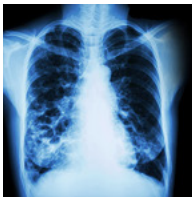

NONTUBERCULOUS MYCOBACTERIAL LUNG DISEASE:
REAL-WORLD APPLICATION OF NEW GUIDELINES AND TREATMENT ADVANCES

OVERVIEW

Nontuberculosis mycobacterial lung disease (NTM-LD) is a frequently fatal lung disease that is now more common than tuberculosis in the United States. Treatment is generally very challenging due to lack of medications approved for first-line therapy, adverse events, drug-drug interactions, need for long-term dual and triple combination therapy, among other issues. This second part of the activity includes case studies to illustrate how to individualize the guideline recommendations so that treatment is initiated and optimized to best meet the needs and characteristics of the individual patient. Throughout the activity, the faculty share their experiences and provide pearls and pitfalls in overcoming the challenges in managing patients with NTM-LD, such as taking medications with ice cream in the evening to improve adherence and promote weight gain.

TARGET AUDIENCE

This activity was developed for pulmonologists, infectious disease specialists, and other healthcare professionals who care for patients with lung diseases.

LEARNING OBJECTIVES

- Describe key treatment concepts as described in the 2020 clinical practice guideline on nontuberculous mycobacterial lung disease (NTM-LD) jointly sponsored by American Thoracic Society, European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases, and Infectious Diseases Society of America
- Summarize the clinical impact of the latest clinical data and therapeutic advances in NTM-LD
- Develop patient-centered treatment strategies for NTM-LD that align with the latest evidence-based guideline recommendations and therapeutic advances
- Collaborate with patients to better individualize treatment over the course of the disease

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Shannon H. Kasperbauer, MD

Consultant: AN2 Therapeutics, Insmed, NTMir, Paratek

Kevin Winthrop, MD, MPH

Consultant: Insmed, Paratek, Red Hill Biopharma, Horizon, Spero

Research Support: Insmed

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Shannon Kasperbauer, MD

Hi, my name is Shannon Kasperbauer, and I'm an assistant professor of medicine at National Jewish Health. And I have with me today, Dr. Kevin Winthrop.

Kevin Winthrop, MD, MPH

Shannon, it's nice to be with you to talk about nontuberculosis mycobacterial lung disease (NTM LD). And I'm a professor here at Oregon Health Science University.

Shannon Kasperbauer, MD

We going to start off, and talk about some of the common treatment challenges that we face in NTM lung disease. Some of them include the resistance that we see with this organism. Kevin, will you clarify or elaborate on that pathogen resistance?

Kevin Winthrop, MD, MPH

Luckily that's not something that's very common, but it is probably at both of our centers because we tend to see people who've been re-treated or have more advanced disease and are more likely to have resistance. But as we mentioned in the prior video, macrolide resistance, and really amikacin resistance, is resistance to the 2 drugs that we really evaluate and we worry about, and we try to protect those drugs. They are the most active drugs against most NTMs.

Most NTMs, MAC, of course, it's what we discussed before, but those are of primary importance with MAC. And then with M. abscessus, azithromycin can be less important because there can be resistance at baseline.

It is a challenge and that's something I always explain to patients. They say, why do I have to take so many drugs? And we're starting someone on a 3-drug regimen, sometimes more than that. And that's the reason I give them. There are other reasons, but the main reason is we have to protect the macrolide or protect the amikacin.

We need to prevent resistance from evolving and, they understand that concept usually after we discuss it. But that is the reason. I wish we had 1 drug that was bulletproof and no bug could develop resistance to it, but that's counter to every evolutionary principle that we understand.

Shannon Kasperbauer, MD

And I think putting it into the context of other infections and certainly things on the spectrum of, in the family of microbacteria, the NTM compared to things like tuberculosis (TB) are much more drug resistant. A lot of patients will say, "Gosh, I'm just so glad I didn't have tuberculosis when I found out that my smear didn't reflect TB." And our usual response is, "Well, we wish this was tuberculosis. This would be a lot easier to treat with 6 months and almost a hundred percent cure rate of treatment." Compared to other pathogens, NTM is definitely harder to treat. And then just as you said, long-term combination therapy is needed because we're trying to prevent resistance developing to our best drugs. And what about therapeutic drug monitoring? Do you think that that is useful?

Kevin Winthrop, MD, MPH

Yes, it's a great question. You'll see a little later when we go through our standard of care card, we do it. I think you guys do it, right?

Shannon Kasperbauer, MD

We do. I would say by the time folks get here, they've already declared themselves as being treatment refractory in most cases. As a referral center, we're doing everything possible to fine-tune their management and making sure there aren't issues with malabsorption. We do typically get therapeutic drug monitoring tests.

There isn't a lot of data to support the use, although there were some studies from Korea that showed the treatment outcomes were better in those individuals that were at least able to get within a therapeutic window on the macrolide.

Less information or no information really, on drug levels on ethambutol or rifampin. But it did show that those individuals that were able to reach a specific target concentration were more likely to have culture conversion. But that certainly needs to be validated.

Kevin Winthrop, MD, MPH

I agree. I think that study plus there's some intuition here that if your level is zero, which sometimes it is. Right? You check these people and I have people on 250 mg a day of azithromycin, and the level is zero 2 hours after they take it. There's not many of them, but there are those people. I think clearly you hit the nail on the head. If someone's not responding the way they should be, that it's at least something that you should evaluate whether or not they're achieving what we think are therapeutic levels.

Shannon Kasperbauer, MD

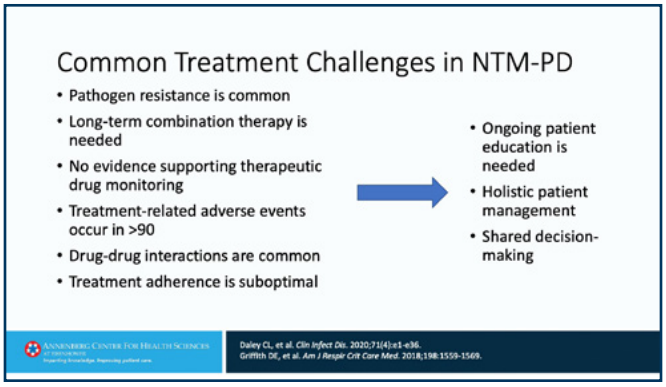
Absolutely. And then adverse events is another challenge in this disease, and is very common. So, creating the regimen that we think is going to be effective, but that a patient will tolerate, that can be tricky.

