COPD Case Study (adapted to PATIENTGPS™)

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PATIENTGPS™: Clinical Paths in the Management of Patients with COPD
Learning Objectives

• After this presentation, the participant should be able to describe how to:
  – Implement evidence-based guidelines to manage dyspnea and activity limitations in patients with COPD
  – Employ strategies to minimize exacerbations in COPD patients
  – Utilize coordination-of-care approaches in patients recently hospitalized due to an exacerbation associated with COPD
  – Review barriers to patient adherence to COPD treatment
  – Implement patient education and patient communication strategies, along with customized treatment plans, to promote patient adherence to COPD therapies
GOLD Objectives

► To provide a non-biased review of the current evidence for the assessment, diagnosis and treatment of patients with COPD.

► To highlight short-term and long-term treatment objectives organized into two groups:
  ➢ Relieving and reducing the impact of symptoms, and
  ➢ Reducing the risk of adverse health events that may affect the patient in the future.

► To guide symptoms assessment and health status measurement.
Chronic Obstructive Pulmonary Disease (COPD)

- COPD is currently the fourth leading cause of death in the world.¹
- COPD is projected to be the 3rd leading cause of death by 2020.²
- More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally.
- Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population.

Pathology, pathogenesis & pathophysiology

► Pathology
  ➢ Chronic inflammation
  ➢ Structural changes

► Pathogenesis
  ➢ Oxidative stress
  ➢ Protease-antiprotease imbalance
  ➢ Inflammatory cells
  ➢ Inflammatory mediators
  ➢ Peribronchiolar and interstitial fibrosis

► Pathophysiology
  ➢ Airflow limitation and gas trapping
  ➢ Gas exchange abnormalities
  ➢ Mucus hypersecretion
  ➢ Pulmonary hypertension
Management of Stable COPD

Once COPD has been diagnosed, effective management should be based on an individualized assessment to reduce both current symptoms and future risks of exacerbations.

Table 4.1. Goals for treatment of stable COPD

- Relieve symptoms
- Improve exercise tolerance
- Improve health status
  
  and

- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality
  
  REDUCE SYMPTOMS

  REDUCE RISK
Key Medical History for Diagnosis of COPD

• Dyspnea that is:
  – Progressive
  – Characteristically worse with exercise
  – Persistent

• Chronic cough
  – May be intermittent, may be unproductive

• Chronic sputum production (any pattern)

• History of exposure to:
  – Tobacco smoke
  – Smoke from home cooking and heating fuels
  – Occupational dusts and chemicals

• Family history of COPD

Spirometry in COPD

• Spirometry is required to make a diagnosis of COPD
  – Reproducible and objective measurement of physiologic lung function

• Criterion for chronic airflow limitation
  – Post-bronchodilator ratio of FEV$_1$/FVC < 0.70

FEV$_1$ = Forced expiratory volume, 1 second; FVC = Forced vital capacity

PATIENT CASE: SHORTNESS OF BREATH
Chief Complaint

• “I feel short of breath when I do things around the house.”
History of Present Illness

- 64-year-old white male with exertional shortness of breath that has been progressing over the past six months
- He has chest tightness with the shortness of breath; he denies wheezing
- The patient’s PCP gave him albuterol roughly a year ago for shortness of breath while climbing stairs, and the patient felt this was somewhat helpful
- He has now been referred for evaluation of shortness of breath that is getting worse

PCP = primary care provider
Review of Systems

• The patient denies change in vision, dizziness, sore throat, headaches, night sweats, fevers, palpitations, chest pain, abdominal pain, dysuria, change in bowel habits

• He admits to a roughly 20-pound weight gain over the past 4 months

• He has cough, sputum most mornings, frequent awakenings at night, snoring, daytime tiredness, increased lower extremity edema, and chronic back pain
Past Medical History

• Coronary artery disease with stent placement in 2006 secondary to myocardial infarction (MI)
• Type 2 diabetes
• Hypertension
• Hypothyroidism
• Exercise-induced asthma during high school
• Appendectomy
• Vertebral fusion L4-S1 in 2008
Social History

• The patient is married and lives in a home with a dog and cat
• His wife is a nonsmoker
• He smoked from age 16–54 years, roughly a pack a day
  – He stopped smoking in 2006 after his MI
• He works as a truck driver for Target
• He drinks roughly 4 beers a day, and has no history of DUI
  – He denies illicit substance abuse
Family History

• Father
  – Coronary artery disease, hypertension, obstructive sleep apnea, cirrhosis, liver cancer, and alcoholism

• Mother
  – Diabetes mellitus, emphysema, hypothyroidism

• Sister
  – Obesity, diabetes mellitus, hypertension
Allergies and Medications

- Allergies: No known drug allergies
- Medications: Aspirin daily; lisinopril daily; metformin twice a day; levothyroxine daily
Physical Examination

- **VITALS:** Temp: 37.6° Celsius, HR: 89, RR: 18, BP: 155/89, SaO₂: 91% on room air at rest, weight: 230 lbs, height: 5’11”, BMI: 32
- **GENERAL:** No apparent distress
- **HEENT:** Sclera clear, EOMI, mouth clear of lesion, neck without bruits or adenopathy
- **LUNGS:** Wheezes bilaterally at end expiration
- **CARDIAC:** RRR no murmur/rub/gallop
- **ABDOMEN:** Nontender, no distention, no rebound
- **EXTREMITIES:** No cyanosis or clubbing, but 1+ lower extremity edema at ankles

