

COPD: Intro to Therapeutic Options Part I

Case related questions.

Scenario:

Mr. H is a 65 year old male with a reported history of COPD. He sees you as a new patient with several months of gradually worsening dyspnea on exertion and a hacking cough. A year ago, Mr. H said he could walk about 2 blocks before getting short of breath, but now can only walk about one block before needing to rest. He has a daily cough productive of clear to whitish-colored mucus. He denies any fevers, upper respiratory infection symptoms, or changes in his mucus production. He has a pulmonologist but has not been to see her in many years. He has only been taking albuterol PRN, now 4 times daily, with some mild to moderate relief. He is a current everyday smoker with a 45-pack-year history. He denies any ER visits or hospitalizations for breathing in the past 5 years. He has never been prescribed oral corticosteroids. In the office, he is comfortable appearing. His resting oxygen saturation on room air is 93%. His other vitals are within normal limits. His pulmonary exam is notable for decreased breath sounds bilaterally without wheezes or rhonchi. He has no evidence of clubbing or peripheral edema. The rest of his exam is normal.

Question 1: What is your differential diagnosis for Mr. H's dyspnea? Compare and contrast emphysema and chronic bronchitis based on the underlying pathophysiology of the disease. Consider the role of non-smoking-related pollutants and host factors in COPD development.

Question 2: What tests do you want to order during his initial visit to assess his dyspnea?

Scenario cont.:

You review the spirometry that was obtained during this initial visit. They are notable for an FEV1 45%, FEV1/FVC 40%, FVC 87%.

Question 3: Once you confirm the diagnosis of COPD, what additional assessments and testing should be considered?

Question 4: What is the GOLD Assessment tool for classifying COPD?

Question 5: What medication(s) would you recommend starting at this point?

Question 6: If Mr. H reported minimal current respiratory symptoms and a history of 2 exacerbations in the past year requiring antibiotics, would that change your recommendation of pharmacotherapy based on the GOLD grading system?

Question 7: Is there any evidence to support starting a combination of ICS+LABA vs. LABA+LAMA in this patient? How do exacerbation history, side effects, and absolute eosinophil count (AEC) impact adding an ICS to bronchodilator therapies?

Scenario cont.:

Mr. H returns for his follow-up visit with you 6 weeks later. He says he has been using his Vilanterol/umeclidinium (Anoro Ellipta) 1 puff daily and albuterol. He is using the albuterol twice daily on average. He obtained additional testing as suggested: PFTs showed a TLC 88%, RV 98% and DLCO 59% predicted. His alpha-1 antitrypsin serum level was normal. A CBC with differential revealed an absolute eosinophil count of 275. His simple exercise testing reports he walked 325 meters with exertional hypoxemia to 87%. Oxygen saturation is 92% at rest. He tells you he was seen by his PCP once since his last visit at and was prescribed a z-pack and 5 days of prednisone with some modest improvement, although he is still not feeling back to baseline. He has cut back on his tobacco use, down to a few cigarettes daily.

Question 8: Characterize the severity of his COPD based on current GOLD criteria and what should be done regarding his inhaler therapy. Should Mr. H be prescribed supplemental oxygen for his exertional hypoxemia?

Question 9: What additional non-pharmacologic interventions should we also consider in Mr. H?

Question 10: Which therapies in COPD have been clearly shown to be disease-modifying (i.e. Change the natural history of COPD by decreasing mortality or slowing the rate of decline in FEV1)?

Question 11: When should you plan to repeat his PFTs? Does Mr. H need any other ongoing monitoring?

Question 12: Mr. H continues complaining of a nagging cough and wants some cough syrup with codeine. Should you give it to him?

Question 13: Why are COPD inhalation therapies so expensive? What are the generic inexpensive options?

COPD: Intro to Therapeutic Options Part I

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Educational Objectives:

1. Review the differential diagnosis and initial evaluation of Chronic Obstructive Pulmonary Disease (COPD)
2. Review the updated 2025 Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria
3. Describe a step-wise approach to initial bronchodilator and inhaled corticosteroid therapy based on a patient's severity of illness and pulmonary dysfunction

Scenario:

Mr. H is a 65 year old male with a reported history of COPD. He sees you as a new patient with several months of gradually worsening dyspnea on exertion and a hacking cough. A year ago, Mr. H said he could walk about 2 blocks before getting short of breath, but now can only walk about one block before needing to rest. He has a daily cough productive of clear to whitish-colored mucus. He denies any fevers, upper respiratory infection symptoms, or changes in his mucus production. He has a pulmonologist but has not been to see her in many years. He has only been taking albuterol PRN, now 4 times daily, with some mild to moderate relief. He is a current everyday smoker with a 45-pack-year history. He denies any ER visits or hospitalizations for breathing in the past 5 years. He has never been prescribed oral corticosteroids. In the office, he is comfortable appearing. His resting oxygen saturation on room air is 93%. His other vitals are within normal limits. His pulmonary exam is notable for decreased breath sounds bilaterally without wheezes or rhonchi. He has no evidence of clubbing or peripheral edema. The rest of his exam is normal.

Question 1: What is your differential diagnosis for Mr. H's dyspnea? Compare and contrast emphysema and chronic bronchitis based on the underlying pathophysiology of the disease. Consider the role of non-smoking-related pollutants and host factors in COPD development.

