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(866) 423-7849

Gaining Control and Co-Managing Severe Asthma

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Gaining Control and Co-Managing Severe Asthma” is part of a video presentation and is provided by the American Academy of Family Physicians and the American Thoracic Society; and. is supported by an independent educational grant from AstraZeneca Pharmaceuticals LP and GlaxoSmithKline. The following program has been edited for our radio listeners, we encourage you to view the video portion of this segment at reachmd.com/CME.

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Here’s your faculty, Drs. Barbara Yawn and Sally Wenzel.

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 4, Gaining Control and Co-Managing Severe Asthma and Co-Managing with our Specialist Colleagues.

Dr. Wenzel:
And I’m Sally Wenzel once again, Professor of Public Health, Medicine and Immunology at the University of Pittsburgh.

Dr. Yawn:
And I’m Barbara Yawn. I am an adjunct professor in the Department of Family and Community Health at the University of Minnesota.

In this module we’re going to review the clinical trial data on the safety and efficacy of the existing targeted therapies, specifically the biologics that are within the last few years to just remind everybody why these are appropriate to consider and for which subtype of patients. So, again, reviewing the clinical trial data, looking at why we think these new medications or newer medications are appropriate for certain groups of people with asthma.

The severe asthma decision tree, is this care by a primary care physician or a specialist physician? We really need to think about this as similar, and sometimes they overlap, but there are certain things that we as primary care physicians definitely need to do in our patients with asthma, especially the ones that are having difficulty and we’re having difficulty getting their symptoms under control. You need to confirm the diagnosis: Is this really asthma? Once you’ve decided it is asthma, then we want to rule out factors that are contributing to their symptoms, their exacerbation and their poor quality of life. And we’ve talked about those things like adherence and triggers.

We want to optimize management. We want to have the management appropriate for the symptoms and the phenotypes now that these patients have, and we want to review their response. It says after 3-6 months, but I think that depends. Sometimes we actually review their response in 4 weeks, and it depends on how symptomatic they are and what kind of changes you’ve made.

If we’ve been through all of those things and we’re still having difficulty or we have a question about, anywhere along the way, of like this wasn’t clearly asthma or not asthma, I can’t make a diagnosis, then we’re going to refer to the specialist who’s going to go through many

of these same steps, like confirming the diagnosis, but also assessing is this severe asthma and what kind of phenotypes may be there, think about appropriate treatment strategies, both nonbiologic treatments that we may not have addressed, thinking about occupational asthma, perhaps, more than we have, or considering add-on biologic for type 2-targeted treatments. They're going to review the response and continue to optimize management.

Now, the one thing that's missing in this slide, of course, is the arrow that goes back to primary care.

Dr. Wenzel:
Absolutely, yep.

Dr. Yawn:
Because these patients, especially as a rural physician, they're not going to drive 60, 70 miles every time they need something with their asthma.

Dr. Wenzel:
Oh, certainly not.

Dr. Yawn:
They're going to come back and see me, so we do need to have this be a loop that we both talk to each other, and now we can do that via the EMR or other easy asynchronous methods, and we don't have to call each other on the phone all the time, but it really is important and appropriate that we go back and forth with: What was your finding? What did you do? What do you expect me to do? If I make a change, I need to let you know I've made a change so we can manage this patient appropriately.

So, when to refer the patient with difficult-to-treat or severe asthma... Well, we've talked about that. Severe asthma can be just as complicated as pulmonary hypertension or pulmonary fibrosis or many other conditions that I don't see very often, and I would like someone helping me decide: What do I do? What are the next steps? And it can be appropriate for the specialist to manage the patient either over a short time, making a diagnosis, changing therapy and sending the patient back, or there are some patients that need to continue having their asthma management really based with a specialist, and I will take care of other things, and if I have an issue with the asthma, I'm going to call you when the patient's there in my office.

Dr. Wenzel:
I hope you do.

Dr. Yawn:
Good. So, atypical or complicated presentation: For example—we've talked about this—when I do the spirometry, they have mixed, obstructive, restrictive disease. They have normal spirometry, but they're very symptomatic. If I happen to get a CT—perhaps they're a smoker and I'm screening for lung cancer and there's nodules, there's evidence of bronchiectasis—they need to go to someone.

Additional testing: The allergy skin testing, we've talked about that is a possibility, but I don't do that in my office. If I need something beyond the blood skin testing, then I might refer for that. Certainly, rhinoscopy, I liked your suggestion of looking with the otoscope, but sometimes you need more definitive.

Dr. Wenzel:
More than that.

Dr. Yawn:
If I think I see something, I need somebody else to see them.

The complete pulmonary function test: This is when we talk about do they need diffusing capacity, do they need total lung volumes, things that can be helpful when I'm trying to distinguish: Is this really asthma or is this asthma and COPD or is there something else going on? And then, certainly, the provocative challenges, the methylcholine, saline, other things, I don't think most of us do those. Those are helpful in a subset of patients and they are important and certainly anybody that needs bronchoscopy.

The other comorbid conditions that we've talked about, the sinusitis, nasal polyps, aspergillosis, severe rhinitis, all of these kinds of things may require a second opinion or actual referral for, "Could you manage this and send it back when you think it's appropriate?" The patient requires confirmation of a history of occupational or environmental inhalants or ingested substances. Sometimes this is necessary for insurance. It's necessary for the employer. This second opinion and this confirmation is another reason I may refer a few patients.

The patient has a life-threatening asthma exacerbation: I don't think any of us have any question about that. They're in the hospital; they're in the ICU; they're on a ventilator; they need somebody else to be helping.

Dr. Wenzel:
Right.

Dr. Yawn:
And they're not meeting their goals after 3-6 months of step 4 therapy. Even if I move to step 5, I think I still need to initiate that referral, and it may take a while. I think that's very important.

The people who use albuterol pretty much every day—and I think we miss that sometimes—that really is not acceptable. That is out-of-control asthma if somebody's having that many symptoms every day. Patients will sometimes say, "Oh, well that's okay. I can control it."

Dr. Wenzel:
They're used to it.

Dr. Yawn:
Yeah, but it is not acceptable.

Dr. Wenzel:
It's not acceptable.