HR = heart rate; RR = respiratory rate; BP = blood pressure; SaO₂ = arterial oxygen saturation; BMI = body mass index; HEENT = head, ears, eyes, nose, throat; EOMI = extraocular movements intact; RRR = regular rate and rhythm.
Objective Data

• Spirometry
  – FVC: 74% of predicted (normal ≥ 80% predicted)
  – FEV₁: 45% of predicted (normal ≥ 80% predicted)
  – FEV₁/FVC: 0.55 (normal ≥ 0.70)

• Chest x-ray
  – Hyperinflation and bronchial wall thickening; no focal opacities
Flow-volume curves from (A) a healthy person or from patients with (B) severe obstruction (emphysema), (C) severe restriction from interstitial disease (radiation fibrosis), (D) upper airways obstruction (tracheal stenosis), and (E) poor effort.
The posteroanterior (A) and lateral (B) chest x-rays of a 71-year-old female with emphysema show increased lung volumes with flattened hemidiaphragms on the lateral examination (arrow) and increase in the retrosternal space (arrowhead). The normal retrosternal airspace is less than 2.5 cm. A prominent pulmonary artery on the posteroanterior view (dashed arrow) reflects secondary pulmonary hypertension.
Case Discussion

• Initial impressions of the patient?
  – Diagnosis?
  – Disease severity?

• Have you had similar patients in your practice?

• What additional procedures and tests would you order? Why?
COPD RISK ASSESSMENT AND CLASSIFICATION
# Classification of COPD Severity

<table>
<thead>
<tr>
<th>Severity</th>
<th>Criterion</th>
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<tbody>
<tr>
<td>-</td>
<td>Smokers with symptoms, FEV&lt;sub&gt;1&lt;/sub&gt;/FVC &gt; 0.7</td>
</tr>
<tr>
<td>GOLD 1</td>
<td>Mild, FEV&lt;sub&gt;1&lt;/sub&gt; ≥ 80% predicted*</td>
</tr>
<tr>
<td>GOLD 2</td>
<td>Moderate, 50% ≤ FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 80% predicted*</td>
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<tr>
<td>GOLD 3</td>
<td>Severe, 30% ≤ FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 50% predicted*</td>
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<tr>
<td>GOLD 4</td>
<td>Very Severe, FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 30% predicted*</td>
</tr>
</tbody>
</table>

*Meets diagnostic criteria of COPD, FEV<sub>1</sub>/FVC < 0.7

Figure 2.4. The refined ABCD assessment tool

- Spirometrically confirmed diagnosis
- Assessment of airflow limitation
- Assessment of symptoms/risk of exacerbations

**FEV₁ (% predicted)**

<table>
<thead>
<tr>
<th>GOLD</th>
<th>≥ 80</th>
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<tbody>
<tr>
<td>GOLD 2</td>
<td>50-79</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>30-49</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>&lt; 30</td>
</tr>
</tbody>
</table>

**Exacerbation history**

- ≥ 2
- ≥ 1 leading to hospital admission
- 0 or 1 (not leading to hospital admission)

**Symptoms**

- mMRC 0-1
- CAT < 10

- mMRC ≥ 2
- CAT ≥ 10
Assessing Patient Symptoms and Risk

CAT = COPD Assessment Test; mMRC = modified Medical Research Council Dyspnea Scale

TREATMENT
Goals of Therapy

- Reduce long-term decline in lung function
- Prevent and treat exacerbations
- Reduce hospitalizations and mortality
- Relieve disabling dyspnea
- Improve exercise tolerance and health-related quality of life

Therapeutic Options

• Smoking cessation
• Pharmacotherapy
• Oxygen therapy
• Surgical intervention
• Pulmonary rehabilitation
• Palliative care

Smoking Cessation

• Greatest capacity to influence natural history of COPD
• Nicotine replacement therapy
  – All forms increase long-term abstinence rates
  – Gum, lozenge, inhaler, nasal spray, transdermal patch, sublingual tablet
• Pharmacologic
  – Increases long-term abstinence rates
  – Should be used in conjunction with support program
  – Varenicline or bupropion
• Counseling
  – Practical counseling, social support with treatment, social support outside of treatment are all effective
  – Dose-dependent relationship with counseling intensity

Short-acting Muscarinic Antagonists

- **Mechanism**: block acetylcholine effects on muscarinic receptors → reduce bronchomotor tone and reflex bronchoconstriction
- **Efficacy**: improve FEV$_1$
- **Side effects**: dry mouth; nasopharyngitis; cardiovascular morbidity/mortality
- **Route**: inhalation

Short-acting $\beta_2$ Agonists

- **Mechanism**: stimulate $\beta_2$ adrenergic receptors → bronchodilation
- **Efficacy**: improve FEV$_1$ and symptoms
- **Side effects**: resting sinus tachycardia; exaggerated somatic tremor in elderly
- **Route**: inhalation, oral

