Chronic Obstructive Lung Disease

Amita Vasoya, DO FACOI FCCP FAASM
Christiana Care Pulmonary Associates
Clinical Assistant Professor of Medicine
Sidney Kimmel Medical College of Thomas Jefferson University
Rowan University School of Osteopathic Medicine
ACOI Board Review 2018
Disclosures

- No Disclosures
Obstructive Lung Diseases

- COPD
  - Chronic Bronchitis
  - Emphysema
- Asthma
- Other
  - Bronchiectasis
  - Bronchiolitis
  - Cystic Fibrosis
  - Alpha 1 anti-trypsin deficiency
Inter-relationship: Inflammation and Bronchial Hyperreactivity

A. Chronic Bronchitis  
Emphysema

COPD (Shaded)

Irreversible or Partially Reversible Airflow Obstruction

Reversible Airflow Obstruction

Asthma

B. Chronic Bronchitis  
Emphysema

COPD (Shaded)

Irreversible or Partially Reversible Airflow Obstruction

Reversible Airflow Obstruction

Asthma

ATS

GOLD

CHEST 2002; 121: 121S-126S
COPD

- THIRD leading cause of death worldwide
- It is the only leading cause of death whose prevalence is increasing!
The 10 leading causes of death in the world
2012

- Ischaemic heart disease: 7.4 million
- Stroke: 6.7 million
- COPD: 3.1 million
- Lower respiratory infections: 3.1 million
- Trachea, bronchus, lung: 1.6 million
- HIV/AIDS: 1.5 million
- Diarrhoeal diseases: 1.5 million
- Diabetes mellitus: 1.5 million
- Road injury: 1.3 million
- Hypertensive disease: 1.1 million

http://www.who.int/mediacentre/factsheets
COPD Risk Factors

- Cigarette smoking
- Occupational exposures
  - Silica, formaldehyde, toluene, nickel, cadmium, etc
- Air pollution
- Biomass fuel
- Hyperresponsive airway
- Asthma
- Genetic factors
Pathogenesis of COPD

Cigarette smoke (and other irritants)

Epithelial cells

Alveolar macrophage

Smoking cessation
Nicotine antagonists & vaccination
CB₁ antagonists

Chemotactic factors

Chemokine & mediator antagonists

Anti-protéases
NE inhibitors
MMP-9 inhibitors

Anti-inflammatory treatments
PDE4, IKK-2, p38 MAPK, PI3K-α inhibitors
PPAR-γ agonists

PROTEASES

Fibroblast

Anti-TGF-β, CTGF

Fibrosis (COB)

CD₈⁺ lymphocyte

Neutrophil

Monocyte

Mucus hypersecretion (Chronic bronchitis)

Retinoic acid
Stem cells

CHEST 2008; 134(8): 1278-1288
# Inflammatory Mediators: COPD

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cells</strong></td>
<td>Neutrophils ++, Macrophages +++ , CD8+ (Tc1)</td>
</tr>
<tr>
<td><strong>Key Mediators</strong></td>
<td>IL-8, TNF, IL-1b, IL-6, NO</td>
</tr>
<tr>
<td><strong>Oxidative Stress</strong></td>
<td>+++</td>
</tr>
<tr>
<td><strong>Site of Disease</strong></td>
<td>Peripheral airways, Lung parenchyma, Pulmonary vessels</td>
</tr>
<tr>
<td><strong>Consequences</strong></td>
<td>Squamous metaplasia, Mucous metaplasia, Small airway fibrosis, Parenchymal destruction, Vascular remodeling</td>
</tr>
<tr>
<td><strong>Response to therapy</strong></td>
<td>Small BD response, Poor steroid response</td>
</tr>
</tbody>
</table>
INFLAMMATION

Small Airway Disease
- Airway inflammation
- Airway remodeling

Parenchyma destruction
- Loss of alveolar attachments
- Decreased elastic recoil

AIRFLOW LIMITATION
Exacerbations represent a further amplification of the inflammatory response in the airways of patients with COPD, and may be triggered by infection with bacteria or viruses or by environmental pollutants.
COPD: Chronic Bronchitis

- Defined as excessive tracheobronchial mucus production associated with cough and sputum expectoration for at least 3 months a year for more than 2 consecutive years
- +/- reversible or fixed airway obstruction
COPD: Chronic Bronchitis

Pathology

- Large (cartilaginous) airways
  - Hyperplasia and hypertrophy of the mucus producing glands in the submucosa

- Small (non-cartilaginous) airway
  - Goblet cell hyperplasia
  - Mucosal/submucosal inflammation
  - Edema
  - Peribronchial fibrosis
  - Plugs
  - Smooth muscle hypertrophy

