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Pharmacologic Management of Poorly-Controlled Asthma

Announcer:
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Dr. Yawn
Welcome to the American Thoracic Society and American Academy of Family Physicians’ educational activity on the topic of severe asthma.

This is module 3, Pharmacological Management of Poorly Controlled Asthma.

Dr. Wenzel
And I am Sally Wenzel, Professor of Public Health Medicine and Immunology at the University of Pittsburgh.

Dr. Yawn
And I’m Barbara Yawn, Adjunct Professor of the Department of Family and Community Health at the University of Minnesota. And you can see our disclosures here.

The learning objectives, as we have talked about, are from module 1 was to talk about the diagnosis, stratification and phenotyping of asthma. In module 2 we talked about effective communication strategies to facilitate patients’ awareness and improve outcomes. In this module 3 we’re going to talk about developing evidence-based treatment plans for severe asthma. And in module 4 we review the clinical data for safety and efficacy of existing targeted therapies for the treatment of severe asthma.

So, again, here in module 3 we’re going to talk about developing evidence-based treatment plans for severe asthma, looking at symptoms, phenotypes, trigger avoidance and lung function.

Reminding you about the definition of severe asthma, that after we confirm the diagnosis, we identify uncontrolled asthma, we try to address all of the modifiable issues and the comorbidities. If after doing that we continue to have asthma which requires treatment with high-dose ICS and a second controller, or systemic corticosteroids to prevent it from becoming uncontrolled, or asthma that remains uncontrolled despite this therapy, we say the patient has severe asthma.

So, what are the manifestations of severe asthma? Well, they are really kind of what you would expect: poor symptom control including nighttime awakenings, which are really, really bothersome and disruptive for patients’ lives, limitations in activities, again very disruptive and definitely what we don’t want to do—patients will tolerate maybe a little wheezing a few days a week, but when they have to change their activities, none of us should tolerate that—

Dr. Wenzel

Absolutely, absolutely.

Dr. Yawn
—overuse of rescue medications. And what's the definition of overuse? It obviously varies, but most people think that they should not be using them daily, and if they do, certainly no more than a couple of puffs a day. What's your sort of barrier or threshold?

Dr. Wenzel
And certainly I would agree with exactly what you said, that I think poorly controlled asthma really is... If you're having to use it every day, that's poorly controlled asthma. And, of course, the more severe the patient is and the moving away from the difficult asthma and moving towards severe asthma, unfortunately that threshold actually can be pretty hard to overcome, so you still have patients taking their albuterol, their short-acting beta agonist, 4, 5 times a day in many cases. That is very poorly controlled asthma. And certainly, we've always said that if you're going through a canister a month of albuterol, that that is a clear sign of poorly controlled asthma.

Dr. Yawn
Well, and just to remind people, a canister a month is an average of 4 puffs every day because there are 120 puffs in that canister, so that is one of the reasons we've said a canister a month is really not acceptable.

Dr. Wenzel
Too much, too much.

Dr. Yawn
Certainly, people who have frequent, severe exacerbations, these are the ones that require systemic corticosteroids, any serious exacerbation which would include a hospitalization and the evidence of airflow limitations, a low FEV1. And amazingly, a lot of these people—we're not talking of an FEV1 of 75% of predicted—we're talking 50, 60 and even less, so these people do have significant evidence of airflow limitations.

Dr. Wenzel
Yes, and I think that is certainly a point to be made, too. I think many times if a physician sees an FEV1 of less than 70% predicted, they will start to call that patient chronic obstructive pulmonary disease or COPD when, in fact, severe asthma can present with that very low lung function and they do not have to get a diagnosis of COPD.

Dr. Yawn
And I think that's very important because asthma and COPD do have different treatment strategies.

Dr. Wenzel
Absolutely they do, right.

Dr. Yawn
And they have different long-term prognoses frequently, so we do want to make the correct diagnosis.

Dr. Wenzel
Correct diagnosis, absolutely.

Dr. Yawn
Evidence-based treatment plans, we certainly have to identify and manage triggers and comorbidities—there's no question about that—and so that's important in the treatment. We have to assess and correct inhaler technique. And we've talked about it a couple of times, that you don't do it just once and then, "Oh, they'll be fine." There's excellent evidence that within 3-6 months, 30-50% of the patients who had pretty good inhaler technique will have at least 1 major error that can affect their ability to get the medicine where it needs to be, so that's important that you do do that recurrently. Address adherence, and again, not by saying, "Well, you are taking your medicines, aren't you?" But one of the ways that I think that probably both of us approach it is, as we've talked about, remembering to take this medication can be difficult. "Are you finding that it's difficult?" and, "How often are you able to take your medicine?" And I think putting some of those terms in there makes it very clear to the patient that we're not blaming them. We're saying, "Hey, we do know this is difficult. Tell us what's going on."

Dr. Wenzel
Absolutely.

Dr. Yawn
And then we add the long-acting bronchodilator therapy or therapies to the anti-inflammatories, which is very helpful, but even that may not do everything we want it to in patients with severe asthma.