Kevin Winthrop, MD, MPH

I'll just say that we're presenting at the American Thoracic Society (ATS) meeting in a few weeks, virtually, where we looked at Medicare data over a 6- or 7-year time period, and I am shocked to see 2 things. Number 1, the proportion of patients who don't start standard ATS-recommended regimens.

And then the second point was that about half of the patients who start a regimen, no matter what it is, are off that regimen by 6 months. We don't know why yet. We're looking into that further, but I think a lot of it has to do tolerability issues.

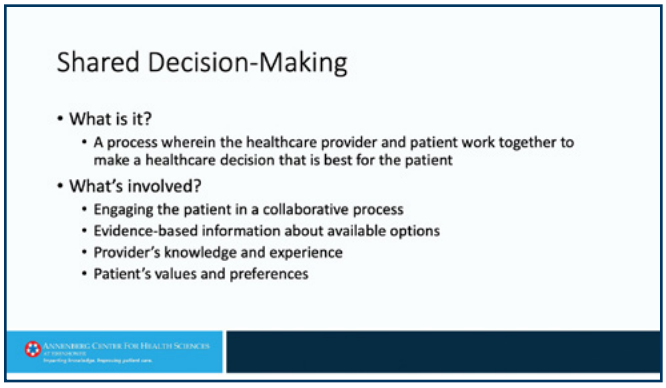
There are some big challenges here and I do think some of the things we're going to talk about here, a lot of the ways to overcome those challenges, are spending extra time with your patient and being creative and flexible and being willing to go the extra mile and troubleshooting some of these issues. That's why I often feel like my center can add value to the clinicians in the region because they maybe don't have the time to do those things. And we do.



Shannon Kasperbauer, MD

Patient education is critical. That holistic management piece, including nutrition, pharmacy, nursing, respiratory therapy, and then, of course, shared decision-making. Let's move on to shared decision-making.

This is such a long journey for individuals. Usually my first question to patients, because they've been on treatment before in a lot of cases, is what's your goal? What do you want to get out of this evaluation? And it's really helpful to start the conversation that way because some patients with cavitary drug-resistant *M. abscessus* come to me and their goal is cure.



And it's really helpful to hear that up front because the likelihood of that happening is almost … it's just very, very low. I think it's important to get their perspective before you dive into a big conversation because if they come to you with that kind of an expectation, it's going to completely change the conversation vs if they come in and say, "I know that I can't cure this. I'm really asymptomatic right now. I just want to think about the likelihood of us pursuing watchful waiting, for example."

How do you frame this in your conversations with patients?

Kevin Winthrop, MD, MPH

I think that's a good way to do it. I view my role as giving them my best opinion and answering their questions so they're informed, and then leaving it to them to make a decision.

And I think a lot of that starts with like what you said, it's what's the goal of therapy. And I, I try to at least tell them what I think the goals could be, what the usual goals are and where they fall in the spectrum of maybe being able to achieve one of those goals. But I've always said that this is an infectious disease, almost unlike any other. And that it's really one in which the patient tells you when they want to be treated.

Shannon Kasperbauer, MD

Right. And on that note of giving patients the tools they need and the information that they need to make these decisions, I've found that it's really helpful to sit down and spend the time going through the images together.

I think a lot of times patients come out to us here at National Jewish and they might've been struggling with this for a decade, but they've never, ever seen their CT before. That is the advantage of working in a center where you have a lot of protected time to educate. But those visual tools are so helpful to patients to understand the severity of their disease. Getting their participation in and just looking at the data and explaining to them what the computed tomography (CT) scan means, having cavities, for example. Going through the microbiology with them. Having someone that's heavily smear-positive and just explaining what does that mean as a predictor for progression, for example.

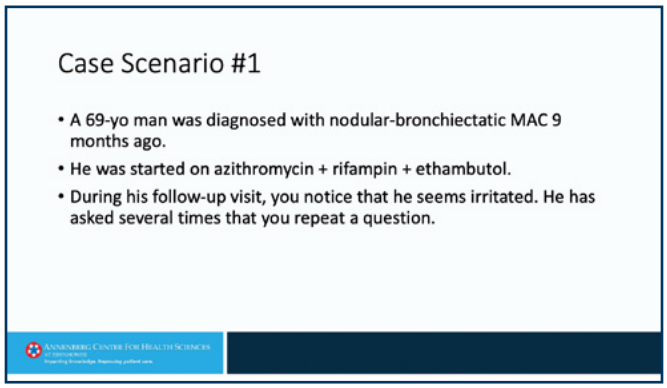
I do agree with you completely on the shared decision-making. I try to lay all this out and give them this information. And then explain what are the treatment options. Doing nothing is always a treatment option as far as nothing in terms of medications. However, I would always emphasize airway clearance and bronchiectasis management in that patient and explain to them that this may actually help your symptoms, and in some cases, may improve your imaging to a certain extent with some of the mucus plugging.

And then talking to them, of course, about their values, their preferences. What's going to get in the way of them getting a peripherally inserted central (PIC) line and starting on twice-daily infusions where they have to drive into an infusion clinic twice a day for months at a time.

Utimately, once you lay that all out, and again, we have the luxury of time with our patients here to go over this. And I feel like they usually have the tools that they need to make that decision, that you are alluding to, letting them make that choice. Then we can circle back and talk to them.

And maybe they decide, as an example, that they do have significant radiographic disease and they have progressed. But they've been down this road so many times they don't want to go back again. Then it's deciding how often you're going to follow them. Maybe you'll see them sooner and get cultures more often because they're not starting on treatment, for example. So, I think those are just kind of the steps as it relates to shared decision-making. I thought it would be helpful to just talk through a case.

The first scenario we're going to talk through is a 69-year-old gentleman who was diagnosed with nodular bronchiectatic MAC 9 months ago. He's started on azithromycin, ethambutol, and rifampin, our 3 standard agents. And in his follow-up visit, Kevin, you notice that he's very irritated. He's asked several times that you repeat a question. What is going through your mind when you hear that scenario?



Kevin Winthrop, MD, MPH

I think this case is kind of hinting at a couple of things. Asking you to repeat your question raises a question if there's some hearing compromise and, of course, we think of MAC compromise and hearing compromise. And so, that'd be something to consider.