- MOSTLY RESPONSIBLE FOR AIRWAY OBSTRUCTION
Mucus membrane swelling
No muscle contraction
Copious mucus secretion
Narrowing of bronchial opening
Emphysema

- Mucus in bronchiole
- Enlarged alveoli
- Fewer capillaries

Lungs

Normal bronchiole and alveoli

© Healthwise, Incorporated
### Morphologic Types of Emphysema

<table>
<thead>
<tr>
<th></th>
<th>Upper lobe</th>
<th>Lower lobe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td><img src="normal.png" alt="Diagram" /></td>
<td><img src="normal.png" alt="Diagram" /></td>
</tr>
<tr>
<td><strong>Centriacinar (Centrilobular) Emphysema</strong></td>
<td><img src="centriacinar.png" alt="Diagram" /></td>
<td><img src="centriacinar.png" alt="Diagram" /></td>
</tr>
<tr>
<td><strong>Panacinar (Panbular) Emphysema</strong></td>
<td><img src="panacinar.png" alt="Diagram" /></td>
<td><img src="panacinar.png" alt="Diagram" /></td>
</tr>
</tbody>
</table>

**Alpha 1 AT**
COPD Definition: GOLD

- Chronic Obstructive Pulmonary Disease (COPD) is a PREVENTABLE and TREATABLE disease with some significant extrapulmonary effects that may contribute to the severity in individual patients.

- Airflow limitation that is NOT fully reversible.

- Airflow limitation is usually persistent and progressive.

- Associated with an abnormal inflammatory response to noxious particles and gases.
A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease.

Spirometric evaluation is necessary for the clinical diagnosis.
COPD Definition: GOLD

- A post bronchodilator FEV1/FVC <70%
- In combination with an FEV1 <80% predicted
- In an individual with cough, sputum production or dyspnea, and exposure to risk factors confirms the diagnosis
## Severity of COPD: GOLD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Severity</th>
<th>FEV1/FVC</th>
<th>FEV1 (%PRED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
<td>&lt; 70%</td>
<td>80% or &gt;</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>&lt; 70%</td>
<td>50 to 79%</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>&lt; 70%</td>
<td>30 to 49%</td>
</tr>
<tr>
<td>4</td>
<td>Very Severe</td>
<td>&lt; 70%</td>
<td>&lt; 30% or &lt; 50 with CRF</td>
</tr>
</tbody>
</table>
## Definition of Reversibility

<table>
<thead>
<tr>
<th>ATS</th>
<th>Increase in FEV1 of 200 cc and a 12% from baseline following BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERS</td>
<td>Greater than 10% improvement in FEV1 post BD</td>
</tr>
<tr>
<td>GOLD</td>
<td>Increase in FEV1 of 200 cc and a 12% improvement in FEV1 post Tx with either BD or ICS</td>
</tr>
</tbody>
</table>
Assessment

- **CAT (COPD Assessment Test)**
  - Numeric scale relating 8 functional parameters
    - Cough, sputum, walking, sleeping, energy, etc
  - Lower score = fewer symptoms
  - Higher score = more symptoms

- **mMRC Questionnaire (Modified Medical Research Council)**
  - Degree of breathlessness using 0-4 scale
  - Higher values indicating decreasing exercise tolerance
How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example:  I am very happy 0 1 2 3 4 5 I am very sad

I never cough 0 1 2 3 4 5 I cough all the time

I have no phlegm (mucus) in my chest at all 0 1 2 3 4 5 My chest is completely full of phlegm (mucus)

My chest does not feel tight at all 0 1 2 3 4 5 My chest feels very tight

When I walk up a hill or one flight of stairs I am not breathless 0 1 2 3 4 5 When I walk up a hill or one flight of stairs I am very breathless

I am not limited doing any activities at home 0 1 2 3 4 5 I am very limited doing activities at home

I am confident leaving my home despite my lung condition 0 1 2 3 4 5 I am not at all confident leaving my home because of my lung condition

I sleep soundly 0 1 2 3 4 5 I don't sleep soundly because of my lung condition

I have lots of energy 0 1 2 3 4 5 I have no energy at all

TOTAL SCORE

CAT

COPO Assessment test and the CAT logo are trademarks of the GlaxoSmithKline group of companies.
© 2000 GlaxoSmithKline. All rights reserved.
**mMRC Questionnaire**

Modified Medical Research Council (mMRC) Questionnaire for Assessing Severity of Breathlessness

<table>
<thead>
<tr>
<th>Score</th>
<th>Description of Dyspnea</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>I get breathless only with strenuous exercise</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>I get short of breath when hurrying on level ground or walking up a slight hill</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>On level ground, I walk slower than other people my age because of breathlessness, or I have to stop for breath when walking at my own pace</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>I stop for breath after walking approximately 100 yards or after a few minutes on level ground</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>I am too breathless to leave the house, or breathless when dressing</td>
<td>Very severe</td>
</tr>
</tbody>
</table>
# GOLD: Severity of COPD

