CRAIG RILEY: Hi. I'm Craig Riley. I'm one of the pulmonologists at UPMC. And I have a subspecialty interest in the care of COPD patients.

NICK DEGREGORIO: And my name is Nick DeGregorio. I'm an internal medicine physician and currently serve as the senior medical director for UPMC For You, which is a Medicaid line of business within UPMC Health Plan, which is part of the greater UPMC Insurance Services Division, currently serving over 3 and 1/2 million members.

CRAIG RILEY: And we're going to be discussing a three-part podcast on best practices for the management of patients with COPD. So this is section three of our three-part series on best practices for COPD. The topic of this section is on intensifying treatment for poorly controlled COPD.

NICK DEGREGORIO: The objectives of section three are to assess changes and treatment for patients with exacerbations or suboptimally controlled symptoms despite initial maintenance therapy and to identify patients who may benefit from subspecialty pulmonary referral.

So first, we want to talk about identifying patients with poorly controlled disease. Poor disease control describes ongoing acute exacerbations or significant symptom burden despite an existing optimal treatment plan. So looking at exacerbation criteria, we would consider that for any hospitalization defined as in a severe exacerbation or more than one outpatient prescription for systemic steroids and/or antibiotic therapy, defined as a moderate exacerbation.

Under symptom criteria, again, we would look at the modified Medical Research Council score of greater than 2 or a CAT score of greater than or equal to 10. And it's reasonable to use respiratory symptoms attributable to COPD that prevent the patient from doing any desired activity they could previously do as more patient-centered criteria.

So again, important to get that detailed history to see if there were things they were previously doing that they stopped doing because of being short of breath. So once again, assessing disease control should be part of any visit in which COPD is addressed.

CRAIG RILEY: So Nick, like you mentioned, we really want to identify patients who have been on optimal regimens already, where it's not getting them where they need to go. And one of the first things to consider, especially if your patient was started on a dual long-acting bronchodilator regimen, as we recommended in section one of the series, is whether or not it would be appropriate to step them up to an inhaled corticosteroid-containing regimen.

Now, in basically no situation does it make sense to get rid of one of those two long-acting bronchodilators so this might include stepping them up to a third separate inhaler or switching them over entirely to LAMA-LABA ICS containing three-in-one inhaler.

The patients who generally benefit from inhaled corticosteroids are those who have some evidence of airway inflammation. That's what inhaled corticosteroids are treating. And that's often evidenced by patients who have a chronic cough, sputum production.

On CT scan imaging, they might have thickened airways, and these patients often have exacerbations, particularly severe exacerbations requiring hospitalization. And those patients' biomarker for inhaled corticosteroid responsiveness are blood eosinophil levels, which we've started to incorporate into our practice.

Almost all patients are going to have a complete blood count with a differentiable at some point in the past year. So taking a look at that, when they're not on systemic steroids which affect that differential, and looking for patients who have more than 150 or 300 cells per microliter.

Again, blood eosinophils are what we're talking about here, which is generally 2% or 3% of the differential. Those are patients who might really benefit from the addition of inhaled corticosteroids. Patients who have very low blood eosinophil levels, less than 100 cells per microliter or less than 1% of their differential, are patients who actually might have harm from inhaled corticosteroids.

If you think about it, if we're trying to treat eosinophilic airway inflammation, and your patient doesn't have that, adding an anti-inflammatory therapy will raise the risk of them having a bacterial pneumonia without improving their symptom control or their exacerbation risk.

And this is something that I think is ready for prime time. This is described in the GOLD Guidelines and is increasingly incorporated into other guidelines for COPD management. Of course, if you're going to use any inhaled medication, you want to, again, make sure that the medication is getting where it needs to go. None of these medications, bronchodilators or inhaled corticosteroids, are very effective if they're in the patient's mouth or breathed back out into the room.

As we mentioned previously, optimal adherence requires that for any prescribed medication, the patient can get it from the pharmacy. They can get the device ready to use. They can remember to use it daily, twice daily, whatever the schedule is, and they have to be able to use the medication properly for it to get to their lower airways.

Studies suggest that patients' actual adherence rates, which are defined as them using and using properly the device at least 80% of the time, are pretty dismal, as low as 6% in one trial. And lower adherence rates, as you mentioned before, are associated with increased hospitalizations and worse outcomes, including death.

NICK DEGREGORIO: So guidelines suggest that we assess the use of inhalers for members with COPD at every visit. And there may be differences among patients in their preference for different inhalers or in which ones may be more effective. So what are your recommendations in evaluating inhalers for individual patients?

