GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE (GOLD):
TEACHING SLIDE SET
December 2011

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Global Initiative for Chronic Obstructive Lung Disease
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Jørgen Vestbo, MD - Chair

Dissemination/Implementation Committee
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Robert Stockley, MD
Claus Vogelmeier, MD
<table>
<thead>
<tr>
<th>Evidence Category</th>
<th>Sources of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Randomized controlled trials (RCTs). Rich body of data</td>
</tr>
<tr>
<td>B</td>
<td>Randomized controlled trials (RCTs). Limited body of data</td>
</tr>
<tr>
<td>C</td>
<td>Nonrandomized trials Observational studies.</td>
</tr>
<tr>
<td>D</td>
<td>Panel consensus judgment</td>
</tr>
</tbody>
</table>
GOLD Structure

GOLD Board of Directors

Roberto Rodriguez-Roisin, MD – Chair

Science Committee

Jørgen Vestbo, MD - Chair

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Jean Bourbeau, MD - Chair

GOLD National Leaders - GNL
http://www.goldcopd.org
Global Initiative for Chronic Obstructive Lung Disease
GOLD Objectives

- Increase awareness of COPD among health professionals, health authorities, and the general public
- Improve diagnosis, management and prevention
- Decrease morbidity and mortality
- Stimulate research
Global Strategy for Diagnosis, Management and Prevention of COPD, 2011: Chapters

- Definition and Overview
- Diagnosis and Assessment
- Therapeutic Options
- Manage Stable COPD
- Manage Exacerbations
- Manage Comorbidities
COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.

Exacerbations and comorbidities contribute to the overall severity in individual patients.
Mechanisms Underlying Airflow Limitation in COPD

Small Airways Disease
- Airway inflammation
- Airway fibrosis, luminal plugs
- Increased airway resistance

Parenchymal Destruction
- Loss of alveolar attachments
- Decrease of elastic recoil

AIRFLOW LIMITATION
COPD is a leading cause of morbidity and mortality worldwide.

The burden of COPD is projected to increase in coming decades due to continued exposure to COPD risk factors and the aging of the world’s population.

COPD is associated with significant economic burden.
Global Strategy for Diagnosis, Management and Prevention of COPD

Risk Factors for COPD

Genes

Exposure to particles

- Tobacco smoke
- Occupational dusts, organic and inorganic
- Indoor air pollution from heating and cooking with biomass in poorly ventilated dwellings
- Outdoor air pollution

Lung growth and development

Gender

Age

Respiratory infections

Socioeconomic status

Asthma/Bronchial hyperreactivity

Chronic Bronchitis
Global Strategy for Diagnosis, Management and Prevention of COPD

Risk Factors for COPD

- Genes
- Infections
- Socio-economic status

Aging Populations

- Cigarette smoke
- Occupational dust and chemicals
- Environmental tobacco smoke (ETS)
- Indoor and outdoor air pollution
Global Strategy for Diagnosis, Management and Prevention of COPD, 2011: Chapters

- Definition and Overview
- Diagnosis and Assessment
- Therapeutic Options
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- Manage Exacerbations
- Manage Comorbidities
A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease.

Spirometry is required to make the diagnosis; the presence of a post-bronchodilator FEV₁/FVC < 0.70 confirms the presence of persistent airflow limitation and thus of COPD.
Diagnosis and Assessment: Key Points

- The goals of COPD assessment are to determine the severity of the disease, including the severity of airflow limitation, the impact on the patient’s health status, and the risk of future events.

- Comorbidities occur frequently in COPD patients, and should be actively looked for and treated appropriately if present.
SYMPTOMS
- shortness of breath
- chronic cough
- sputum

EXPOSURE TO RISK FACTORS
- tobacco
- occupation
- indoor/outdoor pollution

SPIROMETRY: Required to establish diagnosis
Assessment of Airflow Limitation: Spirometry

- Spirometry should be performed after the administration of an adequate dose of a short-acting inhaled bronchodilator to minimize variability.

- A post-bronchodilator FEV$_1$/FVC < 0.70 confirms the presence of airflow limitation.

