

[MUSIC PLAYING]

**FRANK
SCIURBA:**

Good evening. I'm Frank Scieurba. I'm a professor of medicine in the Department of Medicine. Today, I'm going to be talking about management of COPD with a primary focus in the outpatient setting. I'd like to thank Dr. Gladwin and the sponsors for the invitation, and hopefully this is useful to you in optimizing your care of our patients with COPD. Thank you.

These are my disclosures. We're going to first talk about the impact of COPD on the health care system and making the diagnosis of COPD, and then I'm going to talk about guideline-based therapy, as well as some of the evolving precision therapies moving forward in COPD.

This is the current definition of COPD, and it gives us some insight really into the more recent trends in thinking about COPD. COPD is a common disease. We need to think of it in terms of it being preventable, of course, but it's also not an irreversible disease, as we described it in the past.

It is not completely reversible, but we need to keep the perspective that it is treatable. It results in persistent respiratory symptoms, as opposed to asthma, which often can be completely reversed with regards to symptoms.

And it involves airflow limitation due to either airway or alveolar parenchymal abnormalities generally caused by exposure to noxious particles or gases in this country greater than 80% due to tobacco smoke. However, in the third world, exposure to indoor cooking in nonventilated homes is a very common cause of COPD.

COPD is more of a syndrome than a specific disease. It's an umbrella term for progressive diseases, including emphysema, parenchymal involvement, chronic bronchitis, more airway-dominant involvement with or without emphysema. Refractory nonreversible asthma can evolve into COPD, and there's an asthma COPD overlap syndrome, which is likely a single entity that involves characteristics of both classic diseases, and then other forms of airway involvement, including bronchiectasis and bronchiolitis.

The most common symptoms of COPD, as most of you know, is dyspnea initially on exertion and evolving to dyspnea at rest, chronic cough, and sputum production, which can occur with or without dyspnea.

COPD 10 years ago was the third leading cause of death in this country, then the epidemic of opioid use resulting in a higher prevalence of traumatic deaths made it the fourth cause. And now in the past year, due to the pandemic, is the fifth cause.

And all this has occurred without the prevalence of COPD, unfortunately, going down, and the number of individuals in this country affected is over 13 million. It now affects women more than men, despite the stereotype of COPD.

Worldwide, it's the fourth leading cause of death, and the prevalence involves about 11% of people in this world. And as we said, in the third world and in many other parts where, actually, tobacco smoking is increasing, the most common cause is still often indoor exposures.

The burden of COPD is not just the classic definition of airflow obstruction, and these different domains of COPD often are the targets of treatment. Lung function decline, symptoms often independent of the degree of lung function impairment.

Some individuals burdened by excessive cough and sputum despite relatively preserved lung function, evolving into activity impairment. Often individuals with exacerbations and flare-ups that can be disproportionate to the level of objective lung function impairment. Quality of life, again, often separate from lung function impairment. And then, of course, mortality, and just the burden of the costs on the health care system into the individual.

COPD is of great attention to the payer system because it is one of the most common causes of hospital readmission and a target of the Medicare readmission program. Approximately 23% of patients with COPD admissions result in readmissions, and that's third only to heart failure and psychiatric disorders.

In order to diagnose COPD, we must get spirometry to objectively define COPD. Many patients admitted to the hospital, if you do an EMR search, have not ever had spirometry. And so we really, while they may have an admitting diagnosis, there is some uncertainty.

And often we find other lung diseases, including interstitial fibrosis and other chronic diseases that are treated as though they have COPD because it is the most common and have not objectively been defined by spirometry. Anybody who has symptoms, cough, shortness of breath, sputum, and risk factors of any kind should get spirometry to objectively define the disease. The disease is defined by, generally, post-bronchodilator spirometry with an FEV1/FVC ratio of less than 0.7, meaning less than 70% of their air on a forced expiration comes out in that first second.

