COPD: Inhaled Strategies in the Clinic

- Discuss the evidence describing the preferred treatment for symptomatic patients with COPD who have a low risk of exacerbations.
- Describe the evidence for the preferred treatment strategy for patients with GOLD grade D COPD.
- Explain the role of supplemental oxygen therapy in patients with COPD.

Guest Faculty Disclosure
Dr. Hansel has indicated that she has received gifts in kind from Austin Air and consulting fees from GlaxoSmithKline, and has performed contracted research for AstraZeneca and Boehringer Ingelheim Vetmedica GmbH.

Unlabeled/Unapproved Uses
Dr. Hansel has indicated there will be no references to unlabeled or unapproved uses of drugs or products in this presentation.
Medicine at the Johns Hopkins University School of Medicine, to talk about inhaled therapy strategies in patients with COPD.

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Learning objectives for this audio program include:

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- Describe the evidence for the preferred treatment strategy for patients with GOLD grade D COPD.
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Dr. Hansel, thank you for joining us today.

DR. NADIA HANSEL: Thank you for inviting me, it’s great to be here.

MR. BUSKER: Before we get started with our patient scenarios, the Global Initiative for Chronic Obstructive Lung Disease, which goes under the acronym GOLD, publishes guidance to help clinicians manage patients with COPD. Very briefly, please explain to us what the GOLD Guidelines are.

DR. HANSEL: The GOLD Guidelines classify patients into categories, A, B, C, or D based on their disease severity. These categories are determined by patients’ symptoms as well as their exacerbation history.

For example, patients who have minimal or low symptoms, as would be determined by either the CAT score, the COPD Assessment Test; or the mMRC, which is a dyspnea scale. So, an mMRC score of 0 or 1 or a CAT score less than 10 would be considered low symptoms. And if that patient also did not have moderate or severe exacerbations in the last year, or only one exacerbation that did not lead to a hospitalization, they will be categorized as GOLD grade A.

GOLD B patients have symptomatic COPD but no or only one history of exacerbation in the last year which does not lead to hospitalization.

GOLD grade C participants have low symptoms but have a history of at least two exacerbations or at least one exacerbation leading to a hospital admission.

A very symptomatic patient who has an mMRC score of at least 2, or a CAT score of at least 10, and have a history of at least two moderate or severe exacerbations, or one leading to a hospital admission, they would be classified as COPD grade D.

MR. BUSKER: The GOLD Guidelines were recently revised. What’s new in GOLD in 2018?

DR. HANSEL: The changes for the GOLD Guidelines 2018 are minor. The focus has transitioned from using spirometry to classify disease severity to more symptom and exacerbation risk-grading criteria.

MR. BUSKER: Thank you. Now let’s see how we can translate what we’ve just talked about, as well as the information you presented in your recent ePulmonology newsletter issue, into clinic practice. Dr. Hansel, please start us out with a patient scenario.

DR. HANSEL: The patient is a 70-year-old gentleman who has a 32-pack year smoking history. He has no other comorbidities and overall feels as if he is in good health. Recently, however, he complains that he can’t keep up with his golfing friends and that he feels that he needs to stop and catch his breath when walking on level ground. His doctor performs spirometry and he has a postbronchodilator FEV1 of 70% predicted, and his FEV1-to-FVC ratio is 60%. He’s wondering whether he should start regular inhaler therapy.

MR. BUSKER: Using the GOLD Guidelines, how would you classify this patient?

DR. HANSEL: This person would most likely fall into GOLD B grading severity. He has symptoms, such as dyspnea, where he feels as if he can’t catch his breath when walking on a level ground, but he does not report a history of frequent exacerbation. So, he falls into GOLD B COPD.
MR. BUSKER: For this patient would you consider regular inhaler therapy? What do the guidelines say?

DR. HANSEL: The current guidelines recommend that symptomatic COPD or GOLD group B with persistent symptoms is time to initiate a long-acting bronchodilator. This could either be treatment with a long acting beta agonist or a long acting muscarinic antagonist.

MR. BUSKER: Either a long-acting muscarinic agonist or a long-acting beta agonist — a LAMA or a LABA. What’s the benefit in choosing one over the other?

DR. HANSEL: That’s a great question. Current guidelines do not recommend one class of long-acting bronchodilator over another for initial relief of symptoms in this group of patients. The risk profile is quite similar whether you choose a LABA or a LAMA medication.

However, you could consider a few things in your choice of starting a LABA or a LAMA. For example, if the patient had a recent exacerbation, a New England Journal of Medicine study showed that tiotropium, or the LAMA, had a 17% reduction in exacerbation risk compared to LABA therapy. So, for patients with persistent breathlessness on monotherapy, using two bronchodilators is recommended. However, you always want to minimize risk, so if the addition of a second bronchodilator does not improve symptoms, we suggest stepping down treatment to a single bronchodilator.