Dr. Wenzel
And I think certainly just to add to the long-acting beta agonist, the data to actually suggest that in truly severe asthma that adding a long-acting beta agonist actually improves their outcomes is actually pretty modest once you get to a certain severity level. And I will have many patients, actually, who continue to take short-acting beta agonists 2 or more times a day despite the fact that they're on their long-acting beta agonist, and in that case I actually get concerned about all of the beta agonist load that they have, and in some cases I will stop their long-acting beta agonist so that they're not being overly burdened with the side effects of beta agonist therapy.

Dr. Yawn
And those certainly are possible. I do want to reassure people that in patients needing long-acting bronchodilators, beta agonists, they really have a very good safety profile overall.

Dr. Wenzel
Oh, absolutely.

Dr. Yawn
But it is this compounding that all of us worry about. You can take anything too much of. Water, if you drink too much of it, is dangerous.

Dr. Wenzel
It's still a bad thing, yep.

Dr. Yawn
Right, and so that's what we're talking about. We're not saying that these are dangerous in people with asthma. We're saying you don't want them to use a long-acting and then have to use 4, 6 puffs a day of the short-acting. That's just more than we would like to have our patients have to use.

Dr. Wenzel
And there are potential for cardiac effects and all of those sorts of things under those extreme conditions.

Dr. Yawn
Right, under those conditions.

Dr. Wenzel
And extreme conditions.

Dr. Yawn
Right, right. So the quick relievers, we have the short-acting beta 2 agonists, the short-acting anticholinergics, and we have the combination. Now, I find that's more helpful in COPD than it is in asthma, but do you use the combination short-acting very often?

Dr. Wenzel
Very rarely to be quite honest with you. I think most patients with asthma actually prefer just the beta agonist. I think if I'm really struggling to reduce the short-acting beta agonist use, then I will throw in an anticholinergic or a combination to try to taper down the amount of short-acting, but in general I'm a fan of using albuterol as the primary reliever.

Dr. Yawn
Well, but that's a good metric to say, well, this is when you might try it. When you've got somebody that is using those 6 puffs a day, can you get them down to 2 puffs a day by using a different combination?

Dr. Wenzel
Correct.

Dr. Yawn
The long-term controller therapy, certainly the primary ones have been the anti-inflammatories because this is an inflammatory condition, so that's what we want to approach first. We've got the inhaled and the systemic corticosteroids. Obviously, we want to avoid the systemic corticosteroids if at all possible. And we have the leukotriene modifiers, which also can be helpful. I think that they can be helpful across the age span, but I do find they are more helpful in younger patients, I think, and certainly in patients with an allergic profile or phenotype that we're going to talk about in a little bit.

Dr. Wenzel
Mm-hmm.

Dr. Yawn

The bronchodilators we've talked about, the long-acting beta agonist, the long-acting muscarinic receptor antagonist, the LAMAs, the LABAs. There are still the methylxanthines, and we don't use them very often in the United States, but certainly around the world there are many places where that's the only thing that's really available and affordable.

Dr. Wenzel
Inexpensive, yeah.

Dr. Yawn
Right. And, of course, then there are the combination therapies that put multiple ones of these drugs together. And now we have a new category that we're going to talk a lot more about, the biologics. And these are monoclonal antibodies. I don't think there's any that are not injection. Are they? They're all injection?

Dr. Wenzel
Injection or infusion, correct.

Dr. Yawn
Infusion, right. So they are a step up for burden of use potentially in some cases, but we'll talk about the fact that maybe having a shot once every 2 or 3 weeks may be a lot easier for patients than other things.

Dr. Wenzel
In some cases.

Dr. Yawn
But they're also very expensive, so you want to select the appropriate person to use them.
Managing patients who remain poorly controlled despite the typical therapy, so we're going to start talking about phenotypes, endotypes, potential biomarkers associated with severe asthma. What can we do that helps better define and identify these people so that we can personalize or individualize therapy? As we talked about way in the beginning, asthma is not asthma is not asthma.

Dr. Wenzel
Right.

Dr. Yawn
It is a very heterogeneous condition, and the more we can do—especially as patients get more symptomatic—to identify their specific individual types of asthma, then the better we can tailor therapy.

Dr. Wenzel
Absolutely.

Dr. Yawn
This is what this just says, that many phenotypes have been suggested. Actually, not very many of the phenotypes are broadly accepted.

Dr. Wenzel
That is correct.

Dr. Yawn
And so we talk about them, and one of the things that primary care people find is that if I have 3 allergists and 2 pulmonologists I refer to, I have 5 different categories of phenotypes.

Dr. Wenzel
Different answers, yep.

Dr. Yawn
And so we all just have to realize when these are important and what can we do, and it's going to change, I think, as we move forward.

Dr. Wenzel
Yep.

Dr. Yawn
We're going to have a lot more well-defined phenotypes and be able to say, yes, you do want to check for this or that or the other. We have some now that we have talked about and will. So, individualizing, tailoring, personalized therapy, whatever you want to call it, we really want to address the clinical manifestations. The people that have more problems this time, that time, the ones that have seasonal

allergic problems, those are kinds of things we think about. The physiological characteristics can vary. And, of course, the outcomes. It seems there are patients whose body can tolerate a lot more than others and they won't be as symptomatic, and you expect them to be but they aren't, so we think about that.
The age of onset is really something we've talked more and more about. I always have to laugh when they talk about elderly asthma beginning at 50. I'm sorry, that isn't elderly.

(laughter)

Dr. Wenzel
Those are young people.