- Where possible, values should be compared to age-related normal values to avoid overdiagnosis of COPD in the elderly.
Spirometry: Normal Trace Showing $\text{FEV}_1$ and FVC

- $\text{FEV}_1 = 4\text{L}$
- FVC = 5L
- $\text{FEV}_1$/FVC = 0.8
Spirometry: Obstructive Disease

Volume, liters

Time, seconds

FEV$_1$ = 1.8L
FVC = 3.2L
FEV$_1$/FVC = 0.56

Normal

Obstructive
Determine the severity of the disease, its impact on the patient’s health status and the risk of future events (for example exacerbations) to guide therapy. Consider the following aspects of the disease separately:

- current level of patient’s symptoms
- severity of the spirometric abnormality
- frequency of exacerbations
- presence of comorbidities.
Assessment of COPD

- Assess symptoms
- Assess degree of airflow limitation using spirometry
- Assess risk of exacerbations
- Assess comorbidities
The characteristic symptoms of COPD are chronic and progressive dyspnea, cough, and sputum production.

*Dyspnea:* Progressive, persistent and characteristically worse with exercise.

*Chronic cough:* May be intermittent and may be unproductive.

*Chronic sputum production:* COPD patients commonly cough up sputum.
Assess symptoms

Use the COPD Assessment Test (CAT) or mMRC Breathlessness scale
Assessment of Symptoms

*COPD Assessment Test (CAT):* An 8-item measure of health status impairment in COPD (http://catestonline.org).

*Breathlessness Measurement using the Modified British Medical Research Council (mMRC) Questionnaire:* relates well to other measures of health status and predicts future mortality risk.
Please tick in the box that applies to you (one box only)
mMRC Grade 0. I only get breathless with strenuous exercise.
mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill.
mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.
mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level.
mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing.
Assessment of COPD

- Assess symptoms
- Assess degree of airflow limitation

Use spirometry for grading severity according to spirometry, using four grades split at 80%, 50% and 30% of predicted value.
Classification of Severity of Airflow Limitation in COPD*

In patients with FEV$_1$/FVC < 0.70:

GOLD 1: Mild \( \text{FEV}_1 \geq 80\% \text{ predicted} \)

GOLD 2: Moderate \( 50\% \leq \text{FEV}_1 < 80\% \text{ predicted} \)

GOLD 3: Severe \( 30\% \leq \text{FEV}_1 < 50\% \text{ predicted} \)

GOLD 4: Very Severe \( \text{FEV}_1 < 30\% \text{ predicted} \)

*Based on Post-Bronchodilator FEV$_1$
Assessment of COPD

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

Use history of exacerbations and spirometry. Two exacerbations or more within the last year or an FEV₁ < 50 % of predicted value are indicators of high risk.
Global Strategy for Diagnosis, Management and Prevention of COPD

Assess Risk of Exacerbations

To assess risk of exacerbations use history of exacerbations and spirometry:

- Two or more exacerbations within the last year or an FEV$_1$ < 50% of predicted value are indicators of high risk.
Combined Assessment of COPD

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

*Combine these assessments for the purpose of improving management of COPD*
Combined Assessment of COPD

Symptoms (mMRC or CAT score)

- mMRC 0-1
  - CAT < 10
  - (A)
- mMRC > 2
  - CAT ≥ 10
  - (B)

Risk (GOLD Classification of Airflow Limitation)

- Risk < 2
  - (C)
- Risk ≥ 2
  - (D)

Risk (Exacerbation history)

- 0
- 1
- ≥ 2
Combined Assessment of COPD

Assess symptoms first

If mMRC 0-1 or CAT < 10:
Less Symptoms (A or C)

If mMRC ≥ 2 or CAT ≥ 10:
More Symptoms (B or D)

Symptoms
(mMRC or CAT score)

mMRC 0-1  mMRC ≥ 2
CAT < 10   CAT ≥ 10
Combined Assessment of COPD

Assess risk of exacerbations next

<table>
<thead>
<tr>
<th>Risk (GOLD Classification of Airflow Limitation)</th>
<th>Symptoms (mMRC or CAT score)</th>
<th>Exacerbation history</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>mMRC 0-1 CAT &lt; 10</td>
<td>0 or 1 exacerbations per year: Low Risk (A or B)</td>
</tr>
<tr>
<td>1</td>
<td>mMRC &gt; 2 CAT ≥ 10</td>
<td>≥ 2 exacerbations per year: High Risk (C or D)</td>
</tr>
</tbody>
</table>

If GOLD 1 or 2 and only 0 or 1 exacerbations per year: Low Risk (A or B)