Table 1 below lists the differential diagnosis for COPD with discriminating features. The biggest challenge is deciphering COPD from chronic asthma. Current pulmonary function testing and imaging do not allow a clear distinction between these conditions, and treatment recommendations are similar to asthma management.¹

Regarding pathology, COPD involves changes in the central airways, peripheral airways, lung parenchyma, and pulmonary vasculature. The different pathogenic mechanisms produce pathological changes, which, in turn, give rise to the following physiological abnormalities in COPD: mucous hypersecretion and ciliary dysfunction; airflow limitation and hyperinflation; gas exchange abnormalities; pulmonary hypertension; and systemic effects.² According to the American Thoracic Society (ATS), **chronic bronchitis** is defined clinically as chronic productive cough for 3 months in each of 2 successive years in a patient in whom other causes of productive chronic cough have been excluded. It may precede or follow development of airflow limitation. **Emphysema** is defined pathologically as the presence of permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis. **Centrilobular emphysema** refers to abnormal dilation or destruction of the central portion of the acinus. It is commonly associated with cigarette smoking, but can also be seen in coal workers' pneumoconiosis. **Panacinar emphysema** refers to enlargement or destruction of all parts of the acinus. It is most commonly associated with alpha-1 antitrypsin deficiency, although it can be seen in combination with proximal emphysema in smokers. In **paraseptal emphysema**, the alveolar ducts are predominantly affected. It may occur alone or in combination with centrilobular and panacinar emphysema. When it occurs alone, the usual association is spontaneous pneumothorax in a young adult.³

The 20% rule of COPD states that 20% of smokers develop COPD and 20% of COPD occurs in people without a smoking history. The latter fact reminds the reader to consider other airborne pollutants (organic dust, inorganic dust, chemical agents, and fumes) and host factors. Lifetime nonsmokers with COPD do not carry an increased risk of lung cancer or cardiovascular disease. Host factors to consider include deficiency of alpha-1 antitrypsin (AATD) and lung growth and development. Historically, the consensus was that "susceptible smokers" reached normal lung function in early adulthood and then developed an accelerated decline in forced expiratory volume in 1 second (FEV1) over time. This likely accounts for only 50% of COPD patients, with the remaining patterns having reduced lung function in early adulthood due to abnormal growth and development with a normal decline in lung function over time.^{4,5}

Table 1. Differential Diagnosis for COPD

Diagnosis	Suggestive features
COPD	Mid-life onset Slowly progressing symptoms Long history of smoking
Asthma	Early onset Varying symptoms Symptoms during the night/early morning Presence of allergy, rhinitis and/or eczema A family history Airflow limitation that is largely reversible
Congestive heart failure	Fine basilar crackles on auscultation Dilated heart on chest radiography Pulmonary oedema Volume restriction not airflow limitation on pulmonary function tests
Bronchiectasis	Large volume of purulent sputum Commonly associated with bacterial infection Coarse crackles/clubbing on auscultation Bronchial dilation and bronchial wall thickening on chest radiography/CT
Tuberculosis	Onset at all ages Lung infiltrate on chest radiography Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	Younger onset and in nonsmokers History of rheumatoid arthritis/fume exposure Hypodense areas on expiration on CT suggestive of bronchiolitis
Diffuse panbronchiolitis	Effects mostly male nonsmokers Almost all have chronic sinusitis Diffuse small centrilobular nodular opacities and hyperinflation on chest radiography and HRCT

CT: computed tomography; HRCT: high resolution computed tomography.

Borrowed from Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper.¹

Question 2: What tests do you want to order during his initial visit to assess his dyspnea?

Recommendation 1:

A diagnosis of COPD should be made by assessing a patient's symptoms, risk factors, and spirometry. COPD should be considered in any patient with symptoms of dyspnea, chronic cough or sputum production, a history of repeated lower respiratory tract infections, and/or a history of exposure to risk factors. **Spirometry is required to make the diagnosis.** The GOLD guidelines define persistent airflow limitation as the presence of a post-bronchodilator FEV1/FVC < 0.70. There are pros and cons of using a fixed ratio compared to a cut-off based on the lower limit of normal (LLN). The pros are that it is simple, independent of reference values, and the standard used in prior longitudinal studies of COPD. The con is that it can underdiagnose COPD in younger patients and overdiagnose it in elderly patients.⁶ This debate is unlikely to be resolved satisfactorily by expert opinion and, more importantly, has not been comprehensively studied in the medical literature. Since COPD ultimately is a clinical diagnosis with spirometry as only one parameter, simplicity and consistency take preference for now. ACP, ACCP, ATS, and ERS recommend obtaining spirometry to diagnose airflow obstruction in patients with respiratory symptoms (Grade: strong recommendation,

moderate-quality evidence). Spirometry should not be used to screen for airflow obstruction in individuals without respiratory symptoms (Grade: strong recommendation, moderate-quality evidence).⁷

Scenario cont.:

You review the spirometry that was obtained during this initial visit. They are notable for an FEV1 45%, FEV1/FVC 40%, FVC 87%.

Question 3: Once you confirm the diagnosis of COPD, what additional assessments and testing should be considered?

In high-prevalence countries, all COPD patients should have a one-time screening test for AATD.⁸ A serum concentration of alpha-1 antitrypsin less than 20% of normal suggests homozygosity.⁹

Additional pulmonary function testing, including lung volumes, preferably by body plethysmography to look for air trapping and diffusion capacity of the lungs for carbon monoxide (DLCO), can assist in characterizing the severity of COPD and identifying COPD phenotypes. However, they are not required for patient management. Although still commonly obtained and used to drive treatment decisions, assessing bronchodilator reversibility is no longer recommended as it does not predict response to bronchodilator or inhaled corticosteroid treatments and cannot be used to differentiate asthma from COPD.^{10,11}

There are no satisfactory biomarkers to follow in COPD. However, the absolute eosinophil count has become useful in guiding pharmacotherapy in symptomatic patients using inhaled corticosteroids.¹²

Simple exercise testing (commonly by a six-minute walk test) is useful to obtain to evaluate baseline exercise capacity and disability as well as to determine the presence of exertional hypoxemia. If this testing is unavailable, similar information can be ascertained using a pulse oximeter and walking with a patient in the clinic hallway.

