease Modifier by FEV₁</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting beta₂-agonists</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>Yes</td>
<td>N/A</td>
<td>Minimal</td>
</tr>
<tr>
<td>Short-acting anticholinergic</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Minimal</td>
</tr>
<tr>
<td>Long-acting beta₂-agonists</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Minimal</td>
</tr>
<tr>
<td>Long-acting anticholinergic</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Minimal</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>Potentially important</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

What we can do

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

COPD Exacerbations

Defined as an acute change in dyspnea, cough and/or sputum sufficient enough to warrant therapy change¹

In a 12-month observational study (n=127), 77% of patients reported having at least one exacerbation²*

The prevention of exacerbations is recognized as a key goal in COPD disease state management³

*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.1

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.3

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Outcomes of AECOPD

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>ICU patients</th>
<th>Hospital mortality</th>
<th>20%-24%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In hospitalized patients</td>
<td>Hospital mortality</td>
<td>2.5%-10%</td>
</tr>
<tr>
<td></td>
<td>In ER patients</td>
<td>Relapse (repeat ER visit)</td>
<td>22%-32%</td>
</tr>
<tr>
<td></td>
<td>In outpatients</td>
<td>Treatment failure rate</td>
<td>13%-33%</td>
</tr>
</tbody>
</table>

Treatment failure is defined as not responsive to initial treatment(s).

Outcomes = health utilizations.

Health Status Changes Following an Exacerbation

SGRQ Score

Further Exacerbation Within 6 Months
No Further Exacerbation

Baseline (At presentation with acute exacerbation)
4 Weeks
12 Weeks
26 Weeks

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 AECOPD
Additive Drug Effects

<table>
<thead>
<tr>
<th></th>
<th>Favors Active Treatment</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRISTAN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calverley</td>
<td>LABA ICS Comb</td>
<td></td>
</tr>
<tr>
<td>Mahler</td>
<td>LABA ICS Comb</td>
<td></td>
</tr>
<tr>
<td>Szafranski</td>
<td>LABA ICS Comb</td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td>LABA ICS Comb</td>
<td></td>
</tr>
</tbody>
</table>

Relative Risk (95% CI) of Exacerbation
Adapted from Sin et al. JAMA. 2003;290:2301-2312.
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: Influenza Vaccination

Prevention of COPD Exacerbations: Pneumococcal and Influenza Vaccination

- Pneumococcal vaccination
- COPD hospitalization
- All-cause mortality
- Pneumococcal + influenza vaccination
- COPD hospitalization
- All-cause mortality

Relative Risk (95% CI)


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
Management of Acute Exacerbations in COPD

Bronchodilators in Acute Exacerbations of COPD

Initiate or increase dose of short-acting inhaled beta₂-agonists (eg, albuterol)
Add anticholinergic (eg, 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
3-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
Bacterial pathogens
– 40%-50%
Viral infection
– 30%-40%
Atypical bacteria
– 5%-10%

20% noninfectious
Environmental factors
Noncompliance with medications

Effect Size

COPD Exacerbations: Antibiotic Therapy

Elmes et al, 1957
Berry et al, 1960
Fear 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

Overall

Favors Placebo  Favors Antibiotic


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 organism


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


An abbreviated history of COPD therapy

- Acute Bronchodilation
- Reduce Hyperinflation
- Improve Health Status
- Prevent/Treat Exacerbations

What we can do
An abbreviated history of COPD therapy

What we can do
- Reduce Hyperinflation
- Preserve Pulmonary Function
- Reduce Mortality
- Prevent/Treat Exacerbations

What we must do
- Acute Bronchodilation
- Symptomatic relief
- Improve Health Status

Lung Function Over Time

Adapted from Fletcher et al. BMJ. 1977;1:1645-1648 (B).
Oxygen reduces mortality in COPD patients with resting hypoxemia