As you mentioned before, they may be on other meds. There may be a drug-drug interaction. Whenever you use rifampin, you got to look at all those meds very carefully. They could be on some antidepressant or anxiolytic or something that might have an interaction. A lot of them don't, but some of them do.

Thyroid medication has an interaction with rifampin. Long ago I realized, why are all my patients fatigued on rifampin? A lot of them were on levothyroxine for the thyroid. And if you check the thyroid stimulating hormone (TSH) level, it is through the roof and they're totally hypothyroid now.

These types of drug-drug interactions we definitely need to be keenly aware of. The MAC hearing issue. We've looked at this in population-based fashion. There, there's no doubt there's a risk of hearing loss. Although my impression is it's with long-term use. I wouldn't expect it really soon after drug start. What are your thoughts?

Shannon Kasperbauer, MD

I agree. It can certainly happen. We're well aware of it. And I also think it's a cumulative exposure and perhaps some individuals may be more vulnerable if they have underlying ototoxicity to begin with for other reasons. Or if they're on other drugs and there's cumulative ototoxicity potentially. And I think you're spot on with the potential issues with this particular individual. One of the other things I thought about was I don't know how long he's been on medications. And sometimes patients, if we haven't really gone through education well about the side effects, they're just overwhelmed. You know, they're completely overwhelmed. We throw 3 drugs at them, maybe daily, and they don't feel well. And they just, they kind of shut down and they're not listening. So, one of the strategies we've found that's helpful is to introduce drugs one at a time.

We introduce drugs on a staggered fashion, typically alphabetically, just to make it easy. With the macrolides first and then the ethambutol, and ultimately the rifampin. I'll go through a drug-drug interaction profile with them, but I also print out the specific medications where there is going to be an interaction.

Like you commented on, if they're on levothyroxine, we're rechecking a TSH in 4 to 6 weeks because we know they'll need to have an adjustment in their hormone replacement. Another agent that I know you published on, Kevin, that has potential discontinuation related to adverse events, is linezolid.

Now, it's not part of our standard treatment for MAC, but we do use linezolid quite a bit in M. abscessus. What do you run into as far as side effects with linezolid?

Kevin Winthrop, MD, MPH

That was just an observational study that you guys and other colleagues all reported their cases within. We found close to half of the people eventually develop peripheral neuropathy. There are actually very few cytopenias. It was mostly peripheral neuropathy. I run into that a lot with linezolid and tedizolid in the treatment of *M. abscessus*. That seems to be time-limiting for that medicine and that's even when you dose it once a day. Even when you give large doses of vitamin B6 alongside it. I tend to keep linezolid in my back pocket of it's active by the susceptibility report. I tend not to use it upfront. I tend to save it for later, knowing that I'm probably going to get a few months out of it anyway. Those are my thoughts on that.

Shannon Kasperbauer, MD

We see neuropathy with ethambutol as well. I don't know that this is appreciated. Everyone is focused on the eyes, but over time, with extensive exposure, we've had several patients develop neuropathies that are rate limiting with ethambutol use as well. Just in general, when you have an adverse event, if it's a significant adverse event, we'll just stop the medication. But let's use optic neuritis with ethambutol as an example. Are there any other options other than just forever putting that on there?

Kevin Winthrop, MD, MPH

Let's talk about that. Ethambutol, what's the risk? Well, we know it's low. We don't know what the true risk is other than there's some observational studies that say it's one in a hundred to one in a

thousand, that kind of thing. We just reviewed our data for the last 15 years and came up with 2.3%.

I was a little surprised it was that high. But it does happen. And it definitely happens with prolonged use. It's definitely dose-related. With the lower dose you see less than at higher doses. I know we all use a low dose. We use the lowest dose recommended. 15 mg per kg, if you're dosing daily.

I think it's pretty rare. It's important to point out—to remind people—that it's reversible, provided you catch it early enough. It's almost the first question I ask everyone as they come in the door because I don't want to forget to ask it. And I always remind them before they leave to let me know of any vision change immediately. We don't necessarily monitor religiously these folks. I don't know what your standard of care is. I will check for people who I don't necessarily trust, or I don't think are as reliable or don't scrutinize their vision the same way, or already have a lot of vision problems to begin with. I do color vision testing on them every time they come in. That's every 2 or 3 months, but I don't do that in a lot of people. I just let them tell me if they notice anything different. How do you guys handle it?

Shannon Kasperbauer, MD

I would say it depends on the provider and it depends on the patient, but somewhere between the range of every 3 to 6 months, we suggest they follow up with an ophthalmologist. But I think your point is well taken. What I always tell my patients is this is something that's going to happen between your ophthalmology appointments. It's going to happen and you're going to notice symptoms subjectively. But the key is that you're reading something in the same font every day. And that you're cognizant that if you start to have any blurred vision or changes in your vision, you're stopping that medicine, calling our clinic, letting us know that you're having some changes and then we're contacting neuro-ophthalmology for an evaluation.

Again, it gets back to the education piece. And we're holding meds while we're sorting through it. But in individuals who have clearly had some issue with ethambutol in the past, would you ever rechallenge them? Let's say years later, because we do know how important ethambutol is as part of their regimen. And there's some data out of Texas to suggest that the different administration confers different risk.

Kevin Winthrop, MD, MPH

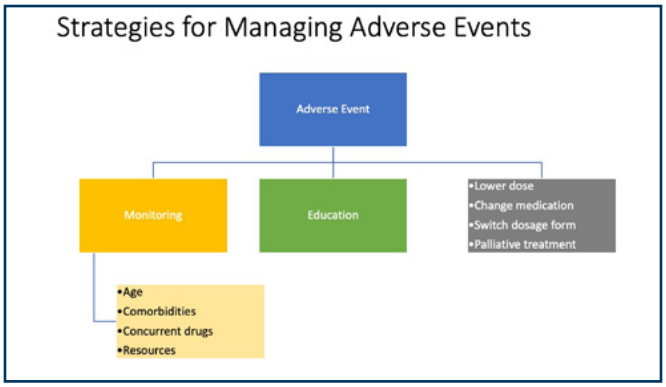
Yes. I, I have reinstituted it in some people. If I can convince them to try it. I've monitored those people very closely with an ophthalmologist. I've printed out a Snellen chart form at home, and I've got an Ishihara color plate. There's a home version, which has fewer color plates, but we use it in TB control all the time.

