COPD
A New Look at an Old Disease

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GOLD: Global Initiative for Chronic Obstructive Lung Disease

GOLD definition of COPD¹
- Common, preventable, treatable—partially reversible
- Characterized by persistent airflow limitation
- Usually progressive and disabling
- Associated with enhanced chronic inflammatory response in airways/lung to noxious particles or gases

COPD is heterogeneous²
- Multiple risk factors, phenotypes, comorbidities
- Exacerbations and comorbidities contribute to severity

The New Look of COPD

- Epidemiology
- Pathophysiology
- Diagnosis and Assessment
- Management
- Novel targets for therapy

COPD: The Old Look

Perception

COPD is a disease of the elderly
COPD is a disease of men

Reality: COPD afflicts the working-age population. Reality: COPD is also a disease of women.

The Impact of COPD in the United States

In 2010, COPD accounted for
- 10.3 million physician office visits/y
- 1.5 million ED visits
- 699,000 hospital discharges

- Costly
  - Direct: $27 billion/y
  - Indirect: $20 billion/y
- 3rd leading cause of death
- 4th leading cause of hospital readmissions

The New Look of COPD

- Epidemiology
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COPD: The New Look

Risk Factors for COPD

- Exposure to inhaled particles:
  - Tobacco smoke (active and passive)
  - Occupational dusts, organic and inorganic
  - Indoor air pollution from heating and cooking with biomass in poorly ventilated dwellings
  - Outdoor air pollution
- Susceptibility genes

COPD: Oxidative Stress is Central to the Destruction of Pulmonary Tissue

Inflammatory and Cellular Mechanisms in COPD due to Cigarette Smoking
**COPD: A Multicomponent Disease**

- Mucus hypersecretion
- Reduced mucociliary transport
- Mucosal damage
- Increased numbers of inflammatory cells
  - CD8+ T-lymphocytes
  - Monocytes/macrophages
  - Neutrophils
  - Mast cells
- Elevated inflammatory mediators: IL-8, TNF-α, LTB-4, and oxidants
- Proinflammatory/anti-inflammatory imbalance

- Goblet cell hyperplasia/metaplasia
- Mucus gland hypertrophy
- Increased smooth muscle mass
- Airway fibrosis
- Alveolar destruction

**Pathophysiology of COPD**

Hyperinflation, central to the pathophysiology of COPD (ie, increased airway resistance), correlates more directly with patient-reported outcomes

- Hyperinflation
- Airflow obstruction
- Deconditioning
- Chronic hyperinflation
- Hypoxemia
- Tachypnea

**The New Look of COPD**

- Epidemiology
- Pathophysiology
- Diagnosis and Assessment
  - Management
  - Novel targets for therapy

**COPD is Underdiagnosed and Undertreated**

- Majority of patients are diagnosed at later stages of COPD

1. NIH, NHLBI. Morbidity and Mortality. 2000 Chartbook on Cardiovascular, Lung and Blood Diseases.
Natural History of COPD

Significant Drops in Lung Function Are Often Required for Patients to Become Severely Symptomatic

- Dyspnea, Cough
- Exercise Intolerance
- Exacerbations
- Hospitalizations
- Systemic Effects
- Respiratory Failure
- Pulm Hypertension

FEV1 (% predicted at age 25 years)

Age (years)