While his clinical history suggests COPD, other chronic diseases must be evaluated as possible **concomitant** causes of his dyspnea, including cardiovascular disease, skeletal muscle dysfunction, and lung cancer.

Furthermore, an initial assessment of his symptoms should be conducted and can easily be assessed by the Modified British Medical Research Council (mMRC) Questionnaire or COPD Assessment Test (CAT).

Question 4: What is the GOLD Assessment tool for classifying COPD?

Historically, a simple spirographic grading system was used to guide treatment recommendations even though the severity of airflow obstruction correlated poorly with functional limitation and quality of life.¹³ The ABCD assessment tool was introduced in 2011 and incorporated patient symptoms and exacerbation history into the management of COPD. This tool still anchored the “letter” grading system to the “numerical” severity of airflow obstruction and was no better at predicting mortality. The 2017 GOLD criteria separated the numerical and letter classifications into 2 separate assessments creating a GOLD 1234 based on spirometry and GOLD ABCD based on symptom burden and risk of

exacerbations.¹⁴ In 2023, this was simplified to ABE eliminating GOLD C who had low symptom burden but exacerbations.¹¹

GOLD 1234 (Classification of airflow limitation severity based on spirometry)

GOLD 1 = FEV₁ ≥ 80%

GOLD 2 = FEV₁ 50-79%

GOLD 3 = FEV₁ 30-49%

GOLD 4 = FEV₁ < 30%

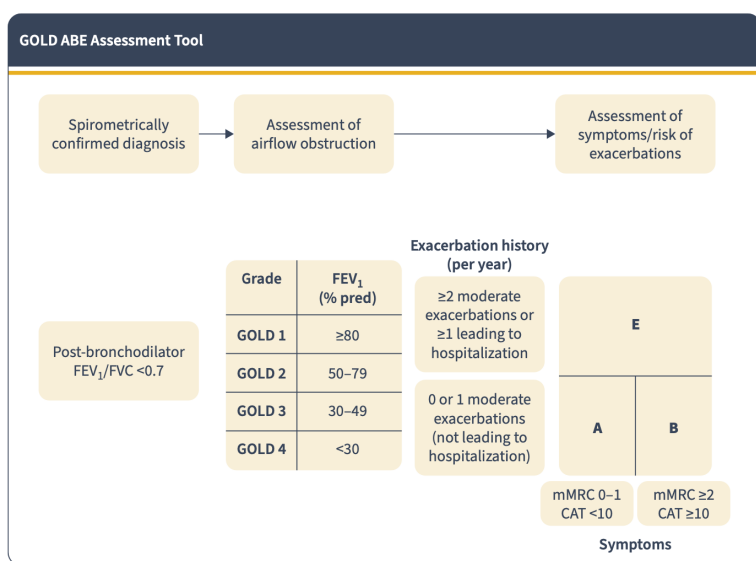
GOLD ABE (Classification based on symptom burden and risk of exacerbations)

GOLD A = mMRC 0-1 or CAT < 10; and 0-1 moderate exacerbations a year

GOLD B = mMRC ≥ 2 or CAT ≥ 10; and 0-1 moderate exacerbations a year

GOLD E = ≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization

Figure 1. The GOLD classification of COPD



Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2023 Report. *Eur Respir J.* 2023;61(4):2300239. doi:10.1183/13993003.00239-2023.

Question 5: What medication(s) would you recommend starting at this point?

Pharmacologic treatment is aimed at reducing symptoms, reducing the risk and severity of exacerbations, and improving overall health status and exercise tolerance in patients with COPD.¹⁵ Inhaled bronchodilators plus/minus inhaled corticosteroids are the mainstay of pharmacologic treatment for COPD.

Table 2. Commonly Used Inhaled Bronchodilators

Beta-2-Agonists	Anticholinergics
Short Acting Beta Agonist (SABA) - Albuterol (ProAir, Ventolin, Proventil) - Levalbuterol (Xopenex) - Fenoterol - Terbutaline	Short Acting Muscarinic Antagonist (SAMA) - Ipratropium bromide (Atrovent) - Oxitropium bromide (Oxivent)
Long Acting Beta Agonist (LABA) - Salmeterol (Serevent) - Formoterol (Foradil) - Arformoterol (Brovana) - Indacaterol (Arcapta Neohaler) - Olodaterol (Striverdi Respimat) - Vilanterol	Long Acting Muscarinic Antagonist (LAMA) - Tiotropium (Spiriva) - Umeclidinium (Incruse Ellipta) - Aclidinium bromide (Turdoza Pressair) - Glycopyrronium bromide (Seebri Breezhaler) - Glycopyrrolate solution (Lonhala Magnair) - Revefenacin solution (Yupelri)
PDE3/PDE4 Inhibitor - Ensifentrine (Ohtuvayre)	

Combination SABA+SAMAIpratropium bromide and albuterol (Combivent respimat)Ipratropium bromide and albuterol solution (Duoneb)Ipratropium and Fenoterol solution (Berodual)**Combination LABA+LAMA**

Formoterol/aclidinium (Duaklir Pressair)

Formoterol/glycopyrronium (Bevespi Aerosphere)

Indacaterol/glycopyrronium (Ultibro Breezhaler)

Vilanterol/umeclidinium (Anoro Ellipta)

Olodaterol/tiotropium (Stiolto Respimat)

Combination LABA+ICS

Formoterol/beclomethasone (Fostair)