If GOLD 3 or 4 or two or more exacerbations per year: High Risk (C or D)
Use combined assessment

Patient is now in one of four categories:

A: Less symptoms, low risk
B: More symptoms, low risk
C: Less symptoms, high risk
D: More symptoms, high risk

Combined Assessment of COPD

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

(mMRC or CAT score)

Symptoms

Risk

(GOLD Classification of Airflow Limitation)

Risk

(Exacerbation history)

(A) mMRC 0-1 CAT < 10
(B) mMRC > 2 CAT ≥ 10
(C) mMRC 0-1 CAT ≥ 10
(D) mMRC > 2 CAT < 10
Global Strategy for Diagnosis, Management and Prevention of COPD

Combined Assessment of COPD

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Characteristic</th>
<th>Spirometric Classification</th>
<th>Exacerbations per year</th>
<th>mMRC</th>
<th>CAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low Risk Less Symptoms</td>
<td>GOLD 1-2</td>
<td>≤ 1</td>
<td>0-1</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>B</td>
<td>Low Risk More Symptoms</td>
<td>GOLD 1-2</td>
<td>≤ 1</td>
<td>≥ 2</td>
<td>≥ 10</td>
</tr>
<tr>
<td>C</td>
<td>High Risk Less Symptoms</td>
<td>GOLD 3-4</td>
<td>≥ 2</td>
<td>0-1</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>D</td>
<td>High Risk More Symptoms</td>
<td>GOLD 3-4</td>
<td>≥ 2</td>
<td>≥ 2</td>
<td>≥ 10</td>
</tr>
</tbody>
</table>
COPD patients are at increased risk for:

- Cardiovascular diseases
- Osteoporosis
- Respiratory infections
- Anxiety and Depression
- Diabetes
- Lung cancer

*These comorbid conditions may influence mortality and hospitalizations and should be looked for routinely, and treated appropriately.*
### Differential Diagnosis: COPD and Asthma

<table>
<thead>
<tr>
<th>COPD</th>
<th>ASTHMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset in mid-life</td>
<td>Onset early in life (often childhood)</td>
</tr>
<tr>
<td>Symptoms slowly</td>
<td>Symptoms vary from day to day</td>
</tr>
<tr>
<td>progressive</td>
<td>Symptoms worse at night/early morning</td>
</tr>
<tr>
<td>Long smoking history</td>
<td>Allergy, rhinitis, and/or eczema also present</td>
</tr>
<tr>
<td></td>
<td>Family history of asthma</td>
</tr>
</tbody>
</table>
Global Strategy for Diagnosis, Management and Prevention of COPD

Additional Investigations

*Chest X-ray:* Seldom diagnostic but valuable to exclude alternative diagnoses and establish presence of significant comorbidities.

*Lung Volumes and Diffusing Capacity:* Help to characterize severity, but not essential to patient management.

*Oximetry and Arterial Blood Gases:* Pulse oximetry can be used to evaluate a patient’s oxygen saturation and need for supplemental oxygen therapy.

*Alpha-1 Antitrypsin Deficiency Screening:* Perform when COPD develops in patients of Caucasian descent under 45 years or with a strong family history of COPD.
Exercise Testing: Objectively measured exercise impairment, assessed by a reduction in self-paced walking distance (such as the 6 min walking test) or during incremental exercise testing in a laboratory, is a powerful indicator of health status impairment and predictor of prognosis.

Composite Scores: Several variables (FEV$_1$, exercise tolerance assessed by walking distance or peak oxygen consumption, weight loss and reduction in the arterial oxygen tension) identify patients at increased risk for mortality.
Global Strategy for Diagnosis, Management and Prevention of COPD, 2011: Chapters

- Definition and Overview
- Diagnosis and Assessment
- Therapeutic Options
- Manage Stable COPD
- Manage Exacerbations
- Manage Comorbidities
Therapeutic Options: Key Points

- Smoking cessation has the greatest capacity to influence the natural history of COPD. Health care providers should encourage all patients who smoke to quit.
- Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates.
- All COPD patients benefit from regular physical activity and should repeatedly be encouraged to remain active.
Appropriate pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.

None of the existing medications for COPD has been shown conclusively to modify the long-term decline in lung function.