Early diagnosis can motivate smoking cessation and also define individuals who may not actually have admitted that they have symptoms, often because they're still smoking. And as you can see, these are the results of the Lung Health Study. If we can get individuals to quit smoking early on, they have less decline in their lung function and, ultimately, better survival, so early diagnosis is an important aspect of this disease.

The severity of disease had traditionally been defined by the severity of objective decline in FEV1 in lung function impairment. While spirometry is really essential to define the disease by the presence of a low ratio, determining severity lung function is only one component.

Other aspects, including shortness of breath symptoms, as we discussed, inactivity, quality of life, exercise impairment. Frequency of exacerbations may indicate severity to some degree independent of FEV1, and as I'll show you in the gold classifications that comes into play as we define the classification of the disease.

Interestingly, COPD is more complex than just lung function impairment. It's a systemic disease that actually is associated with comorbidities disproportionate to just the level of tobacco smoking. If an individual has COPD, they're much more likely to have osteoporosis, anxiety, depression.

Lung cancer is more common if you have COPD in a smoker than an individual with equivalent tobacco exposure. Here's a list of diseases that are disproportionately associated with COPD, and these conditions can make it very difficult in defining what's causing an exacerbation or in treating a person both in the outpatient and following exacerbations in the inpatient setting.

The level of impairment in COPD, again, goes just beyond lung function impairment. The level of deconditioning due to withdrawal from activity can create what we call the inactivity dyspnea spiral. Individuals have a sense of shortness of breath, they begin to withdraw from activity, they get more symptoms and shortness of breath, they withdraw further from activity. And this is a representation of why exercise training, pulmonary rehab and conditioning really is a very important component of treating this disease.

This is the GOLD class A, B, C, D classification, which, as you can see-- lung function, while it defines the presence of the disease, in this classification, doesn't categorize the class or severity of the disease. This, on the horizontal scale, shows a symptom scale, either the mMRC or the CAT, which are two patient-related outcome scales. And then, on the y-axis, is the frequency of exacerbation.

So patients in level A may have objective obstruction, but are not symptomatic and don't have exacerbations. Whereas those GOLD class D are both very symptomatic and have greater than two outpatient-- greater than or equal to two outpatient or one admission related to an exacerbation for COPD. And these classifications, due to some extent, begin to define the level of therapy that we give to our patients.

This shows the discrepancy between GOLD obstruction, class GOLD 4 being severe obstruction and GOLD 2. Many patients in GOLD 4 do not have exacerbations, whereas still 20% of patients in just GOLD 2 will still have exacerbation. So while there's an association, they can be very separate.

This slide shows the greatest predictor of an exacerbation is a prior exacerbation. You can see individuals who've not had an exacerbation in the prior year have less than 25% chance of having an exacerbation in the next year. Whereas if you have two or more exacerbations, you have greater than a 75% chance of having an exacerbation in the following year, or one admission to the hospital.

Treatment of COPD will first start with more guideline-based therapy. The goals are to reduce symptoms, improve activity, reduce exacerbations, and quality of life. Less certain, although there's strong trends in the data that we can slow the decline in lung function over time, and also a strong trend in optimal guideline-based therapy to reduce mortality, but these are less definite proven goals of therapy.

We always start, of course, with the nonpharmacologic interventions. I'm not going to give a lecture on smoking cessation today, but obviously in patients who continue to smoke that, is a fundamental goal of treatment. Influenza vaccination every year, pneumococcal vaccination. These folks are mechanically immune compromised and predisposed to infections.

I, generally, particularly in those over 65, will give both PCV-13 and Pneumovax vaccinations. Avoidance of indoor and occupational pollution and exposures. And we can't iterate this point enough, encouraging physical activity, really, to optimize their quality of life and level of activity.

The specific chemical classes used to treat COPD, in general, have not changed in the last 25 years. However, the drugs have gotten longer acting and more potent, and, in fact, they have meaningful effects on clinically important outcomes in these patients compared to the shorter acting bronchodilators that we had 15 to 20 years ago.