Formoterol/budesonide (Symbicort)

Formoterol/mometasone (Dulera)

Salmeterol/fluticasone (Advair)

Vilanterol/fluticasone furoate (Breo Ellipta)

Triple Combination LABA+LAMA+ICS

Fluticasone/umeclidinium/vilanterol (Trelegy Ellipta)

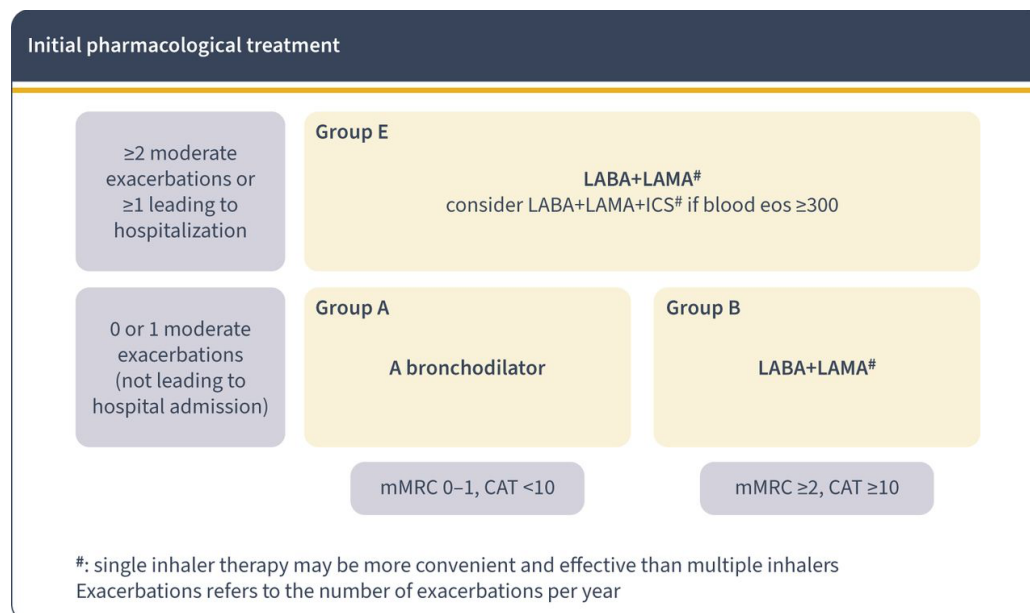
Beclomethasone/formoterol/glycopyrronium (Trimbow)

Budesonide/formoterol/glycopyrrolate (Breztri Aerosphere)

Choice of pharmacotherapy in COPD is determined using the ABE grading system shown in Figure 2 based on the Modified British Medical Research Council Questionnaire (mMRC) or the COPD Assessment Test (CAT) and the number of exacerbations in the last year. His

GOLD 1234 is 3 based on his FEV1 of 45%. Based on the history provided, his mMRC is ≥ 2 and his CAT score is ≥ 10 with no reported exacerbations or hospitalizations in the past year classifying him as GOLD Group B.

Figure 2. Initial Pharmacologic Treatment Based on GOLD Classification



Initial pharmacological treatment. Abbreviations: mMRC: modified Medical Research Council Dyspnea Questionnaire; CAT: COPD Assessment Test; LAMA: long-acting anti-muscarinic antagonist; LABA: long-acting β_2 receptor agonist; ICS: inhaled corticosteroid; eos: eosinophils.

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Based on his GOLD classification, it is recommended that he be started on a **combination LABA+LAMA inhaler**.

Combination treatment with a LABA and LAMA increases FEV1, reduces symptoms (Evidence A), and reduces exacerbations (Evidence B) compared to monotherapy.¹⁶ If LABA+LAMA combination is not considered appropriate, GOLD recommends bronchodilator treatment based on its effect on breathlessness. This can be either a short or long-acting bronchodilator, however if available and affordable, a long-acting bronchodilator is preferred. When choosing between LAMA vs LABA monotherapy, studies have shown LAMA to be more effective than LABA in preventing exacerbations.¹⁷

Furthermore, the following recommendation from the ATS also supports use of combination therapy over monotherapy:

ATS Recommendation 1: In patients with COPD who complain of dyspnea or exercise intolerance, the ATS recommends long-acting B2-agonist (LABA)/long-acting muscarinic antagonist (LAMA) **combination therapy** over LABA or LAMA monotherapy (strong recommendation, moderate certainty evidence).¹⁵

A new class of long-acting inhaler was approved by the FDA in 2024 following the publication of the ENHANCE trials¹⁸ that studied a PDE3/PDE4 inhibitor delivered as a nebulized suspension for patients with Gold B COPD (MMRC ≥ 2) in addition to any existing inhalers. This study did meet its primary endpoint of improvement in FEV1 and also showed a reduction in exacerbations. Unfortunately, the study population was very heterogeneous with 30-45% of patients not using any long-acting inhaler prior to the study so the role for this inhaler in Gold B COPD remains unclear at this time. Currently GOLD recommends its use for persistent dyspnea despite LABA+LAMA.

Given Mr. H's dyspnea, it is reasonable and supported by the ATS and GOLD guidelines that he be started on LAMA+LABA combination. Due to the severity of his dyspnea on presentation, Mr. H was subsequently started on combination therapy with the LABA+LAMA combination vilanterol/umeclidinium (Anoro Ellipta).

Question 6: If Mr. H reported minimal current respiratory symptoms and a history of 2 exacerbations in the past year requiring antibiotics, would that change your recommendation of pharmacotherapy based on the GOLD grading system?