PT # 1
59 y
FEV1: 28 %
PaO2: 70 mmHg
6MWD: 540 mt
BMI: 30

PT # 2
60 y
FEV1: 33 %
PaO2: 57 mmHg
6MWD: 348 mt
BMI: 21

PT # 3
70 y
FEV1: 35 %
PaO2: 66 mmHg
6MWD: 210 mt
BMI: 34

PT # 4
72 y
FEV1: 34 %
PaO2: 66 mmHg
6MWD: 140 mt
BMI: 24

COPD Heterogeneity

FEV1 < 35% predicted

Airway Disease

Emphysema

BMI < 21

BMI > 35

Sedentary

Active

Recent Trials to Identify Phenotypes

COPDGene
COPD Genetic Epidemiology

ECLIPSE
Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints

Spiromics
COPD Phenotypes

Disease attributes that describe the diverse symptoms and outcomes of patients

- Frequent Exacerbations
- Systemic Inflammation
- Chronic Respiratory Failure
- Comorbidities
- Asthma COPD Overlap Syndrome (ACOS)
- Symptom Burden
- Chronic Hypoxemia
- Exercise/Acivity Intolerance/Hyperinflation
- Chronic Cough and Sputum
- Radiologic Airway (CT, Bronchiectasis, Emphysema)

Ideal Phenotypic Construct

- Clinical Phenotype Defined by Similar Outcome
- Symptomatic, Physiologic, and/or Radiologic Characterization of Phenotype
- +/- Development of Therapy

Assessment of COPD

- 2015
- 2010
- Airflow Limitation: Spirometry for diagnosis and assessment
- Symptoms: Validated patient questionnaires (mMRC and CAT)
- Exacerbation Risk: History of exacerbations or spirometric classification

Global Strategy for Diagnosis, Management and Prevention of COPD: Assessment of COPD

- Assess symptoms

mMRC: Modified Medical Research Council Dyspnea Scale
CAT: COPD Assessment Test
Assessment of COPD: Symptoms

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description of Breathlessness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>I only get breathless with strenuous exercise</td>
</tr>
<tr>
<td>1</td>
<td>I get short of breath when hurrying on level ground or walking up a slight hill</td>
</tr>
<tr>
<td>2</td>
<td>On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace</td>
</tr>
<tr>
<td>3</td>
<td>I stop for breath after walking about 100 yards or after a few minutes on level ground</td>
</tr>
<tr>
<td>4</td>
<td>I am too breathless to leave the house or I am breathless when dressing</td>
</tr>
</tbody>
</table>

Modified Medical Research Council Dyspnea Score

Assessment of COPD: Lung Function

- Assess symptoms
- Assess degree of airflow limitation using spirometry

Severity of Obstruction

Patient with FEV1/FVC < 0.70:

- GOLD 1: Mild FEV1 > 80% predicted
- GOLD 2: Moderate 50% ≤ FEV1 < 80% predicted
- GOLD 3: Severe 30% ≤ FEV1 < 50% predicted
- GOLD 4: Very Severe FEV1 < 30% predicted

*Based on Post-Bronchodilator FEV1

Global Strategy for Diagnosis, Management and Prevention of COPD: Assessment of COPD

- Assess symptoms
- Assess degree of airflow limitation using spirometry
- Assess risk of exacerbations

Frequent Exacerbations Drive Disease Progression

Patients with frequent exacerbations

- Lower quality of life
- Increased inflammation
- Increased risk of recurrent exacerbations
- Faster disease progression
- Increased likelihood of hospitalization


Patients with frequent exacerbations
- Increased risk of recurrent exacerbations
- Increased mortality rate
- Increased inflammation
- Faster disease progression
- Lower quality of life

GOLD: Combined COPD Assessment
Assessment Using Symptoms, Breathlessness, Spirometric Classification, and Risk of Exacerbations*

<table>
<thead>
<tr>
<th>Risk</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAT  &lt; 10</td>
<td>High risk, Less symptoms</td>
<td>High risk, More symptoms</td>
</tr>
<tr>
<td>mMRC 0-1</td>
<td>Low risk, Less symptoms</td>
<td>Low risk, More symptoms</td>
</tr>
</tbody>
</table>

* When assessing risk, choose the highest risk according to GOLD grade or exacerbation history.

Global Strategy for Diagnosis, Management and Prevention of COPD: Assessment of COPD

- Assess symptoms
- Assess degree of airflow limitation using spirometry
- Assess risk of exacerbations
- Assess comorbidities
These comorbid conditions may influence mortality and hospitalizations; the patient should be assessed for them routinely and treated appropriately.