Dr. Yawn:
They most likely can have a better quality of life, and we want to get them there. And then the 2 or more bursts of oral steroids... One of the things I do ask primary care to think about—and I think we see this—is sometimes people with an asthma exacerbation don't get a burst of oral steroids. They got called bronchitis and they get 10 days of antibiotics, so I think we need to be really suspicious. If we have somebody who has asthma and we see, "Oh, yeah, they've gotten antibiotics for bronchitis twice," until proven otherwise, I think that's 2 exacerbations.

Dr. Wenzel:
In many cases it is.

Dr. Yawn:
And I think they need to be evaluated with that in mind.

Dr. Wenzel:
Yeah.

Dr. Yawn:
The complicated therapy: Certainly, your office may have more opportunity for education and support than I do for allergy avoidance, for example. I hear all the time, "Oh, it's dust mites." "Well, throw it in hot water." That doesn't work.

Dr. Wenzel:
It doesn't work in most cases, correct.

Dr. Yawn:
No, it has to be hotter than 132 degrees, I think it is.

Dr. Wenzel:
Yep, boil those little bugs.

Dr. Yawn:
And almost all of us have governors on our hot water heater, and it never gets above, oh, maybe 116.

Dr. Wenzel:
It never gets that high.

Dr. Yawn:
So you're not going to be killing those dust mites. It takes somebody who knows that and has that experience frequently, even for something as common as a dust mite allergy.
When the patient is being considered for immunotherapy, certainly I think they need a consultation. If they have significant psychiatric, psychosocial, family problems—well, the referral may not be to the allergist. It may be to a mental health professional to help me co-manage. And then, certainly, if a patient is being considered for biologics, I think they need a specialist referral.

Dr. Wenzel:

Right. So, when that patient comes to me, there are certain things that I'm going to do as that specialist that you've referred the patient to, and I think the first thing that I'm going to do—other than, again, making sure that the asthma diagnosis is correct and we've addressed all the comorbidities—I'm going to try to phenotype that patient. I'm going to want to understand is that patient a type 2 high asthmatic or a type 2 low asthmatic, and I'm going to do my blood counts; I'm going to do my exhaled nitric oxide—I have it in my office; I use it all the time; I find it actually very, very helpful—and spirometry pre and post bronchodilator.

And again, I think if I have a patient who has normal pulmonary function testing and they've got evidence on whatever test, ACT, APGAR, etc., that their asthma is not well-controlled, I'm going to want to do a bronchoprovocation test. I'm going to want to do a methacholine test to determine, "Gee, do they really have asthma?" "Is something else going on here?" I don't do as many of them as I used to because I think with our combination of inflammatory biomarkers, exhaled nitric oxide and blood eosinophils, we can do less now.

Dr. Yawn:
Well, and your inspiratory loop on your spirometry.

Dr. Wenzel:
And your inspiratory loop, etc., but it still remains a test that can be valuable in some cases. You want to distinguish, again, is this difficult asthma, which is really asthma with a lot of comorbidities, or is it truly refractory asthma that you've got them well-managed and you still can't get them under control. And then again, you want to distinguish that severe asthma patient from somebody with a similar illness, so things like EGPA, eosinophilic granulomatosis and polyangiitis, hypersensitivity pneumonitis—actually not that uncommon and again very much exposure-related, similar to the occupational asthma—asthmatic granulomatosis, which is actually a type of asthma variant that we described at the University of Pittsburgh now getting close to 10 years ago which has granulomas in the lung in asthma and seems to be very unresponsive to typical therapies; sarcoidosis, you can have airway involvement in the sarcoid and that can masquerade as severe asthma; and then the allergic bronchopulmonary aspergillosis, ABPA, which is a type of asthma but leads to actually substantial bronchiectasis and which can actually be diagnosed on a CT scan and with blood testing. So, again, all of those things really should be identified as either the actual diagnosis or the confounding diagnosis, because again, the treatment for these are going to be different than just treatment for asthma.

Sometimes CT imaging can be helpful. I probably would say that, of the patients that I see with difficult asthma, I probably have a CT scan on somewhere around three-quarters of those patients they will actually get a CT scan. I think it's especially important when there is an abnormal presentation to the symptoms, and I would always get a high-resolution noncontrast CT scan. There's almost no reason to give a patient contrast for these types of diagnostic patterns.

Sinus CAT scans can actually be very helpful, especially in adult-onset asthma patients. Patients may not know or appreciate that they have any sinus problems, but then you look at their sinus CT scan and their sinuses are completely plugged with mucus. And again, there's obviously different treatment approaches to that. Laryngoscopy: Typically, again, if you have provocative challenge that you're looking to see is this asthma, what I'll do is put a laryngoscopy at the end of that methacholine challenge such that I've irritated their airways, irritated their vocal cords, and if I find they have a flat response—they actually don't have a drop in their FEV1 during their methacholine challenge—I will go in and do a laryngoscopy at the very end to see if they have closure of their vocal cords. Many times you'll be able to pick it up on that testing.

Sometimes, if you have people who—even though they're on high doses of proton pump inhibitors or H2 blockers, they can still have refractory reflux disease. I think it's time to send a patient to a gastroenterologist if that's the case. And then we've already heard a little bit about the methacholine and the lung volume testing.

All right, so we're pretty sure this patient has severe asthma. We've done all the right tests. How are we going to manage this patient? Well, obviously, the first thing you want to do is make sure that they have been tried on all of the appropriate nonbiologic treatments, and if they have not been on high-dose therapy, you can certainly increase their dose for at least 3-6 months. And sometimes I've seen people respond to higher than the standard dose inhaled corticosteroid so that they're on their combination therapy, and there's a maximum amount of inhaled corticosteroids that you can use in combination therapies, so you'll add a second inhaled corticosteroid. Sometimes that works, although, actually, relatively small percentage of the time. Things like long-acting muscarinics, if they have a persistent bronchodilator response, again leukotriene modifiers, if there's concomitant allergies or upper airway issues, and sometimes in patients who have aspirin-exacerbated respiratory disease and nasal polyps, these drugs can be helpful too. And then macrolide antibiotics, of course, have been talked about quite a bit, so things like azithromycin, clarithromycin can help, and they can help astonishingly well in some patients, but we still don't really know how to target who are the patients that respond.