In this hypothetical situation, Mr. H would be classified as GOLD E. Combination LAMA+LABA reduces exacerbations compared with monotherapy (Evidence B).^{16,19} In general LAMA+LABA would remain the recommended pharmacotherapy unless the patient has an eosinophil count ≥ 300 , then it would be reasonable to start triple inhaler therapy with LAMA+LABA+ICS.

Question 7: Is there any evidence to support starting a combination of ICS+LABA vs. LABA+LAMA in this patient? How do exacerbation history, side effects, and absolute eosinophil count (AEC) impact adding an ICS to bronchodilator therapies?

The following are recommendations from the ATS regarding treatment strategies regarding inhaled corticosteroids:

ATS Recommendation 2: In patients with COPD who complain of dyspnea or exercise intolerance despite dual therapy with LABA+LAMA, the ATS recommends the use of triple therapy with LABA+LAMA+ICS over dual therapy with LABA+LAMA in those patients **with a history of one or more exacerbations in the past year** requiring antibiotics or oral steroids or hospitalization (conditional recommendation, moderate certainty evidence).

The **2025 GOLD guidelines** recommend against the use of LABA+ICS and recommend using triple therapy if there is an indication for ICS. Triple therapy improves lung function, symptoms, and health status and reduces exacerbations compared to, LAMA/LABA+ICS, LAMA+LABA combination therapy, or LAMA monotherapy (Evidence A) in symptomatic patients with a history of frequent and/or severe exacerbations. The most recent GOLD guidelines include an absolute eosinophil count (AEC) ≥ 100 as part of their recommendations for starting triple therapy in patients with persistent exacerbations. They recommend considering triple therapy in GOLD E patients with an AEC ≥ 300 . Anyone with a history of asthma should be maintained on an ICS.

Initiating ICS therapy in COPD patients is not without potential complications. ICS therapy, compared to bronchodilators, has more adverse reactions. Oral candidiasis, voice changes, and bruising are more common and troublesome for patients.²⁰ Importantly there is a higher risk of developing pneumonia. Using the absolute eosinophil count to guide ICS therapy has become more recognized. For instance, COPD patients with frequent

exacerbations and an AEC ≥ 300 significantly benefit from using an ICS compared to those on bronchodilator therapy alone. Although less impactful, there still appears to be a benefit in COPD patients using an ICS with at least 1 moderate exacerbation a year and an AEC above 100. However, the risks of ICS use outweigh their benefits in COPD patients with an AEC below 100 and in those with a history of pneumonia or mycobacterial infection.^{21,22}

At this time, Mr. H has not reported a history of exacerbations. Based on current guidelines, triple therapy is not indicated at this time.

Scenario cont.:

Mr. H returns for his follow-up visit with you 6 weeks later. He says he has been using his Vilanterol/umeclidinium (Anoro Ellipta) 1 puff daily and albuterol. He is using the albuterol twice daily on average. He obtained additional testing as suggested: PFTs showed a TLC 88%, RV 98% and DLCO 59% predicted. His alpha-1 antitrypsin serum level was normal. A CBC with differential revealed an absolute eosinophil count of 275. His simple exercise testing reports he walked 325 meters with exertional hypoxemia to 87%. Oxygen saturation is 92% at rest. He tells you he was seen by his PCP once since his last visit at and was prescribed a z-pack and 5 days of prednisone with some modest improvement, although he is still not feeling back to baseline. He has cut back on his tobacco use, down to a few cigarettes daily.

Question 8: Characterize the severity of his COPD based on current GOLD criteria and what should be done regarding his inhaler therapy. Should Mr. H be prescribed supplemental oxygen for his exertional hypoxemia?

Based on his prior spirometry, Mr. H has severe airflow limitation and is GOLD 3. Based on his symptoms and exacerbations (only 1 moderate exacerbation), he remains GOLD B. However, his GOLD classification does not bind him to specific treatment options, and escalation or de-escalation strategies are based on response to symptoms of dyspnea or exacerbations. It is important to note that follow-up treatment does not depend on the initial GOLD group at diagnosis. Because he still feels significant dyspnea and has had 1 moderate exacerbation despite being on combination LABA+LAMA therapy, it is reasonable to escalate to triple therapy with ICS+LABA+LAMA. His AEC of 275 is also supportive of this change.

Figure 3. GOLD Guidelines Recommendations on Which Patients May or May Not Benefit from ICS Therapy

Factors to consider when initiating ICS treatment	
Factors to consider when adding ICS to long-acting bronchodilators: (note the scenario is different when considering ICS withdrawal)	
Strongly favors use	History of hospitalization(s) for exacerbations of COPD [#]
	≥2 moderate exacerbations of COPD per year [#]
	Blood eosinophils ≥300 cells·μL ⁻¹
	History of, or concomitant asthma
Favors use	1 moderate exacerbation of COPD per year [#]
	Blood eosinophils 100 to <300 cells·μL ⁻¹
Against use	Repeated pneumonia events
	Blood eosinophils <100 cells·μL ⁻¹
	History of mycobacterial infection
[#] : despite appropriate long-acting bronchodilator maintenance therapy (see Figure 4 and GOLD report Table 3.4 for recommendations). Note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.	
Adapted from and reproduced with permission from [103].	

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The role of supplemental oxygen in moderate chronic resting room air hypoxemia (SpO₂ 89-93%) and severe exertional room air hypoxemia (SpO₂ ≤ 88%) were clarified by the LTOT trial published in 2017.²³ There was no impact on mortality in providing supplemental oxygen in either scenario. The ATS Executive Summary regarding home oxygen “suggested” against LTOT supplemental oxygen (> 15hr/day) in those with moderate resting hypoxemia (conditional recommendation, low-quality evidence) and suggested prescribing ambulatory oxygen in those with severe exertional hypoxemia (conditional recommendation, low-quality evidence).²⁴ The argument for the latter was small but significant improvements in exercise capacity and quality of life in those prescribed oxygen. As with any therapy associated with significant patient and caregiver burden shared decision making is the prudent course.