You're being inundated, I'm sure, and the direct-to-consumer commercials are showing many, many different chemicals and products. In general, the long-acting muscarinic antagonist, the anticholinergics, and the long-acting beta-agonists. There's not huge differences. Often, we are obligated by their payers as to which they use. An individual, and we'll show you information, may, however, respond better to one than the other, or the device that is used to administer the drug can differ based on the individual.

The third class of drugs that is guideline-based is inhaled corticosteroids, and we'll give you some information on the use of those. There are adverse effects associated with it, but the right patient can benefit from inhaled steroids, and we'll discuss that.

In addition to those three drugs, inhaled corticosteroids, LAMAs, and LABAs, the only new class of drug that has been approved for COPD in the last 10 years are PDE-4 inhibitors, roflumilast, and they have a limited role that we'll discuss.

We wrote a review article on the outpatient management of COPD, and I'll use some of the tables in that to discuss our thoughts on the guideline-based treatment. You can see in this slide that short-acting bronchodilators have not been proven at all to improve quality of life or decrease exacerbation rate. They do result in a short-term improvement in lung function.

And certainly your patients do get short-term improvement in symptoms, but in order to optimally treat this disease, we really need to go to longer acting agents. Those agents, the long-acting muscarinic antagonists and beta-agonists, have been shown to improve quality of life and decrease exacerbation risk.

Here, we show anti-muscarinic agents and their impact on lung function, quality of life-- which is the St. George Respiratory Questionnaire used-- and exacerbation. Long-acting beta-agonists, actually, somewhat less effective than single agent muscarinic antagonists.

But really, in any patient with COPD-- as I'll mention-- the use of both a LAMA/LABA dual agent is better than the LABA alone or the LAMA alone, and really recommended in any patient with symptoms and diagnosed obstructive lung disease.

So you say, well, is one better than the other? There's now four, five drugs in each of these classes. And what's interesting, this is a crossover trial looking at two of the most common combined LAMA/LABA agents. This is vilanterol, umeclidinium. And this is olodaterol/tiotropium. This is the Stiolto and the Anoro product. And you can see, this is the difference between treatment being 0, and this is within the error of measurement.

You can see that, actually, using both the device and the chemicals alone, a greater proportion of patients seem to have a meaningful response to the umeclidinium product. However, there's a significant number of individuals that actually responded better to the olodaterol/triotropium.

And my-- reading of this, this may be device related, it may be individual responsiveness to the chemicals. But having both available and having a multipharmacy available, I think, allows us to give the most effective treatment to an individual patient, and to try different products because there are individual differences that can be meaningful.

The use of inhaled corticosteroids is a little bit more nuanced these days than just giving Advair to everybody. And looking at it in triple therapy versus the LAMA/LABA alone, across the board, there is a reduction in exacerbation rate, improvement in quality of life.

But, really, one of the first use of precision therapy I'll show you is that this is not all individuals, and some individuals may be more responsive than others. And we'll talk in more detail about the use of inhaled corticosteroids.

As far as other medications, inpatients who, despite triple therapy, continue to exacerbate, there are currently two options that are used. One, there's the PDE-4 inhibitors that can result in about a 20% further reduction in exacerbation rate. And, in some patients, regular use of azithromycin has been shown to decrease exacerbation in the properly selected patient.

So one of the biomarkers that you have available in your laboratory EMR database is the peripheral blood, absolute eosinophil count just from the CBC. And the panel on the left shows basically, analysis of multiple clinical trials looking at the ICS budesonide LABA formoterol combination versus formoterol alone in the reduction.

So the reduction, based on the eosinophil level with increasing eosinophils, you can see that that reduction in the higher level of eosinophils is significant. Where those that get the ICS LABA have a lower exacerbation rate, whereas those with 100 or less eosinophils, there's very little difference in the treatment of adding the ICS to just the LABA alone.