Long-acting Muscarinic Antagonists

- **Mechanism**: block acetylcholine effects on muscarinic receptors → reduce bronchomotor tone and reflex bronchoconstriction
- **Efficacy**: reduce exacerbations and related hospitalizations; improve symptoms, health status, and effectiveness of pulmonary rehabilitation
- **Side effects**: dry mouth; nasopharyngitis; cardiovascular morbidity/mortality
- **Route**: inhalation

Long-acting $\beta_2$ Agonists

• **Mechanism**: stimulate $\beta_2$ adrenergic receptors $\rightarrow$ functional antagonism to bronchoconstriction

• **Efficacy**: improve FEV$_1$, dyspnea, HRQoL, exacerbation rate

• **Side effects**: resting sinus tachycardia; exaggerated somatic tremor in elderly; minor falls in PaO$_2$; increase in cough

• **Route**: inhalation, transdermal

HRQoL = health-related quality of life; PaO$_2$ = partial pressure of oxygen
Inhaled Corticosteroids

- **Mechanism**: bind to glucocorticoid receptor ➔ regulate gene expression ➔ modulate airway inflammation
- **Efficacy**: reduce frequency of exacerbations
- **Side effects**: oral candidiasis; hoarse voice; skin bruising; pneumonia
- **Route**: inhalation

Methylxanthines

• **Mechanism**: (possible) PDE inhibition, non-bronchodilator mechanisms
• **Efficacy**: improve inspiratory muscle function, symptoms; reduce exacerbations
• **Side effects**: arrhythmias; grand mal convulsions; headaches; insomnia; nausea; heartburn
• **Route**: oral

PDE = phosphodiesterase

Phosphodiesterase-4 Inhibitors

• **Mechanism**: inhibit breakdown of intracellular cyclic AMP → reduce airway inflammation

• **Efficacy**: (as add-on therapy) in patients with chronic bronchitis and severe COPD reduces exacerbations; bronchodilation not clinically significant

• **Side effects**: nausea; reduced appetite; abdominal pain; diarrhea; sleep disturbances; headache; unexplained weight loss

• **Route**: oral

AMP = adenosine monophosphate

Combination – LAMA/LABA

• **Mechanism**: possible synergistic bronchodilator effects

• **Efficacy**: improve lung function; reduce exacerbations

• **Side effects**: similar to components

• **Route**: inhaler


Combination – LABA/ICS

• **Mechanism**: possible synergistic effect – ICS may reduce desensitization and degradation of $\beta_2$ receptors from chronic $\beta_2$ agonist use

• **Efficacy**: improve lung function and HRQoL; reduce exacerbations; greater improvements than monotherapy

• **Side effects**: similar to components

• **Route**: inhaler

<table>
<thead>
<tr>
<th>Drug</th>
<th>Inhaler (mcg)</th>
<th>Solution for nebulizer (mg/ml)</th>
<th>Oral</th>
<th>Vials for injection (mg)</th>
<th>Duration of action (hours)</th>
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</thead>
<tbody>
<tr>
<td><strong>Beta₂-agonists</strong></td>
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<tr>
<td><strong>Short-acting</strong></td>
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<tr>
<td>Fenoterol</td>
<td>100–200 (MDI)</td>
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<td>2.5 mg (pill), 0.05% (syrup)</td>
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<td>Levalbuterol</td>
<td>45–90 (MDI)</td>
<td>0.1, 0.21, 0.25, 0.42</td>
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<td>Salbutamol (albuterol)</td>
<td>90, 100, 200 (MDI &amp; DPI)</td>
<td>1, 2, 2.5, 5 mg/ml</td>
<td>2, 4, 5 mg (pill), 8 mg (extended release tablet) 0.024%/0.4 mg (syrup)</td>
<td>0.1, 0.5 mg</td>
<td>4–6, 12 (extended release)</td>
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<td>Terbutaline</td>
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<td>2.5, 5 mg (pill)</td>
<td>0.2, 0.25, 1 mg</td>
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<td><strong>Long-acting</strong></td>
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<tr>
<td>Arformoterol</td>
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<td>0.0075^¹</td>
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<tr>
<td>Formoterol</td>
<td>4.5–9 (DPI)</td>
<td>0.01^</td>
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<td>Indacaterol</td>
<td>75–300 (DPI)</td>
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<tr>
<td>Olodaterol</td>
<td>2.5, 5 (SMI)</td>
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<td></td>
<td>24</td>
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<tr>
<td>Salmeterol</td>
<td>25–50 (MDI &amp; DPI)</td>
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<td></td>
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<td><strong>Anticholinergics</strong></td>
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<td><strong>Short-acting</strong></td>
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<tr>
<td>Ipratropium bromide</td>
<td>20, 40 (MDI)</td>
<td>0.2</td>
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<td>6–8</td>
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<tr>
<td>Oxitropium bromide</td>
<td>100 (MDI)</td>
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<td>7–9</td>
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<tr>
<td><strong>Long-acting</strong></td>
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<td></td>
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<tr>
<td>Aclidinium bromide</td>
<td>400 (DPI), 400 (MDI)</td>
<td></td>
<td>1 mg (solution)</td>
<td>0.2 mg</td>
<td>12–24</td>
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<tr>
<td>Glycopyrronium bromide</td>
<td>15.6 &amp; 50 (DPI)</td>
<td>1</td>
<td></td>
<td>12</td>
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<tr>
<td>Tiotropium</td>
<td>18 (DPI), 2.5 &amp; 5 (SMI)</td>
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<tr>
<td>Umeclidinium</td>
<td>62.5 (DPI)</td>
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<tr>
<td><strong>Combination of short-acting beta₂-agonist plus anticholinergic in one device</strong></td>
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<td></td>
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<tr>
<td>Fenoterol/ipratropium</td>
<td>50/20 (SMI)</td>
<td>1.25, 0.5 mg in 4ml</td>
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<td>6–8</td>
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<tr>
<td>Salbutamol/ipratropium</td>
<td>100/20 (SMI), 75/15 (MDI)</td>
<td>0.5, 2.5 mg in 3ml</td>
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<td>6–8</td>
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## Combination of long-acting beta₂-agonist plus anticholinergic in one device