Given the mortality benefit associated with LTOT in patients with COPD and severe resting hypoxemia, it is important to identify these patients. Resting pulse oximetry has a false negative rate of 10% in this population, particularly in active smokers due to the presence of carbon monoxide or patients with darker skin pigmentation.²⁵ GOLD recommends performing an ABG in patients with an oxygen saturation of ≤ 92%.

Question 9: What additional non-pharmacologic interventions should we also consider in Mr. H?

Smoking cessation, vaccinations, and pulmonary rehab are cornerstones of COPD therapy (see below).

Question 10: Which therapies in COPD have been clearly shown to be disease-modifying (i.e. Change the natural history of COPD by decreasing mortality or slowing the rate of decline in FEV1)?

One of the pulmonologist's most important roles is to accurately diagnose a patient's disease process and prioritize disease-modifying therapies. In COPD, there are few, and they must be prioritized. The most important intervention is smoking cessation. A \$500 once-daily triple inhaler has nothing on abstinence from smoking! Although not the purpose of this module, the reader is encouraged to read the ATS Practice Guidelines on Pharmacotherapy in Tobacco dependent adults.

Another definitive disease-modifying therapy in COPD patients is long-term oxygen therapy (> 15 hrs/day) in those with severe chronic resting room air hypoxemia ($\text{SpO}_2 < 88\%$ or $\text{PaO}_2 < 55$ mm Hg OR $\text{SpO}_2 89\%$ or $\text{PaO}_2 56-59$ plus one of the following: edema, HCT > 55% or P pulmonale on ECG).²⁴

Alpha-1 antitrypsin augmentation has been shown to slow the progression of emphysema in those with the ZZ genotype (Evidence B).²⁶ Due to cost and lack of availability, the pragmatic recommendation is to consider such therapies in those who are not actively smoking and have an FEV1 of 35-60%.⁸

Surgical lung volume reduction (LVRS) has been shown to reduce mortality in COPD patients with upper lobe predominant emphysema, substantial air trapping ($\text{RV} > 150\%$), and low exercise capacity despite pulmonary rehabilitation.²⁷ Bronchoscopic lung volume reduction (BLVR) has become an attractive alternative to thoracic surgery. Still, it does not have a definitive mortality benefit, albeit recent trials show marked and consistent increases in FEV1 with the procedure at the expense of a 20% risk of pneumothorax.²⁸

Hypercapnic, stable COPD patients ($\text{PaCO}_2 > 52$ mm Hg) have a survival benefit with the addition of non-invasive positive pressure ventilation (NPPV) when NPPV can reduce PaCO_2 levels by 20% of baseline.²⁹

Although not specifically disease modifying for COPD, lung cancer screening aside from smoking cessation will likely have the most important impact to improving mortality in the COPD population. A COPD diagnosis is a substantial risk factor for lung cancer with 1% of COPD patients diagnosed with cancer annually.³⁰

Recently, there have been debates on the role of pharmacotherapy as disease modifying. Specifically triple inhaler therapy compared to LAMA+LABA was shown to reduce mortality in symptomatic patients with frequent and severe exacerbations. In the IMPACT and ETHOS trials, mortality was not the primary outcome but a pre-specified outcome.^{31,32} The majority of patients enrolled in these trials were already on triple therapy prior to randomization meaning that half of them had their ICS withdrawn with a known exacerbation risk. Regardless, the results support the role of triple therapy in GOLD E patients unless there is a good reason not to use an ICS.

Question 11: When should you plan to repeat his PFTs? Does Mr. H need any other ongoing monitoring?

There are no guidelines recommending any regular monitoring of PFTs annually or semi-annually. Spirometry should be performed if there is a substantial change in symptoms or a new complication. ABGs should be checked in all patients with an $\text{FEV}_1 < 40\%$ or signs/symptoms of respiratory failure or heart failure. Key history should focus on clinical

symptoms, exacerbation history, current treatment regimen/adherence, and any new comorbidities. He should be offered lung cancer screening at this time. A pulmonary rehabilitation referral is also recommended. Vaccination history should be reviewed. According to CDC guidelines, annual influenza vaccinations (Evidence B) are recommended, as is the COVID-19 vaccination. Vaccines for pneumococcal pneumonia should also be up to date. It is also important for patients to be up to date on all other recommended age-appropriate vaccinations, including Tdap and Shingrix.³³

Question 12: Mr. H continues complaining of a nagging cough and wants some cough syrup with codeine. Should you give it to him?

No. The cough in COPD is thought to have a significant protective role and is thus cough suppression is contraindicated in stable COPD.³⁴

Question 13: Why are COPD inhalation therapies so expensive? What are the generic inexpensive options?

In 2008, the FDA banned production and sale of chlorofluorocarbon (CFC) based inhalers due to concerns of environmental harm.³⁵ The ultimate consequence was that all generic CFC inhalers were replaced with expensive and patented hydrofluoroalkane (HFA) inhalers. Patent law favors protecting pump design, delivery systems and formulations creating substantial challenges to the generic market. For example, although Advair went off patent in 2010, a generic alternative was released in early 2019. Generic drugs are held to the same high standards of safety and packaging as brand names versions. For inhalers that require a complex delivery mechanism, this requires an added cost that will be reflected in the overall cost of the medication. Generic inhalers will never achieve a comparable affordability as pills or solutions.