Influenza and pneumococcal vaccination should be offered depending on local guidelines.
Counseling delivered by physicians and other health professionals significantly increases quit rates over self-initiated strategies. Even a brief (3-minute) period of counseling to urge a smoker to quit results in smoking quit rates of 5-10%.

Nicotine replacement therapy (nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenge) as well as pharmacotherapy with varenicline, bupropion, and nortriptyline reliably increases long-term smoking abstinence rates and are significantly more effective than placebo.
Brief Strategies to Help the Patient Willing to Quit Smoking

- **ASK** Systematically identify all tobacco users at every visit
- **ADVISE** Strongly urge all tobacco users to quit
- **ASSESS** Determine willingness to make a quit attempt
- **ASSIST** Aid the patient in quitting
- **ARRANGE** Schedule follow-up contact.
Global Strategy for Diagnosis, Management and Prevention of COPD

Therapeutic Options: Risk Reduction

- Encourage comprehensive tobacco-control policies with clear, consistent, and repeated nonsmoking messages.
- Emphasize primary prevention, best achieved by elimination or reduction of exposures in the workplace. Secondary prevention, achieved through surveillance and early detection, is also important.
- Reduce or avoid indoor air pollution from biomass fuel, burned for cooking and heating in poorly ventilated dwellings.
- Advise patients to monitor public announcements of air quality and, depending on the severity of their disease, avoid vigorous exercise outdoors or stay indoors during pollution episodes.
### Therapeutic Options: COPD Medications

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta$_2$-agonists</strong></td>
<td></td>
</tr>
<tr>
<td>Short-acting beta$_2$-agonists</td>
<td></td>
</tr>
<tr>
<td>Long-acting beta$_2$-agonists</td>
<td></td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td></td>
</tr>
<tr>
<td>Short-acting anticholinergics</td>
<td></td>
</tr>
<tr>
<td>Long-acting anticholinergics</td>
<td></td>
</tr>
<tr>
<td>Combination short-acting beta$_2$-agonists + anticholinergic in one inhaler</td>
<td></td>
</tr>
<tr>
<td><strong>Methylxanthines</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Inhaled corticosteroids</strong></td>
<td></td>
</tr>
<tr>
<td>Combination long-acting beta$_2$-agonists + corticosteroids in one inhaler</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic corticosteroids</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Phosphodiesterase-4 inhibitors</strong></td>
<td></td>
</tr>
</tbody>
</table>
Bronchodilator medications are central to the symptomatic management of COPD.

Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms.

The principal bronchodilator treatments are beta$_2$-agonists, anticholinergics, theophylline or combination therapy.

The choice of treatment depends on the availability of medications and each patient’s individual response in terms of symptom relief and side effects.
Long-acting inhaled bronchodilators are convenient and more effective for symptom relief than short-acting bronchodilators.

Long-acting inhaled bronchodilators reduce exacerbations and related hospitalizations and improve symptoms and health status.

Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.
Regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function and quality of life and reduces frequency of exacerbations for COPD patients with an FEV₁ < 60% predicted.

Inhaled corticosteroid therapy is associated with an increased risk of pneumonia.

Withdrawal from treatment with inhaled corticosteroids may lead to exacerbations in some patients.
An inhaled corticosteroid combined with a long-acting beta$_2$-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in moderate to very severe COPD.

Combination therapy is associated with an increased risk of pneumonia.

Addition of a long-acting beta$_2$-agonist/inhaled glucorticosteroid combination to an anticholinergic (tiotropium) appears to provide additional benefits.
Chronic treatment with systemic corticosteroids should be avoided because of an unfavorable benefit-to-risk ratio.
In patients with severe and very severe COPD (GOLD 3 and 4) and a history of exacerbations and chronic bronchitis, the phosphodiesterase-4 inhibitor (PDE-4), roflumilast, reduces exacerbations treated with oral glucocorticosteroids.
Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators and is not recommended if those drugs are available and affordable.

There is evidence for a modest bronchodilator effect and some symptomatic benefit compared with placebo in stable COPD. Addition of theophylline to salmeterol produces a greater increase in FEV₁ and breathlessness than salmeterol alone.

Low dose theophylline reduces exacerbations but does not improve post-bronchodilator lung function.
Influenza vaccines can reduce serious illness. Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older and for COPD patients younger than age 65 with an FEV$_1$ < 40% predicted.