The other thing is a lot of ethambutol-related optic neuritis before, really it wasn't! That's the other group where you really kind of hear the story, or you call up the prior physicians and talk to them, and it's pretty clear that it probably wasn't related to ethambutol. And in those cases, I feel fine about reinstituting it if I can convince the patient to do it.

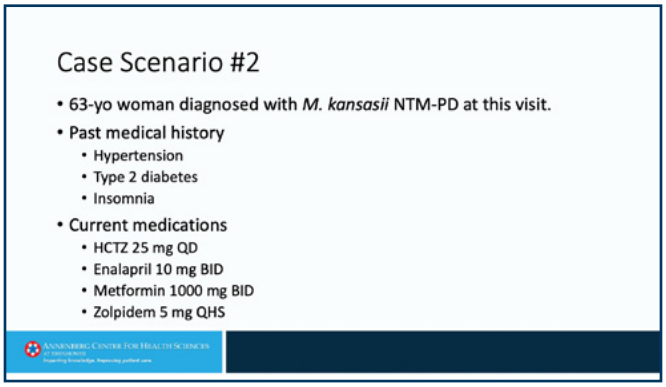
Shannon Kasperbauer, MD

We will do the same. And we'll also strongly consider thrice weekly as opposed to daily ethambutol in those individuals that we think are at risk or may have had optic neuritis before. And I have been successful in a handful of patients with reinstituting ethambutol. Very close monitoring. But as a thrice weekly administration.

Those are just some strategies for managing adverse events. We talked about choosing the lowest dose recommended. I'd be cautious going below the recommended dosages in a smaller individual without therapeutic drug monitoring to support an unusual dose strategy. And a good example of that is some patients that have come to our practice, who were formerly treated with like half-dose rifampin. Three days a week. They are on 300 mg, 3 days a week. And that I think is dangerous for all the reasons we know in infectious diseases that you're really giving them subtherapeutic dosing and promoting resistance.



This is a 63-year-old woman who was diagnosed with *M. kansasii* at the current clinic visit where you're seeing her and she has hypertension and type 2 diabetes, insomnia, and is on several of the usual medications for those comorbidities, including hydrochlorothiazide, enalapril, metformin and zolpidem.



How would you counsel her as you're getting ready to start knowing your *M. kansasii* regimen in someone with these particular medications and comorbidities? And maybe just how, in general, Kevin, your standard of care assessment would be in that individual.

Kevin Winthrop, MD, MPH

I think for her you're going to talk to her about the usual drugs used for *M. kansasii*, which I believe we covered in the last hour of our

conversation. You know, the choice to use rifampin or not, obviously rifampin is your choice drug for *M. kansasii*. And she may have some drug-drug interactions.

She may not. And actually looking here, she's probably fine. You'd have to look at all the drugs here closely, but I don't think there's a lot of interactions there to worry about with rifampin.

But it's something, particularly with other hypertension medicines, and beta blockers and calcium channel blockers. Those are 2 big ones that interact that you have to be aware of. The other thing with rifampin, you always worry about pain medicines, opiates, steroids …

Shannon Kasperbauer, MD

I can't count how many times folks have been on chronic prednisone for their RA, we start their MAC treatment and they just have a horrific RA flare or their asthma flares. It's underappreciated how wicked the drug-drug interactions are with rifampin.

Kevin Winthrop, MD, MPH

That is something to always look for. And it's funny. I know a lot of them, but I always look them up because every once in a while there's a new drug or just one that I haven't thought about. Like, what about azithromycin and warfarin?

There are a few that pop up where you're just like, oh yes! When was the last time I had a patient on warfarin? I don't know. But that one comes up every once in a while. I will go back to rifampin. The new antiplatelet agents, those are a big one.

Shannon Kasperbauer, MD

I think, and on that topic, Kevin, I think that atrial fibrillation (AFib), NTM, and lung disease combination is a balancing act. Same situation where someone's cardiologist is just cranking up their calcium channel blocker in an attempt to control their rate and the rifampin's taking out at least 60% to 70% of that calcium channel blocker. And then, you have to be very careful when you stop the rifampin. Right?

Kevin Winthrop, MD, MPH

Yes.

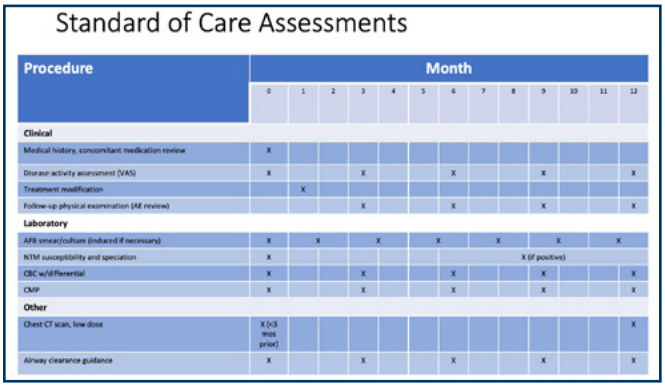
Shannon Kasperbauer, MD

Or you're going to make that patient bradycardic because, all of a sudden, the rifampin is gone. On the front end and on the back end, looking at those drug-drug interactions is key.

I know with the study that you're doing right now we're following the standard of care assessments. How often do you see people in clinic and how often are you getting cultures and labs?

Kevin Winthrop, MD, MPH

I should tell you how we developed this document. This was put together as part of our national, PCORI funded 2 vs 3 (2v3) trial. And we developed a standard of care card to guide clinicians and people collecting the data in the trial. And it was put together by our steering committee for this study, which is a group of a few patients, a few pulmonary NTM experts, pulmonologists, and infectious disease folks, and a few patient-advocacy group type people.