According to GoodRx reporting, the average price of inhalers has increased 35% from 2013 to 2018 from \$280 to \$380.³⁶ There are generic options for both inhalers and nebulizers, and both GoodRx (goodrx.com) and Mark Cuban's CostPlus Drug Company (costplusdrugs.com) are useful resources for patients with prohibitive out-of-pocket drug costs. As is evident from Table 3, the cost of generic combination inhalers remains expensive and quite limited.

The reader is encouraged to look through the list of available medication on GoodRx and try to cost out the most affordable regimen for a patient.

Table 3. Prices of Commonly Used Inhalers

Short-acting bronchodilators	Average Cost with GoodRx coupon
Albuterol Generic for Proair HFA	\$24.52 (1 inhaler)
Albuterol Generic for Ventolin	\$41.50 (1 inhaler)
Albuterol Generic for Proventil	\$21.20 (1 inhaler)
Albuterol Accuneb solution	\$14.99 (25 vials)
Levalbuterol Generic for Xopenex HFA	\$55.43 (1 inhaler)
Levalbuterol Generic for Xopenex solution	\$41.77 (25 vials)
Ipratropium Generic Atrovent solution	\$17.33 (25 vials)
Atrovent HFA	\$470.92 (1 inhaler)
Ipratropium/Albuterol Duoneb solution	\$16.80 (30 vials)
Combivent respimat	\$487.86 (1 inhaler)

ICS+LABA	
Fluticasone / Salmeterol generic as Airduo	\$32.33 (1 respiclick inhaler)
Wixela Inhub Generic Advair	\$110.63 (1 diskus)
Budesonide/ Formoterol generic Symbicort)	\$210.48 (1 inhaler)
Breo Ellipta	\$171.62 (1 inhaler)
Dulera	\$347.86 (1 inhaler)
LAMA	
Spiriva Handihaler	\$517.29 (1 inhaler)
Spiriva Respimat	\$513.06 (1 inhaler)
Tudorza Pressair	\$665.92 (1 inhaler)
Incruse Ellipta	\$373.18 (1 inhaler)
Seebri	\$425.09(1 inhaler)
Longhala Magnair	\$1300.01 (60 vials)
Yupelri	\$1254.87 (30 vials)
PDE3/PDE4 Inhibitor	
Ohtuvayre suspension	TBD (60 ampules)
ICS	
Flovent HFA	\$124.16 (1 inhaler)
Pulmicort Flexhaler	\$256.47 (1 inhaler)
QVAR redihaler	\$286.30 (1 inhaler)
Budesonide Generic solution of Pulmicort	\$75.49 (60 vials)
LAMA+LABA	
Formoterol/glycopyrronium (Bevespi Aerosphere)	\$431.41 (1 inhaler)
Vilanterol/umeclidinium (Anoro Ellipta)	\$454.14 (1 inhaler)
Olodaterol/tiotropium (Stiolto Respimat)	\$471.04 (1 inhaler)
LABA	
Salmeterol (Serevent)	\$448.46 (1 diskus)
Formoterol generic Perforomist	\$344.62 (60 vials)
Arformoterol generic Brovana	\$293.03 (60 vials)
Olodatero (Striverdi Respimat)	\$247.37 (1 inhaler)
ICS+LAMA+LABA	
Fluticasone/umeclidinium/vilanterol (Trelegy Ellipta)	\$640.44 (1 inhaler)
Budesonide/formoterol/glycopyrrolate (Breztri Aerosphere)	\$631.21 (1 inhaler)

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COPD: Intro to Therapeutic Options - Part I

Post-Test Case Related Questions

1. A 65-year-old man is seen in your clinic for evaluation of COPD. His PFTs show obstruction with an FEV1 of 45% predicted. He has had 1 exacerbation in the last year and only uses albuterol as needed (which he requires up to 4-5 times daily). He can walk 2-3 blocks before becoming winded. Which of the following would be the appropriate next step according to the official ATS guidelines with the strongest evidence?
 - a. Start an inhaled steroid alone
 - b. Start a long-acting beta-agonist alone
 - c. Start a long-acting muscarinic antagonist alone
 - d. Either B or C
 - e. Either A or B
 - f. Combination of B and C
 - g. Start any combination of 2 of the above medications

2. A 55-year-old female with COPD (FEV1 55%) comes to see you in the clinic for a follow-up. She currently has a 5-6 block exercise tolerance and is maintained on tiotropium with as-needed albuterol for rescue. She is overall doing well but tired of taking her inhalers every day. She asks you what good this tiotropium is doing her anyway. Based on the known literature, which of the following is(are) true regarding the benefit of this medication in patients with COPD?
 - a. Improved mortality
 - b. Improved symptoms (dyspnea and quality of life)
 - c. A decreased decline in FEV1
 - d. All of the above

3. A 70-year-old female (FEV1 40%, not on home O2) comes to your office for follow-up. She is currently maintained on a maximum dose combination fluticasone-salmeterol and tiotropium. She continues to need her albuterol inhaler 2-3 times daily. Her score on the mMRC dyspnea scale is 4 (she is short of breath after walking a few minutes on flat ground). She has had 1 exacerbation this past year that was managed as an outpatient with a course of antibiotics and steroids.
 - 3a. Which of the following most accurately classified her COPD according to the GOLD spirometry criteria?
 - a. Gold 1
 - b. Gold 2
 - c. Gold 3
 - d. Gold 4
 - 3b. Which of the following most accurately classified her COPD according to the most recent GOLD guidelines (Grade ABE based on symptoms, mMRC grade or CAT score, and exacerbation history)?
 - a. Gold A
 - b. Gold B
 - c. Gold E

COPD: Intro to Therapeutic Options - Part I

Post-Test Case Related Answers

- 1) F
- 2) B
- 3) C and B

UPLIFT Trial

The UPLIFT trial (NEJM 2008) showed that tiotropium relieves dyspnea, improves lung function and quality of life, and reduces exacerbations compared to placebo. However, there was no significant difference in rate of FEV1 decline or mortality.