The use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is currently not indicated.
Alpha-1 antitrypsin augmentation therapy: not recommended for patients with COPD that is unrelated to the genetic deficiency.

Mucolytics: Patients with viscous sputum may benefit from mucolytics; overall benefits are very small.

Antitussives: Not recommended.

Vasodilators: Nitric oxide is contraindicated in stable COPD. The use of endothelium-modulating agents for the treatment of pulmonary hypertension associated with COPD is not recommended.
All COPD patients benefit from *exercise training programs* with improvements in exercise tolerance and symptoms of dyspnea and fatigue.

Although an effective pulmonary rehabilitation program is 6 weeks, the longer the program continues, the more effective the results.

If exercise training is maintained at home the patient's health status remains above pre-rehabilitation levels.
**Oxygen Therapy:** The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival in patients with severe, resting hypoxemia.

**Ventilatory Support:** Combination of noninvasive ventilation (NIV) with long-term oxygen therapy may be of some use in a selected subset of patients, particularly in those with pronounced daytime hypercapnia.
Lung volume reduction surgery (LVRS) is more efficacious than medical therapy among patients with upper-lobe predominant emphysema and low exercise capacity.

LVRS is costly relative to health-care programs not including surgery.

In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve quality of life and functional capacity.
Global Strategy for Diagnosis, Management and Prevention of COPD, 2011: Major Chapters

- Definition and Overview
- Diagnosis and Assessment
- Therapeutic Options
- Manage Stable COPD
- Manage Exacerbations
- Manage Comorbidities
Identification and reduction of exposure to risk factors are important steps in prevention and treatment.

Individualized assessment of symptoms, airflow limitation, and future risk of exacerbations should be incorporated into the management strategy.

All COPD patients benefit from rehabilitation and maintenance of physical activity.

Pharmacologic therapy is used to reduce symptoms, reduce frequency and severity of exacerbations, and improve health status and exercise tolerance.
Manage Stable COPD: Key Points

- Long-acting formulations of beta$_2$-agonists and anticholinergics are preferred over short-acting formulations. Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators.

- Long-term treatment with inhaled corticosteroids added to long-acting bronchodilators is recommended for patients with high risk of exacerbations.
Long-term monotherapy with oral or inhaled corticosteroids is not recommended in COPD.

The phosphodiesterase-4 inhibitor roflumilast may be useful to reduce exacerbations for patients with FEV$_1 < 50\%$ of predicted, chronic bronchitis, and frequent exacerbations.
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Goals of Therapy

- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

Reduce symptoms
Reduce risk
Avoidance of risk factors
- smoking cessation
- reduction of indoor pollution
- reduction of occupational exposure

Influenza vaccination
### Manage Stable COPD: Non-pharmacologic

<table>
<thead>
<tr>
<th>Patient</th>
<th>Essential</th>
<th>Recommended</th>
<th>Depending on local guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Smoking cessation (can include pharmacologic treatment)</td>
<td>Physical activity</td>
<td>Flu vaccination Pneumococcal vaccination</td>
</tr>
<tr>
<td>B, C, D</td>
<td>Smoking cessation (can include pharmacologic treatment) Pulmonary rehabilitation</td>
<td>Physical activity</td>
<td>Flu vaccination Pneumococcal vaccination</td>
</tr>
</tbody>
</table>
### Global Strategy for Diagnosis, Management and Prevention of COPD

**Manage Stable COPD: Pharmacologic Therapy**

*Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.*

<table>
<thead>
<tr>
<th>Patient</th>
<th>First choice</th>
<th>Second choice</th>
<th>Alternative Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SAMA prn or SABA prn</td>
<td>LAMA or LABA or SABA and SAMA</td>
<td>Theophylline</td>
</tr>
<tr>
<td>B</td>
<td>LAMA or LABA</td>
<td>LAMA and LABA</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA or LAMA</td>
<td>LAMA and LABA</td>
<td>PDE4-inh. SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA or LAMA</td>
<td>ICS and LAMA or ICS + LABA and LAMA or ICS+LABA and PDE4-inh. or LAMA and LABA or LAMA and PDE4-inh.</td>
<td>Carbocysteine SABA and/or SAMA Theophylline</td>
</tr>
</tbody>
</table>
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