CRAIG RILEY: There's been some attention paid to this. Dry powder inhalers are typically very simple devices. The patient doesn't have to prime or assemble the device in the first place, at least for multi-use dry powder inhalers. They just have to open it, blow their air out, suck in strong and forcefully to desegregate the medication and get it to their airways, and hold their breath long enough for the medicine to stick there.

And in some cases, that could theoretically lead to better adherence. Once daily versus twice daily regimens. Once daily are probably easier for patients to use, but nobody has really convincingly shown that this improves adherence rates.

So ultimately, what I pay attention to is whether the patient feels like they're able to use their device properly and then objectively assessing whether or not that's the case. Patients who like their devices and who are able to use them generally adhere to it better than people who find their devices to be bothersome or difficult to assemble and use.

One thing that's also gotten a lot of attention is assessment of inspiratory flow rates. So dry powder inhalers require patients to forcefully inhale to get that medication to their lungs, whereas other devices like pressurized metered dose inhalers or Soft Mist Respimat inhalers have either a propellant or a spring action that pushes the medication out into a fine aerosolized mix that the patient can then slowly and deeply inhale to their lungs.

Some patients have trouble within inspiratory flow rates being adequate for use of dry powder inhalers, but in our practice, this has turned out to be a relatively small percentage of people. What's probably a bigger problem, a bigger issue, is that patients often don't know how they're supposed to inhale to ideally get medication to their lower respiratory tract.

And a relatively simple, inexpensive device called the In-Check DIAL is used in my practice, both through UPMC and through the Veterans Affairs Administration, not just to determine whether patients are going to have trouble with adequate inspiratory flow rates regardless of their effort, but to tweak their effort and train them to inspire the proper way to get the full benefit from these medications. Although, right now I don't believe that devices like this are being used commonly in most primary care practices.

I think that if you have an identified point person, a champion for inhaler training within your practice, this might be something to invest in, because it is a very easy teachable technique that can measure how the patient does and allow that person to correct their technique in real time. And really, it takes seconds to use a device like this.

One other way that we can help patients to adhere to their devices is to have options to switch between different device types within a single therapeutic class. So one of the nice benefits of having a redundant formulary is that some patients, regardless of inspiratory flow issues, they just don't respond as well to one type of inhaler. And as a result, they may not be as adherent to it. So having multiple options and the ability to switch can make a big difference for some patients, for reasons that we still don't fully understand.

NICK DEGREGORIO: So for metered dose inhalers, the use of spacers can decrease oropharyngeal deposition and better ensure that the medication is getting down into the lower respiratory airways so they can increase both the efficacy and decrease side effects of the inhalers as well.

Generally, spacers should be considered for all patients who are prescribed metered dose inhaler devices. In terms of insurance coverage, there is usually no issue for commercial insurance products or for Medicaid insurance products, but because of a CMS regulatory issue, these are generally not covered for Medicare patients, although they can be purchased relatively inexpensively.

So that's something certainly to consider in Medicare patients who might benefit from the use of a spacer. So Craig, in terms of using nebulizer therapy instead of spacers, what patients might benefit or for whom might nebulizers be indicated?

CRAIG RILEY: So we talked a little bit about the use of nebulized medications for inpatients in the setting of acute exacerbations. But it seems like a lot of patients use nebulizers outside of the hospital. And while this might make sense in the setting of a COPD action plan for outpatient management of exacerbations, a lot of patients have confusion about how they're supposed to be using nebulized therapy.

In my opinion, nebulized medications are probably best used long term for patients who either, despite repeated training, have trouble using their inhaled devices properly or patients who can just never, even under the best of circumstances, hold their breath for five seconds or for some patients, who for cognitive or behavioral reasons or due to neuromuscular disease, just have a lot of difficulty in using inhaler products.

In those patients, what I'm talking about is really not using albuterol and ipratropium long term but using long-acting nebulized medications which have recently become available across classes. And these are things like LABAs like arformoterol, LAMAs like glycopyrrolate and revefenasin.

And these medications are much easier for somebody to use than short-acting medicines which wear off between doses and really do not last long enough to allow patients to be able to function with their lives outside of the home. I think that these medications hold some potential opportunity in the acute exacerbation setting, but that's a discussion for another time.

NICK DEGREGORIO: We also had alluded earlier to some of the comorbid conditions with COPD and particularly those that can mimic uncontrolled COPD. Other pulmonary diseases like pulmonary fibrosis, pulmonary hypertension, bronchiectasis, and asthma that may require different treatment plans. Comorbid cardiac disease that again has shared risk factors with COPD. And it also can mimic the dyspnea and cough that you see with COPD as well.

Obstructive sleep apnea can lead to fatigue and activity limitation. And GERD can be a contributor to chronic cough and aspiration that can lead to lung injury and pneumonia. We spoke earlier of depression and anxiety, the importance of screening for depression and anxiety because of the link that they have with medication on adherence as well as perceptions of higher symptom burden, lower quality of life, increased hospitalizations at similar levels of lung function impairment.

