This educational activity is supported by an educational grant from AstraZeneca Pharmaceuticals LP.
The Learning Objectives for this Program are:

• Discuss best practice approaches for early diagnosis and management of COPD to prevent and reduce exacerbations.
• Review current and emerging therapeutics in the treatment of COPD.
• Describe patient-centered strategies for creating personalized treatment and management plans for COPD to improve patient adherence.

Chapter 1
Early Diagnosis
55 y.o. with recurrent episodes of bronchitis.

Does she have COPD? History suggests she may have COPD.

Factors to consider:
- Heavy smoking history
- Recurrent bouts of acute bronchitis? COPD exacerbations
- Dyspnea on exertion
- Co-morbidities associated with COPD-hypertension and hyperlipidemia
- Abnormal chest exam with wheezing and rhonchi heard

The diagnosis of COPD requires spirometry confirmation.

Does she meet the criteria for COPD set by international (GOLD) guidelines?

“Definition: COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.”
COPD... characterized by persistent airflow limitation

How Do We Measure Airflow Limitation (Obstruction)?

SPIROMETRY

GOLD Classification of COPD

Staging by Spirometry

The diagnosis requires evidence of airflow limitation (obstruction): FEV₁/FVC less than 70%

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>FEV₁/FVC</th>
<th>FEV₁ Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I:</td>
<td>Mild</td>
<td>&lt; 0.70</td>
<td>≥ 80% predicted</td>
</tr>
<tr>
<td>Stage II:</td>
<td>Moderate</td>
<td>&lt; 0.70</td>
<td>50% ≤ FEV₁ &lt; 80% predicted</td>
</tr>
<tr>
<td>Stage III:</td>
<td>Severe</td>
<td>&lt; 0.70</td>
<td>30% ≤ FEV₁ &lt; 50% predicted</td>
</tr>
<tr>
<td>Stage IV:</td>
<td>Very Severe</td>
<td>&lt; 0.70</td>
<td>FEV₁ &lt; 30% predicted or FEV₁ &lt; 50% predicted plus chronic respiratory failure</td>
</tr>
</tbody>
</table>
Case 1

55 y.o. with recurrent episodes of bronchitis. Does she have COPD?

Office spirometry:

<table>
<thead>
<tr>
<th>Current studies</th>
<th>Pre-bronchodilator</th>
<th>Post-bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>2.44 L (82% predicted)</td>
<td>2.52 L (85% predicted)</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>71%</td>
<td>72%</td>
</tr>
</tbody>
</table>

NO Airflow Obstruction
No COPD!
FEV₁/FVC (%)=73%

While this patient does not meet criteria for COPD she is symptomatic and needs a different clinical approach.
Clinical and Radiologic Disease in Smokers With Normal Spirometry

• COPDGene study described this patient who appears to have what was formerly “GOLD 0”

• Findings:
  • worse quality of life
  • lower 6-minute walk distance
  • half had CT evidence of emphysema or airway thickening

“There are 35 million current and former smokers older than 55 years in the United States who may have unrecognized disease or impairment.”

Smokers with a Normal FEV₁

SPIROMICS Study

• Ever- or former smokers compared to never smokers with normal FEV₁/FVC,%
• Abnormal QOL score (COPD assessment test) was observed in 50% of smokers; prevalence of CMH* 33% in symptomatic smokers
• They had significantly less physical activity, slightly lower lung function, more respiratory exacerbations, and HRCT** findings consistent with greater airway wall thickening and low percentage emphysema.

*CMH=chronic mucus hypersecretion **HRCT Hi Resolution CT scan

Why Do We Need Spirometry?

**Spirometry is useful for:**
- Screening individuals at risk for pulmonary disease
- Confirmation of COPD diagnosis
- Assessing severity of pulmonary dysfunction
- Guiding selection of treatment
- Assessing the effects of therapeutic interventions

Who Should Be Screened for COPD?

Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40:
- Dyspnea that is progressive, usually worse with exercise, and persistent
- Chronic cough (may be intermittent and unproductive)
- Chronic sputum
- Frequent attacks of “winter bronchitis” or “chest colds”
- History of tobacco smoke exposure
- Exposure to occupational dusts and chemicals
- Exposure to smoke from home cooking and heating fuels
Spirometry is Underutilized

174 years after its invention.

WHY?

Hutchinson 1846

Spirometry for a Diagnosis of COPD

- Spirometry should be performed after the administration of an adequate dose of a short-acting inhaled bronchodilator (such as 4 puffs of albuterol recommended)

- A post-bronchodilator FEV₁/FVC <0.70 confirms the presence of airflow limitation that is not fully reversible

- Where possible, values should be compared to age-related normal values to avoid over-diagnosis of COPD in the elderly (FEV₁/FVC may be slightly less than 0.70 due to loss of elastic lung recoil with aging)
Measures of Pulmonary Function Used in COPD

- **FVC**
  - Forced vital capacity (FVC): total volume of air expired after a full inspiration. Patients with obstructive lung disease usually have a normal or only slightly decreased vital capacity.