Dr. Yawn:
And there was just a publication talking about using them in children, and the response wasn't nearly what people had hoped for.

Dr. Wenzel:
Had hoped it would be, yeah.

Dr. Yawn:
And so that doesn't look like it's something we're going to be doing very regularly.

Dr. Wenzel:
And I would say, at least again in my experience, it's patients who develop their asthma in adulthood and often give you a history of, "I had a bad cold, it went to my chest, and I've never been better since." In those cases it's probably worth giving a try. Again, it's a relatively inexpensive, relatively benign medication, and some of those patients will, in fact, get better.

And then don't forget to discontinue ineffective add-on therapies. I can't tell you how many times, again, rather than take anything away people just keep piling on medications, and there's no way... We talk about adherence. If a patient is on 6 different medications—I don't care how good you are—you're never going to be able to be adherent to all of those medications.

But then now we're fortunately at the era where there are alternatives, and this is where we can start considering these biologic agents. And I think these biologic agents really emerged with our better understanding of the inflammatory molecular phenotypes that underlie patients who have severe, difficult asthma. And the whole concept now is: Bring the right drug to the right patient. Don't expose patients to drugs that might have some side effects if it's not the right drug for that patient, but on the other hand, if it is the right drug for that patient, get them on that as soon as possible.

Now, most of these drugs have been trialed in large-scale clinical trials. Thousands of patients have been treated with these medications by now. And really, all of these drugs have shown an ability to reduce steroid-requiring exacerbations, probably the most important outcome, and there is some impact on other outcomes, things like asthma quality of life, symptoms, upper airways, as well as lung function testing, so they have been able to hit all of the right things.

Dr. Yawn:
Well, and you had the SNOT there. In case people don't know what that is, that is like a control test for—

Dr. Wenzel:
For your nose.

Dr. Yawn:
—for your nose, yeah, and it's kind of what it sounds like.

Dr. Wenzel:
Yep, it absolutely is. So there are currently 5 FDA-approved biologic agents based on what the FDA has approved, and the GINA guidelines. The oldest of these is anti-IgE, omalizumab. Many of you are probably familiar with that. It was first asthma biologic. It's been available for, shockingly, nearly 20 years, so a very long time, and it was developed to target allergic asthma. We'll get into that a little bit more.

Then there are 3 drugs that actually target the IL-5 pathway, one of which targets the cytokine itself, anti-IL-5, 2 of which target the anti-IL-5, and one of which targets the receptor, the anti-IL-5 receptor. The data show that increasing blood eosinophils are associated with increasing risk of asthma exacerbations. That's why it's really important to get the eosinophils on the CBC. But I think most of the data would say that they are primarily effective in patients with elevated eosinophils, and most studies would say greater than or equal to 300 eosinophils in the peripheral blood and sometimes even in patients who have a little bit lower than that. That's why, again, it gets back to this measuring it several times because many of the times when you measure 175 or 200 eosinophils on 1 measurement, if you keep measuring it, it will be about 300 on the next or another time.
And then there's one drug that targets the anti-IL-4 receptor, which is the receptor that actually binds 2 different cytokines, interleukin 4 and interleukin 13. They are present on many cell types. It's a broad therapy that targets the single receptor—and again blocks both IL-4 and IL-13—and it appears to work in patients with slightly lower levels of blood eosinophils, greater than or equal to 150 per microliter, or elevated exhaled nitric oxide around 20 parts per billion.

So let's go through the evidence that supports these different biologics. Again, omalizumab, the first of these, targeted the IgE molecule. It's administered via subcutaneous injection every 2-4 weeks. The dosing is actually dependent upon the size of the patient, their blood IgE levels, and again, somewhat dependent upon their age as well. It's useful for patients age 6 and above, or at least it's been indicated for patients 6 and above, but you can have patients that are too heavy to use it. If you're really over 300 pounds even with a relatively low IgE level, it's going to be hard to dose it appropriately, and then if you have a very high IgE level, it's not recommended for patients with very high IgE levels because you can't dose it high enough in both of those cases.

The overall response rates are somewhere between 60% and 70% in patients with allergic asthma, but interestingly, allergies have never been a very good predictor of who responds to omalizumab even though it was developed that way, which I always find fascinating. It seems to be in a post-hoc analysis—probably needs to be repeated in a prospective manner—that if you have high evidence or evidence for high type 2 biomarkers or high exhaled nitric oxide, high blood eosinophils, those are the patients that are going to do the best with that whether or not they have allergies by traditional measures.

Dr. Yawn:
Well, and you can sort of understand though, we're talking about something that's been around for 20 years. That means the testing of it probably started 25 or 30 years ago.

Dr. Wenzel:
Of course.

Dr. Yawn:
And we weren't looking at—

Dr. Wenzel:
We weren't doing it.

Dr. Yawn:
—pheno and blood eosinophils at that time, so the best marker we had of those 2 things was they have allergies.

Dr. Wenzel:
They have allergies, exactly, but we've learned since then.

Dr. Yawn:
We have.

Dr. Wenzel:
There is a safety notation. There is a risk of anaphylaxis in a small percentage of patients, and all patients are advised to have an EpiPen available at the time of dosing. It's dosed in a clinic, it's not dosed at home, and so that's important you have a clinic that can do that. It's indicated for moderate to severe persistent asthma in patients, again, over the age of 6 or above with a positive skin test or evidence for specific IgE to perennial or seasonal allergens and whose symptoms are not adequately controlled on moderate to high-dose inhaled corticosteroids. There are a few other indications, but we're not going to particularly talk about them.

Dr. Yawn:
Well, and this one has been around a long time, and after a patient is stabilized and established on this and we have gone from weekly injections to every 2-4 weeks, I think sometimes these patients end up back in my office for me to give them this, and the reason is that, again, the nearest allergist is 60, 70, 80 miles away.

Dr. Wenzel:
Sixty miles away, right.

Dr. Yawn:
And in Minnesota in the winter, that can be a blizzard away.

Dr. Wenzel:
Daunting, that can be daunting.

Dr. Yawn:
Yes, and so, as long as we are comfortable with the very unlikely occurrence of anaphylaxis and feel like we could handle it—we have a crash cart, we know what to do—I'm comfortable with a patient after they have been on this for 6 months to a year to have the injections actually in my office.

