Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/improving-outcomes-ntm-ld-strategies-diagnosis-individualized-treatment-plans-and-patient-adherence/11948/

Released: 11/06/2020
Valid until: 11/06/2021
Time needed to complete: 60 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Improving Outcomes in NTM-LD: Strategies for Diagnosis, Individualized Treatment Plans and Patient Adherence

Narrator:
Welcome to CME on ReachMD. This activity titled *Improving Outcomes in NTM-LD: Strategies for Diagnosis, Individualized Treatment Plans and Patient Adherence*, is provided by National Jewish Health and supported by an educational grant from Insmed. This replay of a live broadcast focuses on how to diagnose, treat and manage NTM. Here are your panelists, Dr. Charles Daley and Dr. Shannon Kasperbauer.

Dr. Daley:
Welcome to today's program titled *Improving Outcomes in NTM: Strategies for Diagnosis, Individualized Treatment Plans and Patient Adherence*. I'm Charles Daley, Chief of the Division of Mycobacterial and Respiratory Infections at National Jewish Health in Denver, Colorado. My colleague, Dr. Shannon Kasperbauer, who is an associate professor in the Division of Mycobacterial and Respiratory Infections at National Jewish Health, will also be joining me in this program.

This program is provided by National Jewish Health and supported by an educational grant from Insmed.

Please look at the accreditation here on this slide.

These are the faculty disclosures.

The learning objectives for this program are to apply strategies to reduce time to diagnosis and initiation of evidence-based treatment of NTM lung disease and to use a patient-centered approach for communications related to diagnosis and development of individualized treatment plans and to integrate strategies to manage adverse events and improve adherence to promote the completion of treatment regimens and improve patient outcomes in our patients with NTM lung disease.

So let us begin today's discussion focusing first on the diagnosis of NTM lung disease.

The first thing we should do is make sure we're all on the same page, and that's, What are nontuberculous mycobacteria, or NTM? Well, mycobacteria represent 200 separate species. These are organisms that are found throughout our environment. They are in water, they are in soil, and we think we're exposed to them almost every day, and the number of species is continuing to climb. But what's also continuing to climb are the number of patients with NTM lung disease. You can see in this figure and data showing a rise in NTM lung disease from 2008–2015. These data come from a very large managed care claims database that included 27 million people annually.

If you look on the Y axis, you'll see the prevalence per 100,000 of NTM lung disease from 2008–2015. The top line are those who are 65 years of age and older. The line right below that are those enrolled in Medicare, so they are both a reflection of age, but you can see high rates developing or increasing over time. The third line are women. They also have a higher rate than other groups, and also, the prevalence is increasing over time. So you can summarize, I think, these data by saying the highest-risk people are those who are 65 and older who are women, and they are also the groups that are seeing the greatest rise. What this means to you as a clinician is you're going to be seeing more and more of these patients in your practice. That means we need to be thinking about this early in the

disease course and try to make earlier diagnosis and reduce the time to treatment.

Now, there are 3 real reasons we should be doing this, and one is that if we don't, we know disease progresses in about 60% of people who meet the criteria for disease based on ATS and IDSA criteria, and they do so in a fairly short period of time, about 3–5 years. The other reason, we know that their function declines. Lung function will decline over time. And finally, mortality is high in this group. The 5-year all-cause mortality is 10–33%, and when it's been compared with the general population, it tends to be higher. And in at least 1 study, mortality was higher in the untreated MAC population than in the treated MAC population.

So, ATS and IDSA, back in 2007, they built these guidelines for us. These diagnostic criteria are just that. They are a guideline for clinicians. They assume that the patient has symptoms, that they have a radiograph that's consistent with NTM lung disease, but importantly, this is a microbiologic diagnosis, so we want to see 2 or more positive sputums that are culture-positive for the same species. Now, in some patients I know you can't get a sputum specimen, and a bronchoscopic specimen can be used in these criteria, but I don't think it's as important as having 2 positive sputum. And in some cases you may have a lung biopsy, and if they show the right histopathologic findings and they have a positive respiratory culture, that also meets disease criteria.

But to begin this diagnostic cascade, we have to begin somewhere, and we have to think about it, and once we think about it, it is still going to take 8–12 weeks for us to get a diagnosis with drug susceptibility results. So, who would you think about this disease in?