- **FEV₁**
  - Forced expiratory volume in 1 second (FEV₁): volume of air expired in the first second during maximal expiratory effort. The FEV₁ is reduced in COPD.

- **FEV₁/FVC**
  - FEV₁/FVC: percentage of the vital capacity which is expired in the first second of maximal expiration. In healthy patients the FEV₁/FVC usually exceeds 70%. In patients with obstructive lung disease FEV₁/FVC decreases and can be as low as 20-30%.

Partial Reversibility* is Common in COPD

- Increase in FEV₁ of 12% or 200 mL

Case 1 Follow-up

55 y.o. with recurrent episodes of bronchitis. She does not meet criteria for COPD. What other diagnosis should be considered?

1. Asthma – unlikely.
   • While she does have elevated eosinophils on her blood work, spirometry showed no reversibility following a bronchodilator; also no history of atopic disease.

2. Bronchiectasis - recurrent bouts of chest infection suggests this diagnosis.
   • A CT scan can confirm this diagnosis.

3. Smokers with normal spirometry.

Case 1 Follow-up

55 y.o. with recurrent episodes of bronchitis.
How can this woman’s outlook be improved?

1. Reduce risk factors
   Smoking cessation
   Avoid occupational dusts and chemicals
   Avoid indoor and outdoor air pollutants
   Yearly influenza vaccination

2. Pharmacologic approach
   Consider long-acting inhaled bronchodilator
Key Points

• A 55 y.o. female smoker had recurrent episodes of bronchitis and a diagnosis of COPD was considered. Spirometry did not confirm a diagnosis of COPD, showing the value of this test in diagnosis and how even with normal lung function, smokers can experience considerable pulmonary morbidity.
• Spirometry is necessary to confirm the diagnosis of COPD and can be used to stage the severity of the disease, select treatment, and assess the response to treatment.
• This case demonstrates a patient who, despite multiple risk factors for COPD (smoking history, frequent bronchitis, exertional dyspnea and daily cough), never had spirometry to investigate for this diagnosis.
• Symptoms of COPD are not specific; other diseases of the airways such as asthma and bronchiectasis must be considered using additional pulmonary function testing and radiographic studies.

Chapter 2
Assessment and Prevention of Exacerbations
Case 2

60-year-old female patient
Chief Complaint: recent attack of COPD

1. Definition
2. Risk factors including COPD co-morbidities
3. Treatment
4. Prevention

• The current definition of an acute exacerbation of COPD (AECOPD) in the GOLD Guidelines is as follows:
  • “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.”

Factors Associated With Increase Risk for Exacerbations

- Severity of airway obstruction (FEV$_1$ impairment)
- Chronic bronchial mucous hypersecretion
- Longer duration of COPD
- Productive cough and wheeze
- Poor health-related quality of life
- Increased age
- Prior use of medications for COPD
- Bacterial colonization
- Comorbid conditions (e.g., cardiovascular disease)
- Antibiotic or systemic corticosteroid use in the past year

COPD Comorbidities Are Common

Death Due to Co-Morbidities is More Common in COPD


ECLIPSE STUDY: Factors Associated With Increased Exacerbation Frequency

**Risk for Subsequent Exacerbations**

Frequency Increases with Declining Lung Function (FEV₁)

Elevated Exacerbation Risk Associated With Cough and Sputum Production

Reproduced with permission of the © ERS 2020: European Respiratory Journal 2003 21: 46s-53s; DOI: 10.1183/09031936.03.00078002


COPD Exacerbations Impact on Survival


Patients with frequent exacerbations

- Lower quality of life
- Increased mortality rate
- Increased inflammation
- Increased risk of recurrent exacerbations
- Faster disease progression
- Increased likelihood of hospitalization
Goals of COPD Management

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

Reduce symptoms
Bronchodilators
ICS

Reduce risk
Smoking cessation
LVRS
O2

Can we prevent exacerbations?
Evidence-Based Measures That Reduce COPD Exacerbations

- Reducing risk factors
- Immunizations
- Long-acting bronchodilators
- Inhaled corticosteroids with long-acting bronchodilator(s)
- Pulmonary rehabilitation
- Integrated patient education programs
- Supplemental oxygen
- Prophylactic antibiotics
- Roflumilast