Dr. Wenzel:
In the primary care, yeah.

Dr. Yawn:
I used to give allergy shots after stabilization too, so I think there is that co-management possibility.

Dr. Wenzel:
Absolutely. And, of course, there are some complicating factors because sometimes the office has to buy and bill for it, and sometimes

there is a pharmacy that buys and bills for it, so all of those things can complicate the situation; but, yeah, I mean, in most cases, if primary care is willing and able to give these drugs, there's no reason that you have to travel the 60 miles to see the specialist when it certainly could be given in the primary care office.

Dr. Yawn:
Well, I have to say that because omalizumab has been around for 20 years, I'm a lot more comfortable with it than I am with the newer agents.

Dr. Wenzel:
Yeah. Well, you know, to be honest with you, I think the newer agents may actually be even safer than the omalizumab from the standpoint of those acute reactions.
So, mepolizumab was the first of the anti-IL-5 antagonists that was developed. It's administered, again, by subcutaneous injection. There is now, just in the last few months, the ability to administer it at home, so you actually get around going to the specialist or the primary care office. It's dosed once a month. It's fixed dosing. There's no adjustment for weight or eosinophils or anything. It's been shown reliably to reduce exacerbations in patients who have elevated blood eosinophils and generally around 300, although may be some wiggle room there. It improves quality of life. It was the first biologic to definitively show that if you have someone who's on daily prednisone, daily Medrol, that you can reduce their oral steroid dose when you start treatment with an anti-IL-5 drug, which was a huge advance. We have had no drugs that have ever really been able to reliably show that.

Dr. Yawn:
That is very, very important for those very symptomatic patients.

Dr. Wenzel:
Very difficult patients.

Dr. Yawn:
And this is the one that has just changed age indications too, isn't it?

Dr. Wenzel:
Correct, so this one now can be used for children age 6 and above based on some very good safety data that has come out in a group of children. It is indicated for maintenance therapy, add-on therapy, in patients with very severe asthma. Again, typically, it's patients who have a history of exacerbations, who are on high doses of inhaled and/or oral corticosteroids who have evidence for high eosinophils in their blood. And it's also recently been approved for eosinophilic granulomatosis with polyangiitis, although the dosing is different in those patients. It's actually 3 times the dose than it is in asthma.

Dr. Yawn:
Well, and this one, as you said, is approved for the patient to administer or the parent to administer at home. Do you start it that way, or do you start them in your office for a few doses?

Dr. Wenzel:
Well, this just has happened, but to be honest with you, my specialist hat would say that I would want to do it in the office probably for 3-4 months to kind of understand is the patient getting better with it and is the patient having reactions to it, whatever, and then when I'm comfortable that they're not, then I would send them out with their home administration kit and allow them to continue it at home.

Some of us have thought that having them come into the office is actually helpful because when there are concerns about adherence, we know that the patients are adherent so long as they are coming into the office, and it's when you start administering at home you don't then really know are they taking their medication any more than you know that they're taking their inhaled corticosteroid, so there's always that sort of element that you have to play with as well.

Dr. Yawn:
Well, and I think that's where some communication back and forth may be helpful because I may have seen this patient for 5, 10 years—

Dr. Wenzel:
Of course, yes.

Dr. Yawn:
—and I have some sense of how well I think they are able to adhere, and if I do have adherence concerns, then I really ought to let you know because I would really not like them to be trying to do something at home when...

Dr. Wenzel:

Home administration, right.

Dr. Yawn:
There are people that just have very chaotic lives for a whole lot of reasons.

Dr. Wenzel:
Yep.

Dr. Yawn:
And this just wouldn't be a good idea.

Dr. Wenzel:
It wouldn't work for them.

Dr. Yawn:
Right, and we need to communicate about that.

Dr. Wenzel:
I think that's... Again, that wonderful team that can exist between primary care and specialists.

Dr. Yawn:
Yes.

Dr. Wenzel:
So there's another anti-IL-5 antagonist which is also on the market. Unlike the mepolizumab, this is administered by a milligram per kilogram dosing, and it's administered as an IV infusion, so you actually have to go into an infusion center, some center who's able to give—start an IV and monitor it. It's given over a 20- to 50-minute period of time, again once a month. Similar to mepolizumab, it's been shown to reduce asthma exacerbations in eosinophilic patients by about 50%, improves lung function testing. It does, like omalizumab, have a black box warning about frequent anaphylaxis, so again, patients are required to be observed after dosing. I would have an EpiPen available if you're going to dose with this drug, but again, this drug is only given in infusion centers. It's indicated for add-on treatment of severe eosinophilic asthma. It is only indicated for adults 18 or above, not indicated for children, and although it could probably be used in patients who have eosinophils less than 400 microliters, it was studied in patients who had eosinophils of at least 400 per microliter, so it was studied in a slightly more eosinophilic group than any of the other anti-IL-5s. It's not indicated for any other diseases.

Dr. Yawn:
One of the things that I always like to be able to do is tell my patients what they could anticipate. So, if one of them comes back and they're on this drug and they have to go to an infusion center, do they also go to your office every month? How does that work? Or do you just send them to an infusion center and see them every 3 months?

Dr. Wenzel:
Every 3-4 months, yes.

Dr. Yawn:
Okay.

Dr. Wenzel:
So, as long as there's no issues with the administration, I will have them go to the infusion center, get their infusions once a month. It's noted in the chart, obviously, that they showed up or didn't, and then I will see them every 3-4 months to monitor their improvements or lack thereof because not everyone responds with these treatments.

And then the third of the anti-IL-5 targeted therapies is benralizumab. It differs from the other ones in that it is a receptor antibody, so it targets the IL-5 receptor as opposed to the cytokine itself. It also differs from the others because it is administered as a subcutaneous injection every 4 weeks but only for the first 3 months, and then so long as the patient looks like they're responding, one would continue it at every-2-month dosing, so it benefits from, again, having a...

Dr. Yawn:
Stretching it out.