<table>
<thead>
<tr>
<th>Combination</th>
<th>Strength</th>
<th>Dose 1</th>
<th>Dose 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formoterol/acldinium</td>
<td>12/400 (DPI)</td>
<td>12</td>
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</tr>
<tr>
<td>Formoterol/glycopyrronium</td>
<td>9.6/18 (MDI)</td>
<td>12</td>
<td></td>
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<tr>
<td>Indacaterol/glycopyrronium</td>
<td>27.5/15.6 &amp; 110/50 (DPI)*</td>
<td>12-24</td>
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</tr>
<tr>
<td>Vilanterol/umeclidinium</td>
<td>25/62.5 (DPI)</td>
<td>24</td>
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<tr>
<td>Olodaterol/tiotropium</td>
<td>5/5 (SMI)</td>
<td>24</td>
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</tbody>
</table>

## Methylxanthines

<table>
<thead>
<tr>
<th>Methylxanthines</th>
<th>Strength</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminophylline</td>
<td>105 mg/ml (solution)</td>
<td>250, 500 mg</td>
<td>Variable, up to 24</td>
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<tr>
<td>Theophylline (SR)</td>
<td>100-600 mg (pill)</td>
<td>250, 400, 500 mg</td>
<td>Variable, up to 24</td>
<td></td>
</tr>
</tbody>
</table>

## Combination of long-acting beta₂-agonist plus corticosteroids in one device

<table>
<thead>
<tr>
<th>Combination</th>
<th>Strength</th>
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<tbody>
<tr>
<td>Formoterol/beclomethasone</td>
<td>6/100 (MDI)</td>
</tr>
<tr>
<td>Formoterol/budesonide</td>
<td>4.5/160 (MDI), 4.5/80 (MDI), 9/320 (DPI), 9/160 (DPI)</td>
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<tr>
<td>Formoterol/mometasone</td>
<td>10/200, 10/400 (MDI)</td>
</tr>
<tr>
<td>Salmeterol/fluticasone</td>
<td>5/100, 50/250, 5/500 (DPI), 21/45, 21/115, 21/230 (MDI)</td>
</tr>
<tr>
<td>Vilanterol/fluticasone furoate</td>
<td>25/100 (DPI)</td>
</tr>
</tbody>
</table>

## Phosphodiesterase-4 inhibitors

<table>
<thead>
<tr>
<th>Combination</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roflumilast</td>
<td>500 mcg (pill)</td>
</tr>
</tbody>
</table>

MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler

* Not all formulations are available in all countries; in some countries other formulations and dosages may be available

* Dose availability varies by country

* Formoterol nebulized solution is based on the unit dose vial containing 20 mcg in a volume of 2.0 ml

* Dose varies by country
**Group C**

- Initial therapy should consist of a single long acting bronchodilator. In two head-to-head comparisons the tested LAMA was superior to the LABA regarding exacerbation prevention, therefore we recommend starting therapy with a LAMA in this group.

- Patients with persistent exacerbations may benefit from adding a second long acting bronchodilator (LABA/LAMA) or using a combination of a long acting beta₂-agonist and an inhaled corticosteroid (LABA/ICS). As ICS increases the risk for developing pneumonia in some patients, our primary choice is LABA/LAMA.
If patients treated with LABA/LAMA/ICS still have exacerbations the following options may be considered:

► Add roflumilast. This may be considered in patients with an FEV1 < 50% predicted and chronic bronchitis, particularly if they have experienced at least one hospitalization for an exacerbation in the previous year.

► Add a macrolide. The best available evidence exists for the use of azithromycin. Consideration to the development of resistant organisms should be factored into decision making.

► Stopping ICS. A reported lack of efficacy, an elevated risk of adverse effects (including pneumonia) and evidence showing no significant harm from withdrawal supports this recommendation (see Chapter 3 for further details).
We recommend starting therapy with a LABA/LAMA combination because:

- In studies with patient reported outcomes as the primary endpoint LABA/LAMA combinations showed superior results compared to the single substances. If a single bronchodilator is chosen as initial treatment, a LAMA is preferred for exacerbation prevention based on comparison to LABAs (for details see GOLD 2017 Chapter 3).