Dr. Yawn
Yes, they are, but there is, it looks like, quite a difference between the people whose asthma started either in childhood or adolescence or young adulthood and those whose asthma started later. We've talked about perimenopausal and postmenopausal asthma as one that is sort of a defining characteristic. And I think people get into concerns when we have someone who develops asthma apparently for the first time at age 50. It seems that a few of those or quite a few of those are also former smokers. And how do I distinguish, "Is this asthma, is this COPD, is this both?"

Dr. Wenzel
And it can be difficult to do that, but I think the general rules of asthma still apply. And unless a patient has smoked more than at least 15 to 20 pack years, I think the previous history of smoking has very little influence on the diagnosis of asthma in a 50-year-old who has new symptoms so long as they meet all the other criteria for asthma, which is obviously reversible airflow limitation and needing a bronchodilator response and having appropriate symptoms. So I think the rules still apply, but you do have to factor in the amount of cigarette smoking that a patient has completed prior to their presentation.

Dr. Yawn
And one of the things that I've heard people talk about is, with asthma, people have good days and bad days. With COPD they have not so good days and worse days. There are not many really good days in people with COPD, so the variability, which we said, that's a major characteristic.

Dr. Wenzel
The variability, yep.

Dr. Yawn
It's one that we sometimes forget.

Dr. Wenzel
I think that's a very good point. I think most people with COPD, the disease is much more steady day to day as compared to asthma where there is a lot of those fluctuations.

Dr. Yawn
Yes, so it's one of the important phenotypes maybe that they should talk about more and think about is the variability. The phenotypes are generally based on clinical and physiological characteristics of the disease. Some of them incorporate biomarkers. We've mentioned eosinophils several times and IgE—and I'll let you talk about those—and then the endotypes, the identification of a particular pathway which defines a disease, and I think endotypes are still very confusing for most of us in primary care. How do I recognize an endotype in asthma? What is it?

Dr. Wenzel
Yeah, and again, we'll talk about that a little bit more as we go through this, but I think there are probably no types of asthma that have yet met the criteria of an endotype. I think we're still talking about molecular phenotypes where we know that there are pathways involved. We know what when we block certain pathways patients get better, but the identification of a specific pathway, that we treat that pathway and everything gets better, I think there are very few, probably no cases of asthma that actually fit into a true endotype.

Dr. Yawn
Well, that's a little reassuring since I'm thinking this is very confusing. I don't know of any, and now you tell me you don't know of any. Okay, I feel much better about endotypes now. And this is what you just finished talking about, the phenotypes' observable characteristics that are a result of an interaction with a genotype and the environment, people who are susceptible to exposure to certain kinds of inhaled triggers, if you want to call them that.

Dr. Wenzel

Right.

Dr. Yawn
The cluster of characteristics that define a disease and its subset—and I know you're going to talk about those Th2 and low Th2 and high Th2—and the endotype, as you just said, we don't have any of those quite yet, so I don't think we have to spend any time except to say we're really hoping that 3-5 years from now—

Dr. Wenzel
Yeah, we will be there.

Dr. Yawn
—maybe we will.

Dr. Wenzel
We will be there, and we'll actually have defined a new disease in my opinion as opposed to a phenotype.

Dr. Yawn
And I think that is important because we call everything under this very large umbrella asthma, and I think all of us know it doesn't look like the same condition or disease.

Dr. Wenzel
It really doesn't, yep.

Dr. Yawn
So I think that will be very exciting in the future. The clinical phenotypes, the obese versus the nonobese, the allergic versus the nonallergic, one of the things that I don't think that I pay enough attention to and a lot of times in primary care is occupational asthma. Frequently, the occupation isn't even recorded in the medical record, but there are several occupations that are clearly significant, recurrent exposures like bakers and all the flour that's all over the place, but I think there are others too that we just don't think of.

Dr. Wenzel
And certainly, in the textbooks you have things like painters and being exposed to isocyanates, people that are in the lumber industry in the same sort of thing, but I think there are new exposures that we don't think about nearly as often as we should, which are people that work in hair salons and all of the sprays that are in the environment, typically in a relatively closed space, not with a lot of good ventilation, and then domestic workers who are exposed to the cleaning fluids on a regular basis. All of those things can certainly influence asthma and the asthmatic symptoms, so things to keep in mind for sure.

Dr. Yawn
Well, and for the healthcare professionals, many of them are exposed to cleaning fluids on a very regular basis, and it may not only be the domestic or housekeeping staff; it may be the nursing staff too.

Dr. Wenzel
Yes, certainly.

Dr. Yawn
So, if you've got somebody where, gee, this doesn't quite all make sense, occupation—

Dr. Wenzel
Think about the occupation.

Dr. Yawn
—needs to be considered. And then, of course, the cell types, we've talked about the eosinophilic; we'll talk about neutrophilic. And then other subdivisions like the aspirin-associated exacerbations, again something I don't think we ask about. Frequently, the patients will come in after a while though and tell you, "I quit using aspirin because I always got into trouble." And then there's premenstrual asthma. Again, frequently those people will come in and tell you after a while, but it can take a long time to figure out, and when someone's having an exacerbation every month and it's a woman, maybe you should think about menstrual association—

Dr. Wenzel
—premenstrual asthma and the hormonal relationship that it bears. And just to make a point about the aspirin-exacerbated respiratory disease too, it's not just aspirin. It's all nonsteroidal anti-inflammatory drugs can do this—perhaps not acetaminophen, but all of the others certainly can, and a patient doesn't have to be taking these regularly to have it be the cause of their asthma. Just having a reaction to it on the times that they do take it is enough to get that diagnosis.