## GOLD Model for Classifying Severity of Disease in COPD

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Characteristics</th>
<th>Spirometric Classification&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Exacerbations Per Year</th>
<th>CAT Score</th>
<th>mMRC Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low risk, fewer symptoms</td>
<td>GOLD 1-2</td>
<td>≤1</td>
<td>&lt;10</td>
<td>0-1</td>
</tr>
<tr>
<td>B</td>
<td>Low risk, more symptoms</td>
<td>GOLD 1-2</td>
<td>≤1</td>
<td>≥10</td>
<td>≥2</td>
</tr>
<tr>
<td>C</td>
<td>High risk, fewer symptoms</td>
<td>GOLD 3-4</td>
<td>≥2</td>
<td>&lt;10</td>
<td>0-1</td>
</tr>
<tr>
<td>D</td>
<td>High risk, more symptoms</td>
<td>GOLD 3-4</td>
<td>≥2/≥1 with hospital admission</td>
<td>≥10</td>
<td>≥2</td>
</tr>
</tbody>
</table>

CAT = COPD Assessment Test; mMRC = Modified Medical Research Council.

<sup>a</sup> Spirometric Classification based on FEV<sub>1</sub>/FVC ratio.
Reasons for delay in Diagnosis

- Patient does not seek medical attention until late in disease process (i.e., emphysema)
- Physicians focus on treatment of symptoms rather than disease prevention
- We may be looking at the wrong thing (waiting too long until PFT, x-rays, spirometry, etc. are abnormal).
Diagnostic Techniques

- History/Physical (symptoms – more sensitive)
- Pulmonary Function Testing
- Imaging: CXR, Chest CT, V/Q scan
- Pulse oximetry at rest and with activity
- ABG
- Alpha 1 Antitrypsin Deficiency Screen
  - COPD in caucasian under age 45 y or with strong family history of COPD
Physical Exam
<table>
<thead>
<tr>
<th></th>
<th>Predominant Bronchitis</th>
<th>Predominant Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>40–45</td>
<td>50–75</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Mild; late</td>
<td>Severe; early</td>
</tr>
<tr>
<td>Cough</td>
<td>Early; copious sputum</td>
<td>Late; scanty sputum</td>
</tr>
<tr>
<td>Infections</td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>Repeated</td>
<td>Terminal</td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td>Common</td>
<td>Rare; terminal</td>
</tr>
<tr>
<td>Airway resistance</td>
<td>Increased</td>
<td>Normal or slightly increased</td>
</tr>
<tr>
<td>Elastic recoil</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Prominent vessels; large heart</td>
<td>Hyperinflation; small heart</td>
</tr>
<tr>
<td>Appearance</td>
<td>Blue bloater</td>
<td>Pink puffer</td>
</tr>
</tbody>
</table>
Volume/Time Curves: Obstruction

- **Normal**
- **Obstructed**
- **Severe Obstruction**

Volume

Time

1 sec
<table>
<thead>
<tr>
<th>Measure</th>
<th>Meas</th>
<th>Ref</th>
<th>%Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>3.66</td>
<td>4.39</td>
<td>83</td>
</tr>
<tr>
<td>FEV1</td>
<td>1.03</td>
<td>2.87</td>
<td>36</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>28</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>FEF25-75</td>
<td>0.33</td>
<td>2.48</td>
<td>13</td>
</tr>
<tr>
<td>PEF</td>
<td>4.29</td>
<td>8.33</td>
<td>52</td>
</tr>
</tbody>
</table>

http://www.vh.org/cgi/cmepractest/Spirometry/SpiroTest.html  11/2/01
Systemic Features of COPD

- Cachexia: loss of fat free mass
- Skeletal muscle wasting: apoptosis, disuse atrophy
- Osteoporosis
- Depression
- Normochromic normocytic anemia
- Increased risk of cardiovascular disease: associated with CRP
Exercise limitation

- Normal individuals never reach a respiratory limitation at peak exercise

- However COPD patients have a reduced maximum ventilation and this can limit their exercise capacity

- These patients can have airflow limitation to exercise

- They can also desaturate with exercise
COPD Treatment: Goals

- Slow disease progression
- Reduce the frequency and severity of disease exacerbations
- Improve quality of life
# GOLD: Severity of COPD