Well, there are 3 groups that we know are at risk, and the first group that I'll review are those who have underlying conditions: people with cystic fibrosis, alpha-1 antitrypsin deficiency, COPD, those who are immunocompromised. Just bronchiectasis with or without CF is a very high risk factor for NTM pulmonary disease. The next group are those who have some innate issue with their immune system. This is a unique group. They are postmenopausal women usually, and they have a phenotype. They tend to be thinner, taller, lighter than other persons. So we call this group the susceptible group, and honestly, most people who have NTM lung disease are susceptible individuals. There is another group, probably not as common, that have just a large dose. They have been exposed to contaminated aerosolized water or soil, maybe even just living in a residence that's endemic for NTM, and we call this the unusual dose group.

Whichever group, they tend to present in 1 of 2 clinical phenotypes. The first, nodular bronchiectatic disease, sometimes called Lady Windermere syndrome, this occurs in older women, typically nonsmokers. They are tall, thin, low body mass, as I mentioned. They may have a CT scan that you see here that has bronchiectasis that predominates in the lingula, in the right middle lobe. The other phenotype is fibrocavitary disease. This is called classic disease, and this occurs in older males. They do tend to be smokers. They have various body builds. The chest x-ray you see here in front of you, you can see right upper lobe cavitation, volume loss, lung destruction. I mean, it looks like tuberculosis, but it turns out this is MAC.

These are the symptoms that most people present with. In almost every study, fatigue and cough occur in 80-plus percent of people. The other symptoms that you see here are quite variable among studies. Weight loss is a very important thing to note because this suggests a subacute or chronic process. One of the issues though in terms of delay in diagnosis relates to the median time from symptoms onset to diagnosis is very long—in this study 10 months—and the range was 1 month to 6 years. There are other studies that suggest it could be up to 20 months on average, so it takes a long time from the time a patient first develops symptoms until we make a diagnosis, and that is something that we need to find a way to shorten.

So, once you think about it, you now need to collect a specimen, and since I'm speaking to a lot of pulmonologists and respirologists, I thought I'd start with bronchoscopy, because this may not be as good as you think it is. First of all, lidocaine is bacteriostatic, so if you use a lot of that, you're inhibiting the growth of the mycobacteria. It's a dilute specimen. There is sampling error, meaning you might be sampling the wrong area of the lung. We can't really determine bacterial load very well from a wash or BAL. And then, of course, there's the risk and the cost of bronchoscopy itself.

How about sputum? Because I think this may be better than you think. First of all, you can get multiple specimens, unlike with a bronchoscopic approach. We recommend in the new guidelines that you get 3 specimens over at least a week, but honestly, we prefer it to be over several weeks. We know that sputum AFB smear status and the number of cultures that we obtain are associated with progression. That again helps sputum over bronchoscopy in terms of deciding who you may want to treat. And then something many people don't know, the culture yield of bronchoscopy is very similar to sputum for both TB and NTM. And the final point I would make is, in those patients who say they can't provide specimens, I bet you can get one if you do sputum induction. And I know you say, "I don't have that available in my practice," but it turns out patients can do this at home. I mean, most of them have bronchiectasis, they're going to be on some type of flutter valve, hopefully getting inhaled hypertonic saline. So, guess what? That's induced sputum. So you can get really good sputum specimens from your patients by having them do this at home.

So now let's get this specimen to the laboratory, and what you're hoping to get back as quickly as possible are culture results, identification, and susceptibility test results. For culture results we recommend liquid and solid media, but unfortunately, most

laboratories in the US only use liquid media, and what that means to you is that's an automatic 15% decrease in sensitivity. Now, with almost 200 mycobacterial species, identification has become more important than it's ever been. You need a laboratory that can provide precise speciation. And then the final thing that you're waiting for are susceptibility results. We would recommend following the CLSI, the Clinical and Laboratory Standards Initiative recommendations. The 2 documents you see here we refer to in the NTM guidelines.

So, if you're going to do susceptibility testing, it is recommended that it be done on every MAC isolate, every one that you believe is causing disease, whether that's an initial isolate or a recurrent isolate. And you can do phenotypic testing. That takes weeks, and in some systems it might take you a month or a couple of months, maybe, to get the results back. We have 2 drugs that are recommended that they be tested. The first are the macrolides, and clarithromycin is a class drug there. The resistant cutpoint is 32 or greater. And note that we have 2 cutpoints now for amikacin. For intravenous, it's 64 or greater, and for liposomal, it's 128 or greater, so this changed a couple of years ago.