MR. BUSKER: Treatment with a bronchodilator — would you expect that to change this patient’s prognosis? Or change his progressive lung function decline?

DR. HANSEL: That’s another great question. Several studies have tried to evaluate whether a bronchodilator can change the progression of lung function decline, and I can summarize them for you briefly.

The UPLIFT trial tested whether tiotropium, which is a LAMA, reduced lung function decline, but it did not reach statistical significance in reducing the rate of lung function loss. In post hoc analysis, however, it reduced the rate of post bronchodilator FEV\textsubscript{1} decline in a subgroup of patients with an FEV\textsubscript{1} between 50% and 70%.

Another study looking at tiotropium in GOLD stage 1 and 2 patients with COPD based on spirometry showed an association with a reduction in post- but not prebronchodilator FEV\textsubscript{1} decline. Similar studies of whether inhaled corticosteroid and LABA combination reduced FEV\textsubscript{1} decline show, perhaps, mild change in the trajectory.

For example, in the TORCH study, inhaled corticosteroid/LABA combination reduced the rate of FEV\textsubscript{1} decline by 16 cc per year vs placebo. And in the SUMMIT trial, once daily inhaled corticosteroid and LABA combination was associated with an 8 cc change in lung function decline. These results are suggestive, overall, but whether early intervention with a LABA or inhaled corticosteroid/LABA therapy alters the long-term course of COPD remains an open question.

MR. BUSKER: Adding an inhaled corticosteroid, an ICS, to a LABA or LAMA — what’s the current thinking on that?

DR. HANSEL: The role of inhaled corticosteroids in COPD has been a longstanding debate. Escalation of therapy to an ICS in addition to a LABA or LAMA or LABA/LAMA combination therapy, suggests that the triple therapy of an inhaled corticosteroid, LABA, and LAMA is more effective at preventing exacerbations than dual bronchodilator therapy alone, and this was seen in the TRIBUTE trial.

Interestingly, I would particularly consider inhaled corticosteroid therapy in a couple of patient categories. One example is patients with an asthma/COPD overlap syndrome, because it’s been shown in patients with asthma that LABA therapy alone may increase risk of asthma morbidity. Therefore, in patients you think may also have a concomitant diagnosis of asthma with COPD, I would strongly consider adding an inhaled corticosteroid regimen.

In addition, studies have suggested in post hoc analysis that inhaled corticosteroid therapy may be effective — or most effective — in patients with COPD who also have eosinophil levels greater than 2% or have a history of chronic bronchitis. So, in subgroups of patients with chronic bronchitis or elevated peripheral eosinophilia — and more important, in those with asthma/COPD overlap syndrome — I think added inhaled corticosteroid should be considered, even for GOLD stage B disease.

MR. BUSKER: Thank you. We’ll return with Dr. Nadia Hansel in just a moment.

MR. BOB BUSKER
This is Bob Busker, managing editor of ePulmonology Review. ePulmonology Review is a combination newsletter and podcast program delivered via email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to clinicians treating patients with pulmonary conditions.

In the month following each newsletter, a case-based podcast discussion, like the one you’re listening to now, is
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Thank you.

MR. BUSKER: Welcome back to this ePulmonology Review podcast. I'm Bob Busker, managing editor of the program.
We've been speaking with Dr. Nadia Hansel from the Johns Hopkins University School of Medicine about how the
inhaled strategies for COPD reviewed in her newsletter issue can translate into improved clinical practice. So, to
continue in that vein, please bring us another patient scenario.

DR. HANSEL: A 60-year-old woman with a diagnosis of COPD. She’s a former smoker with a 30-pack year smoking history.
She last saw a pulmonologist one year ago after being hospitalized for COPD exacerbation. She has no other
comorbidities, but her lung function shows severe obstruction, with an FEV₁ of 45% predicted and an FEV₁ to FVC ratio of
50%.

After hospital discharge one year ago, she was started on ICS and LABA combination therapy. After starting on regular
inhaled therapy, she reported improved quality of life and exercise tolerance; however, she continued to complain of daily
cough and phlegm production, and shortness of breath with exertion. Furthermore, she still had two exacerbations in the
last year which required ED visits. She would like to know whether there is anything that can be done to her medical
management to reduce her risk of future exacerbations.

MR. BUSKER: Changing her medications to reduce her risk of exacerbations — that's certainly a reasonable request.
How would you respond? What medicines would you choose?