Dr. Wenzel:
Stretching it out a bit. It reduces exacerbations, again, similar to the other agents, somewhere between 40-50%. Like mepolizumab, it

has been shown to decrease your dependency on oral corticosteroids in a very nice steroid-sparing study. There's probably more prolonged suppression of blood eosinophils with benralizumab than there is with either mepolizumab or reslizumab, and we don't understand exactly why that is, but seemingly targeting the receptor and actually involved in killing the eosinophil as part of that you probably have a better and more prolonged effect on blood eosinophils.

There is a higher rate of hypersensitivity reactions, again about 3%. Again, anaphylaxis is not completely uncommon, but they don't have a black box warning yet. It may get to that level eventually, but right now it does not.

Again, indications are very similar to the others that we've been talking about, add-on maintenance therapy for severe asthma but over the age of 18 with an eosinophilic phenotype. And typically, again, the eosinophils are defined as greater than or equal to 300 with some indication that it may be beneficial in those with greater than 150.

It's not indicated for any other disease either, but it seems to work best in patients who have adult-onset disease, interestingly, so we have eosinophils and adult-onset disease. If you have eosinophils, adult-onset disease, nasal polyps and oral steroid dependency, those are probably the patients that actually do the best with adding on this anti-IL-5 receptor antibody.

Dupilumab is the last of the new biologics. It's different from any of the others. It blocks the alpha subunit of the IL-4 receptor. It, like the others, is a subcutaneous injection, but unlike the others, except for the new indications with mepolizumab, it is self-administered, so you start out right from the beginning giving the patient instructions on how to self-inject and then sending them out with their medications, and they inject every 2 weeks. It's not an every-4-week drug. It's an every-2-week drug. The data are pretty clear on that. It starts with a loading dose, and there are 2 different doses that have been approved, a 200 mg every other week and a 300 mg every other week. The differences in their efficacy are actually modest, and the reasons that there are 2 doses are based on its use in eczema, atopic dermatitis, and its use in the steroid-sparing study where it was done at 300 mg. So it's available as 2 different doses, but I would always start with the 200 mg dose to be quite honest with you.

Dr. Yawn:
But would know that if this is a steroid-dependent patient and you don't get what you want, you can go up.

Dr. Wenzel:
You could certainly increase the dose.

Dr. Yawn:
It isn't that, well, there's nothing else here; I have to go somewhere else.

Dr. Wenzel:
You can increase the dose.

Dr. Yawn:
How long would you wait before you would increase the dose?

Dr. Wenzel:
I would probably wait at least 3 months before I increase the dose.

Dr. Yawn:
Okay.

Dr. Wenzel:
Again, like the others, there are consistent reductions in asthma exacerbations, maybe a little bit more than with some of the other drugs of about 60%. It does, in fact, improve lung function, probably more so than the other drugs do, but again, works best in patients with more and more evidence of type 2 inflammation, so if you have high blood eosinophils, if you have high exhaled nitric oxide, those are the patients who this drug is going to work in, at least more likely to work in. There is also data to suggest that you can reduce your dependency on oral corticosteroids just like the mepolizumab and the benralizumab with really pretty similar data.

You can have hypersensitivity reactions, surprise, surprise. All of these drugs seem to give you some possibility of having that sort of reaction. It is, again, indicated for add-on maintenance therapy in moderate to severe asthma, so their indication actually at the FDA level was moderate to severe asthma, age 12 and above, and again with a type 2 high phenotype.

It is approved for other diseases. It's approved for eczema, atopic dermatitis, from 12 and above, and it's also now recently been approved for add-on treatment with uncontrolled chronic rhinosinusitis and nasal polyps. So, even if there's no evidence of asthma but you have really severe upper airway disease, especially with nasal polyps, there is an indication for it in that disease process as well but again, in adults, not in children.

Dr. Yawn:
Can you talk about the moderate? To me, the idea of, “I’m going to go to a biologic for moderate asthma” is a little bit of a concern because they’re expensive.

Dr. Wenzel:
They’re very expensive. They’re very expensive. I was a little surprised to see that. It’s based on the patients that were in the clinical trials because the patients in the clinical trials were on moderate to high doses of inhaled corticosteroids. It did work in those patients, but I’m in complete agreement with you, that until you’ve gotten to high-dose inhaled corticosteroids and combination therapy and shown that the patient is not doing well with that, I would not use any biologic until you get to that threshold. That’s what the FDA indications are.

Dr. Yawn:
Yes. Well, and there’s always FDA indications and what you do in the real world of clinical practice.

Dr. Wenzel:
Absolutely, absolutely. Well, now we start our patient on our biologic. They’re expensive. We really don’t want to continue the patient on the biologic for extended periods of time if it’s not working. It does have potential for side effects—they all do—and they’re very expensive, so you really want to reevaluate the patient every 3-6 months for sure.
You want to monitor asthma symptom control, exacerbations in lung function, but to be honest with you, the biggest signal for these drugs is on exacerbations. It gets a little complicated when you’re monitoring patients for exacerbations. If they have 2-3 exacerbations per year and they’ve been on the drug for 3-4 months but they don’t feel better, do you know whether to continue that drug or not? They haven’t gone a long enough period of time to know whether they’ve had a reduction in their exacerbations, so it can get pretty complicated. And you can have those rooms of pulmonologists and allergists and they will probably fight about that one to figure out exactly when is the threshold to try a different biologic.

But you certainly want to assess your type 2 comorbidities. You want to see if there is an effect on the upper airway. Dupilumab actually has a pretty good effect on the upper airways. Atopic dermatitis, obviously; eosinophilic esophagitis, interestingly very controversial whether these drugs are going to help eosinophilic esophagitis, maybe with the anti-IL-4 receptor antibody, but the anti-IL-5s to date have not shown efficacy in that area; again, nasal polyps with the indication for dupilumab in relationship to nasal polyps.
Have they been able to taper back on their oral corticosteroids? That’s a really good indication of response to therapy. Is the patient satisfied? Does the patient feel like “I’m doing better on it”? That’s another really important question to answer. And then, obviously, you want to continue to optimize their overall management and amend their treatment plan as needed.

I think you can step down if they’ve got a good response to type 2 targeted therapy, but you’re really going to have to be careful with how much you step down because they’re going to have to stay, at least for now, on their background combination therapy, typically at high dose, or many insurance companies will not give you medication support for that drug because they want you optimized on the combination therapy, so if you start stepping down, then they’ll say, “Well, you could have done okay just on that high-dose combination therapy. We’re not going to pay for the biologic anymore.” So it gets complicated.