Why don't you speed this up? Why don't you use genotypic testing or molecular testing? And I'm just showing an example here of a line probe. This is a test that we use at National Jewish. In a study from South Korea, they showed that for identification of the rrl mutation, it's associated with macrolide resistance, very good sensitivity and specificity. The sensitivity dropped with the aminoglycoside detection, but they had very few cases, and our clinical experience using this now for several years, the sensitivity is also close to 100%. So these molecular-based tests are becoming more and more available, they are fast, and they are very accurate.

So let me summarize. NTM, including MAC, are increasing in prevalence in many areas. The most common symptoms are cough and fatigue in almost all patients. There are 2 clinical phenotypes: the nodular bronchiectatic disease and the fibrocavitary. But in all honesty, there's a lot of overlap between those 2 categories. The laboratory is critical for you as a clinician, and they need to provide you with precise speciation, in some cases subspeciation, and determination of in vitro susceptibility testing to at least the macrolides and amikacin. But ultimately, the diagnosis of NTM-related lung disease includes the synthesis of clinical, radiographic, and microbiologic information, and with that you can move on and make a decision to treat or not to treat.

So let's do that. Let's transition and talk about individualized treatment and a patient-centered approach, and we're going to focus on MAC. So I'd like to introduce the new NTM guidelines that were recently published in both *Clinical Infectious Diseases* and the *European Respiratory Journal*. The scope of the guidelines is that this was pulmonary disease in adults who are not immunocompromised and do not have cystic fibrosis. We took those 2,000 species and we had to narrow them down a bit, so we focused on the 4 you see here: M. avium complex, kansasii, xenopi, and abscessus. Why? Because these are the most common and cause lung disease. We use the GRADE methodology, which is a rigorous approach to guideline development. This resulted in 22 PICO questions and 31 recommendations, 7 of which really focus on MAC. And I'd like to point out that these guidelines were the product of sponsorship from 4 different professional societies that you see here.

So the first question is, Should you treat this person to begin with, or should you just do what's called watchful waiting and see if the patient progresses over time? This is literally the first question that you have to ask yourself when someone comes in and they meet those diagnostic criteria. So, in this setting we suggest initiation of treatment over watchful waiting, particularly in the setting of someone who has a positive AFB smear or has cavitary disease.

Now, when we reviewed the evidence to support this recommendation, we noted that there are both host and organism factors that relate to progression of disease. For example, some NTM species, like mycobacterium kansasii, are more pathogenic than other species, like mycobacterium gordonae. We also know that immunocompromised patients are at greater risk of progression than immunocompetent. We now have cohort studies that have been able to identify that bacterial load and radiographic extent of disease are 2 very important factors that predict progression, and you're going to have that as part of your evaluation of your patient. We also have some other factors that have been associated with progression, like older age, low body mass index, which is very common in this population, comorbidities, low albumin, anemia, and elevated inflammatory indices. And what you see now is a figure that is a representation of basically natural history in about 500 patients with MAC pulmonary disease who met those ATS and IDSA criteria.

A couple of points: The first is the majority progressed, and they did so over about a 3- to 5-year time period. Granted, not everyone progressed, so about a quarter of them were stable during that time period, and half of those spontaneously converted their cultures to negative, so I think it's important to note that most people progress who meet those criteria and that there are predictors of who is more likely to progress than not, at least during that short time. And I think I'll leave with this point. This is only 3–5 years. Over a person's life, many more of those patients would have progressed.

So, do you treat this person with empiric therapy or susceptibility-based therapy? Well, in the setting of pulmonary MAC, we suggest susceptibility-based treatment for the macrolides and amikacin. And we looked at data. We know that macrolide resistance correlates with poor treatment outcomes, and we have known this for many years, going way back to the monotherapy trials and our HIV-infected patients who had disseminated MAC, but that was followed by retrospective studies of non-HIV-related pulmonary disease that showed

the same thing. Amikacin resistance is associated with a specific mutation, and we now have data that correlate that mutation and high MIC with poor clinical outcomes, but most of the other drugs that we do use we do not have good cutpoints for resistance that would correlate with a poor outcome. So, for example, in this figure you see data from the CONVERT study. This was a randomized-controlled trial that randomized treatment-refractory MAC pulmonary patients to either 1 of 2 regimens. They would get guideline-based therapy alone, or they would get guideline-based therapy with the addition of amikacin liposome inhalation suspension, or ALIS. What you see on the Y axis are the patients, and across the X axis is the increasing MIC. The gray bars are those who converted, and the black are those who did not, and the first thing you'll note is that the gray bars go all the way out to an MIC of 64, meaning that we saw conversion in patients up to an MIC of 64. In the 1 patient—and there was only 1—that had MIC greater than 64 there was no conversion. Similar data were published in the phase II trial, so we now have a cutpoint that we can correlate with outcomes.