FIRST CHOICE

Exacerbations per year

<table>
<thead>
<tr>
<th>GOLD 4</th>
<th></th>
<th></th>
<th>GOLD 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 2</td>
<td></td>
<td></td>
<td>GOLD 1</td>
</tr>
</tbody>
</table>

A: mMRC 0-1
B: mMRC > 2
C: CAT < 10
D: CAT > 10

- **ICS + LABA** or LAMA
- **SAMA prn** or SABA prn
- **LABA** or LAMA
- **ICS + LABA** or LAMA
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

SECOND CHOICE

- **GOLD 4**
  - mMRC 0-1
    - CAT < 10: LAMA and LABA
  - mMRC > 2
    - CAT > 10: ICS and LAMA or ICS + LABA and LAMA or ICS + LABA and PDE4-inh or LAMA and LABA or LAMA and PDE4-inh or LAMA and LABA or LAMA and PDE4-inh.

- **GOLD 3**
  - LAMA or LABA or SABA and SAMA

- **GOLD 2**
  - mMRC 0-1
    - CAT < 10: LAMA and LABA
  - mMRC > 2
    - CAT > 10: LAMA and LABA

- **GOLD 1**
  - mMRC 0-1
    - CAT < 10: LAMA and LABA
  - mMRC > 2
    - CAT > 10: LAMA and LABA
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

ALTERNATIVE CHOICES

- **GOLD 4**
  - mMRC 0-1
  - CAT < 10
  - PDE4-inh., SABA and/or SAMA, Theophylline

- **GOLD 3**
  - mMRC 0-1
  - CAT < 10
  - Theophylline

- **GOLD 2**
  - mMRC > 2
  - CAT > 10
  - SABA and/or SAMA, Theophylline

- **GOLD 1**
  - mMRC > 2
  - CAT > 10
  - Carbocysteine, SABA and/or SAMA, Theophylline

Exacerbations per year

- 0
- 1
- > 2
Global Strategy for Diagnosis, Management and Prevention of COPD, 2011: Chapters

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An exacerbation of COPD is:

“an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.”
The most common causes of COPD exacerbations are viral upper respiratory tract infections and infection of the tracheobronchial tree.

Diagnosis relies exclusively on the clinical presentation of the patient complaining of an acute change of symptoms that is beyond normal day-to-day variation.

The goal of treatment is to minimize the impact of the current exacerbation and to prevent the development of subsequent exacerbations.
Short-acting inhaled beta$_2$-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators for treatment of an exacerbation.

Systemic corticosteroids and antibiotics can shorten recovery time, improve lung function (FEV$_1$) and arterial hypoxemia (PaO$_2$), and reduce the risk of early relapse, treatment failure, and length of hospital stay.

COPD exacerbations can often be prevented.
Consequences Of COPD Exacerbations

- Negative impact on quality of life
- Impact on symptoms and lung function
- Increased economic costs
- Increased lung function decline
- Increased Mortality

EXACERBATIONS
**Global Strategy for Diagnosis, Management and Prevention of COPD**

**Manage Exacerbations: Assessments**

**Arterial blood gas measurements (in hospital):** $\text{PaO}_2 < 8.0$ kPa with or without $\text{PaCO}_2 > 6.7$ kPa when breathing room air indicates respiratory failure.

**Chest radiographs:** useful to exclude alternative diagnoses.

**ECG:** may aid in the diagnosis of coexisting cardiac problems.

**Whole blood count:** identify polycythemia, anemia or bleeding.

**Purulent sputum** during an exacerbation: indication to begin empirical antibiotic treatment.

**Biochemical tests:** detect electrolyte disturbances, diabetes, and poor nutrition.

**Spirometric tests:** not recommended during an exacerbation.
Oxygen: titrate to improve the patient’s hypoxemia with a target saturation of 88-92%.

Bronchodilators: Short-acting inhaled beta$_2$-agonists with or without short-acting anticholinergics are preferred.