And then, again, not to forget about the risk of osteoporosis in these individuals from their underlying disease as well as from the steroids that are used to treat the disease. And not to consider this only in women but especially in men, where particularly after the age of 70 or earlier in folks with COPD where we can see osteoporosis.

The other thing I would mention, certainly in this era where we've seen an opioid crisis, is the impact of opioid use in patients with COPD. And not uncommonly, we've seen individuals with COPD on significant doses of opioids long term.

So there are a few studies. One was in *Chest* in August 2019 that looked at opioid use within seven days prior to an exacerbation. So it appeared that the use of opioids within a seven-day period increased the association or risk of an acute exacerbation of COPD.

Another study looked at opioids alone and benzodiazepines alone, which both increased the risk for exacerbations when taken either 30, 60, or 90 days before the index event. And particularly notable was that the combination of opioids plus benzos, which had more of an adverse effect. And the risk of exacerbation actually increased in proportion to the dose. So the higher the MED, the increased the odds of an exacerbation of COPD.

And finally, there was a study in the European respiratory journal in 2016 that looked at opioids plus COPD and identified about a five-time increased risk of death in folks with COPD who were also on opioids. So something to keep in mind, particularly if opioids are not particularly indicated. And it's not part of a palliative care or hospice care plan.

CRAIG RILEY: I get very nervous when I see a patient with advanced lung disease who is on multiple respiratory sedating medications. It's so easy to tip these patients over.

NICK DEGREGORIO: The other thing we had discussed earlier was the fact that pulmonary rehab, despite its benefits, is so underutilized in COPD, with less than 5% of eligible patients really receiving the training, which is typically three sessions a week for 12 weeks, to both increase strength and endurance along with respiratory-specific education and coping strategies.

CRAIG RILEY: Pulmonary rehab is well-established in terms of the benefits that it provides and quality of life symptom control improvement for patients with COPD. The magnitude is much higher for pulmonary rehabilitation participation than for any of the pharmacologic therapies alone.

And to a high degree, this might be because it can reverse the muscle dysfunction, which is common in patients with significant dyspnea. And it gets them moving, and it gets them interacting with other people. I tend to think that pulmonary rehab is appropriate for most patients who have residual symptoms despite being on dual long-acting bronchodilators. So that's my entrance criteria for thinking that their medication regimen is optimized enough that they might derive some benefit from pulmonary rehabilitation.

But there's no question that for patients who have been hospitalized for a COPD exacerbation that pulmonary rehabilitation is appropriate and is probably a marker of giving high-quality COPD care. The readmission risk for patients who participate in pulmonary rehab is as little as half the patients who do not participate in pulmonary rehabilitation.

And it's been associated with lower mortality. So this is something that I think should really be mandatory for patients who are able to participate following discharge from the hospital.

Because access is such a problem, we're increasingly studying tele-based or home-based pulmonary rehab programs. And the earlier evidence suggests that these capture a lot of the benefits of formal in-person structured programs. But we have more work to do to figure out how we can best tailor these to the needs of our patients, especially in situations where patients have the option to participate in person at a formal pulmonary rehab but might choose to participate in a remote home-based program instead.

For patients who don't have a pulmonary rehab facility within a reasonable driving distance or just can't get there, I think that home-based pulmonary rehab is going to rapidly become a standard of care option.

NICK DEGREGORIO: So are there any other things we can do or other treatments that can reduce exacerbations and keep people out of the hospital with COPD?

CRAIG RILEY: So this is getting to the point where I think that patients often might benefit from referral to pulmonary for consideration. But two of the common medical options that I'll consider and that I think that many primary care providers might be comfortable prescribing are long-term azithromycin and roflumilast.

So long-term azithromycin has been shown to decrease exacerbation rates for patients with COPD. And it's been studied at doses of either 250 milligrams daily or 500 milligrams three times weekly. This benefit in subgroup analysis really only seems to extend to patients who are not currently smoking, which is not a surprise. The damages of ongoing smoking outweigh many of the benefits of these COPD therapies that we're going to be discussing. And azithromycin has some concerns for QT prolongation on EKG.

And at least a baseline EKG should be checked to make sure that patients don't have preexisting QTC issues. Azithromycin, when used long term, is also associated with decreased hearing acuity. And we generally don't recommend screening audiology at initiation of azithromycin, because most of this hearing loss seems to be reversible. But it's something to ask patients about, because you don't want to be blamed for their hearing loss, which has actually been going on for years prior to starting azithromycin.