DR. HANSEL: I think there are two options. There was the FLAME trial, which showed that a LABA/LAMA combination is
more effective at reducing exacerbations than an ICS/LABA combination. In addition, very recently publication of the
TRILOGY study showed that triple therapy with ICS, LABA, and added LAMA had a rate of moderate to severe
exacerbations 23% lower than that in patients treated with ICS/LABA combination alone.

MR. BUSKER: Explain the differences between LABA/LAMA therapy vs ICS plus LABA plus LAMA therapy.

DR. HANSEL: As I mentioned in the previous case, I would consider inhaled corticosteroids for specific subgroups like
those with asthma/COPD overlap syndrome. In addition, the TRIBUTE trial showed that triple therapy with ICS/LABA/LAMA
reduced the risk further of exacerbations by 15% compared to the LABA/LAMA therapy. There was also improvement in
lung function and quality of life, even though there was no change in the frequency of need for rescue medication or short-
acting beta agonist use.

There was also no significant difference in adverse events, including no increase in pneumonia risk or cardiovascular
events.

MR. BUSKER: Are there any specific factors that might predict how patients will respond to any of these medications
you've been discussing?

DR. HANSEL: The FLAME trial, which compared the LABA/LAMA combination to the inhaled corticosteroid/LABA
combination, found no difference in post hoc subgroup analysis. However, in the TRIBUTE trial studying whether triple
therapy with ICS/LABA/LAMA was better than LABA/LAMA therapy without inhaled corticosteroids, those who had either
chronic bronchitis or peripheral eosinophil levels greater than 2% showed an increased benefit from adding an inhaled
corticosteroid than those in the LABA/LAMA group alone.

MR. BUSKER: What alternative treatment choices might clinicians consider?

DR. HANSEL: Roflumilast and azithromycin have both been studied as add-on therapies. In patients with chronic bronchitis,
severe COPD, and an FEV₁ less than 50% predicted, roflumilast, a phosphodiesterase-4 inhibitor, may reduce risk of future
exacerbation. However, this combination has not been shown to be effective in patients without a history of chronic
bronchitis. When using this combination, it is important to monitor for weight loss, diarrhea, or mood disturbances.

Azithromycin has also been evaluated as additional therapy for treating patients with COPD who have a history of
exacerbations. It is most effective in patients who have quit smoking, and similarly to roflumilast, it is suggested to monitor
for side effects. Specifically, with azithromycin you should monitor hearing, as well as QTC prolongation by EKG.

Several studies have investigated the effects of biologics for treating COPD. In particular, recent studies have looked at the effect of anti-IL5 therapies for treating patients with COPD and eosinophilia. These results are encouraging and it is left to be seen whether biologics will be a therapeutic option for COPD in the future.

**MR. BUSKER:** This patient you presented, a 60-year-old woman with COPD and two exacerbations in the past year, what treatment was she given and how did she respond?

**DR. HANSEL:** After her last consultation she was started on triple therapy, an inhaled corticosteroid, LABA, and LAMA. She was very pleased with this change in her medical regimen and over the next year did not report any exacerbations. However, she still continues to complain of dyspnea on exertion or shortness of breath with activity.

Her physician performed an ambulatory oxygen saturation test in the office and noted a resting oxygen saturation of 92% on room air. With ambulation, her oxygen saturation decreased to 86% on room air, and she is wondering whether she should start supplemental oxygen therapy.

**MR. BUSKER:** That's an interesting question. In your opinion, is supplemental oxygen therapy likely to improve her life expectancy?

**DR. HANSEL:** Supplemental oxygen is definitely recommended for people with severe hypoxemia; that is, an oxygen saturation less than 88% or a PAO$_2$ of less than 55 mmHg at rest. However, in this patient, her oxygen saturation is 92% at rest and she only desaturates with exertion.

A recent study showed no mortality benefit with supplemental oxygen in those with resting oxygen saturations between 89% and 93% at rest, or in those who only have desaturation with exercise, as long as the oxygen levels remain greater than 80% on room air.

**MR. BUSKER:** Longevity aside, might she receive other benefits from supplemental oxygen therapy?

**DR. HANSEL:** That's a great question. As I mentioned, no mortality benefit was shown in the study. Interestingly, there was also no difference in all-cause or COPD-related hospitalization rates. There was also no change in quality of life, anxiety, depression, lung function, or distance walked in six minutes or other measures of functional status. Despite this largely negative study, the immediate effects of oxygen on symptoms or exercise performance were not assessed.

In addition, it is important to note that stable oxygen saturations at sea level does not exclude the possibility of hypoxemia during air travel. Therefore, if patients are planning a trip abroad or an airplane flight, they should consult their physician.