## GOLD Model for Classifying Severity of Disease in COPD

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Characteristics</th>
<th>Spirometric Classification&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Exacerbations Per Year</th>
<th>CAT Score</th>
<th>mMRC Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low risk, fewer symptoms</td>
<td>GOLD 1-2</td>
<td>≤1</td>
<td>&lt;10</td>
<td>0-1</td>
</tr>
<tr>
<td>B</td>
<td>Low risk, more symptoms</td>
<td>GOLD 1-2</td>
<td>≤1</td>
<td>≥10</td>
<td>≥2</td>
</tr>
<tr>
<td>C</td>
<td>High risk, fewer symptoms</td>
<td>GOLD 3-4</td>
<td>≥2</td>
<td>&lt;10</td>
<td>0-1</td>
</tr>
<tr>
<td>D</td>
<td>High risk, more symptoms</td>
<td>GOLD 3-4</td>
<td>≥2/≥1 with hospital admission</td>
<td>≥10</td>
<td>≥2</td>
</tr>
</tbody>
</table>

CAT = COPD Assessment Test; mMRC = Modified Medical Research Council.

---

ACP MKSAP 17
## Optimizing Treatment: A

<table>
<thead>
<tr>
<th>Patient Category&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Recommended First Choice</th>
<th>Alternative Choice</th>
<th>Other Possible Treatments&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| A                           | Short-acting anticholinergic PRN  
                             | or                      | Long-acting anticholinergic  
                             | or                      | Long-acting β<sub>2</sub>-agonist  
                             | or                      | Short-acting β<sub>2</sub>-agonist and  
                             | or                      | Short-acting anticholinergic  
                             | Theophylline             |
## Optimizing Treatment: B

<table>
<thead>
<tr>
<th>Patient Category&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Recommended First Choice</th>
<th>Alternative Choice</th>
<th>Other Possible Treatments&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Long-acting anticholinergic&lt;br&gt;&lt;i&gt;or&lt;/i&gt;&lt;br&gt;Long-acting β&lt;sub&gt;2&lt;/sub&gt;-agonist</td>
<td>Long-acting anticholinergic &lt;i&gt;and&lt;/i&gt;&lt;br&gt;Long-acting β&lt;sub&gt;2&lt;/sub&gt;-agonist</td>
<td>Short-acting β&lt;sub&gt;2&lt;/sub&gt;-agonist&lt;br&gt;&lt;i&gt;and/or&lt;/i&gt;&lt;br&gt;Short-acting anticholinergic&lt;br&gt;&lt;i&gt;or&lt;/i&gt;&lt;br&gt;Theophylline</td>
</tr>
</tbody>
</table>
## Optimizing Treatment: C

<table>
<thead>
<tr>
<th>Patient Category&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Recommended First Choice</th>
<th>Alternative Choice</th>
<th>Other Possible Treatments&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Inhaled glucocorticoid +</td>
<td>Long-acting anticholinergic &lt;i&gt;and&lt;/i&gt; Long-acting β&lt;sub&gt;2&lt;/sub&gt;-agonist</td>
<td>Short-acting β&lt;sub&gt;2&lt;/sub&gt;-agonist &lt;i&gt;and/or&lt;/i&gt; Short-acting anticholinergic</td>
</tr>
<tr>
<td></td>
<td>Long-acting β&lt;sub&gt;2&lt;/sub&gt;-agonist &lt;i&gt;or&lt;/i&gt;</td>
<td>Long-acting β&lt;sub&gt;2&lt;/sub&gt;-agonist &lt;i&gt;or&lt;/i&gt; Long-acting anticholinergic and Phosphodiesterase-4 inhibitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long-acting anticholinergic &lt;i&gt;or&lt;/i&gt; Phosphodiesterase-4 inhibitor</td>
<td>Long-acting β&lt;sub&gt;2&lt;/sub&gt;-agonist &lt;i&gt;and&lt;/i&gt; Phosphodiesterase-4 inhibitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Theophylline</td>
</tr>
</tbody>
</table>
## Optimizing Treatment: D

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Recommended First Choice</th>
<th>Alternative Choice</th>
<th>Other Possible Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td><strong>Inhaled</strong> glucocorticoid + Long-acting β₂-agonist and/or Long-acting anticholinergic</td>
<td>Inhaled glucocorticoid + Long-acting β₂-agonist and Long-acting anticholinergic</td>
<td><em>N</em>-acetylcysteine or Short-acting β₂-agonist and/or Short-acting anticholinergic or Theophylline</td>
</tr>
</tbody>
</table>
# Medication side effects