Roflumilast is phosphodiesterase 4 inhibitor that decreases exacerbation rates by decreasing airway inflammation. We generally think about this medication in patients who have signs of airway inflammation-- so bronchietic symptoms-- who have had severe exacerbations are already on maximal inhaled therapy, which is generally going to include an inhaled corticosteroid. And most of the benefit seems to be in people who have severe obstruction. So an FEV-1 less than 50% or 60% predicted.

Roflumilast is associated with a lot of GI discomfort, a lot of nausea and diarrhea. So we usually start it at a half dose for the first four weeks, which is 250 micrograms daily. And then after that, step the dose up to 500 micrograms once daily. This seems to improve tolerance, as most of these GI side effects improve with time.

It also seems that phosphodiesterase inhibitors can worsen psychiatric disease. So patients who have very poorly controlled depression or prior suicidal ideation might not be appropriate candidates for roflumilast.

NICK DEGREGORIO: So what about use of theophylline and chronic prednisone in COPD?

CRAIG RILEY: So for quite a while, we've thought that theophylline, although it doesn't seem to have any role in bronchodilator action or symptom control on top of optimal medical therapy, we thought that maybe it had a role to prevent hospitalization or exacerbation rates. And a recent study that was published in *JAMA* suggested that in a randomized control trial, theophylline had no advantage to controlling exacerbations over conventional medical therapy, including optimal inhaler treatment.

So because it also has a narrow therapeutic index, and it doesn't seem to have any significant benefit, theophylline really does not have a role in management of COPD, at least in a resource-rich setting like the United States. It still might have a role in places where inhalers are unobtainable but that's not the case for the patients that we're seeing here.

Similarly, chronic prednisone has a risk-benefit ratio that's unfavorable in almost all patients. There are a handful of patients with severe asthma that it's very hard to get off of chronic prednisone. But COPD is just not typified by that type of steroid responsive eosinophilic airway inflammation.

And in patients with that sort of issue, where we may be considering an asthma-COPD overlap type of phenotype, we might even consider using asthma-directed biologics to target that type of airway inflammation.

NICK DEGREGORIO: So COPD patients who primary care doctors might consider for referral to pulmonology may include those appropriate, particularly if there are any diagnostic or therapeutic questions in regard to the patient or the diagnosis.

It's recommended for patients with severe obstruction, oxygen dependence, chronic hypercapnea, or refractory symptoms or exacerbations despite optimal inhaled therapy and pulmonary rehab. And additionally, it's recommended for any patient with comorbid pulmonary disease like bronchiectasis, fibrosis, or pulmonary hypertension.

CRAIG RILEY: So I think that what we have to offer for those types of patients, in addition to evaluating their inhaled and oral medications, evaluating adherence and appropriateness of repeat courses or continued pulmonary rehabilitation, other services that some specialists can provide are evaluating patients for advanced therapies, which might include bronchoscopic or surgical lung volume reduction, nocturnal non-invasive ventilation for patients with chronic hypercapnic respiratory failure, and also evaluation for appropriateness for lung transplantation referral.

So in summary, there are several things that should be considered for patients who have refractory disease despite optimal medical therapy. In particular, smoking cessation, the importance of this cannot be overstated. There are only a few therapies that show a mortality reduction in this advanced COPD patient population. And smoking cessation is certainly one of them.

Optimal inhaled medical therapy, including dual long-acting bronchodilators and inhaled corticosteroids in appropriate patients, while it has not demonstrated a specific mortality reduction, we certainly know that suboptimally treating these patients, patients who are not put on long-acting bronchodilator regimens, do seem to do worse.

Oxygen therapy, again, for patients with resting hypoxemia, is associated with increased survival and as a result should probably screen patients for hypoxemia at least yearly to make sure that they have not developed new or worsening hypoxemia.

And pulmonary rehabilitation, especially in the post-hospitalization patient cohort, is critically important and seems to be associated with a lower risk of death. Finally, avoiding medications that can worsen respiratory status, including opioids, benzodiazepines, and other sedating medications is really important, because these patients' respiratory status can be fragile and tenuous. And tipping them over with medications that make their breathing even more difficult is probably not in their best interest.

Now in some cases, patients, despite all of these interventions, are just not where they want to be from a breathing standpoint. And in that case, referral for palliative or hospice-directed services might be appropriate.

And in that case, the use of medications like morphine or oxycodone specifically for dyspnea, when managed by appropriately skilled providers, can be a critical therapy to alleviate suffering at the end of life. Outside of that circumstance, though, I approach respiratory sedating medications in patients with significant COPD with extreme caution.

So this concludes part three of our three-part series on best practices for COPD. Please log in to get CME credit to the website. Use the code COPDSEC3. Again, that's COPDSEC3, and answer the evaluation question. Thank you.