**MR. BUSKER:** What about other nonpharmacological approaches that might improve her outcomes?

**DR. HANSEL:** Pulmonary rehabilitation and exercise are definitely to be considered in patients that have severe COPD, and data from pulmonary rehabilitation studies have definitely shown that acute pulmonary rehabilitation programs can improve patients’ quality of life and exercise endurance.

It is also important to consider that patients receive adequate nutrition, particularly in patients with cachexia or emphysema. It is also very important to ensure that patients receive flu vaccination and appropriate pneumococcal vaccination.

Though our patient had already quit smoking, it is important to reassess smoking status in patients and continue to encourage smoking abstinence as smoking cessation has definitely been shown to be the most effective strategy to improve outcomes in patients with COPD.

In select patients, potential surgical interventions such as lung volume reduction surgery can be considered in some patients with severe emphysema.

**MR. BUSKER:** Thank you, Dr. Hansel, for today’s cases and discussion. Let me ask you one more question, and that’s about the future of therapeutic strategies in the treatment of COPD. What do you see as being needed to improve outcomes?

**DR. HANSEL:** The field of COPD should move toward personalized medicine, and we need to continue to do a better job at understanding which patients or groups of patients will respond better to specific therapy. Already we know that patients with chronic bronchitis, but not emphysema, are likely to respond to roflumilast treatment. Former smokers may be more likely than current smokers to respond to azithromycin therapy. And patients with peripheral eosinophilia may or may not respond better to inhaled corticosteroid therapy and may respond to biologics such as mepolizumab.

However, together we need to continue to make advances in the strategies for the treatment of COPD and better delineate which patients may respond better to a particular therapy.
MR. BUSKER: Thank you for sharing your thoughts. Let’s wrap things up now by reviewing today’s discussion in light of our learning objectives. To begin: the evidence describing the preferred treatment for symptomatic patients with COPD who have a low risk of exacerbations.

DR. HANSEL: We were reviewing the GOLD Guideline recommendations from 2018, which divide patients into four grades of COPD severity, A, B, C, or D, based on their symptomatology as well as their exacerbation risk. Patients who do not have frequent exacerbations or who report zero or one exacerbation that did not lead to a hospital admission, could be categorized into GOLD A or B; A would be those that have few symptoms, and GOLD B would be those with more symptoms or an mMRC of at least 2, or a CAT score of at least 10.

In this category of GOLD B COPD, current guidelines recommend treatment with a long acting bronchodilator, a LABA or LAMA therapy, or in those with more persistent symptoms, combination therapy with a LAMA and LABA.

MR. BUSKER: And our second learning objective: evidence for the preferred treatment strategy for patients with GOLD grade D COPD.

DR. HANSEL: Patients who have frequent exacerbations, or two or more exacerbations or at least one that’s led to a hospital admission in the last year, fall under GOLD grade C or D, with the GOLD C patients having fewer symptoms and the GOLD D patients having a history of exacerbation and more symptoms. Again, an mMRC of at least 2 or CAT score of at least 10.

For patients in group D, three recent trials help guide our therapy and informed the GOLD criteria. The FLAME trial showed that a LABA/LAMA or dual bronchodilator therapy is better than ICS/LABA therapy at reducing exacerbation risk. Similarly, the TRILOGY study showed that triple therapy including ICS and LAMA plus LABA is better than the ICS/LABA alone at reducing exacerbation risk. More recently, the TRIBUTE trial showed that the ICS/LABA/LAMA triple combination therapy was better than the LABA/LAMA dual therapy at reducing exacerbation risk. So, in the most severe cases, triple therapy with ICS/LABA/LAMA may be the treatment of choice.

MR. BUSKER: Finally: the role of supplemental oxygen therapy in patients with COPD.

DR. HANSEL: In patients with COPD we have to think of the best therapeutic medication strategy, but we also need to think about nonpharmacologic approaches treating patients with COPD. We talked about pulmonary rehabilitation and vaccination and appropriate nutrition, but also the role of supplemental oxygen therapy in patients with hypoxemia is important to consider.

As mentioned, it is well established that in patients with severe hypoxemia or resting oxygen saturation < 88%, that supplemental oxygen is indicated. A recent study, however, shows that supplemental oxygen therapy in patients with mild or moderate hypoxemia such as resting saturations of 89% to 93% on room air, or desaturation only with exercise but maintaining above 80%, supplemental oxygen showed no clear medical benefit compared to those not receiving supplemental oxygen therapy.

MR. BUSKER: Dr. Nadia Hansel from the Johns Hopkins University School of Medicine, thank you for participating in this ePulmonology Review podcast.

DR. HANSEL: You are very welcome, it was a great pleasure to be here with you today.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.epulmonologyreview.org

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