Dr. Yawn
And that's really an important one because it is one you can avoid.

Dr. Wenzel
Yes.

Dr. Yawn
And that's what we're always looking for is something we can identify and then avoid easily.

Dr. Wenzel
Correct.

Dr. Yawn
So, the clinical phenotypes, the work-related, we've talked about those, the sensitized-induced, the irritant-induced, and I think we worked—we mentioned pretty much all of those. We didn't say anything about the nail technicians.

Dr. Wenzel
But same thing.

Dr. Yawn
And it's the same thing. They just are in a very enclosed space. The accurate and timely diagnosis really is important for appropriate management. If you don't know this is an issue, you're not going to deal with it particularly well.

Dr. Wenzel
Right.

Dr. Yawn
Some of these people really do have to change occupation before they're going to get sufficient relief. So there are immunological and inflammatory markers that you can look at for these, and I know you're going to talk about those. And the functional airway changes before and after work times, that's something we can do in primary care because if someone comes in and we decide, "Oh, she is a hairdresser and I want to think about that," well, have her stop by on the way after work some day and see what it is and then have her come by—and I'm assuming it's a him, it could be a her too—have them stop by when they have been off work for 3 or 4 days—

Dr. Wenzel
Yes, absolutely.

Dr. Yawn
—and see what the difference is, something that's... I'm not saying it's quick and easy.

Dr. Wenzel
But it's doable.

Dr. Yawn
But it's very doable in primary care.

Dr. Wenzel
And you can even give them a peak flow meter, and they can actually record their peak flows on the weekend or whatever when they're at home and not exposed to the work environment. See what it is over the weekend and then have them record it every day as they are exposed to their work environment to see if there's a decline in their peak flow.

Dr. Yawn
And I think that's important, because most of us have sort of written off peak flow meters because it's very difficult to give a patient a peak flow meter without any specifics like this and just say, "Well, take it whenever." They lose them. But when you have something like this that's very specific, "Okay, we're just going to do this over the next 2 weeks, and I want you to keep track. Is it after work, during work, when you've been off?" then I think you get really good engagement with the patient.

Dr. Wenzel
Mm-hmm, correct.

Dr. Yawn
And I think they'll do it because they'd like their asthma to be better, so I think that's an excellent tip for people to try to do. The avoidance of the inciting agent, you have to figure out what the inciting agent is first if you're going to avoid it, and you try to keep their

exposure at a minimum, and there are some ways to do that besides stopping their occupation entirely.

Dr. Wenzel
Yes, of course.

Dr. Yawn
And I think it's important to try to address those.

Dr. Wenzel
Right. And sometimes it may be just working with their employer to develop a better ventilation system, right?—to move from being in the back machine shop to being in the up-front office related to their profession, and then obviously respirators and the baggage that comes along with having to wear a mask while you're working, but if people really like what they do, these are sometimes alternatives to actually having to change their profession.

Dr. Yawn
And for them maybe a very appropriate alternative because this may be the only profession that is feasible for them.

Dr. Wenzel
Correct, correct.

Dr. Yawn
So, challenge regarding clinical phenotypes: Well, there's really no specific test for many of these phenotypes. Obesity-induced asthma: There are a fair number of people who are obese, and it may or may not be a major role in their asthma.

Dr. Wenzel
Absolutely.

Dr. Yawn
So that's kind of difficult. And there are no universally accepted definitions of some of the phenotypes. There are of a few—

Dr. Wenzel
A few, sure.

Dr. Yawn
—but not all of them. And it can change over time. I mean, that's the tricky part is that, okay, it was this now and now it's something different. And we really tend not to think about these phenotypes, and as we've said, especially the occupational ones that we just plain ignore.

Dr. Wenzel
Right, right. So, in 2019, going into 2020, I think we're trying to expand on our understanding of phenotypes by becoming a little bit more molecular in our approaches, and so we can now begin to think about asthma as being defined by certain cells or certain molecules in association with that phenotype, which hopefully, at the end of the day, will make it much more objective in how we identify patients and allow us to target therapies appropriate for that specific molecular phenotype.

When they are defined by biomarkers, it's important that we measure these biomarkers over time, because just like the clinical aspects, these aspects can change over time, so we want to see patterns. And it's very important to note that when we're using eosinophils as a biomarker, eosinophils in the blood on that complete blood count, CBC, that we've been mentioning several times now, it's actually very important to note when you're drawing that blood count in relationship to oral steroids or oral prednisone, Medrol, etc., because prednisone, Medrol, other steroids should, in fact, wipe out all of your eosinophils, and so you'll have patients come up with zero eosinophils, and you'll say, "Well, they don't have eosinophilic asthma," and it's because the steroids have actually suppressed them. And even patients on very high doses of inhaled corticosteroids you can have suppression of eosinophils on the basis of that, so it is important to know where in time you're measuring these biomarkers.