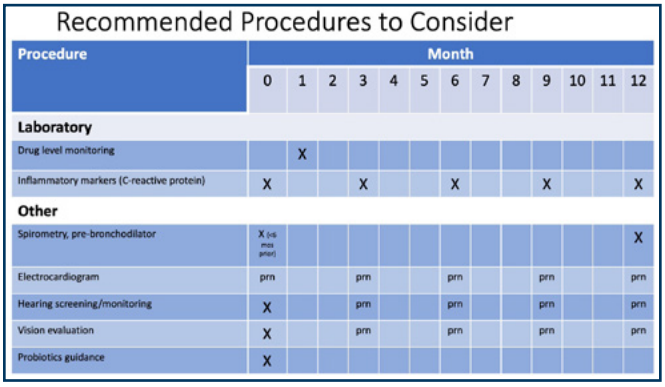

Standard of Care Assessments

Procedure	Month											
	0	1	2	3	4	5	6	7	8	9	10	11	12
Clinical													
Medical history, concomitant medication review	X												
Disease activity assessment (VAS)	X			X			X			X			X
Treatment modification		X											
Follow-up physical examination (AE review)				X			X			X			X
Laboratory													
AFB smear/culture (induced if necessary)	X		X		X			X			X		X
NTM susceptibility and speciation	X									X (if positive)			
CBC w/differential	X			X			X			X			X
CMP	X			X			X			X			X
Other													
Chest CT scan, low dose	X (<3 mos prior)												X
Airway clearance guidance	X			X			X			X			X

In terms of the clinical visits, somewhere between every 2 to 4 months. We have a little "X" in the every-3-months box here. I think that's based on surveying both patients and doctors, how frequently they see these individuals.

A lot of people's sputum dries up and people stop surveying it, but we really need them to do it. I know that you guys, and we are, Texas, a few others are very aggressive about trying to collect sputum and we do so every month or 2. And we think that should be the standard of care. As we talked in the last session, we really need to know when people convert their sputum, so that we know how long to treat them. That is reflected there as well. Some of the laboratory monitoring being a minimum every 3 months. And that monitoring is looking for adverse events associated with the drugs. Most of them are pretty infrequent.

But also the fact that there may be a few who have other comorbidities and problems. I can't tell you how many things I pick up by this lab monitoring that may be totally unrelated to NTM. But I'm glad that I picked it up. That kind of every-3-months monitoring seems reasonable.


Recommended Procedures to Consider

Procedure	Month											
	0	1	2	3	4	5	6	7	8	9	10	11	12
Laboratory													
Drug level monitoring		X											
Inflammatory markers (C-reactive protein)	X			X			X			X			X
Other													
Spirometry, pre-bronchodilator	X (<6 mos prior)												X
Electrocardiogram	prn			prn			prn			prn			prn
Hearing screening/monitoring	X			prn			prn			prn			prn
Vision evaluation	X			prn			prn			prn			prn
Probiotics guidance	X												

And then, there's also things on this card that we just discussed here. Drug level monitoring. We recommend considering it at the start, but we don't know that this is that important at the start. But consider it. Inflammatory markers. Some of us check those things. One of the points of this effort is we're trying to collect some data around some of these things to see if we can come up with better ways to monitor and classify disease activity.

There are a few other things, such as vision and hearing screening, electrocardiogram (EKG), things that we just talked about. The EKG. Maybe we should talk about it specifically. We just wrote "as needed" (PRN) in the boxes there. I think a lot of us don't do EKGs unless there's a reason to, unless their on multiple QT-prolongating agents, where they have underlying cardiac issues that would make you want to do that. That's the nuts and bolts of this card. It is a bit loosey-goosey, but I think if you haven't ever treated someone like this before, I think this card would be helpful to give you a recipe as to how to go forward.

Shannon Kasperbauer, MD

Absolutely. It is in line with what most of us are doing. That a lot of the questions we get from community providers are related to how often to image individuals. And I know that also varies amongst the experts. I think a baseline CT scan is important. I think an end of treatment CT scan is important. And I do think an interval CT scan at some point, whether or not that's 6 months, 9 months into treatment is... I usually do it at 6 months because I want to have a point in time where we're usually assessing for treatment failure and that's defined by our microbiologic outcome. But because that's such an important milestone, I'm typically getting a CT scan at 6 months. What is your practice at OHSU?

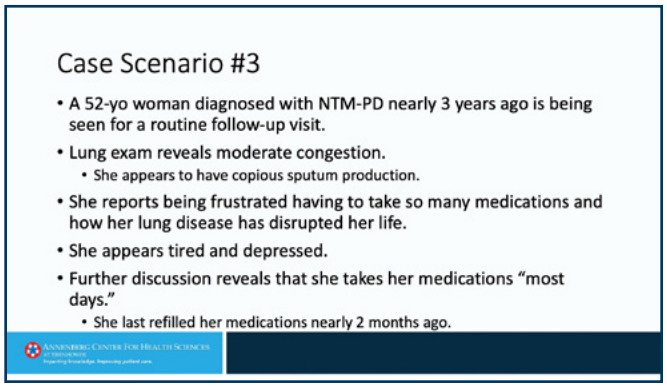
Kevin Winthrop, MD, MPH

I do it always between 4 and 6 months. I mean, I think I just had enough patients early in my career where I thought everything was going great and they thought everything was going great. And then I scanned them and their cavity was twice as big as it was before. That is not usual, but it happens in particular with cavitary disease. I am very keen on repeating that scan in the interval you suggested because I want to make sure those cavities are going in the right direction.

Shannon Kasperbauer, MD

This is a 52-year-old woman who was diagnosed with NTM 3 years ago and is being seen at a routine follow-up. She has moderate congestion on her physical exam, copious sputum production, and she's describing that she's just frustrated because she has to take so many medications. The timing around the meals. And it's complicated and she's quite fatigued.

As you're really digging into her adherence, she reveals that she takes her medications on most days. When I start to worry about adherence, I think we underutilize pharmacy records, and they can be helpful. I think patients have an inherent desire to please us, as



the providers, and yet we find out sometimes they're not filling their meds.

She, in fact refilled her medications 2 months ago. She has not been taking her medications regularly.

Are there strategies that we can give our patients or that you find that help promote adherence?

Kevin Winthrop, MD, MPH

I keep it extremely simple and I've always done this. I don't start drugs one by one. I don't tell them to take things at different times of the day. I tell everybody to take all their medicines at the same time, with a bowl of ice cream, 2 hours before bed.

And I've been doing that for years, and we've looked. Adherence in my practice is 95 plus percent. It's remarkable to me how few patients in our group have failed to complete a regimen. Almost all of them do.

I think one of the biggest things I learned early on is people were very stressed out trying to figure out when to take azithromycin and when to do the rifampin. "And the pharmacist told me I should take the rifampin on an empty stomach." "And they told me I needed to take this one, like 2 hours after any vitamin." And all of a sudden it makes it very complicated. And then all these people are on all these other drugs that are on some of these scenarios here so it's already complicated for them. I just decided, long ago, that the best thing I could do for them is make it not complicated at all!

