

COPD Part II: Advanced COPD Therapy

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*Literature review current through June 2023
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Educational Objectives:

1. Summarize current evidence for triple inhaler therapy
2. Describe pharmacologic and nonpharmacologic adjunctive therapies
3. Identify which patients should be prescribed supplemental O₂ therapy
4. Outline the benefits of pulmonary rehabilitation
5. Identify patients who may benefit from lung volume reduction
6. Determine which patients in whom to consider nocturnal non-invasive nocturnal ventilation

Scenario:

Ms. H is a 65-year-old woman with COPD (FEV₁ 45% of predicted). You have been following her for several years and have treated her with fluticasone/salmeterol 250/50 mcg 1 puff twice daily, tiotropium 18 mcg (1 capsule) inhaled daily, and albuterol 2 puffs or a nebulizer treatment every 6 hours as needed. Despite using her inhalers regularly, she feels that her symptoms have gotten progressively worse over the last year. She has been admitted to the hospital twice in the last year for COPD exacerbations but has never been intubated or required BiPAP. Since her last hospitalization, she feels like she hasn't recovered to her previous baseline and is using an albuterol rescue inhaler 5-6 times daily. She has a chronic cough and brings up a moderate amount of pale-yellow mucus daily. Some days, she has trouble getting the mucus up but breathes a bit better once she does. She quit smoking 16 years ago and had a 30-pack-year history. In the office, she is comfortable appearing. Her resting saturation is 93% breathing ambient air. Her other vitals are within normal limits. Her pulmonary exam is notable for decreased breath sounds bilaterally with a prolonged expiratory phase but no wheezes or rhonchi. She has no clubbing or peripheral edema. The rest of the exam is normal.

Question 1a: Is her current inhaler therapy appropriate?

Yes. An extensive evidence base supports the use of long-acting bronchodilators (LABAs and LAMAs) and inhaled corticosteroids (ICS) in patients with COPD. Robust data confirms that these medications decrease exacerbation rates, reduce symptom burden, and increase exercise tolerance. While they historically have not shown a mortality benefit compared to placebo in randomized trials, these studies mainly focused on reduction in symptoms, exacerbation rates, and improvement in quality of life. Regardless, these medications form the foundation of pharmacologic treatment for COPD.

Several trials ^(1; 2; 3) have now demonstrated the benefit of so-called “triple therapy,” consisting of an ICS, LABA, and LAMA, in patients with COPD *and* a history of exacerbations. Specifically, triple therapy consistently reduces the rate of moderate to severe exacerbations and increases health status compared to either dual therapy with LABA/LAMA or LABA/ICS. In addition to proving the benefit of triple therapy over dual therapy, secondary analyses of the original RCTs have shown triple therapy reduces mortality. Whether the convincing benefit of triple therapy extends to patients without a history of exacerbations is not known, as the above studies were enriched with patients with a recent history of exacerbation. ICS-containing regimens may not benefit all patients, particularly those with consistently low serum eosinophils (<100 cells/uL) ⁽⁴⁾. Given the increased risk of pneumonia in patients on an ICS, it is important to consider which patients should be on an ICS ⁽⁵⁾.

In summary, symptomatic patients with severe COPD and a history of recent exacerbations benefit from triple therapy, as is the case with our patient. This is also consistent with the GOLD guidelines, most recently updated in 2023⁽⁶⁾.

Question 1b: What other pharmacologic treatment options are available to help Ms. H given that she is already on maximal bronchodilator therapy (LAMA/LABA/ICS with albuterol rescue)? What evidence supports their use?

Roflumilast (Daliresp)	Chronic azithromycin
<p>REACT TRIAL⁽⁷⁾ (Lancet, 2015): 1,945 subjects with severe COPD, chronic bronchitis and at least 2 exacerbations in the previous year:</p> <ul style="list-style-type: none"> • Fewer exacerbations in the treatment group with borderline significance • Significant reduction in the number of severe exacerbations • Side effects: Diarrhea (10%), nausea, reduced appetite, abdominal pain, sleep problems, and weight loss. 	<p>Albert et al.⁽⁸⁾ (NEJM, 2011): 1,142 subjects with moderate to severe COPD and either continuous oxygen therapy or at least one exacerbation in the last year:</p> <ul style="list-style-type: none"> • Time to first exacerbation was significantly longer in the treatment group (266 days vs 174 days) • Exacerbation rate was lower in the treatment group • Side effects: hearing loss, nausea, diarrhea, development of bacterial resistance

There is no comparative efficacy data to help guide the choice between roflumilast and chronic azithromycin. In most cases, the choice is made based on consideration of side effect profile, insurance coverage, and the patient’s out-of-pocket cost. One important caveat is that the benefit of azithromycin may be attenuated in patients who are still actively smoking⁽⁹⁾.