- A LABA/LAMA combination was superior to a LABA/ICS combination in preventing exacerbations and other patient reported outcomes in Group D patients (for details see GOLD 2017 Chapter 3).

- Group D patients are at higher risk of developing pneumonia when receiving treatment with ICS.
Figure 4.1. Pharmacologic treatment algorithms by GOLD Grade [highlighted boxes and arrows indicate preferred treatment pathways]

Group C

LAMA + LABA → LABA + ICS
Further exacerbation(s)
LAMA

Group D

Consider roflumilast if FEV₁ < 50% pred. and patient has chronic bronchitis

Further exacerbation(s)
LAMA + LABA + ICS
Persistent symptoms/further exacerbation(s)
LAMA
LABA + ICS

Group A

Continue, stop or try alternative class of bronchodilator
evaluate effect
A bronchodilator

Group B

LAMA + LABA
Persistent symptoms
A long-acting bronchodilator (LABA or LAMA)

In patients with a major discrepancy between the perceived level of symptoms and severity of airflow limitation, further evaluation is warranted.

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Non-pharmacologic Therapy

• Oxygen, continuous
  – Indicated for patients who have PaO$_2$ $\leq$ 55 mmHg or SaO$_2$ $\leq$ 88%
    • Measurements twice in 3 weeks
  – Goal SaO$_2$ 88%–92%

• Surgery
  – Lung volume reduction surgery
  – Lung transplantation

PaO$_2$ = partial pressure of oxygen

Pulmonary Rehabilitation

• Exercise training
  – 6–12 weeks; longer programs result in larger effects
  – 20–30 min walking per session, to limits of symptoms

• Patient education
  – Smoking cessation, COPD natural history and management, self-management, exacerbations

• Assessment and follow-up

• Nutritional support
  – Some evidence of benefit for patients, especially if malnourished

Palliative Care

• COPD characterized by gradual decline in health status and progressive, life-limiting symptoms
• Mortality after exacerbation is 23%–80%
• Discussion of palliative care can begin at diagnosis
• Hospice services may be beneficial for some patients

Managing Stable COPD

• Routine follow up is essential
• Reduce exposure to risk factors (eg, cigarette smoke)
• Reduce symptoms with pharmacotherapy
  – Long-acting bronchodilators favored over short-acting
  – Patients with high risk of exacerbations – add inhaled corticosteroid
  – Patients with GOLD 3 or 4 severity, chronic bronchitis, and frequent exacerbations – consider adding roflumilast
• Implement physical activity
• Consider pulmonary rehabilitation
• Administer annual influenza vaccine

Table 3.4. Bronchodilators in stable COPD

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms (Evidence A).
- Regular and as-needed use of SABA or SAMA improves FEV₁ and symptoms (Evidence A).
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV₁ and symptoms (Evidence A).
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates (Evidence A).
- LAMAs have a greater effect on exacerbation reduction compared with LABAs (Evidence A) and decrease hospitalizations (Evidence B).
- Combination treatment with a LABA and LAMA increases FEV₁ and reduces symptoms compared to monotherapy (Evidence A).
- Combination treatment with a LABA and LAMA reduces exacerbations compared to monotherapy (Evidence B) or ICS/LABA (Evidence B).
- Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance (Evidence B).
- Theophylline exerts a small bronchodilator effect in stable COPD (Evidence A) and that is associated with modest symptomatic benefits (Evidence B).
<table>
<thead>
<tr>
<th>Table 3.5. Anti-inflammatory therapy in stable COPD</th>
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<tbody>
<tr>
<td><strong>Inhaled corticosteroids</strong></td>
</tr>
<tr>
<td>• An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD <em>(Evidence A)</em>.</td>
</tr>
<tr>
<td>• Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease <em>(Evidence A)</em>.</td>
</tr>
<tr>
<td>• Triple inhaled therapy of ICS/LAMA/LABA improves lung function, symptoms and health status <em>(Evidence A)</em> and reduces exacerbations <em>(Evidence B)</em> compared to ICS/LABA or LAMA monotherapy.</td>
</tr>
<tr>
<td><strong>Oral glucocorticoids</strong></td>
</tr>
<tr>
<td>• Long-term use of oral glucocorticoids has numerous side effects <em>(Evidence A)</em> with no evidence of benefits <em>(Evidence C)</em>.</td>
</tr>
<tr>
<td><strong>PDE4 inhibitors</strong></td>
</tr>
<tr>
<td>• In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations:</td>
</tr>
<tr>
<td>» A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations <em>(Evidence A)</em>.</td>
</tr>
<tr>
<td>» A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations <em>(Evidence B)</em>.</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
</tr>
<tr>
<td>• Long-term azithromycin and erythromycin therapy reduces exacerbations over one year <em>(Evidence A)</em>.</td>
</tr>
<tr>
<td>• Treatment with azithromycin is associated with an increased incidence of bacterial resistance <em>(Evidence A)</em> and hearing test impairments <em>(Evidence B)</em>.</td>
</tr>
<tr>
<td><strong>Mucolytics/antioxidants</strong></td>
</tr>
<tr>
<td>• Regular use of NAC and carbocysteine reduces the risk of exacerbations in select populations <em>(Evidence B)</em>.</td>
</tr>
<tr>
<td><strong>Other anti-inflammatory agents</strong></td>
</tr>
<tr>
<td>• Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy <em>(Evidence A)</em>. However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications <em>(Evidence C)</em>.</td>
</tr>
<tr>
<td>• Leukotriene modifiers have not been tested adequately in COPD patients.</td>
</tr>
</tbody>
</table>
### Table 3.6. The inhaled route