Another trial, the impact trial, showed individuals with greater than 150 eosinophils had significant separation in reduction in exacerbation in either of the ICS-containing regimens versus just the bronchodilator regimen alone. Whereas those with lower eosinophil count showed really relatively little added benefit of the inhaled corticosteroid versus the LAMA/LABA alone.

And so using eosinophils and we give a cut off, if you have 100 or less, you're actually not likely to benefit from the addition of inhaled corticosteroids. And you might say, well, there's not really a lot of adverse events associated with ICS, why should I try and discriminate that?

Well, the fact is that here's the impact trial looking at a triple therapy including inhaled corticosteroid, a double therapy with the inhaled corticosteroid, and a single bronchodilator. And you can see, 8% and 7% of those patients had pneumonia versus just the dual bronchodilator.

And that's consistent in multiple clinical trials, that adding an ICS to the regimen increases the frequency of pneumonia by about 2%. So there is a price to pay, and we'd like to give the ICS to those individuals who are likely to benefit from it.

This is a flowchart. This really summarizes what we've already discussed. And I'm not going to go over each part of it, but in our JAMA review article, you can get a perspective of this in the context of all that we've discussed, and that reference is in your handout.

So we talked about the chemicals, how about the devices? There's dry powder inhalers, soft mist inhalers, metered dose inhalers. Do they make a difference? And the fact is that compliance, error rate, individual characteristics can lead to using one versus the other.

And, independent of the chemicals, if you're not getting the drug into the lungs, it's not going to do a whole lot of good. The error rate with metered dose inhalers, the requirement of timing, the hand coordination results in an error rate that's been shown to be over 80%. Whereas dry powder inhalers, which are activated by the inspiration, has a lower rate.

On the other hand, you need, given inspiratory flow rate, you have to have good enough lung function to adequately deliver that inspiratory flow to pop the packets in these dry powder inhalers. And some individuals are too frail and not able to coordinate or generate that.

And those individuals should be considered to benefit more from the soft mist inhaler, which is the olodaterol/tiotropium or even MDIs. Or nebulizer therapy, which I use in some of my most advanced patients, which requires very little coordination. And there are now long-acting inhalers in all three classes available by nebulizer.

We use a little device in clinic that can measure inspiratory flow rate, it's called an in check. And individuals who have a flow rate less than 60, and particularly less than 40, we're not going to give a dry powder inhaler to. And those folks we'll give either an MDI, soft mist, or put them on nebulizer therapy. We have found individuals who've really stated that their inhaler is not doing anything, and we switch them to a device requiring less inspiratory flow, and they do well.

Adherence is really important. There are studies showing that individuals who do not adhere to their regimen are - and this is not rocket science, but if they're not complying and they're not adhering, their negative outcomes are going to be higher. Hospitalizations and exacerbation rate is higher in those with poor adherence.

And so this was a little editorial that we wrote that really advocates for a multipharmacy to allow us to give the most appropriate inhaler based on both chemical and device to have a selection for the given patient who's in front of you.

It's shocking when you look at discharge planning and what patients get. And some of this, it's confused, again, between what they were using in the outpatient setting, what they were using in the inpatient setting. But only 45% of patients were prescribed maintenance bronchodilator therapy, despite the strong evidence in the guideline in reducing exacerbations and improving quality of life.

Nonpharmacologic treatments of COPD. Again, pulmonary rehab, I can't emphasize enough, really is critical. In the pandemic era, bringing them in on-site can be more difficult. We've actually been able to go to more remote pulmonary rehab, or encouragement, really, of activity at home is really critical.

Multiple studies have shown that, ultimately, the impact on quality of life and symptoms with the pulmonary rehabilitation is significantly greater than what bronchodilators can offer and even oxygen therapy in individuals. Despite this, fewer than 5% of patients are prescribed pulmonary rehab who are candidates for it.

There has been multiple Cochrane reviews on quality of life. Hospital readmissions, exercise tolerance that have shown unequivocal benefit of pulmonary rehab. The last Cochrane review said we're not going to do any more of these because pulmonary rehab works and we should use it.