**Comorbidities of COPD**
- Anxiety, depression
- Pulmonary hypertension
- Anemia
- Diabtes
- Metabolic syndrome
- Cachexia
- Cardiovascular disease
- Peripheral muscle wasting and dysfunction
- Osteoporosis
- Peptic ulcers
- GI complications

**Exploring the Links Between COPD and Its Comorbidities**

**Risk Factors**
- Smoking and lifestyle factors
- Genetic susceptibility

**COPD**
- Chronic airway infection
- Acute exacerbations

**Mechanisms**
- Airway and systemic inflammation
- Lung hyperinflation and endothelial dysfunction
- Oxidative stress

**Comorbidities**
- Ischemic heart disease
- Stroke and heart failure
- Hypertension and diabetes
- Muscle weakness and osteoporotic fractures
- Depression

**Outcomes**
- Worse symptoms
- Worse health status
- Reduced activity
- Reduced survival

**Comorbidities of COPD and Systemic Inflammation**
- Acute-phase proteins
- CRP
- ESR

**Assessing Comorbidities in COPD**
- Look for COPD
- If Smoker
- Look for Comorbidities

References:
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Goals of Management

- Airflow Limitation
- Symptom Burden
- Exacerbations
- Functional Limitations

- Improve Lung Function
- Slow FEV1 Decline
- Improve Symptoms
- Prevent and Manage Exacerbations
- Improve Health Status and Exercise Tolerance
- Reduce Hospital Admissions and Mortality

Adapted from Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. www.goldcopd.org.

Improving Outcomes in COPD

- Early diagnosis and accurate assessment
  - Identifying patients at risk
  - Using appropriate diagnostic approaches, ruling out other mimickers
  - Early treatment
- Implementing optimal management
  - Reducing exposures to risk factors and triggers
  - Non-pharmacological approaches
  - Pharmacological treatments
- Incorporating self-management skills through education and collaboration with a health care team
  - Improve adherence

Nonpharmacologic Therapy To Manage COPD

- Smoking Cessation
- Patient Education
- Vaccination
- Oxygen Therapy
- Pulmonary Rehabilitation
- Surgical and Non-surgical Alternatives


Non-pharmacological Options for COPD

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>low risk, fewer symptoms</td>
<td>low risk, more symptoms</td>
<td>high risk, fewer symptoms</td>
<td>high risk, more symptoms</td>
</tr>
<tr>
<td><strong>GOLD 1-2</strong></td>
<td>mMRC 0-1 or CAT 10</td>
<td>mMRC 2-3 or CAT 20</td>
<td>mMRC 0-1 or CAT 10</td>
<td></td>
</tr>
<tr>
<td><strong>GOLD 3-4</strong></td>
<td>mMRC 2-3 or CAT 20</td>
<td>mMRC 2-3 or CAT 20</td>
<td>mMRC 2-3 or CAT 20</td>
<td></td>
</tr>
</tbody>
</table>

**Essential Smoking cessation** for all patients who smoke

- The key intervention for smokers
- Can include pharmacologic treatment

**Recommended**

- Pulmonary rehabilitation

- Physical activity

- Influenza vaccination

- Pneumococcal vaccination

**Outcomes of Pulmonary Rehab in COPD**

- Reduces dyspnea
- Improves deconditioning, muscle fatigue
- Increases exercise capacity
- Improves quality of life
- Improves depression
- Reduces acute exacerbations
- Reduces hospitalizations
- May reduce mortality
- Does not improve PFTs or ABGs

Pharmacological Management of COPD

- Guideline-recommended COPD treatment
  - Improves lung function
  - Minimizes symptoms
  - Improves QoL
  - Prevents exacerbations

- Wide variety of options including new agents
  - Appropriate treatment selection hinges on GOLD staging
  - Before stepping up/modifying treatment, re-evaluate

- Treatment goals:
  - Clinical phenotype
  - Comorbidities
  - Adherence

Adapted from Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. www.goldcopd.org.
COPD Pharmacological Agents Approved in the U.S.