Dr. Yawn
But other things like having an upper respiratory infection or... because you have... Yes, you may specifically get this just for their asthma, but when we look back, they have had several CBCs with differential over the past. Does a URI shoot the eosinophils up high?

Dr. Wenzel
It can depend on what's the cause of the URI, and I think a lot of times things are called URIs when they're actually just a flare of the chronic rhinosinusitis that goes along with severe asthma, and in many of those cases you will see a bump in eosinophils that occurs during that time. I think if it's a bacterial infection in the sinuses, then you're certainly less likely to see it, but again, it doesn't hurt to

check. It's an inexpensive test, and it clearly gives you information. And I think we understand that eosinophils are really at the heart of the inflammation that we describe as asthmatic inflammation in many cases. Probably at least 50% of asthma has an eosinophilic component to it, and steroids inhibit this eosinophilic inflammation. That's one of the reasons why corticosteroids are effective, is that in most people mild to moderate asthma, those eosinophils will be suppressed by the corticosteroids.

On the other hand, people have talked about neutrophilic asthma. This is to me a bit of a quagmire at the present time. It's very poorly defined. There are no simple tests to define it. You cannot look at the neutrophils on a blood count and say, "Oh, this is neutrophilic asthma," because there's no thresholds, there's huge variability, steroids make the neutrophils go up, so it's a bit of an unknown area at the present time.

Dr. Yawn
And you're not going to ask me to do sputum neutrophils.

Dr. Wenzel
Nor would I do sputum neutrophils because even sputum neutrophils are highly variable, don't track very well with symptoms or lung function changes or whatever. I think eosinophils we can feel pretty comfortable with. Neutrophils we're still struggling with.

But based on this concept of eosinophilic inflammation and based on the drugs that have been developed over the last 5-10 years, I think we can pretty clearly say that asthma can be broken down into those patients that have evidence of type 2 inflammation or those patients that have no or very little evidence for type 2 inflammation. And what do I mean by type 2 inflammation? I mean type 2 inflammation that is associated primarily with an eosinophil as the end cell that we're measuring but which is probably driven by a specific group of cytokines called type 2 or Th2 cytokines. They used to be thought only to be made by T-helper cells, but now we know they're made by other things too, so they have come to this type 2 cytokines which are IL-4, IL-5 and IL-13 in the most simple and logical sense.

So this is an example of type 2 inflammation. This is your typical diagram that every asthma presentation that you've ever been to has had at least one of these slides of the pathobiology of asthma.

Dr. Yawn
Right, you have to.

Dr. Wenzel
And I think we realize that the patients with type 2-high asthma have some mix of these cytokines and these cells involved. In most cases these pathways involve activation of mast cells, eosinophils, certain lymphocyte subsets, Th2 cells, and now this new type of lymphocyte called an innate lymphoid cell or an ILC2 cell. And again, this type of inflammation seems to be associated with about half of the asthma population, and I think in the severe asthma population it's probably a little higher than that. It's probably closer to 60-70%. But that's why measuring these biomarkers, the blood eosinophils or things like exhaled nitric oxide and exhaled breath can be so important because they help us to identify who are the patients that have this type 2 asthma versus those that don't. And when it comes to our new treatment options, it's going to be very important to know, "Does this patient fall into that broad category of type 2 asthma versus non type 2 or less type 2 asthma?"

So we've really, I think, transitioned from this concept of clinical phenotyping to molecular phenotyping, to this personalized precision approach to the treatment of asthma that, again, starts with an appropriate diagnosis of making sure the patient has asthma, do they in fact have severe asthma or refractory asthma, and then starting to put them into little bins based on their clinical characteristics, their phenotypes, their molecular phenotypes, what do their biomarkers look like—and maybe someday we'll get to genotype, but we really aren't to that place yet—and then identifying on the basis of those biomarkers whether they are a type 2-high patient or a type 2-low patient. Although people talk about sputum and how you can identify eosinophils and neutrophils in sputum and put a patient into certain categories using that, it's probably not ever going to become mainstream in any practice in the United States, certainly not in specialist care and I would doubt very highly in primary care, because they're difficult tests to do. They're difficult tests to standardize. Many people can never bring up sputum to begin with, and so, again, we're really going to sort of ignore the sputum analysis of molecular phenotyping at this point and focus on tests that are a little bit easier to obtain.

Dr. Yawn
Well, when we can do spit eosinophils, then we might have a chance.

Dr. Wenzel
Spit eosinophils, people have even been talking about getting it in your nose and could you identify eosinophils in the nose, but the bottom line is the blood is pretty good.

Dr. Yawn
And that's pretty easy.

Dr. Wenzel
The blood is pretty easy and it's pretty inexpensive.

Dr. Yawn
Right.

Dr. Wenzel
I would encourage every person who has an electronic medical record, as you've been saying all along, is to go back through the electronic medical records and look over the last 5 years at the eosinophils, the complete blood counts—chances are the patient has had 1 or 2 of them in the past, maybe more—and see if there was ever evidence for elevated eosinophils above traditionally 300 as a sort of starting point, but could be a range, and then also addressing the allergy component. So things like IgE levels, total IgE levels, but specific IgE levels are probably more important to look to see whether the patient is actually making specific IgE antibodies to things like dust mites, cats, dogs, etc. And then we've already talked about induced sputum and we've dismissed that. We're not going to talk about that anymore. And then exhaled breath, I think there is going to be a movement in exhaled breath over the next several years. Now, the only thing that we measure in exhaled breath right now is nitric oxide.