Macrolides Prevent COPD Exacerbations

Median time to 1st exacerbation
271 days Macrolide; 89 days Placebo

Proportion of Participants Free from Acute Exacerbations of COPD for 1 Year


Roflumilast and Exacerbations

Mean rate exacerbations (moderate or severe) per patient per year

1.5

1.23

-21%
(CI -31;-9)
P=0.0011

Significant Reduction in Exacerbations When Added to LABA

REACT Trial= 13% Reduction with LABA/ICS
Martinez et al Lancet 2015;385:857-85

Preventing Hospital Readmissions for COPD: An Integrated Goal-Directed Program

During the hospital visit, COPD care includes:

- Confirm diagnosis and staging with spirometry (if not done)
- Establish goals/review care plan for recovery period
- Confirm smoking cessation efforts/avoidance of risk factors
- Bedside teaching of inhaler devices used
- Teach relaxation techniques and coping skills
- Confirm next appointment with primary care practitioner or specialist and communicate with their personal physician


Key Points

• An exacerbation of COPD is an acute event with worsening of the patient’s respiratory symptoms that leads to a change in medication.
• Risk factors for an exacerbation include severity of airflow obstruction, daily productive cough, coexisting medical illnesses, and most importantly a previous exacerbation within the last year.
• Frequent exacerbations can lead to a poor quality of life and higher mortality.
• Several therapeutic measures can reduce the risk of COPD exacerbations including inhaled long-acting bronchodilators coupled with inhaled corticosteroids, pulmonary rehabilitation, antibiotics, the PDE-4 inhibitor such as Roflumilast, immunizations, and in certain cases, supplemental oxygen.

Chapter 3
Current and Emerging Therapeutics in the Treatment of COPD
Case 3

- 65 year old man from East Texas with multiple visits to physician for flare ups of breathing problems including frequent prednisone and antibiotics about every 2 months
- Main exercise is walking down to basement to watch TV or outside to smoke
- Smoked 2 packs of cigarettes since age 13, but now down to 3-4 cigarettes a day
- Has a daily cough, productive of ¼ cup of sputum
- PMH: HTN, Chol, prior MI
- FAM Hx: no COPD or other lung disease
- Medications: albuterol/ipratropium nebulizer; statin; diuretic; asa
- PE: obese, with BMI 38; vital signs normal except for HR ~105 and oxygen saturation 90% at rest

Following Tests were Ordered

- Spirometry: FEV1/FVC is 0.40; FEV1 is 42% predicted
- ABG: 7.40/45/58
- CBC: WBC 11; HCT 53%; PMN 8; L 1 M 1; Eos 1.0
Additional Therapies to Consider

• No change or LAMA or LABA/ICS or LABA/LAMA or LABA/LAMA/ICS? Any acceptable but at least one long term inhaler should be selected
• Have the patient join a pulmonary rehab program to improve exercise tolerance
• See the patient back to evaluate success of therapy
6 months later

- Patient is walking 30 minutes a day
- Feels less short of breath
- Only had one AECOPD
- Still smoking
- Exam similar, but less cough and wheeze

What should be done at this visit?

- Inhalers: if not on triple therapy, should you escalate?
- Are ICS now indicated?
- Other medication: if on triple therapy consider new treatment such as roflumilast to prevent exacerbations; azithromycin not indicated because of continued smoking; discuss common side effects of roflumilast and starting dosage
- Emerging therapies:
  - Anti-IL5 therapy for eosinophilia and asthma overlap (COPD indication is under investigation)
Additional non-pharmacologic therapies

- Smoking cessation and needs lung cancer screening until 80 years old
- Lung volume reduction (surgical or bronchoscopic)
- Home non-invasive ventilation (BPAP) for respiratory failure and hypercarbia?

Eosinophils


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Eosinophil


Risk ratio exacerbations COPD patients receiving ICS vs. non-ICS treatment ≥2% eosinophils (all association studies). ES, effect size


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Receiver operating characteristic (ROC) curves of levels of blood eosinophils as a marker of mean annual severe exacerbation risk of 1 or more in the chronic obstructive pulmonary disease population.

Published in: Signe Vedel-Krogh; Sune F. Nielsen; Peter Lange; Jørgen Vestbo; Børge G. Nordestgaard; Am J Respir Crit Care Med 193:95-974. DOI: 10.1164/rccm.201509-1862OC Copyright © 2016 by the American Thoracic Society

Anti-IL5 therapy reduces eosinophils and prevents exacerbations

Moderate or Severe Exacerbations According to Blood Eosinophil Count Category at Screening

Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease

Noninvasive Therapies


EBV on CXR
Non-invasive Ventilation at Home

Kaplan-Meier Survival Plot of Time to Readmission or Death From Randomization to the End of Trial Follow-up at 1 Year. The median follow-up times were 8.1 months (interquartile range, 2.3-12.6 months) for the home oxygen therapy alone group and 12.2 months (interquartile range, 8.9-12.9 months) for the home oxygen therapy plus home noninvasive ventilation (NIV) group. Adjusted for number of chronic obstructive pulmonary disease readmissions within past year, prior use of long-term oxygen therapy, age, and body mass index.