Systemic Corticosteroids: Shorten recovery time, improve lung function (FEV$_1$) and arterial hypoxemia (PaO$_2$), and reduce the risk of early relapse, treatment failure, and length of hospital stay. A dose of 30-40 mg prednisolone per day for 10-14 days is recommended.
Antibiotics should be given to patients with:

- Three cardinal symptoms: increased dyspnea, increased sputum volume, and increased sputum purulence.
- Who require mechanical ventilation.
Noninvasive ventilation (NIV):

- Improves respiratory acidosis, reduces respiratory rate, severity of dyspnea, complications and length of hospital stay.
- Decreases mortality and needs for intubation.
Manage Exacerbations: Indications for Hospital Admission

- Marked increase in intensity of symptoms
- Severe underlying COPD
- Onset of new physical signs
- Failure of an exacerbation to respond to initial medical management
- Presence of serious comorbidities
- Frequent exacerbations
- Older age
- Insufficient home support
Global Strategy for Diagnosis, Management and Prevention of COPD, 2011: Major Chapters

- Definition and Overview
- Diagnosis and Assessment
- Therapeutic Options
- Manage Stable COPD
- Manage Exacerbations
- Manage Comorbidities
COPD often coexists with other diseases (comorbidities) that may have a significant impact on prognosis. In general, presence of comorbidities should not alter COPD treatment and comorbidities should be treated as if the patient did not have COPD.
Cardiovascular disease (including ischemic heart disease, heart failure, atrial fibrillation, and hypertension) is a major comorbidity in COPD and probably both the most frequent and most important disease coexisting with COPD. Cardioselective beta-blockers are not contraindicated in COPD.
Osteoporosis and anxiety/depression: often under-diagnosed and associated with poor health status and prognosis.

Lung cancer: frequent in patients with COPD; the most frequent cause of death in patients with mild COPD.

Serious infections: respiratory infections are especially frequent.

Metabolic syndrome and manifest diabetes: more frequent in COPD and the latter is likely to impact on prognosis.
Global Strategy for Diagnosis, Management and Prevention of COPD, 2011: Chapters

- Definition and Overview
- Diagnosis and Assessment
- Therapeutic Options
- Manage Stable COPD
- Manage Exacerbations
- Manage Comorbidities
Global Strategy for Diagnosis, Management and Prevention of COPD, 2011: Summary

- Prevention of COPD is to a large extent possible and should have high priority

- Spirometry is \textit{required} to make the diagnosis of COPD; the presence of a post-bronchodilator \( \text{FEV}_1/\text{FVC} < 0.70 \) confirms the presence of persistent airflow limitation and thus of COPD

- The beneficial effects of pulmonary rehabilitation and physical activity cannot be overstated
Assessment of COPD requires assessment of symptoms, degree of airflow limitation, risk of exacerbations, and comorbidities.

Combined assessment of symptoms and risk of exacerbations is the basis for non-pharmacologic and pharmacologic management of COPD.
Treat COPD exacerbations to minimize their impact and to prevent the development of subsequent exacerbations.

Look for comorbidities – and if present treat to the same extent as if the patient did not have COPD.
WORLD COPD DAY
November 14, 2012

Raising COPD Awareness Worldwide
http://www.goldcopd.org
ADDITIONAL SLIDES PREPARED BY
PROFESSOR PETER J. BARNES, MD
NATIONAL HEART AND LUNG INSTITUTE
LONDON, ENGLAND
PATHOLOGY OF COPD

Peripheral lung

Normal

COPD

Alveolar wall

Bronchiole

Loss of attachments

EMPHYSEMA

Fibrosis

Inflammation

Chronic obstructive bronchitis

Dr Manuel Cosio
ASTHMA AND COPD PATHOLOGY

Asthma death

+++ Inflammation +++

+++ ASM +

+++ BM -

+++ Fibrosis +

+++ Alveolar disruption +

Severe COPD

Courtesy of Jim Hogg
<table>
<thead>
<tr>
<th>INFLAMMATION</th>
<th>ASTHMA</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cells</strong></td>
<td>Mast cells</td>
<td>Neutrophils</td>
</tr>
<tr>
<td></td>
<td>Eosinophils</td>
<td>CD8⁺ T cells</td>
</tr>
<tr>
<td></td>
<td>CD4⁺ T cells</td>
<td>Macrophages +++</td>
</tr>
<tr>
<td></td>
<td>Macrophages +</td>
<td></td>
</tr>
<tr>
<td><strong>Mediators</strong></td>
<td>LTD₄, histamine</td>
<td>LTB₄</td>
</tr>
<tr>
<td></td>
<td>IL-4, IL-5</td>
<td>IL-8, TNF-α</td>
</tr>
<tr>
<td></td>
<td>ROS +</td>
<td>ROS +++</td>
</tr>
<tr>
<td><strong>Effects</strong></td>
<td>All airways</td>
<td>Periph airways</td>
</tr>
<tr>
<td></td>
<td>Little fibrosis</td>
<td>Lung destruction</td>
</tr>
<tr>
<td></td>
<td>Ep shedding</td>
<td>Fibrosis +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sq metaplasia</td>
</tr>
<tr>
<td><strong>Response to steroids</strong></td>
<td>+++</td>
<td>-</td>
</tr>
</tbody>
</table>
AIR TRAPPING IN COPD