- When a treatment is given by the inhaled route, the importance of education and training in inhaler device technique cannot be over-emphasized.
- The choice of inhaler device has to be individually tailored and will depend on access, cost, prescriber, and most importantly, patient's ability and preference.
- It is essential to provide instructions and to demonstrate the proper inhalation technique when prescribing a device, to ensure that inhaler technique is adequate and re-check at each visit that patients continue to use their inhaler correctly.
- Inhaler technique (and adherence to therapy) should be assessed before concluding that the current therapy is insufficient.
Pharmacologic treatment

Table 4.5. Key points for the use of bronchodilators

- LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea (Evidence A).
- Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator treatment should be escalated to two (Evidence A).
- Inhaled bronchodilators are recommended over oral bronchodilators (Evidence A).
- Theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable (Evidence B).

Table 4.6. Key points for the use of anti-inflammatory agents

- Long-term monotherapy with ICS is not recommended (Evidence A).
- Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators (Evidence A).
- Long-term therapy with oral corticosteroids is not recommended (Evidence A).
- In patients with exacerbations despite LABA/ICS or LABA/LAMA/ICS, chronic bronchitis and severe to very severe airflow obstruction, the addition of a PDE4 inhibitor can be considered (Evidence B).
- In former smokers with exacerbations despite appropriate therapy, macrolides can be considered (Evidence B).
- Statin therapy is not recommended for prevention of exacerbations (Evidence A).
- Antioxidant mucolytics are recommended only in selected patients (Evidence A).
OVERALL KEY POINTS (2 of 3):

► Influenza vaccination decreases the incidence of lower respiratory tract infections.
► Pneumococcal vaccination decreases lower respiratory tract infections.
► Pulmonary rehabilitation improves symptoms, quality of life, and physical and emotional participation in everyday activities.
► In patients with severe resting chronic hypoxemia, long-term oxygen therapy improves survival.
► In patients with stable COPD and resting or exercise-induced moderate desaturation, long-term oxygen treatment should not be prescribed routinely. However, individual patient factors must be considered when evaluating the patient’s need for supplemental oxygen.
Outcomes of Adherence

- Good adherence associated with reduced mortality

<table>
<thead>
<tr>
<th>Therapy</th>
<th>3-year Mortality Rates (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good Adherence</td>
<td>Poor Adherence</td>
<td></td>
</tr>
<tr>
<td>Salmeterol</td>
<td>10.7</td>
<td>25.2</td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>12.9</td>
<td>28.7</td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>9.5</td>
<td>24.9</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>12.0</td>
<td>26.7</td>
<td></td>
</tr>
</tbody>
</table>

Alpha-1 antitrypsin deficiency (AATD)

AATD screening

► The World Health Organization recommends that all patients with a diagnosis of COPD should be screened once especially in areas with high AATD prevalence.

► AATD patients are typically < 45 years with panlobular basal emphysema

► Delay in diagnosis in older AATD patients presents as more typical distribution of emphysema (centrilobular apical).

► A low concentration (< 20% normal) is highly suggestive of homozygous deficiency.
PATIENT CASE: ASSESSMENT AND PLAN
Summary of Problems and Additional Considerations

• Shortness of breath:
  – PFTs, walk oximetry, ECG, echocardiogram, CBC
• Chest tightness:
  – Cardiac stress test, methacholine challenge
• Lower extremity edema:
  – Echocardiogram, chemistry panel, LFTs
• Frequent awakenings at night, snoring, daytime fatigue:
  – Sleep study, TSH
• Obesity:
  – Counseling on diet and exercise, offer physical therapy to help with back pain and to help develop exercise program, refer to nutritionist
• Alcohol intake greater than 2 beers per day for male:
  – Counsel on alcohol intake and how it affects health

PFT = pulmonary function test; ECG = electrocardiogram; CBC = complete blood count; LFT = liver function test; TSH = thyroid stimulating hormone
Case Discussion

- How would you treat this patient?
- Is pharmacologic intervention warranted at this time?
  - Why or why not?
Initial Plan

• He was started on a long-acting bronchodilator (tiotropium daily), and he continued albuterol as needed
• PFTs, walk oximetry, CBC and echocardiogram were all completed
• He was counseled on weight loss and his need to try and decrease his alcohol intake
• Sleep study ordered, but scheduled for 4 months from now due to availability
Results of Tests

- **PFTs**
  - TLC: 170%; FRC: 110%; RV: 210%; FVC: 72%; FEV\(_1\): 46%; Ratio: 0.65
  - After bronchodilation, FVC: 80%; FEV\(_1\): 50%; ratio: 0.57 without any significant bronchodilator response; DLCO: 60% of predicted