Dr. Yawn:
Which is sort of a catch-22. They didn’t get on the biologic hopefully—

Dr. Wenzel:
Of course.

Dr. Yawn:
—unless they weren’t doing well.

Dr. Wenzel:
Exactly.

Dr. Yawn:
And now saying, “Well, wait a minute, you have to go back to what you weren’t doing well on before”—

Dr. Wenzel:
Right, right, because this one...

Dr. Yawn:
—it sounds somewhat circular.

Dr. Wenzel:
It's a very circular argument. All right, let's move on to our case studies.

Dr. Yawn:
All right.

Dr. Wenzel:
We're going to revisit old Liam here. So Liam is still a 12-year-old with asthma, poorly controlled on moderate-dose ICS and leukotriene receptor antagonists, issues with the various exposures, incorrect inhaler use, but they have all been resolved. His APGAR is still 4, so we're still in that uncontrolled range, still having day and nighttime symptoms, not able to be as active as he'd like to be, his FEV1 is not normal even on a good day, his allergy testing is negative, can't really do much of that, and he's not had a CBC yet. So, how do we manage him? Do we increase his combination therapy? He's on moderate-dose ICS. Do we refer him to a specialist?

Dr. Yawn:
Well, I think that... You know, he's 12, and we know that there are at least 2 of the biologics now that are possible in a 12-year-old, so I know in the back of my mind that if I refer, that is a possibility that that is something that could be appropriate for him, and he is still quite symptomatic.

Dr. Wenzel:
He's still pretty symptomatic.

Dr. Yawn:
Yeah, and when he can't do the things he wants to do and his FEV1 is... Really, for a 12-year-old, I don't like 75%.

Dr. Wenzel:
That's very obstructed for a 12-year-old.

Dr. Yawn:
That doesn't make me happy at all. So I think it really is time that I send Liam on to a specialist with telling the parents exactly what we just talked about, that he's not doing well, he can't do his activities. They've modified and done a great job of trying to address everything that they and Liam could.

Dr. Wenzel:
Is addressable.

Dr. Yawn:
And it's still just not working.

Dr. Wenzel:
Yeah, he's still not where we'd all like him to be. Would you increase his combination therapy?

Dr. Yawn:
Well, I'm pretty high up on his combination therapy right now. Again, I probably would because it's going to take him 3 months to get the referral.

Dr. Wenzel:
To get to see me.

Dr. Yawn:
That's right. So, yeah, I think during that 3 months I am going to try because now he will have been on high dose, the highest dose therapy that's acceptable for him. I'm going to check his CBC. No, I'm not going to do his pheno because I don't have pheno in my office. I'm not going to do a CT or any of those things.

Dr. Wenzel:
Right.

Dr. Yawn:
But I certainly can get at least 1 CBC with differential and try; and, yes, then I'm going to do 2 things at once.

Dr. Wenzel:
Right. So you repeat his spirometry and he's 73%, again that same level of obstruction. He's got good reversibility. This time his allergy

testing comes up positive. Who knew? Sometimes allergy testing can change. In this case it does come up positive. His exhaled nitric oxide is 54. That's very elevated.

Dr. Yawn:
I was going to say, that's quite high.

Dr. Wenzel:
That's very elevated, but his blood eosinophils are kind of in that borderline zone. They're 250 per microliter. And he clearly has some nasal congestion, but you don't see polyps. Well, what is his phenotype? Well, he's 12. He's had asthma for much of his life. He's certainly going to be an early-onset disease with evidence for type 2 inflammation. He's got allergies, he's got high exhaled nitric oxide, and his blood eosinophils are in that borderline on 1, on 1 blood count.

So at that point you've got a child who's got type 2 high asthma, and at this point it looks like he has some upper airway issues going on, so again, obviously I think you're going to treat his nasal symptoms and put him on nasal rinses and nasal steroids.

And by the way, I'd be interested to know how often primary care uses nasal irrigations or nasal rinses. Is this something that gets talked about very often?

Dr. Yawn:
It does. It gets talked about a lot more now, and there are several over-the-counter products. We do talk to patients about, "Be sure you're using sterile water when you do those."

Dr. Wenzel:
Yes, yes, distilled water.

Dr. Yawn:
You don't just run it under the tap and do it.

Dr. Wenzel:
Yep.

Dr. Yawn:
I think that one's critical. But I think this is something with some of the newer devices that they can do it very easily in the shower or bathtub, whatever, so yes, I think they are getting used more and more with the saline. Now, I'm not doing a steroid nasal rinse necessarily. I'm doing the saline and then having them use the nasal steroid separately.

Dr. Wenzel:
Right, right, right, but I think they can, in fact, be very helpful for many patients.

Dr. Yawn:
I agree.

Dr. Wenzel:
And it's such a simple, inexpensive thing to do.

Dr. Yawn:
It is. Well, and kids aren't as bad as adults about shooting something up their nose. They have been doing that since they were very little.

Dr. Wenzel:
For a long time, yeah.

(laughter)

Dr. Wenzel:
Exactly, exactly. So the dose was increased to high-dose combination therapy, and 3 months he still had to go to the emergency room, still went to the emergency department because of an asthma attack. And again, you're doing all the right things here. You clearly are. He was treated with omalizumab by the specialist that he finally got in to see. Boy, those specialists have those long waits. Anyway, and you saw that now a couple months later his lung function improved a little bit. He's got less allergy symptoms, and his exhaled nitric oxide dropped a little bit. But now he goes back to you, and now you're there with him and his mom, and they report, "Well, we've seen that specialist, but maybe we're still not doing quite as well as..."

Dr. Yawn:
And I'm going to agree with them, and I'm not going so say, "Well, we're going to see a different specialist because that one didn't do the right thing." We're going to talk about the fact that what was done seemed appropriate first step in a biologic. This is the one that's been around for a very long time, and people who are a little bit uncomfortable with medications, if I can tell them, "Look, this has been used for 20 years," they're going to be a little more comfortable.

Dr. Wenzel:
Yes.

Dr. Yawn:
So I think that this was an appropriate trial—

Dr. Wenzel:
Very appropriate.