Dr. Yawn
Right.

Dr. Wenzel
And that is an indicator of type 2 inflammation in the airways. Nitric oxide is produced by cells that line the airways of patients with asthma, and you can measure it in their breath on a relatively simple, relatively inexpensive piece of equipment. I don't know whether it will become mainstream in primary care or not. In many specialists' offices they don't still have it, so I don't know whether it will go to primary care or not, but the point is just by having a patient exhale into a machine you can get some indication of what type of asthma that they have, and I think we're going to be able to become more granular with this approach, measuring things in the breath—which again children can do, it's noninvasive, you're not sticking a needle in folks—and potentially get a lot of additional information.

Dr. Yawn
And I think when we find that we can get really useful information, I think it has a chance, because as you said, it is very doable, it is not difficult and doesn't take nearly as long as spirometry does, for example, to do.

Dr. Wenzel
Right, right, it can be done in 5 minutes.

Dr. Yawn
Right. It's just that right now, if you don't use it frequently, then it seems it's expensive to do on a per-test basis.

Dr. Wenzel
Right, and it should guide your therapy. If you're not making a change in therapy on the basis of measuring it, then it's probably not...

Dr. Yawn
Then don't bother.

Dr. Wenzel
Not worry about it either. So again, why should we use biomarkers? To guide therapy. That's exactly what we're talking about here, that biomarkers should be associated with a diagnosis and a specific treatment that follows it. I think you want to document the characteristics of the biomarker, and we should be able to identify its association with clinical patterns to the disease, not just, "Oh, there's an eosinophil there." What does it associate with it? It should identify a phenotype which responds better to certain therapies, so again back to that point of it should be guiding therapy. And then it should ideally be a monitoring biomarker so that if we start a therapy and the biomarker goes down, we know that that therapy is actually working, that there's a molecular process that is being targeted by that therapy and that biomarker is now getting better. So you can have a predictive biomarker, something that predicts response to treatment, and then a monitoring biomarker which responds to that treatment if, again, that treatment is appropriate for that person.

Dr. Yawn
And exhaled nitric oxide really does do both.

Dr. Wenzel

Yes, exhaled nitric oxide absolutely does both. It gives you a type 2 phenotype, and in either the case of corticosteroids or some of these new type 2 biologics will go down in response to therapy.

So really only 4 asthma biomarkers have been validated and are readily available. They include blood eosinophils, total and specific IgE levels, which again Dr. Yawn has been talking about throughout the presentations, and exhaled nitric oxide. There's not specific guidelines about how often to measure these biomarkers, how regularly to measure these biomarkers, but at least from my perspective, if you have someone where you have no history of what their inflammatory biomarkers look like, you should at least measure them 3 to 4 times over a period of a year or 2 years or whatever to get a pattern of whether they are elevated or not and do they correlate in any way to their clinical symptoms, to their clinical presentations, to the stability of their asthma. And again, avoid measuring during systemic corticosteroid burst, even including up to 2-4 weeks after the prednisone has been stopped because you will have a long-term effect on it.

I like to recommend that every adult asthmatic has a complete blood count with a differential at least once, and if you have a blood count of greater than 300 eosinophils per microliter, that should be considered evidence of type 2 inflammation. And I think you have to be careful because on the laboratory printouts or readouts, the laboratories have different thresholds for what's normal and abnormal, and even in our laboratories there are some that go up to 700 for normal eosinophils. A 700 is not a normal eosinophil count.

Dr. Yawn
I was going to say...

Dr. Wenzel
And so a busy physician who kind of looks down and says, "What's abnormal?" it may not even be checked as abnormal, so you actually have to specifically look for it. And again, if a patient is on oral corticosteroids, the eosinophils should be zero, and if the eosinophils are not zero in that case, you certainly have to address adherence—are they taking their medications. But do they have a very refractory type of asthma, which we absolutely do see where even though they are taking systemic corticosteroids they still have elevated eosinophils. Those are patients you really get concerned about.

Dr. Yawn
And these are ones that really go to the specialist immediately.

(laughter)

Dr. Wenzel
If you say so.

Dr. Yawn
I say so, yes.

Dr. Wenzel
Anyway, okay, so managing patients with severe asthma: How do we decide who goes where? Who stays in primary care? Who should be referred to a specialist? And, of course, the answers aren't always straightforward. So let's start with Tara. So, Tara is a 46-year-old woman. She developed asthma about 5 years ago, didn't really have any previous history of breathing problems, no history of seasonal allergies, never required any prescription therapy, but she developed symptoms when she was 41, so she was older, certainly. Five years ago she developed increasing wheeze, cough, shortness of breath, things that go along with an asthma diagnosis. She was, in fact, prescribed low-dose inhaled corticosteroids and short-acting beta agonist, very appropriately, but despite that therapy her symptoms worsened. She's now been marched up the scale, and she's now on high-dose inhaled corticosteroids plus a long-acting beta agonist plus a leukotriene receptor antagonist, and she's still using her albuterol twice a day, so she's at our threshold of going through that canister a month, and she wakes up at least once a week.