Question 1c: What non-pharmacologic treatment options are available to help Ms. H?

In addition to additional pharmacologic management, it is also important to discuss the following:

- Smoking cessation in patients with active tobacco use, consider pharmacotherapy to increase success at quitting
- Oxygen therapy for patients with resting hypoxemia

- Pulmonary rehabilitation
 - Influenza, pneumococcal, and SARS-CoV-2 vaccination
 - Mucus clearance education, if pertinent
 - Pursed lip breathing techniques
1. Regarding supplemental oxygen: All patients, regardless of stage of disease, should be evaluated for evidence of oxygen desaturation with ambulation/exercise. For those with resting hypoxemia ($SpO_2 \leq 88\%$ or $paO_2 \leq 55$), continuous oxygen therapy reduces mortality if used for $>15h$ per day^(10; 11) and should be initiated in all patients who meet these criteria. The LOTT trial⁽¹²⁾ found no decrease in time-to-death or time-to-first hospitalization in patients with stable COPD and moderate desaturation at rest (SpO_2 89-93%) or with exercise (SpO_2 80-90%). For this group, deciding whether to initiate oxygen therapy should be individualized.

Question 1d: What additional considerations apply when caring for women with COPD?

Since 2000, the age-adjusted rate for COPD-related deaths has improved in men⁽¹³⁾. However, it is unchanged in white women and has increased in black women. Women are often underdiagnosed, and spirometry testing and pulmonary referrals are less common. This is an important consideration as female patients could be more likely to present with more advanced disease at the time of initial consultation⁽¹⁴⁾.

Scenario continued:

You confirm that Ms. H's oxygen saturations remain 90% or greater on room air with exertion. She begins therapy with roflumilast. She has had some diarrhea for the first couple of weeks on the medication, but this has improved, and she denies significant side effects. After further discussion, she decides to enroll in pulmonary rehab.

Question 2: What is pulmonary rehabilitation, and in what ways is it beneficial for COPD patients?

The American Thoracic Society's document on pulmonary rehabilitation⁽¹⁵⁾ defines it as "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors."

Health behavior change is vital to any intervention in chronic disease care. Pulmonary rehabilitation provides a framework for patients to cultivate self-efficacy, learn positive adaptive behaviors, and reduce the impact of the disease on their daily lives.

Regular aerobic exercise is essential for patients with COPD of any severity. Pulmonary rehabilitation should be offered to all COPD patients with severe obstruction ($FEV_1 < 50\%$) and considered for patients with $FEV_1 \geq 50\%$ if symptomatic and/or exercise limited. Multiple studies have shown that pulmonary rehabilitation improves exercise capacity, health-related quality of life, and recovery after acute exacerbation. It also reduces dyspnea, hospitalizations, depression, and anxiety associated with COPD (see GOLD guidelines, 2023 update, for a summary of primary studies)⁽⁶⁾.

In patients with more severe exercise impairment, optimizing medical treatment of their COPD and other comorbid conditions may maximize the effectiveness of pulmonary rehabilitation. Prior to referral for pulmonary rehabilitation, assessing for non-pulmonary sources of dyspnea (such as coronary artery disease) is also important.

Scenario continued:

Ms. H had strong participation in pulmonary rehabilitation and increased her 6-minute walk distance. Unfortunately, she still struggles with severe dyspnea and limited exertional capacity. A friend suggested she ask you about lung volume reduction and she wonders if she is a candidate.

Question 3a: What is lung volume reduction and how can it be performed?