And so that has been my algorithm. There's no randomized controlled trial data saying that's the best way to do it, but it seems to work for my practice. And I think patients love being told they have to eat ice cream!

Shannon Kasperbauer, MD

And a lot of patients are struggling to gain weight. Our nutritionists often give them that freedom to stop shopping for fat-free food and actually eat something with fat and calories in it every day. I didn't know about your ice cream bowl strategy. That is news to me, but I do use a similar approach. I tell folks, take it at night because you're going to be reaching your peak concentration in the middle of the night. If it is going to give you a little gastrointestinal (GI) upset, it's not in the middle of breakfast. I think consolidating meds to bedtime is wise. I have told them, take it with some saltines, take it

with some crackers, if that helps them to tolerate any distress. And sometimes it's they just cannot do all 3 drugs at once. It's okay to put the azithromycin in the morning, for example, and rifampin and ethambutol in the evening. What we don't want people doing is taking their 2 red capsules of rifampin and splitting that dose throughout the day because we are trying to reach a peak concentration.

Kevin Winthrop, MD, MPH

And then a lot of people too, they come to you and they're splitting up their ethambutol. I agree with you. That's always one thing upfront to cover with patients that you have to keep the medicines, the individual doses of an individual medicine, taken together.

Shannon Kasperbauer, MD

You are talking to your patients at your visits about adherence. Some patients find, I don't do this a lot, but when it is really complicated and they have all different, a huge polypharmacy, a huge list of medicines, I sometimes suggest they keep a treatment diary.

Our nursing staff will sometimes just create a little spreadsheet of something they can put on the fridge to remember, don't take this medicine with that medicine, for example. Don't take your meds with all of your vitamins and minerals is one example. And then any ways that we can reduce complexity, which you just said very nicely, just trying to take them all at bedtime. They don't have to worry about spacing them from meals, etc.

Kevin Winthrop, MD, MPH

But the only thing I'd add to that is the reflux issue. I always try to tell them to do it a few hours before bed, so that they don't get reflux from their ice cream or one of their medicines.

Shannon Kasperbauer, MD

And revisiting what we just heard in this last case about why poor adherence can actually be dangerous. And if they decide to take the red pills on Sundays and the white pills on other days, they can actually be promoting drug resistance.

The rifampin might just make them feel so lousy that they're splitting their dose, or they're not taking that particular medication. Well, that's a time to think of an alternative medicine, like clofazimine (no longer available in the US) to put in its place. A lot of times I find—I don't know if you see this as well—in that first visit with patients that you're talking to them about the fact that … they have this orphan disease … they're going to be on meds for 1 to 2 years … 3 different drugs.

I've sort of lost them at bullet number one. Having a caregiver or partner, daughter, whoever, present during those visits can be really helpful to absorb some of that information. And then just as far as communication strategies, I usually break it down into 2 visits. The first visit I have with patients, if it's a new patient and they're treatment-naive, is just to talk to them about their vulnerability.

They have this other disease called bronchiectasis and we're going to start airway clearance. And we're going to just introduce what is NTM infection, but honestly, most of the time in that first visit, I'm just getting to know them and their goals. We don't even have the bandwidth to go into all of the nuts and bolts of NTM treatment.

I try to keep it simple and just focus on the bronchiectasis and the airway clearance, and then set up a second visit to talk to them. How is the airway clearance going? Do you notice that your cough is better? And it may be 2 weeks or 3 weeks later.

And then we schedule that longer visit just to go into all the education of NTM treatment and what that's going to look like.

Kevin Winthrop, MD, MPH

I think that strategy mirrors ours as well. I think it's overwhelming for the patient, a newly diagnosed patient to think about all these things at the same time. I mean, going back to what you said before, too, I think going through the scan, like you said, is really helpful. It helps me explain to them what is bronchiectasis.

It is not everyone, but the majority of those people don't even know what that is. They think they've been told they have bronchitis, or they may have been told the word but they don't know what it is, or they've just never been told.

I think going through that scan and really showing them what that means in the areas that are involved and then how that directly relates to the strategies of airway clearance and hygiene you were mentioning.

There's mucus plugging, there's this buildup of gunk on inside of your airway, just like your sink pipe at home, I mean, that kind of thing. They can see it, and then they can understand why these things we're going to ask them to do might actually help.

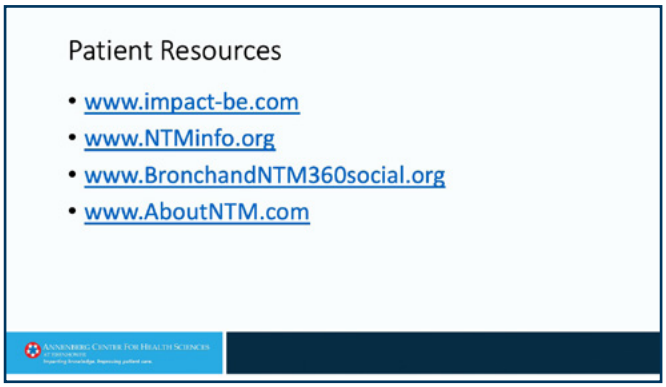
I am with you. I tend to focus a lot on that stuff that you mentioned earlier and then have them come back 4 weeks later or 6 weeks later and think about starting treatment.

Shannon Kasperbauer, MD

And that interval of time might be longer for certain people. If I see their initial CT scan and they're in that mild category, I'm going to talk about the bronchiectasis, talk about treating that. And maybe I don't see them back for 4 to 6 months. At that time point we are assessing, we'll have had time to say, did the cough go away on airway clearance? Are they feeling dramatically better? And, in fact, their CT scan is the same or better, that person you may not treat with the NTM.

But I think that that interval of 6 months—I think that's an approach that I know our colleagues around the US and Asia as well have adopted in the milder phenotypes—to repeat imaging at 6 months and then decide, is it time to start treatment? Do they have evidence of progression?