She reports that her symptoms are worse just before the weekend. She's actually been to the emergency department twice, both on Friday nights, interestingly, so good to know, and her family history, no real history that significant for asthma. But interestingly, when you do ask that question about what is her occupation, she says that she worked at the Counter Bakery about 5 years ago, but there's no current updates, so we don't really know. We look back through the medical records and, yeah, she was working in the bakery but 5 years ago.

So we do the testing. We do our spirometry because she's pretty symptomatic at this stage. She's on a lot of medication, so it's important for us to do spirometry, and her lung function shows she is pretty obstructed. Her FEV1 is 64% of predicted, she's got a big bronchodilator response, and her eosinophils, to my point, are reported as normal at 300 eosinophils per microliter.

Dr. Yawn

Which is not normal.

Dr. Wenzel
Which is not normal. And again, she still reports this, “I feel better on Monday, but by Fridays I require albuterol 4 times a day.” Still working at the same job, so you ask her, “Where are you working?” “Oh, I’m still working at the bakery.” But then you dig a little bit deeper, and now she’s actually working in the bakery. She’s not selling the pastries at the front counter. She’s actually baking the bread. And she’s exposed to flour; she’s exposed to yeast. She’s exposed to yeast. She doesn’t wear a mask because she never really thought about it. And sort of the lightbulb goes off and you say, “Hmm, this could be baker’s asthma. This could be an occupational-related lung disease.” And so you ask her to monitor your peak flows from Monday through Friday, and there’s clearly a drop as the week progresses, which confirms the diagnosis of occupational baker’s asthma in this situation.

And so, what are the treatment options? Well, if she really wants to be a baker, then she should wear a respirator if she’s really enjoying baking the bread, but she could also potentially have another location in the bakery. She could go back to the counter where she started work 5 years ago and, in fact, that may be enough to reduce her symptoms. You could ask the owners to install better ventilation, or probably worst case scenario she could change jobs. Asking patients to change jobs is a horrible situation.

Dr. Yawn
Yes.

Dr. Wenzel
None of us like to be in that. So she returned to the counter. She’s now selling donuts as opposed to making them and her symptoms improved. She’s only using her albuterol 1 time per day, and she’s clearly better, and this is, again, a case where you’ve intervened, you’ve improved the asthma by just having her change her occupational location, actually, as opposed to her occupation.

Interestingly, she will probably continue to have some symptoms because she is still going to be exposed to the yeast and the flour even though she’s at the front counter, but with occupational asthma there’s good data to say even if she completely leaves that position and finds another job, she’s still going to have some symptoms, so the asthma response has been triggered and it’s very unlikely it will actually ever go away.

All right, 1 more case, Charles. Would you refer Charles? So, Charles is 22. He’s had his asthma since the age of 6, childhood onset—getting back to that, “When did you get your asthma?”—again very important, very easy question to ask. He has had problems with recurrent exacerbations despite moving away from home where dad smokes. He’s been using montelukast and high-dose combination therapy, and he says he uses it most of the time. And, in fact, you actually call the pharmacy, and he’s refilled it 10 times over 12 months, which, again, that’s close to 80%.

Dr. Yawn
That’s pretty good.

Dr. Wenzel
That’s pretty good. And his inhaler technique is okay, but he’s coming up on his third exacerbation of the year; 3 exacerbations in 1 year where he’s gotten oral steroids, prednisone, and his ACT is 16, which is uncontrolled asthma. You review possible comorbidities and find only maybe some seasonal allergies, but it’s really not strong, and he’s been to the emergency room at times where he’s not in his season of his allergies. So, Dr. Yawn, what would you do as your next steps?

Dr. Yawn
Well, certainly you’re going to think back through making sure he has asthma for one thing. The fact that he started at 6, he has a very typical history of asthma starting in childhood and going on. The triggers and the allergy testing, which we may do for seasons, for example, if they match, that’s pretty suggestive. Sinus disease, postnasal drip, he has the kinds of comorbidities that we see. Does he have GERD? I don’t know. Occupational, I don’t know what he does.

Dr. Wenzel
He’s young, but he’s still a student at this stage.

Dr. Yawn
Okay, he’s still a student. Well, that for anxiety, but the other exposures, probably not occupational. The spirometry, the pre and post bronchodilator, I need to do that.

Dr. Wenzel
Yes (inaudible)*45:14

Dr. Yawn
Because I really want to make sure that he does have the reversibility that I expect, and I just want to see what his FEV1 looks like. How low is it? As I said, I find that they are usually lower than I expect them to be, and I think that's true for most of us. Blood eosinophil count because I'm now starting to think I believe that he definitely has asthma, it looks like asthma that is getting uncontrolled. He does seem to be adherent. I, of course, have to check his inhaler technique.

Dr. Wenzel
Mm-hmm.

Dr. Yawn
And when we check it, it looks pretty good, so now I'm in the realm of I don't see a comorbidity that exactly explains this, adherence doesn't explain it, inhaler technique doesn't explain it, so I'm starting to get concerned, so the blood eosinophils are important. Pheno, if I happen to have it available, that will be great. And we talked about the allergy testing, which I think is real important.

Dr. Wenzel
Right.

Dr. Yawn
So I'm now starting to think that he is sort of at the top. He's at step 4 or 5 depending on what you think is high-dose inhaled corticosteroids.