**Normal**
- small airway
- alveolar attachments

**COPD**
- Inspiration
  - thickened airway
  - loss of alveolar attachments
  - loss of elasticity (emphysema)
- Expiration
  - airway closure
AMPLIFICATION OF INFLAMMATION IN COPD

- Neutrophils
- Macrophages
- Cytokines
- Mediators
- Proteases

Inflammation levels:
- Non-smokers
- Normal smokers
- Mild COPD
- Severe COPD
- Exacerbation
NEUTROPHILS IN COPD

CXCL1, CXCL5, CXCL8

CXCL8

Chemotaxis

CXCR2

CD11B

Migration

Inflammation

LTB4

ROS

MMP8 MMP9

Emphysema

Neutrophil elastase

Mucus secretion

Oxidative stress
NF-κB IN COPD

Stimulus

Cigarette smoke

Oxidative stress

Irritants

TNF-α

IL-1β

IKK2

NF-κB

LκB

Inflammatory genes

mRNA

Inflammation

Cytokines

TNF-α, IL-1β, GM-CSF

Chemokines

IL-8, GRO-α, MIP-1α, MCP-1

Adhesion molecules

ICAM-1

Enzymes

MMP-9
OXIDATIVE STRESS IN COPD

- Anti-proteases
  - SLPI
  - α₁-AT
  - Proteolysis

- Mucus secretion

- Isoprostanones

- Plasma leak

- O₂⁻, H₂O₂, OH⁻, ONOO⁻

- NF-κB
  - IL-8
  - TNF-α
  - Neutrophil recruitment

- CORTICOSTEROID RESISTANCE
  - AGING

- B/C
EFFECTS OF MMP-9

- Macrophage
  - Pro-MMP-9
  - Latent TGF-β
  - MMP-9
  - Active TGF-β

- Chemotactic peptides (ac-PGP)
  - ↓ α1-AT
  - Elastolysis
  - Emphysema
  - COPD

- Small airway fibrosis (chronic obstructive bronchiolitis)

- Neutrophils
  - Neutrophil elastase
ALVEOLAR MACROPHAGES IN COPD

Cigarette smoke
Wood smoke

↓ HDAC
↓ Steroid response

ROS
NO

↑ Numbers (25X)
↑ Secretion
Steroid resistance

↓ Phagocytosis

Elastolysis
MMP-9, MMP-12
Cathepsins B,L,K

Neutrophils
Monocytes
CD8+ cells

Emphysema

LTB₄
CXCL1
CXCL8
CCL2
CXCL9
CXCL10
CXCL11
CXCR2
CCR2
CXCR3

Emphysema
CD8+ CELLS IN COPD

IFN-γ

Bronchiolar epithelial cells

Macrophage

CXCL10, CXCL9, CXCL11 (IP-10) (Mig) (I-TAC)

CXCR3

Cytotoxic T cell (CD8+: Tc1 cell)

Perforins

Granzyme B

Emphysema (apoptosis of type I pneumocytes)
Th17 CELLS

- RORγt
- STAT3
- IL-23
- TGFβ
- IL-6
- IL-17A
- IL-17F
- IL-21
- IL-22

- Th17
- Neutrophils
  - CXCL1
  - CXCL8
  - Epithelial cells
  - ↑ IL-10
  - ↑ acute phase proteins

- B cell
- CD8+ cell
Nrf2 AND ANTIOXIDANT GENE REGULATION

BZip transcription factor

Nrf2(-/-): ↑ emphysema in smoking mice
Rangasamy T et al: JCI 2004;
Ishii et al: J Immunol 2005

Nrf2 activity in lung
↑ in normal smokers
↓ in COPD patients
Malhotra et al: AJRCCM 2008

No ↑ with ox stress in COPD
Due to Nrf2 acetylation
(linked to ↓ HDAC2 and SIRT1)