Should you use a regimen that contains a macrolide or one that does not? We recognize that there are really no well-designed studies that have addressed this, but we recommend a 3-drug regimen that includes a macrolide. We know that macrolide susceptibility has been a strong predictor of treatment success. This has been noted in multiple cohorts. And on the other side, if you lose the macrolide, that is associated with a markedly reduced rate of sputum conversion. You go from about 80% to 5–36%. We also have a systematic review that included 21 studies, and that review showed that sustained culture conversion incidence rate ratio was higher in the macrolide-containing regimens compared to macrolide-free regimens, and that difference got more and more as the quality of that study improved.

So, if we're going to say use macrolide, which one are we going to recommend? Well, we suggest using an azithromycin-based regimen as opposed to clarithromycin. We know there is equal efficacy in multiple cohort studies. We know there's better tolerance with azithromycin, less drug interactions, lower pill burden, and single daily dosing. We thought that all added up to azithromycin preferred to clarithromycin. We use that same systematic review because they show there's no difference in sputum culture conversion at 6 months, end of therapy or sustained out to 12 months, and there was no difference in acquired macrolide resistance.

What about aminoglycosides? The previous guidelines did suggest consideration of intravenous or parenteral aminoglycoside in cavitary disease, so we broadened that a bit in the new guidelines. So, for patients who have cavitary disease or advanced, severe bronchiectatic disease or macrolide-resistant disease, we suggest using a parenteral amikacin or streptomycin. This would be included as part of a multidrug regimen. It turns out we actually have a randomized, placebo-controlled trial that has addressed this. This was a study that randomized people to a macrolide-based, 3-drug regimen, and it either had intramuscular streptomycin for 3 months at the beginning versus placebo, and they showed higher rate of culture conversion in those who got streptomycin. We also know from cohort studies that if you include an aminoglycoside in a regimen with someone who has macrolide resistance, they also have a higher culture conversion rate. So you'll see in this figure, this is that randomized study from Japan. Those who got streptomycin, about 70% of them converted their cultures to negative. It was more like 50% in those who got placebo. They looked at both avium and intracellulare, and not surprisingly, really no difference there, so it does look like addition of an aminoglycoside at the beginning of therapy does have a bacteriocidal effect. In more severe disease we would use it.

Now, what about inhaled amikacin? Well, we didn't address this in the previous guidelines from 2007. We have 2 recommendations as part of this. The first was that in patients who have untreated disease, treatment-naive disease, that we would not suggest the use of either inhaled parenteral amikacin or ALIS. On the other side of this though, what about those people who are failing therapy? We define this as at least 6 months of guideline-based therapy and still they are culture positive. Here we do recommend addition of ALIS to that regimen, and it's based on these data and others. This again is the CONVERT trial, which I mentioned before. Here what we're looking at are the proportion of people that are converting their culture after they were randomized to receive ALIS plus guideline-based therapy or just guideline-based therapy. And as you can see, going across the X axis, that the culture conversion even at 1 month was separating from those who did not get ALIS, and by 4 months it was 30% conversion in those who received ALIS plus guideline-based therapy, but it was only about 9% in those who stayed the course and did not have ALIS added to the regimen. This led to FDA approval several years ago, and we basically follow that in our recommendations in the new guidelines.

How many drugs will you get? Three versus two. This is a very commonly asked clinical question, so we thought it was very important to address it, and we suggest that you use 3 drugs including a macrolide and ethambutol over a regimen with 2 drugs. If for some reason you are using 2 drugs to treat the patient, it should be a macrolide and ethambutol. We do not recommend a macrolide and rifampin or a macrolide and a quinolone because those regimens have been associated with a higher rate of acquired macrolide resistance. Most studies, as it turns out, that have been published, they looked at 3 drugs. We don't have many regimens or many trials that looked at 2, but we actually do have 1 randomized study. It compared 2 versus 3 drugs. It compared clarithromycin and ethambutol versus the same 2 drugs plus rifampin. Unfortunately, it was quite underpowered. There were several methodologic weaknesses that the committee reviewed. We were also concerned about acquired macrolide resistance developing in a 2-drug regimen, hence our recommendation to stay the course and continue the previous guidelines recommendation of 3 drugs. But I do want

to show you a figure from this because it turns out it did look like it worked.