Dr. Yawn:
—and it didn't work, but they should be kind of used to that by now because we've had to try several things, and so, what I would say to them is, "This is not a failure of biologics. This is a first trial with a biologic, and I think that you need to go back and see the specialist again, and let's talk about whether or not there is a different biologic that might be more appropriate for you and your special type of asthma and might be more helpful. So let's don't give up. Let's try again."

Dr. Wenzel:
"Let's try again." And again, I think this gets back to how we're trying to come up with biomarkers that better predict this is the right medicine for Liam, but we're not quite there yet, and there still is going to be a little bit of trial and error. We've identified pretty easily that he's a type 2 high asthmatic, but we don't really know what the best therapy for him is. And clearly, omalizumab has been around for the longest amount of time and it has the absolute longest experience in children, and everyone wants to consider safety first—

Dr. Yawn:
Of course.

Dr. Wenzel:
—when you're dealing with a 12-year-old, so I absolutely think that that was correct.

Dr. Yawn:
And I think that they can understand because maybe one of the parents has hypertension, for example, and it's unlikely that the first medicine that parent got on for their hypertension is the one they're on now, and so you can kind of explain this is all us needing to try and see what's best for you, and most of the time we do have to try more than one thing.

Dr. Wenzel:
Unfortunately, that is too often still the case. All right, new case.

Dr. Yawn:
Yes.

Dr. Wenzel:
Terry, 45-year-old man, no history of childhood asthma or allergies. Unlike Liam, his asthma actually started in his mid 30s, had a history of sinus disease, postnasal drip, and some good family practice doctor looked in his nose and saw nasal polyps.

Dr. Yawn:
And I would be so excited if I saw a nasal polyp. I think I'd call the specialist immediately and say, "I saw one. I saw one."

(laughter)

Dr. Yawn:
They're not easy to see.

Dr. Wenzel:
No, they're not, but sometimes they are almost hanging out in the nose.

Dr. Yawn:
Right, right.

(laughter)

Dr. Wenzel:
So anyway, but... Unfortunately, Terry has not been very good with taking his medications. He has been taking his LABA ICS 1 time per day, not twice a day as prescribed. Obviously, there are some LABA ICS which are once a day, but he was on a twice-a-day one and he was only taking it half as often as he needed to, but he's beginning to adhere better. He's now on high-dose combination therapy and actually taking it twice a day or as written. Those issues have resolved, but his asthma is still not very well-controlled. His ACT is 15, and he has had 2 exacerbations in the last year.

So, what do we do now? So I'm going to weigh in on this one first because this guy came to me now, and so, as the specialist, I'm going to assess him.

Dr. Yawn:
Well, yeah, because if we saw those polyps, you got him.

(laughter)

Dr. Wenzel:
So he's been wheezing with upper respiratory tract infections over the last couple of years, especially if he takes an ibuprofen. A nonsteroidal anti-inflammatory drug will make his asthma symptoms worse. We do a sinus CAT scan, and goodness knows you can hardly even see his maxillary sinuses anymore. They're completely occluded with mucus, and his ethmoid sinuses have some obvious polyps that you can see there. His blood eosinophils aren't just 300. They're twice that. They're 600. And the review of his chart reveals that he's been up to a thousand on a few occasions. Now, a thousand ought to make everybody sort of step back and take notice. His exhaled nitric oxide is really high.

Dr. Yawn:
That would make you stop too.

Dr. Wenzel:
And it does; it makes me stop.

Dr. Yawn:
It would make me do it again and say, "Is this wrong?"

Dr. Wenzel:
Oh, trust me, some of these patients can have exhaled nitric oxide of above 200—

Dr. Yawn:
Whoa.

Dr. Wenzel:
—on all these medications and their exhaled nitric oxide is still above 200. His IgE level is maybe minimally elevated but certainly not very high. In contrast to Liam, he is an adult-onset, type 2 high, very eosinophilic asthma patient with aspirin-exacerbated respiratory disease. I mean, his history is pretty clear. He takes ibuprofen and he gets increased wheezing.

So he returns. You make sure he doesn't take any ibuprofen, but like most people with AERD, he is still wheezing, and he's still short of breath, and he's not taking any aspirin or nonsteroidals, and his asthma is not better. He also has GERD. You repeat his evaluation with another CBC and, oh, they haven't improved. They're still high. They're still 800. His IgE is a little bit higher now, slightly elevated, and his exhaled nitric oxide has come down a little, but it's still very high. He's still at 50. And he's taking his combination therapy, back to taking it once a day, and it's really supposed to be twice a day.

So, does Terry have severe asthma? Well, I would say there's every evidence in the world that Terry has severe asthma. We've treated his sinus problems already. We treated him with nasal steroids and nasal rinses. We've treated his GERD, but he continues to have more courses of oral prednisone, more courses of steroids, and he is certainly needing his referral.

So the treatment decision as to which biologic he should be on, he's a candidate for any of the type 2 biologics at this stage. The only, perhaps, direction that you might have is that the anti-IL-4 receptor antibody was recently approved for the treatment of nasal polyps. The anti-IL-5s have not been approved for the treatment of nasal polyps, but certainly, anti-IL-5 receptor antibodies have been shown to work best in people with nasal polyps, although the impact on their nasal polyps has not yet been demonstrated. They should certainly continue to avoid all aspirin and other nonsteroidal anti-inflammatory drug products and continue his nasal rinses and his nasal steroid with possible referral to an ear, nose and throat physician. Although, just removing nasal polyps isn't a very good treatment for them.

They typically grow back. So you remove them once, and within 6 months or so they can certainly come back.

All right, here is, I believe, our final case, Joan. This is a 37-year-old woman, uncontrolled asthma, again despite addressing all these comorbidities, adherence, inhaler technique. She's referred for an allergist evaluation, and when this person is seen, they're already on a biologic and high-dose combination therapy, but she comes to you because, guess what, she's having an asthma exacerbation.

I'm going to hand it off to you now. What do you do? She's on a biologic already. I don't know which one, but she could be on any of them. What do you as her primary care physician do? On this day she's coming back to you and she's in the middle of an asthma exacerbation.