- **Walk oximetry**
  - On room air the patient started at 92%, but he desaturated to 82% at minute 3, and 2 LPM of NC O\(_2\) was needed to maintain SaO\(_2\) ≥90% throughout the 6 minutes

- **CBC**
  - WBC: 9; Hgb: 11; HCT: 33%; PLT: 250,000

- **Echocardiogram**
  - LVEF was 45%; stage 2 diastolic dysfunction; LA severely dilated; RVSP estimated as 60 mmHg; and RV also moderately dilated

TLC = total lung capacity; FRC = functional residual capacity; RV = residual volume; DLCO = diffusing capacity of the lung for carbon monoxide; LPM = liters per minute; NC = nasal cannula; WBC = white blood cell; Hgb = hemoglobin; HCT = hematocrit; PLT = platelet; LVEF = left ventricular ejection fraction; LA = left atrium; RVSP = right ventricular systolic pressure; RV = right ventricle
Follow-up in Clinic After Testing

- The patient felt that the tiotropium was helpful, but he was still having daily shortness of breath that seemed to acutely worsen during the past week
  - He stated that he was unable to sleep last night due to the shortness of breath
- His wheezing was increasing, and he was starting to produce more mucus over the past few days
- He was now needing his albuterol rescue several times a day
- During the clinic visit, the patient’s breathing was visibly labored, and his oxygen saturation was 84%
- Lower extremity edema was worse
Next Step

• The patient was informed that he has COPD based on his PFTs and may need more medications to control his symptoms
• He was informed that he qualified for O₂ therapy with activities
• He also has mild anemia
• The patient was told that his worsening shortness of breath over the past several days with more mucus is concerning, so he is being referred to the ED for a COPD exacerbation
MANAGEMENT OF EXACERBATIONS
Risk of Exacerbation

• Exacerbation = Acute event characterized by worsening of respiratory symptoms
  – More than day-to-day variation
  – May lead to change in medication
• Increased risk of exacerbation linked to:
  – History of previous exacerbations
  – Female sex
  – Poorer lung function
  – More dyspnea
  – Comorbidities: myocardial infarction, heart failure, depression

Risk of Exacerbation and Poor Outcome Increases with Worsening Airflow Limitation

<table>
<thead>
<tr>
<th>Severity of COPD*</th>
<th>Exacerbations (per year)†‡¶</th>
<th>Hospitalizations (per year)†¶</th>
<th>3-year Mortality†‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1 (Mild)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GOLD 2 (Moderate)</td>
<td>0.7 – 0.9</td>
<td>0.11 – 0.2</td>
<td>11%‡</td>
</tr>
<tr>
<td>GOLD 3 (Severe)</td>
<td>1.1 – 1.3</td>
<td>0.25 – 0.3</td>
<td>15%†</td>
</tr>
<tr>
<td>GOLD 4 (Very Severe)</td>
<td>1.2 – 2.0</td>
<td>0.4 – 0.54</td>
<td>24%†</td>
</tr>
</tbody>
</table>

*Spirometric severity (post-bronchodilator):  \( \text{FEV}_1/\text{FVC} < 0.70 \) and
  - Mild: \( \text{FEV}_1 \geq 80\% \) predicted
  - Moderate: \( \text{FEV}_1 50\% – 79\% \) predicted
  - Severe: \( \text{FEV}_1 30\% – 49\% \) predicted
  - Very Severe: \( \text{FEV}_1 < 30\% \) predicted or respiratory failure

†Placebo arm of the Toward a Revolution in COPD Health (TORCH) study
‡Placebo arm of the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study
¶Placebo arm of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study

OVERALL KEY POINTS (2 of 3):

► Maintenance therapy with long-acting bronchodilators should be initiated as soon as possible before hospital discharge.

► Systemic corticosteroids can improve lung function ($FEV_1$), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not be more than 5-7 days.

► Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should be 5-7 days.

► Methylxanthines are not recommended due to increased side effect profiles.
COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy.

Classified as:
- **Mild** (treated with SABDs only)
- **Moderate** (treated with SABDs plus antibiotics and/or oral corticosteroids) or
- **Severe** (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure.

Blood eosinophil count may also predict exacerbation rates (in patients treated with LABA without ICS).
# Pharmacotherapy Examples

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
<th>Typical Dosage</th>
</tr>
</thead>
</table>
| Antibiotic, broad spectrum    | Consider if sputum is purulent or after treatment failure; if resistance to narrow-spectrum agents | **Amoxicillin/clavulanate**: 875 mg po bid or 500 mg po tid X 5 d  
**Levofloxacin**: 500 mg qd X 5 d |
| Antibiotic, narrow spectrum   | Consider if sputum is purulent or after treatment failure; if no signs of resistance and no recent antibiotics | **Amoxicillin**: 500 mg po tid X 3-14 d |
| Muscarinic antagonist, short-acting | May add to $\beta_2$ agonist; increase dosage if already taking             | **Ipratropium**: 500 mcg by nebulizer q4h PRN; 2 puffs by MDI q4h PRN |
| $\beta_2$ agonist, short-acting | Increase dosage                                                              | **Albuterol**: 2.5 mcg by nebulizer q1-4h PRN; 4-8 puffs by MDI q4h PRN |
| Corticosteroid                | Moderately ill patients, especially those with purulent sputum              | **Oral prednisone**: 30 to 60 mg qd  
**IV methylprednisolone**: 60 to 125 mg 2-4x/d |
Prevention of Exacerbations (cont)

• Inhaled pharmacotherapy in patients with moderate to severe COPD
  – Use of long-acting β₂ agonist
  – Maintenance therapy with inhaled corticosteroid and long-acting β₂ agonist
  – Maintenance therapy with long-acting muscarinic antagonist alone or combined with long-acting β₂ agonist

What to Do Next?