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
N = 140

Non High Risk Patients
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

\[ R_R = 0.57 \]

\[ P = 0.01 \]

\[ P_{2\ yr} = 0.01 \]

\[ P_{5\ yr} = 0.003 \]
## Alpha One Replacement Therapy Product Comparison

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Dosage</th>
<th>Typical Volume</th>
<th>Specific Activity*</th>
<th>AlphaNet Support</th>
<th>Year of Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSL Behring</td>
<td>Zemaira</td>
<td>60 mg/kg/week IV</td>
<td>100 ml</td>
<td>&gt;0.70</td>
<td>Yes†</td>
<td>2004</td>
</tr>
<tr>
<td>Talecris</td>
<td>Prolastin</td>
<td>60 mg/kg/week IV</td>
<td>200 ml</td>
<td>&gt;0.35</td>
<td>Yes</td>
<td>1987</td>
</tr>
<tr>
<td>Baxter</td>
<td>Aralast</td>
<td>60 mg/kg/week IV</td>
<td>250 ml</td>
<td>&gt;0.55</td>
<td>No</td>
<td>2003</td>
</tr>
</tbody>
</table>

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

## TORCH: All-cause mortality at 3 years

COPD: The Importance of Co-morbidities

Percent Change in Age-Adjusted US Death Rates

What Do COPD Patients Die From?

Mild COPD
GOLD Stage I

Moderate COPD
GOLD Stage II

Severe COPD
GOLD Stage III


The Relationship Between COPD & CVD

NHANES 1; N=1,861
Overall causes of death in TORCH as adjudicated by the Clinical Endpoint Committee

- Respiratory: 35%
- Cardiac: 27%
- Cancer: 21%
- Other: 10%
- Unknown: 7%


Total Number of Co-Morbidities

- Household (N=1,003)
- Patient Org (N=2,029)

$p < .001$ 58
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%

Degree of Dyspnea grouped by # of Co-Morbidities
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
- Mediators - histamine, IL-4, IL-5, IL-13
- Effects all airways, little fibrosis, epithelial shedding

**COPD**
- Cells - neutrophils, lymphocytes, +++macrophages
- CD8 T-lymphocytes
- Mediators - LTβ4, IL-8, TNF-alpha
- Effects - peripheral airways, lung destruction, fibrosis and squamous metaplasia
### Asthma vs COPD

#### Physiologic Responses

<table>
<thead>
<tr>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversible</td>
<td>Partially reversible</td>
</tr>
<tr>
<td>Bronchodilator response</td>
<td>Bronchodilator response</td>
</tr>
<tr>
<td>BA&gt;AC</td>
<td>AC&gt;BA</td>
</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>
</tr>
<tr>
<td>Normal DLCO</td>
<td>Reduced DLCO in emphysema</td>
</tr>
</tbody>
</table>

#### Therapy

<table>
<thead>
<tr>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS- first line therapy</td>
<td>Bronchodilators- first line therapy</td>
</tr>
<tr>
<td>Smoking asthmatics less responsive</td>
<td>Add ICS if recurrent exacerbations</td>
</tr>
<tr>
<td>Add bronchodilators-Beta agonists</td>
<td>ICS not first line therapy unless overlap</td>
</tr>
<tr>
<td>Leukotriene modifiers</td>
<td>+/- Theophyllines</td>
</tr>
<tr>
<td>+/- Theophyllines</td>
<td>+/- Theophyllines</td>
</tr>
</tbody>
</table>
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

Airflow Limitation

Adapted by Christopher B. Cooper, MD.
Am J Respir Crit Care Med. 2003;167:787-797 (C).

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

COPD: What's New

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

Investigational device only. Not currently approved for sale.
**Spiration intra-bronchial valve**

**EBV Procedure Overview**

- Bronchial diameter less than outer diameter of sizing gauge
- Main body of retainer completely engaged within target bronchus
- Advance housing into target segment, confirm sizing using gauges
- Confirm Zephyr EBV positioning and sizing
- Zephyr EBV allowing air to exit from during expiration
- Zephyr EBV preventing air from entering during inspiration
Minimally Invasive Lung Volume Reduction

Bronchoscopic Stent Placements
Airway Bypass Procedure

Airway View

Airway Bypass Procedure

Airway View
Airway Bypass Procedure

AIRWAY VIEW

Airway Bypass Procedure
OPTICAL ELECTRONIC PLETHYSMOGRAPHY
OEP
COPD 2009

Treatable and Preventable
Together We Can Make a Difference