There are a lot of resources out there for patients and I find some patients are very savvy. They're already connected. They're in a

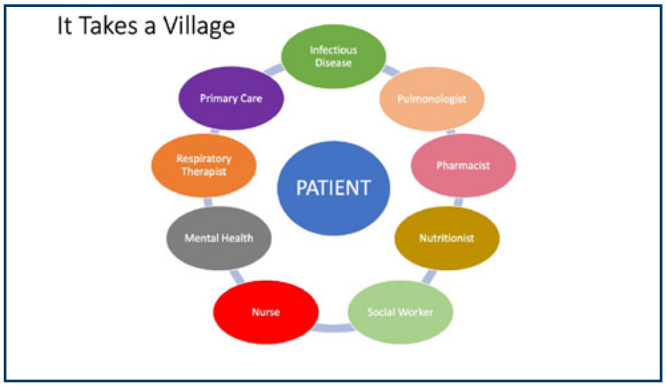


support group by the time they meet us. But there's a lot of folks who have no idea that there are resources out there for them.

I did include some of those for our listeners that in those patients that would benefit from seeing these resources, our patient advocacy group, which is NTM Info & Research. They're found at www.NTMinfo.org. There's a www.BronchandNTM360social.org website and another industry-supported website called www.AboutNTM.com.

This segues into the multidisciplinary approach of the other individuals that we get involved when we see a patient with NTM lung disease, because it really is, we've all said many times, it does take a village. There are often comorbidities, of course, with bronchiectasis.

There are a lot of mental health challenges in our patients, too, that I think we've only really started to scratch the surface on, Kevin, with some research that I know you've been a part of, and that we've heard about at our consortium meetings. A lot of folks struggle with depression and anxiety. How do you think about that in your clinic and what are your preferences to refer?



Kevin Winthrop, MD, MPH

I think it's under appreciated. And like you said, my colleague Emily Henkle, MD, is really interested in this and has driven several research studies ahead to try to better quantify the prevalence of this and see how these things change during treatment, for example.

And there are some patient-report outcome tools that we're using as part of studies, but also as part of routine clinical care now. Although, truth be told, it's still kind of a study because we don't really know how to use these tools yet. I'm more aware of it now than I was a few years ago because of these studies we've been doing. And I definitely try to bring it up with the patient and usually their spouse or whoever's with them in the room, their daughter, whoever it is.

And then, of course, try to triage them to get help if they need it. A lot of that is working with the primary care doctor. And, of course, if it's more advanced, then it ends up in a psychiatrist realm. I think the support groups can be really helpful. One of my first patients here started the Northwest support group. And it's grown and it's a great resource for not just my patients, but me.

Shannon Kasperbauer, MD

The luxury of being at a center where we have patients come out for 2 weeks at a time, we routinely have at least an initial screening visit with the psychologist or psychiatrist, depending on our concerns.

And then they really help us determine where we need to go from there. If the patient should be establishing care with a specialist at home, or if it's something that we think can be managed with a primary care provider. But there's lots of screening tools that I think we've discussed, as a group, we should just start embedding them into our questionnaires when we first meet with patients.

We should all just be mindful of that. This is a chronic disease. It can have quite a mental toll on our patients. And it's helpful to get that assistance if they need it. The other person in this team that I think we rely on quite a bit here at National Jewish is our respiratory therapist. When we see people back every 6 months, we schedule a respiratory therapy visit as part of their routine follow-up. And that is for 2 reasons. One is they're the ones performing the sputum induction with that patient, that they go over their technique. They will review how they're using their flutter valve, whether or not that's an Aerobika or other device.

We have moved to using the Aerobika simply because we're able to do inline nebulization with this particular PEP valve. I have a pretty low threshold to add hypertonic saline to my patient's therapy at home.

And I find that it improves their airway clearance, it also improves their ability to submit a high yield specimen when they're following them.

Kevin Winthrop, MD, MPH

With these valves, my biggest problem is you prescribe them and then patients show up few months later, say, "Oh, we never got them. Like where, where was I supposed to get it?" You know, the medical supply store. They don't always ship it. They're hard to find. It's not as easy as getting something in a pharmacy, so they can be hard to get. We have taken the time to actually directly ship them to patients now, particularly with the pandemic.

We have a randomized control trial funded by NTMir, enrolling these patients into a hypertonic saline study for 3 months vs observation, vs placebo essentially, to see what it actually does.

We all think it does something like you mentioned. And I do use it a lot, particularly people with more advanced bronchiectasis. But there's very little data. We are hopeful this data that's being collected

in people with MAC might provide some talking points for us, for where we're trying to convince our patients to do this in the future. The sputum induction issue you brought up is also really important because it is hard for us folks to produce sputum. That home induction kind of idea will help, I think. And we often rely on that as well.

Shannon Kasperbauer, MD

It's such an important data point and I hear the same thing from individuals that they're in a community environment. They're not at an academic center, there's really no place to get a sputum induction. It's just they can only get inpatient sputum inductions, according to the community pulmonologist. They just don't get it. It's such a simple tool for our patients to have at home and feel that we're appropriately monitoring their response to treatment. That is another important reason to use it.

Kevin Winthrop, MD, MPH

I guess I'd only emphasize the "it takes a team" slide here. Obviously, your center, you're bringing people there for 2 weeks at a time. You have some luxuries there to have a huge team and spend a lot of time with patients.

I think for other centers, and certainly in the community, there's not that luxury or the resources aren't as easy to access. But I think this should be a reminder that these people are out there and you can consult them and get them to help you with your patient, as needed. I don't have a dedicated nutritionist, but I have some nutritionists that I rely on for certain people when they need that, because it's beyond just kind of the usual "eat ice cream." You need an extra thousand calories a day and they need more guidance. A nutritionist can also be helpful.

Shannon Kasperbauer, MD

There's actually a great case that illustrates how important weight is for our patients. This is an 80-year-old female with chronic MAC. She has bronchiectatic nodular MAC disease, macrolide susceptible. She has what looks like early cavitation.

She's been on therapy when she comes to see you, with clarithromycin, ethambutol, and rifampin. And she's been on this treatment for at least 6 months. And she states that her weight loss actually got worse when she started treatment. She has incredible loss of appetite now. She has a metallic taste in her mouth. Her BMI on exam is 16.5 kg/m^2. Any thoughts on what you could do to alter her regimen, to help with some of the side effects?

Kevin Winthrop, MD, MPH

I see this all the time and that's why we recommend azithromycin as the macrolide of choice in the guidelines. And there's data to back this up, but we all believe azithromycin is better tolerated than clarithromycin. The metallic taste in the mouth is classic with clarithromycin. It's definitely harder to tolerate on the gut. It's what I think. Oftentimes just switching them to azithromycin, it's like magic!