Dr. Yawn:
Well, I'm probably going to try to contact my colleague and say, "Hey, there's a problem," but I am going to treat the acute exacerbation. I am going to give her oral corticosteroids. There is no contraindication—

Dr. Wenzel:
Absolutely not.

Dr. Yawn:
—just because she is on the biologic for her... No contraindication for her to have the oral steroid, so you still treat the exacerbation, but I think it's really important that I don't just treat it and then say, "Well, just keep your usual appointment." I think I need to let her allergist or pulmonologist, whichever one saw her, let them know what's going on because they may choose to have her come back sooner—or especially if this is a person who is doing their therapy at home.

Dr. Wenzel:
Right.

Dr. Yawn:
There are some real questions about maybe adherence. If she's going to an infusion center, she may not be seen in the allergist or pulmonologist's office except every 3-6 months.

Dr. Wenzel:
Correct.

Dr. Yawn:
And so this is one that I think we need to make sure, because if someone's on a biologic and they're having exacerbations, they need to be reevaluated in my opinion.

Dr. Wenzel:
Correct. Yes, I would completely agree with all of that. And again, the golden rule is, if there's a problem with asthma exacerbations, there's no change in the treatment of the asthma exacerbation from what there would be if they weren't on a biologic.

Dr. Yawn:
Right. You don't want to sit around and wait because maybe the specialist can't call you back for 2 days because they're tied up with something or other. You don't want to not treat the patient for 2 days.

Dr. Wenzel:
No, treat that asthma exacerbation.

Dr. Yawn:
You want to treat it now.

Dr. Wenzel:
Absolutely, absolutely. All right. Well, there is one final case here. This is Marco. Marco is 43. He's got a sprained ankle. During his review of his medications, he tells you that he stopped using all of his asthma medications because dagnabbit those biologics are working so well that he's the happiest he's been in a long time and he doesn't need any of those other medications. Now what do you do?

Dr. Yawn:
Well, I certainly don't think I'm going to reinforce stopping all his inhalers. I think that's a little drastic because we don't know what's going to happen 3-6 months from now, so I am going to let his specialist know that he has stopped them. I'm going to see if I can convince him that we will step down from what he was taking but still leave him... If he was on high-dose combination therapy, can we

step down to medium-dose combination therapy and get him back to the specialist, but I'm not going to say, "Oh, that's terrific, just stop everything"—

Dr. Wenzel:
Right.

Dr. Yawn:
—because, as you said, this can be very problematic, and asthma is variable.

Dr. Wenzel:
It's highly variable.

Dr. Yawn:
What's well-controlled this month may not be doing so well 2 months from now, and I want him to have those medications to continue.

Dr. Wenzel:
And I completely agree. And like we said, sometimes insurance will not pay for the medications if you're not taking even high-dose inhaled corticosteroids, but I think there's no data to suggest that these drugs will work in the absence of background inhaled corticosteroids, so I think it is very important to at least have the patient on medium-dose inhaled corticosteroids while they're on these medications...

Dr. Yawn:
Well, and to let you know. I assume you think that's pretty important too.

Dr. Wenzel:
Yes, absolutely.

Dr. Wenzel:
My job is to try to figure out what is the best first biologic, and it's not so easy, and I'm going to make mistakes, but there are certainly some indications, as we've talked about. Certain drugs seem to work better in people with adult-onset disease and nasal polyps, and there are some people that may have concomitant comorbidities that would drive us down one path or another. Obviously, if somebody's got severe atopic dermatitis and asthma, one might consider an anti-IL-4 receptor antibody.

I think it's my job to monitor the dosing to make sure that they're taking it as they're supposed to, as it's prescribed, to monitor safety, to monitor efficacy, and I'm the one that should be deciding when is enough enough, when do I change to a different biologic, and that's complicated. And again, there aren't definitive guidelines on that.

And then, obviously, this is a co-management issue. My role is to communicate with you or whatever primary care physician regarding all of the above to keep you in the loop so when that patient does show up in your office with an asthma exacerbation or poor control or whatever it is, you know what treatment the patient is on, how long they have been on it, have they had side effects, etc., so I think all of that is important.

So, in summary, I think we now have a total of 5 different biologic therapies for severe asthma. Other than rheumatoid arthritis, I don't think there's any other disease that has quite as many—chronic disease that has quite as many biologic therapies available for it.

Dr. Yawn:
Right.

Dr. Wenzel:
There's a lot of data to support their safety and efficacy, and in fact, they have changed lives, absolutely. I'm very comfortable saying that people have come in and said these are game-changers. But choosing the right biologic for the right patient is still challenging. It's not candy. It is challenging, and there may be more than 1 choice for what works as well; but again, patients who respond can truly have a life-changing impact. And then monitoring, following and changing therapy I think is, in fact, a team effort between primary care and specialist, and unless I get feedback from you and you get feedback from me, we may not always make the best decisions.

Dr. Yawn:
So the optimal diagnosis and management of severe asthma of course begins, I'd like to think, in the primary care office, making sure that we've made the accurate diagnosis, looking to see if there are other diagnoses. We need to confirm that it is uncontrolled asthma and optimize treatment, the comorbidities, the triggers, the adherence, the inhaler technique, ruling out other possible explanations for the presentation. I may do some of that, but then I may also say, "I need help with this." And I think that we can't stress enough that effective communication is crucial to all of this—and yes, communication with the patient, if they're a child or adolescent, with their

parents too, but then with my colleague that I'm co-managing with. How can you call it co-anything if you're not talking to each other? And it doesn't have to be on the phone anymore. It can be through the EMR, through all kinds of different ways to communicate, and so I think it's really important.

And we haven't talked a lot about asthma action plans, but I did want to just emphasize that I think we don't use them often enough in primary care. I'm hoping that all of my patients that I refer and they come back on biologics have an asthma action plan, and maybe it will help me learn to use them more effectively.

Dr. Wenzel:
Referral to an asthma specialist when symptoms and exacerbations remain uncontrolled can be helpful if further diagnostic testing is required. If additional biomarkers, other approaches to phenotyping the patients can be helpful in identifying which additional therapies might be beneficial, and then obviously considering the biologic therapy. And I think most people would acknowledge that once you are to the biologic therapy route, that a specialist probably should be involved in that management.

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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