<table>
<thead>
<tr>
<th>Bronchodilators</th>
<th>Tachycardia and hypokalemia (usually dose dependent), but generally well tolerated by most patients</th>
<th>Generally used as needed for mild disease with few symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled short-acting β₂-agonists (albuterol, fenoterol, levalbuterol, metaproterenol, pirbuterol, terbutaline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled short-acting anticholinergic agents (ipratropium)</td>
<td>Dry mouth, mydriasis on contact with eye, tachycardia, tremors, rarely acute narrow angle glaucoma; this drug class has been shown to be safe in a wide range of doses and clinical settings</td>
<td>Not to be used with tiotropium; generally used as needed for mild disease with few symptoms; avoid using both short- and long-acting anticholinergics</td>
</tr>
</tbody>
</table>
### Medication side effects

| Inhaled long-acting anticholinergic agents (tiotropium, aclidinium, umeclidinium, glycopyrronium) | Dry mouth, mydriasis on contact with eye, tachycardia, tremors, rarely acute narrow angle glaucoma | Not to be used with ipratropium; use when short-acting bronchodilators provide insufficient control of symptoms for patients with an FEV₁ <60% of predicted |
| Inhaled long-acting β₂-agonists (salmeterol, formoterol, arformoterol, indacaterol, olodaterol) | Sympathomimetic symptoms such as tremor and tachycardia; overdose can be fatal | Use as maintenance therapy when short-acting bronchodilators provide insufficient control of symptoms for patients with an FEV₁ <60% of predicted; not intended to be used for treatment of exacerbations of COPD or acute bronchospasm |
## Medication side effects

<table>
<thead>
<tr>
<th>Methylxanthines (theophylline, aminophylline; sustained and short-acting)</th>
<th>Tachycardia, nausea, vomiting, disturbed pulmonary function, and disturbed sleep; narrow therapeutic index; overdose can be fatal with seizures and arrhythmias</th>
<th>Used as maintenance therapy; generally use only after long-acting bronchodilator treatment to provide additional symptomatic relief of exacerbations; may also improve respiratory muscle function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral β₂-agonists (albuterol, metaproterenol, terbutaline)</td>
<td>Sympathomimetic symptoms such as tremor and tachycardia</td>
<td>Used as maintenance therapy; rarely used because of side effects but may be beneficial for patients who cannot use inhalers</td>
</tr>
</tbody>
</table>
**Medication side effects**

<table>
<thead>
<tr>
<th>Oral Phosphodiesterase-4 Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Roflumilast</strong></td>
</tr>
<tr>
<td>Diarrhea, nausea, backache, decreased appetite, dizziness</td>
</tr>
<tr>
<td>Used to reduce risk for exacerbations in patients with severe COPD (blood levels not required) with chronic bronchitis and history of exacerbations; roflumilast should not be used with methylxanthines owing to potential toxicity; very expensive and should be used only in select patients</td>
</tr>
</tbody>
</table>
# Medication side effects

<table>
<thead>
<tr>
<th>Anti-Inflammatory Agents</th>
<th>Side Effects</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled glucocorticoids (fluticasone, budesonide, mometasone, ciclesonide, beclomethasone)</td>
<td>Dysphonia, skin bruising, oral candidiasis, rarely side effects of oral glucocorticoids (see below)</td>
<td>Most effective in patients with a history of frequent exacerbations and when used in conjunction with long-acting bronchodilators; not approved by the FDA for treatment for COPD</td>
</tr>
<tr>
<td>Oral glucocorticoids (prednisone, prednisolone)</td>
<td>Skin bruising, adrenal suppression, glaucoma, osteoporosis, diabetes mellitus, systemic hypertension, pneumonia, cataracts, opportunistic infection, insomnia, mood disturbance</td>
<td>Use for significant exacerbations of COPD with taper; avoid, if possible, in stable COPD to limit glucocorticoid toxicity; consider inhaled glucocorticoids to facilitate weaning of systemic glucocorticoids</td>
</tr>
</tbody>
</table>
# Therapy at Each Stage of COPD

<table>
<thead>
<tr>
<th>Stage</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt; (%)</th>
<th>Treatment Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Mild</td>
<td>&lt; 70%</td>
<td>≥ 80% predicted</td>
<td>Active reduction of risk factor(s); influenza vaccination; <em>Add</em> short-acting bronchodilator (when needed)</td>
</tr>
<tr>
<td>II: Moderate</td>
<td>&lt; 70%</td>
<td>50% ≤ FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 80% predicted</td>
<td><em>Add</em> regular treatment with one or more long-acting bronchodilators (when needed); <em>Add</em> rehabilitation; <em>Add</em> inhaled glucocorticosteroids if repeated exacerbations</td>
</tr>
<tr>
<td>III: Severe</td>
<td>&lt; 70%</td>
<td>30% ≤ FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 50% predicted</td>
<td></td>
</tr>
<tr>
<td>IV: Very Severe</td>
<td>&lt; 70%</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 30% predicted or FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 50% predicted plus chronic respiratory failure</td>
<td><em>Add</em> long term oxygen if chronic respiratory failure; <em>Consider</em> surgical treatments</td>
</tr>
</tbody>
</table>

*Add* indicates additional treatment to be considered as necessary.
Additional Treatment for COPD