Dr. Wenzel
Right.

Dr. Yawn
And he's not doing well, so yes, this is kind of patient that I very well may say, "Help."

Dr. Wenzel
Right. And I think from my specialist—wearing my specialist hat, I think if you have a patient who is on a reasonable regimen of asthma medications, the 4- to 5-step sort of category, you've addressed the comorbidities, you've addressed adherence and that patient is still having issues, then it's probably time to have someone step in who has potentially more comfort with some of the more complicated testing that can be done.

Dr. Yawn
Well, I think it's not just comfort. I think hopefully you have more expertise. You've spent a lot of time working in this area.

Dr. Wenzel
Right, correct.

Dr. Yawn
And one of the things that I think many of us realize is that you may also have people in your office... If I was worried about adherence or inhaler technique or things like that, you may have an asthma educator or someone else who can spend the time.

Dr. Wenzel
More time.

Dr. Yawn
And I may not have anybody in my practice—

Dr. Wenzel
Correct.

Dr. Yawn
—who has that kind of time or expertise, so we as primary care refer both for your expertise but also for some of the resources you have in your office.

Dr. Wenzel
Correct, correct, and I think just being able to spend more time with the patient sometimes is a true advantage. So again, things you want to address, the comorbidities, you want to address lifestyle changes, exposures at work, the occupational piece, do that spirometry. If there is a large bronchodilator response, then you might consider adding a long-acting muscarinic. If blood eosinophils and the exhaled nitric oxide are high, well, you can consider systemic corticosteroids. They'll probably go down, but the long-term side effects of

systemic corticosteroids are really not something we want to have to face.

Dr. Yawn
It's not an acceptable long-term plan.

Dr. Wenzel
Solution, correct. And then things like allergy testing, you still want to match your symptoms with your allergy testing, so if somebody says that they are, whatever, the spring is always their worst season but they have no grass allergies, well, it's probably not a true grass allergy, so the symptoms should match the testing. And if they do, then you might want to consider allergy referral or consider for biologic therapy. And I think in all of these cases, once you've, again, got this patient in front of you who's remaining uncontrolled despite addressing all of these issues, on high-dose medication, think about referral to a specialist.

So, when they see that specialist, that specialist now will have on his or her opportunities to treat this patient type 2 targeted therapies. And we sort of talked about type 2 biomarkers. Now we can talk about the biologic therapies that are targeted to those patients that have elevations in those type 2 biomarkers.

So there are 5 currently available biologic therapies for the treatment of patients with severe refractory type 2-high asthma. They are most effective in patients with evidence of type 2 inflammation, including those who have high elevated eosinophils. Typically, 300 was the starting point, 300 or above, but there are some now that can go down as low as 150 and above, and then at least one of them was developed on the basis of 400 and above. High exhaled nitric oxide in that breath, exhaled breath, probably greater than 20 parts per billion if you're going to use a biologic, type 2 targeted biologic on the basis of that exhaled nitric oxide, and then demonstrated allergy for anti-IgE.

You likely will benefit by having 3 or more recent complete blood counts to determine whether the patient is eosinophilic or type 2 high. And again, just don't do 1 CBC and rely on that. It's helpful to have more than one. And again, this need for blood eosinophil testing over time when a patient is symptomatic before starting corticosteroids, that's really a good time to get that complete blood count. I always argue that when a patient goes to the emergency room, before they get their IV Solu-Medrol and you're putting that IV in, draw a complete blood count. Draw a CBC and get that differential because that's the easiest time to get it and the patient is very symptomatic at that time.

Dr. Yawn
And that's a real change because for many, many years we've said, "Don't bother. The WBC isn't going to give you any information of how you're going to treat the asthma exacerbation," and now we're saying, "Well, it isn't just the total white count. It is the eosinophils specific."

Dr. Wenzel
Eosinophils, correct.

Dr. Yawn
And you could get... Instead of the CBC, you could get an absolute eosinophil count, but I've always found those are more expensive.

Dr. Wenzel
They're more expensive than a CBC.

Dr. Yawn
So why bother?

Dr. Wenzel
Correct, correct, absolutely. And sometimes you'll find something else like they have a low hemoglobin or something, which can be helpful too, so get the CBC with a differential. And again, if the patient is already on oral steroids, they really should have no evidence of blood eosinophils.

So, in summary, I think we've begun to now start to identify different subphenotypes of asthma, that to do that we need to address poor inhaler technique, adherence, comorbidities, again to make sure we've addressed all the "easy things," which really aren't so easy, that we want to optimize the pharmacologic management before you get to the biologic agents. Additional diagnostic testing, at least things like spirometry and CBC and specific IgE testing I think can be very helpful, and then using all of that information that we have obtained, including how the patient is doing, to identify whether it's time to refer that patient to a specialist or not.

Dr. Yawn
And I think it's fine to err on the side, perhaps, of more referrals instead of fewer referrals, and I think we now err on the side of waiting

too long, so I think with these new abilities to identify phenotypes, it is a little easier to say, “Whoa, I have this phenotype and they may be candidates for therapy that I’m not comfortable addressing,” so earlier referral frequently.

Dr. Wenzel
On behalf of the American Thoracic Society and the American Academy of Family Physicians, thank you so much for joining us for this very important educational program.

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