An interesting database review of the Medicare database in individuals prescribed pulmonary rehab after discharge versus those that were not showed a significant difference in 90-day mortality. This was using a propensity matching analysis. So while not randomized data, there's even a suggestion of potential survival benefit.

Why doesn't everybody get pulmonary rehab? Well, health system resources if everybody was referred are actually not adequate to provide it to everybody. Travel distance and transportation can be a problem. Patient's perception that they get short of breath and suffer when they walk can often impair or impede them getting involved.

And education of physicians, to you right now as well as patients, letting them know the benefits and pushing through that discomfort will make the rest of their day go better and can significantly reduce their symptom burden.

We're not going to talk a lot about supplemental oxygen use, but we generally customize their delivery to prescription at rest with exertion and often do a nocturnal pulse oximetry to optimize delivery throughout the day.

We're not going to talk about non-invasive ventilation, but your patients who are hypercapnic with PCO₂s greater than 50, there's significant European data showing decreased hospitalization rate and prolonged survival. Although, generally, referral to pulmonary to go through the administrative gauntlet to get NIV for our patients really is necessary because it's not easy to get.

How about treatment of exacerbation in the outpatient setting? The latest discussion on that was based on this reduced trial, which showed that there was noninferiority of a five-day regimen of 40 milligrams a day compared to a more prolonged course with a taper.

And, really, in individuals who have infrequent exacerbations, this is generally what we do. We give a five-day course of 40 milligrams rather than your two-week prolonged taper. Patients with recurrent exacerbations and difficulties, this doesn't really work that well, but in your patients with less frequent exacerbation, that's our general approach.

The factors that influence readmission, the number of comorbidities and the socioeconomic status. Individuals with a Medicaid product versus private insurance are more likely to be readmitted often having less social support at home. And individuals with increasing number of exacerbations, as we discussed in the past, are often readmitted.

What's very interesting is that the cause of readmissions for COPD is most commonly not a recurrent COPD exacerbation, but other issues, such as congestive heart failure due to volume overload, hypoglycemia from the steroids, frailty, and falls, pulmonary emboli, those issues because of the frequency of comorbidities in these patients.

To prevent hospital readmissions, we really encourage a phone call within a day or two of discharge. And now that we have telemedicine, that's acceptable within that week following discharge to interact with your patient either on-site or by telemedicine.

And then, for your more difficult patients, consider referral to pulmonary for some of our more advanced options and to consider other alternatives. Patients with multiple hospitalizations, very high baseline symptoms disproportionate to their lung function, and patients who are younger, consider referral to pulmonary.

The impact of COVID and the pandemic on our patients goes beyond getting infected with COVID. We all know, I mean, these patients are coming in later, often there's less access. During their exacerbations, they stay home. They're reluctant to come in. And in the long run, by really having diminished care, they developed flare-ups or deterioration in their chronic condition. Also, these patients are much more susceptible to the psychiatric, and mental anxiety, and depression issues that is common to all of us in our dealing with this.

Treatments beyond guideline-based therapy are evolving. Precision treatment are in a state of evolution, but we hope in the next 10 years that we will be able to have precise therapies for individuals. This is the traditional way of looking at treatment option where you see a mean change in the population.

But if we look more precisely in a precision approach, we may see those are the same exact dots. Some patients actually deteriorated with the treatment. The red dots had significant improvement, the yellow may not be cost-effective, and many of the white dots had no benefits. So we want to find those red dots in our patients.

Use of supplemental oxygen, frequent exacerbations, therapies for that are the beginnings of developing precision therapy, but we'd really like to get beyond that looking at specific clinical attributes and maybe biomarkers that can guide us into precision therapy.

This is the results of the roflumilast trial, where there's greater than 20% reduction in exacerbation rate in the subgroup of patients who have chronic bronchitis and low FEV1. In azithromycin, again, in patients who are on guideline-based therapy who continue to exacerbate, what we're finding is-- if you're a former smoker, you can have a significant benefit by having either daily 250 or three times a week 500 milligrams of azithromycin, whereas smokers do not benefit from this therapy.