- Smoking cessation
- Pulmonary rehabilitation
- Oxygen therapy
  - $\text{PaO}_2 \leq 55\text{mmHg or } \text{pox} \leq 88\%$
  - $\text{PaO}_2 \leq 59$ with polycythemia or clinical evidence of cor pulmonale
- Surgery (LVRS – upper lobe dz, Lung Transplant)
Pharmacological Interventions

- Nicotine replacement
- Bupropion HCL
- Varenicline
- Clonidine HCL
- Nortriptyline
Assess COPD Comorbidities

- Cardiovascular disease
- Osteoporosis
- Respiratory infections
- Anxiety and Depression
- Diabetes
- LUNG CANCER

These comorbid conditions influence mortality and hospitalizations; and should be looked for routinely and treated appropriately.
Vaccination: COPD

- **Pneumococcal vaccination**
  - All adults 65/+y and high risk <65y
  - PPSV23
  - PCV13
  - PCV13 is more effective in preventing invasive pneumococcal disease than PPSV23

- **Flu vaccine**
  - Given yearly
Asthma
Prevalence of Asthma: 2011

Prevalence of Lifetime Asthma

Percentage of Population with Asthma

Source: 2011 National Health Interview Survey Data (NHIS)

Question: "Has a doctor or other health professional ever told you that you had asthma?"
Prevalence of Asthma: 2015

Current Asthma Prevalence Percents by Age, Sex, and Race/Ethnicity, United States, 2015

- Child: 8.4%
- Adult: 7.6%
- Male: 6.5%
- Female: 9.1%
- White: 7.8%
- Black: 10.3%
- Hispanic: 6.6%

Source: National Health Interview Survey, National Center for Health Statistics, Centers for Disease Control and Prevention
Asthma

- Is an **obstructive** pulmonary disease with the following characteristics:
  - Airway obstruction that is reversible (in most patients)
  - Airway inflammation
  - Increased airway responsiveness

- **Major Symptoms:**
  - Cough
  - Wheeze
  - Dyspnea
  - Hypocapnea (usually)
TRIGGERS

**inflammatory factors**
- respiratory infections
- allergens
- work
- medication
- food additives
- pollutants

**irritants**
- temperature change
- strong odors
- cold air
- exercise
- stress and emotions
- gastric reflux

**others**
- exercise
- cold air
- stress and emotions
Pathology of Advanced Chronic Asthma

- Hyperinflation
- Increased number of mucus glands
- Thick tenacious mucus
- Mucus plugs
- Muscular hypertrophy
- Thickened basement membrane
- Peribronchial Eosinophilic infiltration

*All are significantly reversible*
Differences in inflammatory cells between COPD and asthma

Ranked in relative order of importance

<table>
<thead>
<tr>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>Eosinophils</td>
</tr>
<tr>
<td>Macrophages</td>
<td>Mast cells</td>
</tr>
<tr>
<td>CD8-T-lymphocytes</td>
<td>CD4-T-lymphocytes</td>
</tr>
<tr>
<td>Eosinophils (exacerbations)</td>
<td>Macrophages, Neutrophils</td>
</tr>
</tbody>
</table>

Similarities and Differences in Asthma and COPD*: The Dutch Hypothesis

CHEST. 2004;126(2_suppl_1):93S-95S.

**Asthma**
- Usually intermittent airflow obstruction but often has a less reversible obstruction
- Improvement in airway obstruction with bronchodilators and corticosteroids
- High levels of bronchial responsiveness
- Cellular inflammation with eosinophils, mast cells, T lymphocytes; in severe disease, neutrophils
- Broad inflammatory mediator responses
- Airway remodeling (epithelial injury and fibrosis)

**COPD**
- Progressive airflow obstruction
- Smaller bronchodilator and corticosteroid response
- Most patients have increased bronchial responsiveness
- Cellular inflammation including neutrophils, macrophages, eosinophils and mast cells may occur
- Cytokine, chemokine, protease responses
- Emphysema (lung destruction) frequent
Two Phases of Asthma

- Early (immediate) response
  - Major problem - bronchospasm

- Late (delayed) response
  - Major problem - inflammation
  - Typically more severe than early response
Characteristics of Early Asthmatic Response

- Occurs in all patients with asthma
- Caused by release of mediators from mast cells (Histamine)
- Occurs 5-10 minutes after exposure
- Lasts 1.5-2 hours
- Responds to:
  - Bronchodilators (b-agonists preferred)
  - Cromolyn sodium (effective prophylactically)
  - Corticosteroids (no effect acutely, partial effect chronically)
Characteristics of Late Asthmatic Response

- Occurs in 50%-90% of patients
- Caused by chemotactic factors recruiting eosinophils, platelets, neutrophils
- Occurs 3-8 hours after exposure
- Lasts a widely varying amount of time
- Responds well to:
  - Cromolyn sodium
  - Corticosteroids
Asthma Syndromes