**Bronchodilators**
- **Short-acting**
  - β-Adrenergic (SABA)
    - Albuterol
    - Pirbuterol
    - Levalbuterol
  - Anticholinergic (SAMA)
    - Ipratropium

**Long-acting**
- β-Adrenergic (LABA)
  - Salmeterol
  - Formoterol
  - Indacaterol
  - Umeclidinium
  - Glycopyrronium

**β-Agonists (SABA)**
- Albuterol
- Pirbuterol
- Levalbuterol

**Anticholinergic (SAMA)**
- Ipratropium

**Anticholinergic (LAMA)**
- Tiotropium
- Umeclidinium
- Glycopyrronium

**LABA + LAMA**
- Umeclidinium + Vilaanterol
- Tiotropium + Oladaterol
- Glycopyrronium + Indacaterol
- Theophylline

**Anti-Inflammatory**
- ICS + LABA
- Fluticasone + Salmeterol
- Budesonide + Formoterol
- Fluticasone Furoate + Vilaanterol

**PDE-4 Inhibitors**
- Roflumilast

**Systemic Steroids**
- Prednisone
- Methylprednisolone

COPD Pharmacological Treatment Options

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting (SAMA or SABA)</td>
<td>Long-acting (LAMA OR LABA)</td>
<td>LAMA</td>
<td>ICS + LABA</td>
</tr>
<tr>
<td>Long-acting (LAMA OR LABA)</td>
<td>Combos of: LAMA + LABA + ICS + PDE-4 inhibitor</td>
<td></td>
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</tr>
</tbody>
</table>

Inhaler Devices Available in the U.S.

A large proportion (48-76%) of patients use their inhalers incorrectly. GOLD guidelines recommend rechecking inhaler technique at each patient visit.


Strategies to Ensure Adherence

- Educate patients about COPD and treatments
- Support self-efficacy: encourage and praise successes
- Set treatment goals
- Train patients on proper use of devices periodically
- Ask about device preference
- Use "teach back" method
- Ask about side effects
- Ugly patients to complete treatment even if they feel better

1. Ellipta
2. Spacer Devices
3. Small Volume Nebulizer
4. MDI

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Unmet Needs with Current Interventions

- Current pharmacotherapies do not change the natural history of COPD
- Many patients remain symptomatic with current therapies
- Inadequate adherence with inhaled therapy is a major cause of poor clinical outcomes in the treatment of COPD
- Cost, compliance, and safety are significant issues

Novel Pharmacological Targets in COPD

- Novel formulations of existing medications
  - Ultra LABAs (indacaterol, oladaterol)
  - Ultra LAMAs (aclidinium,umeclidinium, glycopyrinium)
  - LABA/LAMA combinations (vilanterol/umeclidinium, indacaterol/glycopyrrolate, formoterol/glycopyrrolate)
  - LABA/ICS combinations (vilanterol/fluticasone)
  - Nebulized bronchodilators and combination therapies
  - MABAs

Drugs Used in Treatment of Comorbidities That May Be Useful in COPD

- Macrolides
- Statins
- ACE Inhibitors
- Beta-blockers
- Peroxisome proliferator-activated receptor (PPAR) agonists
Summary

• COPD continues to be a major public health problem
• The pathophysiology of COPD involves chronic airway inflammation and lung destruction driven by several inflammatory cells and mediators
• COPD is a heterogeneous disease with multiple phenotypes
  – Phenotypic characterization of COPD will improve personalized approach to the disease

Summary

• Clinical approach to COPD includes assessment of symptoms, lung function, exacerbation risk and comorbidities
• Several non-pharmacological and pharmacological interventions are available which should be implemented according to disease severity
• Multiple novel targets of therapy are being evaluated and may be available in the future