We'd like to look at unique biologic attributes and biomarkers to guide therapy in the future. A proportion of patients actually have the TH2 inflammatory response that we classically see in asthma, and there's other therapies that are evolving toward TH1 treatment.

We talked about eosinophils. About 40% of patients with COPD will have elevated eosinophils that can be a potential target for TH2 therapy. The one clinical trial, IL-5 modulation-- in these patients, there were sister studies that showed a 20% reduction in exacerbation rate.

While overall the FDA did not feel this was sufficient to approve the drug, in fact, if you looked at subgroups of patients with increasing eosinophil, the improvement is-- or the reduction in exacerbations is even better with up to 36% reduction in individuals who had a historical eosinophilic count of greater than 300.

Device therapy in COPD is really evolving. And surgical volume reduction was our first approach where individuals who had asymmetric emphysema and had surgical resection of that emphysema allowed the compressed, better quality lung to re-inflate into the chest. These have been shown to decrease mortality rate and declines in lung function, particularly in those patients with asymmetric upper-lobe dominant disease.

Because the surgical complications are not insignificant, we've attempted to find alternative bronchoscopic, less invasive approaches to do the same thing and reduce and eliminate the more affected emphysema in this area allowing the less involved areas to expand into the chest.

And in the past couple of years, endobronchial valves placed into the most effective regions of the lung-- there's two types of valves, the pulmonics and the spiration valves. These are now FDA approved. And other technologies, either still in clinical trials or had insufficient effect in clinical trials, are also being evaluated.

One aspect that we learned about using endobronchial valves is that these fissures that separate the upper- from the lower-lobe, if they're not complete-- which had previously been an anatomic curiosity-- by putting the valves in a lobe, we cannot get that lobe to collapse and cannot get the volume-reducing benefit of volume reduction surgery.

So we look at both radiographically and we do a physiologic test in the bronchoscopy suite to confirm that there's complete fissures. The valves are then placed in patients to collapse a lobe, and the patients have significant improvement in lung function and exercise tolerance.

This shows our first discovery that, when the fissures are complete, we can get on average nearly a litre reduction in volume in that lobe with expansion of the ipsilateral lobe, less so in patients who do not have complete fissures.

And this was the pivotal trial that the FDA used to approve endobronchial valves in the treatment of COPD with approximately 50% of patients having clinically important improvement in FEV1. You can see an improvement, a drop in the SGRQ as an improvement in quality of life that's nearly three times the clinically important difference, and then improvement in 6-minute walk relative to the normal deterioration over time in these individuals. So clearly, in the properly selected individual, they can get a significant improvement.

Other biologic therapies are in evolution. The TH2 IL-5, IL-4/13 modulators used in asthma or in ongoing clinical trials. Other more innate immunity or TH1-type responses are also being studied to look at impact on exacerbation rate in cough and mucus symptoms.

Other bronchoscopic trials targeted lung denervation, in which we do RFA ablation of the vagus nerve or bronchial rheoplasty where an electrical signal reduces goblet cells in the epithelium are currently in clinical trials.

This is the targeted lung denervation where we put a cooled catheter that creates a heat signal outside on the exterior surface of the airway where the vagus nerve runs and can decrease exacerbation rates.

This is the randomized trial in the European data showing significant reductions in exacerbations in individuals following targeted lung denervation. We're currently doing the pivotal trial of this in Pittsburgh, if you have patients for referrals.

So in conclusion, the COPD burden includes mortality, exacerbations, hospitalizations, and readmissions, as well as symptoms, and costs, not just improvement in lung function. Existing and emerging treatments are increasingly effective in altering the burden of COPD.

Attention to maintain inhaler device selection and adherence is as important as the specific drug. And precision therapy is emerging, ranging from biologics targeting specific molecular pathways and devices targeting specific physiologic attributes. So I thank you for your attention and look forward to any questions you may have. Thank you.