• Refer to cardiac/pulmonary rehab
• Counsel on need to continue $O_2$ therapy, as non-compliance is common when first starting
• Continue tiotropium, fluticasone/salmeterol, and albuterol, but consider adding home nebulization therapy
• Order a sleep study given his symptoms and past echocardiogram showing elevated RV pressures
PATIENT ADHERENCE TO TREATMENT
Patient Adherence in COPD is Multifactorial

- Medication adherence is ~40-50% in clinical practice
- Most common causes of non-adherence are forgetting or deciding not to take medication

**Patient**
- Health beliefs
- Cognitive ability
- Self-efficacy
- Comorbidities
- Psychological profile
- Conscientiousness

**Society**
- Patient-prescriber relationship
- Social support
- Access to medication
- Device training
- Follow-up

**Treatment**
- Method of administration
- Dosing regimen
- Polypharmacy
- Side effects

Medication-Related Barriers to Treatment Adherence

- Higher frequency of dosing
- Polypharmacy
- Inhaled route of administration
  - Improper inhaler technique
  - Dissatisfaction with device
- Side effects
- Cost of treatment
- Oxygen therapy – bulky and embarrassing equipment

Patient-Related Barriers to Treatment Adherence

- Older age
  - More comorbid conditions
  - Polypharmacy
  - Cognitive decline
- Psychiatric conditions
  - Up to 40% of patients with COPD have depression, anxiety
- Perception of lack of disease severity
- Lack of disease understanding
- Perceived and actual social support

Healthcare Provider-Related Barriers to Treatment Adherence

- Lack of continuity in care
- Poor or no written instructions for medication dosing
- Poor or no explanation of rationale for therapeutic plan
- Poor healthcare provider-patient communication

Strategies to Improve Adherence

• Dosing
  – Simplified (eg, once or twice daily)
  – Synchronized schedule of multiple therapies
  – Combination therapies

• Self-management education

• Patient understanding of expected benefits

• Multidimensional interventions have largest effect on adherence
  – Combination of self-management education, coordinated care, written instructions, and instruction on inhaler use

Strategies to Improve Adherence

- Healthcare professional
  - Patient perception of support from healthcare professional
  - Communicate about chronic nature of COPD, rationale for treatment
  - Provide patient opportunity to identify and discuss concerns
  - Written education and treatment information
  - Monitor medication adherence and provide feedback

Summary

• COPD is characterized by a gradual decrease in lung function and progressive, activity-limiting symptoms
• Dyspnea is cardinal symptom
• Diagnosis made with spirometry
• Risk of exacerbations increases with COPD severity
• Management depends on symptoms and exacerbations
• Specific therapeutic strategies to prevent subsequent exacerbations
Summary (cont)

• Therapeutic options for COPD include smoking cessation, pharmacotherapy, oxygen, surgery, and pulmonary rehabilitation

• Barriers to therapy adherence influenced by medication, patient factors, and healthcare provider factors

• Patient adherence to therapy can increase through medication choice, communication, education
Choice of thresholds

- COPD Assessment Test (CAT™)
- Chronic Respiratory Questionnaire (CCQ®)
- St George’s Respiratory Questionnaire (SGRQ)
- Chronic Respiratory Questionnaire (CRQ)
- Modified Medical Research Council (mMRC) questionnaire

**Figure 2.3. CAT Assessment**

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.

<table>
<thead>
<tr>
<th>Example:</th>
<th>I am very happy</th>
<th>I am very sad</th>
</tr>
</thead>
<tbody>
<tr>
<td>I never cough</td>
<td>0 0 0 0 0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>I have no phlegm (mucus) in my chest at all</td>
<td>0 0 0 0 0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>My chest does not feel tight at all</td>
<td>0 0 0 0 0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>When I walk up a hill or one flight of stairs I am not breathless</td>
<td>0 0 0 0 0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>I am not limited doing any activities at home</td>
<td>0 0 0 0 0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>I am confident leaving my home despite my lung condition</td>
<td>0 0 0 0 0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>I sleep soundly</td>
<td>0 0 0 0 0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>I have lots of energy</td>
<td>0 0 0 0 0</td>
<td>0 0 0 0 0</td>
</tr>
</tbody>
</table>

**Table 2.5. Modified MRC dyspnea scale**

PLEASE TICK IN THE BOX THAT APPLIES TO YOU (ONE BOX ONLY) (Grades 0–4)

- **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.