Lung volume reduction is a consideration in patients with severe COPD (FEV1 <45% predicted), significant air trapping (RV >150% predicted), and exercise limitation despite maximal pharmacologic therapy and regular aerobic exercise⁽¹⁶⁾. Historically it was only performed via lung volume reduction surgery (LVRS), a surgical procedure involving resection of up to a third of severely emphysematous lung tissue from one or both upper lung zones. More recently, bronchoscopic approaches to lung volume reduction have emerged^(17; 18; 19) (called BLVR for bronchoscopic lung volume reduction). This is performed via insertion of one-way valves into the airways to collapse regions of emphysematous lung tissue. The decision as to whether a patient is a candidate for surgical versus bronchoscopic lung volume reduction is complex and involves a multidisciplinary discussion involving interventional pulmonologists and thoracic surgeons.

Several possible mechanisms explain the benefits of lung volume reduction. First, expansion of remaining lung may increase elastic recoil, which holds small airways open to reduce airway resistance and dynamic hyperinflation. Second, reducing overall volume of the chest returns the diaphragm and chest wall closer to normal resting position, restoring mechanical advantage during breathing. Third, removal or collapse of excess dead space may improve V/Q matching and gas exchange despite the decrease in overall alveolar surface area.

Question 3b: What patient characteristics are favorable (and unfavorable) for lung volume reduction?

	Favorable characteristics	Unfavorable characteristics
LVRS	<ul style="list-style-type: none"> • Severe, apical predominant emphysema • Severe obstruction ($FEV_1 \leq 45\%$ pred) • Severe air trapping ($RV > 150\%$ pred) • Apical hypoperfusion on V/Q ($< 10\%$ perfusion to upper lung thirds) • Apical air trapping on V/Q (long tracer half-life in upper lung thirds) • Low exercise capacity after pulmonary rehab (< 25 W on cycle ergometry for women, < 40 W for men) • Single organ disease • No tobacco in the last 6 months 	<ul style="list-style-type: none"> • Airways disease phenotype (i.e. severe obstruction but only mild emphysema) • Homogenous or basilar predominant emphysema • Insufficient obstruction ($FEV_1 > 45\%$ pred) • Insufficient air trapping ($RV < 150\%$) • Preserved apical perfusion on V/Q ($\geq 20\%$ perfusion to upper lung thirds) • FEV_1 and DLCO <u>both</u> $< 20\%$ predicted • Severe comorbid illness • Active smoking • $pCO_2 > 60$ • Pulmonary hypertension or systolic heart failure • Prior thoracic surgery
BLVR	<ul style="list-style-type: none"> • Severe, heterogenous emphysema • Severe obstruction ($FEV_1 \leq 45\%$ pred) • Hyperinflation ($TLC > 100\%$ pred) • Severe air trapping ($RV > 150\%$ pred) • Completed or enrolled in pulmonary rehab • MMRC ≥ 2 • BMI < 33 • Optimized on maximal inhaler therapy • 6MWD < 500m • Lack of collateral lobar ventilation 	<ul style="list-style-type: none"> • $FEV_1 < 15\%$ predicted • DLCO $< 20\%$ predicted • Homogenous emphysema • Presence of large bullae ($> 30\%$ hemithorax) • 6MWD < 100m or > 500m • Pulmonary HTN (PASP > 45mmHg) • Concerning nodule in target lobe • Hypercapnia (PACO₂ > 60 mmHg) • Systolic heart failure (LVEF $< 45\%$) or unstable arrhythmia, CAD • BMI > 35 • Active smoking • Daily prednisone > 20mg • Prior chest surgery (e.g. transplant, LVRS, lobectomy, sternotomy)

(Compiled from references 16 – 19)

Question 3c: What evaluation is necessary prior to consideration for lung volume reduction?

Patient selection: The main indication for lung volume reduction assessment referral is severe dyspnea despite aggressive treatment with bronchodilators, oxygen as necessary, and exercise (preferably pulmonary rehabilitation).

Testing should include:

- Full pulmonary function tests with plethysmography to evaluate lung volumes (gas dilution methods may significantly underestimate volumes)
- High-resolution chest CT without contrast to assess severity and distribution of emphysema as well as software analysis of emphysema and lobar integrity if BLVR is being considered
- Arterial blood gas to exclude significant hypercapnia
- Echocardiogram to exclude significant pulmonary hypertension or LV dysfunction
- Quantitative perfusion analysis by ventilation/perfusion nuclear scan or SPECT scan if surgical approaches are being considered.