- **Allergic Asthma**
  - Most common form of asthma in adults
  - Atopy, positive FH

- **Cough Variant**

- **Exercise Induced Bronchospasm**
  - Triggered by drying of airways

- **Occupational Asthma**
  - Farmers, factory workers, hairdressers

- **Aspirin Sensitive Asthma (Samter triad)**
  - Asthma, asa sensitivity, sinusitis/nasal polyposis

- **Reactive Airways Dysfunction Syndrome**
  - Exposure to high concentration of irritant; short lived

- **Virus-Induced bronchospasm**

- **Allergic Bronchopulmonary Aspergillosis**
  - Colonization of aspergillus sp
  - Mucus plugging, bronchiectasis, asthma, fleeting infiltrates
Contributing Factors

- GERD
- Sinus disease
- OSA/Obesity
- Chronic aspiration
- Vocal Cord Dysfunction
  - Mid-chest tightness, dyspnea, dysphonia/stridor, partial response to asthma medication
  - Adduction of VC on laryngoscopy
Four Components of Asthma Management

- Objective measures
- Patient education
  - Trigger avoidance
  - Peak flow measurements
- Environmental control measures
- Pharmacotherapy
  - Medications
  - Secretion clearance
# Asthma Management Therapies

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Properties and Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABAs</td>
<td>Albuterol, levalbuterol</td>
<td>Relax airway smooth muscle; treatment of choice for acute symptoms</td>
</tr>
<tr>
<td>LABAs</td>
<td>Salmeterol, formoterol</td>
<td>Bronchodilation lasting for ≥ 12 hours; usually used in combination with ICS after step 2</td>
</tr>
<tr>
<td>ICS</td>
<td>Beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone</td>
<td>Reduce airway hyperresponsiveness, decrease inflammatory cell migration and activation, block late-phase reactions to allergens</td>
</tr>
<tr>
<td>OCS</td>
<td>Prednisone</td>
<td>Systemic anti-inflammatory effects; used for moderate to severe exacerbations to accelerate recovery and prevent late-phase response; may be used for long-term control</td>
</tr>
<tr>
<td>Mast cell stabilizers</td>
<td>Cromolyn sodium, nedocromil</td>
<td>Interfere with release of inflammatory mediators from mast cells; maintenance therapy for mild to moderate asthma or as prophylaxis for exercise-induced asthma</td>
</tr>
<tr>
<td>Leukotriene modifiers</td>
<td>Montelukast, zafirlukast, zileuton</td>
<td>Interfere with leukotriene mediators released from mast cells, eosinophils and basophils; prophylaxis of exercise-induced asthma and long-term treatment as alternative to low doses of ICS</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>Theophylline, aminophylline</td>
<td>Mild to moderate bronchodilation; toxic at higher doses</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Ipratropium bromide</td>
<td>Enhance effects of SABAs in acute attacks by inhibiting muscarinic cholinergic receptors and reducing vagal tone of airway</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>Omalizumab</td>
<td>Binds to IgE, forming complexes that prevent initiation of allergic cascade by inhibiting mast cell and basophil degranulation; reserved as add-on therapy for patients ≥ 12 years with refractory asthma (steps 5 and 6)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ICS, inhaled corticosteroids; LABAs, long-acting beta-agonists; OCS, oral corticosteroids; SABAs, short-acting beta-agonists

Corticosteroid
Mechanism of Action

- Prevents the activation and directed migration of inflammatory cells
- Interferes with arachidonic acid metabolism and the synthesis of leukotrienes and prostaglandins
- Increase the responsiveness of the $\beta$-receptors of airway smooth muscle
Systemic vs. Inhaled Corticosteroids

Major Adverse Effects

- High dose, short-term, oral therapy:
  - Reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, rounding of the face, mood alteration, hypertension, peptic ulcer, and aseptic necrosis of the femur

- Lowest possible dose, long-term, oral therapy:
  - Osteoporosis, hypertension, Cushing’s syndrome, cataracts, myopathy, hypothalamic-pituitary-adrenal axis suppression, impaired immune mechanisms (rare)

- Aerosolized therapy:
  - Infrequent systemic adverse effects
  - Local adverse events include oropharyngeal candidiasis, dysphonia, occasional coughing resulting from upper airway irritation caused by aerosol inhalation
LT Antagonist: Clinical Utility

- Prophylaxis of mild to moderate asthma
- Aspirin induced asthma
- Prevention of antigen and exercise induced asthma
- Not effective in relieving acute asthma exacerbations
- Bronchodilation
- Anti-inflammatory action
- Less effective than inhaled corticosteroids
- Potentiate oral corticosteroid action
LT Antagonist Side Effects