Shannon Kasperbauer, MD

It is. And, in fact, that is exactly the lovely ending to this story. All we did was switch her from clarithromycin to azithromycin. Her appetite was better within a week. She was eating hamburgers again. And 3 months later, when we saw her in clinic, she had gained 10 pounds which, given her baseline weight, was huge. And I think this is something that it's just a pearl of treating this all the time that we share with our fellows. Weight is like an antibiotic in these individuals. It is as important as any of these medicines that we're using, and if we're giving them something to lose weight, we are not doing our patients a service.

We know that multiple studies in MAC and *M. abscessus* have shown that a low BMI is a predictor for progression. That is where nutrition comes in. And it is the little things that we can do to help folks gain weight. I'll easily make this macrolide switch, but if they're in that severe a malnourished state, I have a low threshold for putting them on some kind of an appetite stimulant. I call it the 3Ms. So, mirtazapine (Remeron), megestrol (Megace) and dronabinol (Marinol, Syndros). Those are the 3 things that we're thinking about for our patients. And the mirtazapine story is really interesting in those individuals. That actually was a recommendation that came from our psychiatrist who had been working with our program for decades.

And when he would identify an individual that had some mild depression that he thought would improve with the mirtazapine and certainly being underweight, it was just a really nice approach because it's well tolerated at low dose. It also can help with sleep. And it stimulates their appetite and they gain weight.

Kevin Winthrop, MD, MPH

When do you give it? At night before bed?

Shannon Kasperbauer, MD

At bedtime.

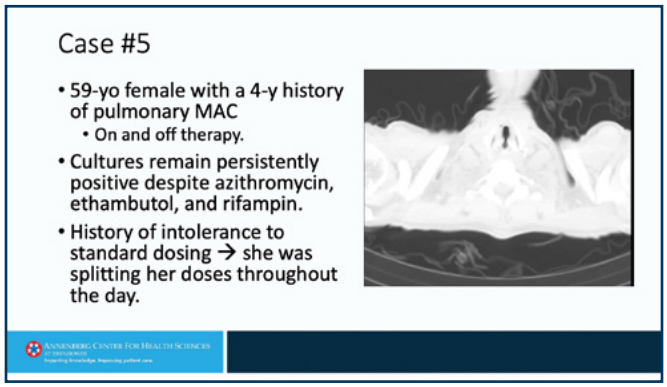
Kevin Winthrop, MD, MPH

I haven't used that for appetite necessarily. In Colorado, you can just walk down the street and get the big M (ie, marijuana). A lot of my patients will just go buy edibles.

Shannon Kasperbauer, MD

This is actually a patient of mine who is a 59-year-old female. She had a 4-year history of MAC. She was on and off treatment throughout that therapy. She was persistently culture-positive at 4 years despite being on azithromycin, ethambutol, and rifampin.

Now she's similar to the prior case we heard about and had a history of some intolerance. She was splitting her doses throughout the day, which makes you worried about the development of drug resistance. On your microbiologic investigations, she's smear positive, she's growing *Mycobacterium avium* and, in fact, her clarithromycin MIC was greater than 32 mcg/mL and her amikacin MIC was 16 mcg/mL.



How would you think about those results? Would you use amikacin? Would you use the macrolide?

Kevin Winthrop, MD, MPH

I still sometimes use a macrolide hoping that there's some susceptible populations there still, so I often do that anyway, if they're tolerating it and if it's otherwise not an issue. The amikacin, that MIC is getting to a level, it's a little bit harder to overcome it using parenterally. You can still—and you may—change the way you dose it. I do. I give it a higher dose twice weekly when I see an MIC of 16 mcg/mL. And I'm talking about parenteral use. Inhalational use, that's fine. There's no problem getting above the MIC. Those are kind of my general thoughts about those 2 drugs and the MICs.

Shannon Kasperbauer, MD

I think we would all feel pretty comfortable putting her into this category of macrolide-resistant MAC, whether or not we use the macrolide or not. But it definitely changes the prognosis in the patient, their ability to cure this infection. And then how aggressive are we?

On her CT scan, she has significant right middle lobe and lingular bronchiectasis. She had never been on amikacin before. In fact, we know that at least from some retrospective data, there were 2 intensification approaches that change prognosis in these individuals. And that was the ability to tolerate prolonged aminoglycosides. And if they had focal disease where we could actually use surgery as an adjuvant to medical therapy. Those are under the 2 things that I think about when I see a patient with macrolide resistance, which are: can I get them on 6 months of amikacin; and can I get them to the operating room (OR) for a debulking procedure? She had 6 months of IV amikacin, she had a right middle lobectomy and lingulectomy and she ultimately got to cure, which is our endpoint. She was on treatment from 2010 to 2014. She had her lobectomies in 2015 and came off treatment after 12 months of negative culture. I have now had the luxury of seeing her 5 years off treatment and she is without recurrence.

Kevin Winthrop, MD, MPH

There is no question that there can be a big benefit of resection when it's done in the right patients, by the right surgeons. Particularly in these cases of resistance where you're never going to cure her, and you may never be able to take her off therapy. Surgery in some of these people really makes them feel better. You remove a huge focus of destroyed lung and their cough is better. They're not producing as much sputum. I think it's really important to consider in most patients.

Shannon Kasperbauer, MD

And I think that that's a unique scenario where we had macrolide resistance. If she didn't have macrolide resistance, I might think about it differently. As far as someone that had diffuse disease and was just persistently culture-positive at that duration, that would be certainly an indication for the FDA-approved agent amikacin liposome inhalation suspension. But when you are dealing with macrolide resistance, I think that puts them into a different category where there is a chance for cure in those patients if you can proceed with at least those 2 approaches that I clarified.

In summary, I think we've talked about a lot of things and those tools that can confer success in patients, including individualizing treatment, shared decision-making, very close monitoring, education upfront, but ongoing education and using some of the support tools that we mentioned with NTMinfo.org or other online support networks.

Holistic management, and then—so important—is that multidisciplinary care approach. Any other closing thoughts that you have, Kevin?

Kevin Winthrop, MD, MPH

It is the art form, that we have been talking about. It's not always straightforward and it's not something that generally takes 15 minutes. It often takes a lot longer and multiple visits and a lot of time outside of clinical visits to try to get people through this.

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