Scenario:

On evaluation, Ms. H has an FEV₁ of 42% pred, TLC 110% pred, RV 145% predicted, and DLCO 32% pred. Her CT shows severe, relatively homogeneous emphysema. Her ABG on room air shows 7.32/65/54. Echocardiogram shows normal RV and LV size/function and an estimated pulmonary artery systolic pressure of 44 mmHg. You explain that she is not a candidate for either LVRS or BLVR due to homogeneous emphysema, insufficient air-trapping, and significant hypercapnia.

Question 4a: Would Ms. H benefit from nocturnal non-invasive positive pressure ventilation?

While robust data support the use of NIPPV (e.g. BiPAP or AVAPS) during acute exacerbations of COPD, the use of NIPPV in chronic stable COPD remains somewhat controversial. Studies evaluating nocturnal NIPPV have produced mixed results, probably due to significant differences in study design. Despite this conflicting data, more recent reviews of multiple trials suggest a benefit in mortality, risk of hospitalization, and dyspnea (20; 21); however, data is conflicting on whether this therapy improves the quality of life(22). A patient like Ms. H with stable COPD and documented hypercapnia might benefit from nocturnal NIPPV. As such, the ATS guideline on nocturnal NIV in stable hypercapnic COPD(23) suggests NIPPV after excluding OSA as the cause of sleep-related hypoxemia. In this patient with chronic retention, NIPPV should be discussed with her.

Question 4b: How would you obtain approval for NIPPV?

To qualify a stable COPD patient for home NIPPV, insurance criteria generally require that the patient have:

- Chronic hypercapnia ($pCO_2 \geq 52$)
- Nocturnal hypoxemia ($SpO_2 \leq 88\%$ for ≥ 5 min of nocturnal recording time on 2 L/min or patients baseline O₂ dose, whichever is higher)
- Documentation that sleep apnea (OSA or central sleep apnea) has been considered and ruled out (formal sleep study is not necessarily required, but documentation must indicate it is not clinically likely).

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Pre/Post-Test Questions:



1. A 56-year-old male presents to your office for ongoing management of severe COPD (FEV1 25%). He is on inhaled fluticasone-salmeterol at the maximum dose as well as tiotropium once daily and PRN albuterol. He is maintained on 2L NC continuous supplemental oxygen. He has had several COPD exacerbations in the last year and thus you are contemplating starting him on either chronic azithromycin therapy or roflumilast. Which of the following is a reported side effect of azithromycin but NOT roflumilast?
 - a. Visual changes
 - b. Hearing loss
 - c. Gastrointestinal upset
 - d. Weight loss

2. A 75-year-old female with severe COPD presents to your office for ongoing management. Her most recent PFTs reveal an FEV1 is 18% predicted, and her DLCO is 20% predicted. Her CT scan shows significant emphysema, most prominent at the apices. A VQ scan is pending. She has no other significant comorbidities but continues to have poor exercise tolerance despite pulmonary rehab. Additional testing includes a normal echocardiogram, and her last ABG was 7.37/58/90 on her baseline 2L NC. You are considering her candidacy for lung volume reduction surgery as she is not a transplant candidate due to her age. Which of the following would make her an unfavorable candidate for this procedure?
 - a. Significant exercise limitations/decreased exercise capacity
 - b. Apical predominance of her emphysema
 - c. Elevated baseline PCO2
 - d. Baseline oxygen requirement
 - e. Reduced FEV1 of 18% and reduced DLCO of 20%
 - f. None of the above. She is a good candidate for this procedure.

3. A 60-year-old male with COPD presents to your office for ongoing management. You are considering his candidacy for nocturnal non-invasive ventilatory (NIV) support via BiPAP. He has had a prior sleep study that excluded obstructive sleep apnea (OSA). His ABG on room air is 7.35/66/80. Which of the following is true regarding his ability to qualify for nocturnal NIV from an insurance standpoint?
 - a. He would likely currently qualify based on his documented hypercapnia alone
 - b. He would qualify if he also has documented nocturnal hypoxemia
 - c. He would not qualify because he does not have a co-existent OSA
 - d. None of the above

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