Study Design: 4-year, randomized, double-blind, placebo-controlled, parallel-group study involving 5993 patients (mean age, 65±8 years) with moderate-to-severe COPD a mean post-bronchodilator FEV1 of 1.32±0.44; 48% of predicted value) that received usual treatment (including LABA, ICS alone or in combination), and were randomized to tiotropium or placebo (control).

Inclusion Criteria: Patients were >40 years old, >10 pk year history, FEV1 ≤70% after bronchodilators, FEV1/FVC≤70

Exclusion Criteria: history of asthma, COPD exacerbation or respiratory infection within 4 weeks before screening, a history of pulmonary resection, use of supplemental oxygen for more than 12 hours per day

Intervention: 4 years of therapy with either tiotropium or placebo

Primary Outcome: Rate of decline in the mean FEV1 before and after bronchodilation beginning on day 30

Secondary Endpoints: FVC, changes in response on St. George's Respiratory Questionnaire (SGRQ), exacerbations of COPD, and mortality

Findings:

- Did not show significant differences in the rate of decline in lung function or HRQL score between the tiotropium and control groups, but achieved a sustained increase in lung function and HRQL over 4 years ($p < 0.001$).
- After day 30, the differences between the two groups in the rate of decline in the mean FEV1 before and after bronchodilation were not significant. FEV1 decline was 40 mL/year for tiotropium and 42 mL/year for the control group

- The mean absolute total score on the SGRQ was improved (lower) in the tiotropium group, as compared with the placebo group, at each time point throughout the 4-year period ($P < 0.001$).
- The difference in 4-year all-cause mortality between the tiotropium and placebo groups was not statistically significant ($p = 0.09$)

At 4 years and 30 days, tiotropium was associated with a reduction in:

- Time to first exacerbation: compared with control, tiotropium significantly delayed time-to-first exacerbation (16.7 vs 12.5 months) and time-to-first hospitalization for exacerbations (lower risk of hospitalization in tiotropium group; HR, 0.86 [95% CI, 0.78–0.95]; $p = 0.002$)
- The mean number of exacerbations by 14% (rate per patient-year, 0.73 vs 0.85; HR, 0.86 [95% CI, 0.81–0.91]; $p < 0.001$), and reduced the number of days with exacerbations (13.64 vs 12.11; HR, 0.89 [95% CI, 0.83–0.95]; $p = 0.001$) compared with control.
- COPD-related hospitalizations (hazard ratios were 0.86 (95% CI, 0.81 to 0.91) in the tiotropium group and 0.86 in the placebo (95% CI, 0.78 to 0.95),

TORCH Trial:

The TORCH trial (NEJM 2007) showed that combination ICS/LABA therapy improved lung function (measured by FEV1) compared to both placebo vs. LABA alone vs. ICS alone. There was no proven mortality benefit to combination therapy in this study (although the p value was close at 0.052)

Study Design: 3-year, double-blind, parallel-group, placebo-controlled study of 6184 COPD patients randomized to salmeterol (500 µg) and fluticasone (50 µg) twice daily, either as monotherapy or in combination vs placebo.

Inclusion Criteria: current or former smokers (at least a 10-pack-year history); 40 to 80 years of age with a diagnosis of COPD (prebronchodilator FEV1 < 60%), an increase of FEV1 with albuterol of less than 10% of the predicted value for that patient, and a ratio of prebronchodilator FEV1/(FVC) equal to or less than 0.70

Primary outcome: all-cause mortality over 3 years

Secondary Outcomes: frequency of exacerbations, health status, and spirometric values

Findings:

- No difference in mortality with LABA–ICS combination therapy versus short-acting bronchodilators (placebo)
 - All-cause mortality rates were 12.6% in the combination therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group, and 16.0% in the fluticasone group; hazard ratio [HR] 0.825, 95% confidence interval [CI], 0.681–1.002; $p = 0.052$)
- Reduction in the annual rate of exacerbations compared with placebo (1.13 in placebo vs 0.85 in the combination regimen; $p < 0.001$)
- Exacerbations requiring hospital admission were reduced with the combination therapy and salmeterol alone compared with placebo ($p \leq 0.03$).

- Combination therapy also improved average HRQL compared with placebo and monotherapies over the 3-year trial period
- A sustained increase in lung function was observed in all active groups compared with the placebo
 - The rate of FEV1 decline was 55 mL/year in the placebo vs 39 mL/year in combination therapy and 42 mL/year for ICS and LABA monotherapy ($p \leq 0.03$).

Adverse events: increased incidence of pneumonia among patients receiving ICS treatment either as monotherapy or combination therapy.

Current guidelines continue to recommend ICS/LABA. However, the role of LAMA-LABA combos needs further study.

- 52-week multicenter RCT of glycopyrronium-indacaterol vs. fluticasone-salmeterol in 3362 patients with mod-severe COPD, high dyspnea scores, and history of at least one mod-severe exacerbation in the year prior (reference 9 above)
 - Glycopyrronium reduced the rate of mild-mod COPD exacerbations by 11% compared to fluticasone arm
 - Few episodes PNA (3.2 vs 4.8%)
 - Similar rates in the sicker patients (hx hospitalization/more severe exacerbation)
- RCT of 592 patients with mod-severe COPD with either tiotropium-formoterol vs. fluticasone-salmeterol (reference 10 above)
 - Lung function better after 6 weeks in the tiotropium-formoterol group