- Elevation of liver enzymes
- Headache
- Dyspepsia
- Rare:
  - Eosinophilic granulomatosis with polyangiitis (formerly Churg-Straus syndrome)
Theophylline: Pharmacologic Properties

- Mechanism of action:
  - Inhibits action of phosphodiesterase which prevents breakdown cAMP, thereby increasing cAMP levels in tissue resulting in smooth muscle relaxation
- Bronchodilation
- Improved airflow
- Increased mucociliary clearance
- Improved respiratory muscle strength and endurance
- Increased cardiac output (in some)
- Moderate respiratory center stimulation
Theophylline - Clinical Utility

- Chronic asthma
- Manage reversible components of chronic bronchitis and emphysema
- Effective at low doses, minimizing potential for serious side effects
- Additive effects with oral and inhaled $\beta_2$-agonists
- Especially useful when given before bedtime for the patient with primarily nocturnal symptoms
Adverse Effects of Theophylline

- Cardiac
  - Tachycardia, arrhythmia
- CNS
  - Seizure, tremors
- GI
  - Nausea, vomiting
- GU
  - Prostatism, detrusor muscle relaxation
- Metabolic
  - Hyperglycemia, hypokalemia
Theophylline Clearance

• **Increased by:**
  ◦ B-agonist
  ◦ Carbamazepine
  ◦ Phenytoin
  ◦ Furosemide
  ◦ Hyperthyroidism
  ◦ Ketoconazole
  ◦ Marijuana
  ◦ Phenobarbital
  ◦ Rifampin
  ◦ Tobacco smoke

• **Decreased by:**
  ◦ Allopurinol
  ◦ Macrolides
  ◦ Ciprofloxacin
  ◦ Isoniazid
  ◦ Propranolol
  ◦ Caffeine
  ◦ Cirrhosis
  ◦ CHF
  ◦ Cimetidine
  ◦ Mexiletine
  ◦ Oral contraceptives
  ◦ Viral infections
Immunomodulators

- Omalizumab
- Monoclonal antibody directed against human IgE
- Prevents IgE binding with its receptors on mast cells and basophils
- Decrease release of allergic mediators
- Used to treat allergic asthma
- Subcutaneous injection
- Expensive
- Not first line therapy
- Anti IL 5: Mepolizumab
# Classifying Asthma Severity and Initiating Treatment in Youths ≥ 12 Years of Age and Adults

Assessing severity and initiating treatment for patients who are not currently taking long-term control medications.

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity ≥ 12 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
</tr>
<tr>
<td>Normal FEV₁/FVC:</td>
<td></td>
</tr>
<tr>
<td>8-19 yr</td>
<td>85%</td>
</tr>
<tr>
<td>20-39 yr</td>
<td>80%</td>
</tr>
<tr>
<td>40-59 yr</td>
<td>75%</td>
</tr>
<tr>
<td>60-80 yr</td>
<td>70%</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2 x/month</td>
</tr>
<tr>
<td>Short-acting beta agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Lung function</td>
<td>Normal FEV₁ between exacerbations</td>
</tr>
<tr>
<td></td>
<td>FEV₁ &gt; 80% predicted</td>
</tr>
<tr>
<td>Risk</td>
<td>Exacerbations requiring oral systemic corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV₁.</td>
</tr>
</tbody>
</table>

**Recommended Step for Initiating Treatment**

- **Step 1**: In 2-6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.
- **Step 2**:  
- **Step 3**:  
- **Step 4 or 5**: and consider short course of oral systemic corticosteroids

*FEV₁ - forced expiratory volume in one second; FVC - forced vital capacity*
**Intermittent Asthma**
Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

**Step 1**
Preferred: Low-dose ICS OR Medium-dose ICS
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

**Step 2**
Preferred: Low-dose ICS + LABA
Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 3**
Preferred: Medium-dose ICS + LABA
Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 4**
Preferred: High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

**Step 5**
Preferred: High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

**Step 6**
Step up if needed.
(first, check adherence, environmental control, and comorbid conditions)
Assess control
Step down if possible
(and asthma is well controlled at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

Quick-Relief Medication for All Patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.
Bronchial thermoplasty

- FDA approved 2010
- Adjunctive therapy despite optimization of asthma treatment
- Bronchoscopically induced catheter applies thermal energy to conducting airways 3mm or greater with goal of reducing smooth muscle thickening
- 3 sessions, 3 weeks apart
- Lung function remains unchanged
- Notable improvement in symptoms
- Adverse effect: temporary bronchospasm after procedure
Also important to review...

- Alpha 1 Antitrypsin deficiency
- Cystic Fibrosis
- Bronchiectasis
  - Right Middle Lobe Syndrome
  - Ciliary Dyskinesia Syndrome
  - Allergic Bronchopulmonary Aspergillosis