Emerging Therapies

• “New” triple therapies
• Phosphodiesterase (PDE) 3 and 4
• Anti-interleukin-33

IL-33/ST2 Pathways


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Key Points

• Patients with high blood eosinophils benefit the most from ICS and IL-5 therapy, but high eosinophil counts are not that common in COPD
• Home non-invasive ventilation may benefit the severe COPD patient who has been admitted to the hospital for respiratory and still has evidence of poor ventilation (inc. PCO2).
• Severe COPD patients may benefit from lung volume reduction and bLVR (valves) are an alternative to surgery
• Triple therapy is better than dual therapy to prevent exacerbations

Chapter 4
Patient Centered Strategies for Selecting Personalized Treatment and Management Plans for COPD to Improve Patient Adherence
Case 4

• 68 year old man from Columbus, Ohio. He is seeing you for the first time. He is weak and feels like he is short of breath while daily activities such as cleaning and dressing. He has no cough or wheezing.
• Main exercise is letting his dog out in the backyard
• Smoked 2 packs of cigarettes from age 19-65
• PMH: osteoporosis, severe hand arthritis, mild cognitive decline
• FAM Hx: brother with COPD
• Medications: albuterol inhaler; doesn’t help him so stopped using
• PE: BMI 27; vital signs normal

Following Tests Ordered

• Spirometry: FEV1/FVC is 0.50; FEV1 is 50% predicted
• ABG: 7.40/38/70
• CBC: WBC 8; HCT 38%; PMN 6; L 1 M 1; Eos 0.1
What would you treat with?

- No change or LAMA or LABA/ICS or LABA/LAMA or LABA/LAMA/ICS? Any acceptable but at least one long term inhaler should be selected
- Have the patient join a pulmonary rehab program to improve exercise tolerance
- See the patient back in 3-4 weeks to evaluate success of therapy
1 month later

- Patient is no better
- Stopped using LABA/ICS combination therapy because no benefit
- No AECOPD
- Still not smoking
- Exam similar


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Motivational Topics

<table>
<thead>
<tr>
<th>Theme of Responses</th>
<th>Representative Quote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theme 1: Participants view coaching conversations as motivating and encouraging.</td>
<td>To have someone there that calls you up and talks to you and encourages you to do things, not push you, just encourage. It gives you a little bit more willpower to keep going and try a little more all the time. It seemed to boost me up a little bit. Give me a little more courage. It would make me want to do it again. Do the exercise better.</td>
</tr>
<tr>
<td>Theme 2: Coaching conversations increased accountability.</td>
<td>Just the fact that come Thursday, I knew I would have to talk to this coach and I was always cognizant of keeping up with some activity, as minor as it might be, and keeping my activity log up-to-date and pedometer readings. It’s like anything else you do where somebody is motivating you or checking on you. You pay a little more attention to what you are doing and you want to be able to report some progress, so it’s helpful in that regard. They make sure you are doing what you are supposed to be doing. I had somebody to report to when I accomplished or didn’t accomplish.</td>
</tr>
<tr>
<td>Theme 3: Through coaching, participants gained increased awareness of health and health behavior.</td>
<td>Probably made me more aware of what I’m doing and not doing, or what I should be doing. It just reinforces to follow the guidelines. Try to do better, let’s put it that way. It certainly made me more aware of setting some goals. Well, my general awareness of what I was doing, I became very aware of my activity levels. She gave me examples of alternative things that I could do. I guess she gave me the insight for other things. It keeps you mindful of what you are trying to do.</td>
</tr>
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</table>
Effect of Motivational Therapy on Treatment Adherence


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Multi-disciplinary Needs

Education (understanding COPD) → Managing symptoms and medications (learning about medications)
→ Healthy lifestyle (diet and exercise, pulmonary rehab, smoking cessation)

Mobility and independence (walkers, wheelchairs, portable oxygen)
→ Managing feelings and worries (treating anxiety and depression)

Social support (personal care, financial support, driving assistance, navigating services)
→ Living positively with COPD (peer support groups)

Thinking about the future (community support and end of life planning)

A Patient Centered Discharge Bundle


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Self management of COPD exacerbations may reduce HCU


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But other studies are less conclusive


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Cochrane Review of COPD Self-Management Action Plans

Key Points

• Many patients don’t use their inhaler properly
• Practice to use inhalers correctly and effectively
• Motivational strategies may help
• Mixed evidence of self-management for COPD