So, if you look at this figure, you'll look at efficacy in both the intention-to-treat and a per-protocol approach, and in the intention-to-treat, 2 drugs was not inferior to three. However, in the per-protocol, that was not statistically significant, in part because there were very few patients left at the end of the trial because of high dropout rates. So, while we could not make a change in the recommendation from 3 to 2 drugs based on this study, this study did lead to a very large study that's occurring right now in the US. It's a randomized study of 2 versus 3 drugs, and it is occurring in about 30 sites in the US, so I hope by the time we have our next guideline, we will have more data to inform us on this decision.

Now, can you give this intermittently or daily? We have 2 recommendations. So, in people who have noncavitary disease, we believe this can be given 3 times a week, but the flipside is that we do not recommend this in cavitary or advanced nodular bronchiectatic disease. The evidence behind this is that we have cohort studies that have demonstrated similar culture conversion rates with intermittent versus daily therapy. We also know that intermittent therapy is associated with less adverse effects and has better completion rates. There is no evidence of increased risk of macrolide resistance. But on the flipside, this isn't the case with cavitary disease. We know there are very low rates of culture conversion with intermittent therapy in cavitary MAC, hence the reason we say use daily therapy if it's cavitary, but you can use intermittent if it's noncavitary.

The final question related to MAC treatment is, How long do you treat the patient? We basically are saying the same thing we did in the 2007 guidelines because we could not find new evidence that would change that recommendation, and that is to suggest that patients receive treatment for at least 12 months after culture conversion. Granted, there are no randomized studies that have evaluated the optimum duration of therapy, but we have cohort data and some systematic review data that show treatment successes higher in people who receive 12 or more months of a macrolide-based regimen compared to those who got less than 12 months. And there was a large postmarketing study in Japan that showed that 5% recurred when they were treated for less than 15 months after sputum conversion, but it was zero if they got over 15 months after sputum conversion, so our recommendation probably lies somewhere in between, but we think we're in the right general zone of what would be a good treatment regimen and the duration.

I'm going to show you the figure from that study from Japan. So the gray bars show you those who recurred, and you can see it was all in those who took less than 15 months of therapy, but probably what I want to point out is, if you look to the right, there weren't many patients who received more than 15, so this is not a definitive study, and I think it highlights a very important research priority, which is, How long should we treat our patients?

So that leads us to these recommendations. For nodular bronchiectatic disease, we recommend 3 drugs, macrolide-containing, azithromycin-preferred, and this regimen can be administered 3 times a week. For cavitary disease, we recommend 3 or 4 drugs. Here is where we would add intravenous amikacin or streptomycin parenterally. We would give this regimen daily, and you can give the aminoglycoside 3 times a week. The new recommendation relates to refractory disease, and here we would use 4 or more drugs. We would use a standard azithromycin, rifampin and ethambutol, and we would add ALIS at this point. And again, we define this as those who have not culture-converted after about 6 months. This is daily therapy, but again, you can give the aminoglycoside, the intravenous aminoglycoside, 3 times a week.

So this is what you expect if you do this. You take a treatment-naive patient; you start him on a 3-drug macrolide-containing regimen; you add IV amikacin if they have cavitary disease. Anywhere from 50–80% of people will culture-convert—80% if they have nodular bronchiectatic disease, 50% if they have cavitary disease. Of those, most are cured, but recurrence is high, 25–50%, the lower number in those with nodular bronchiectatic disease, and among those that recur, reinfection is very common. Half or more of patients seem to come back with a new isolate. Among those who do not culture-convert and stay positive for 6 or more months, we call those treatment-refractory patients, and this is a patient population that we would add ALIS to their treatment regimen.

So, before we conclude this section, let's hear from a patient on their perspective about living with NTM.

Patient Speaker:
Well, I was first diagnosed about 14 years ago, and, uh, I actually saw an allergist. I was very lucky, and then I was referred for a bronchoscopy, and that's when it came back and I was diagnosed with NTM. And I'm now on my fourth round of drugs. I still play tennis every day, um, at a pretty competitive level, and I know it's back when I start coughing again. The other way you know that NTM is back is because you—if affects eating. It always comes back, unfortunately, and to be—not to wait if you start to feel... After you get off the drugs, if you start getting sick again, not to—to see the doctor right away because, uh, that's when the bronchiectasis increases, and it's, you know, cyclical. Your profession has become being a patient, which is really depressing, you know, because you do spend a lot of time going back and forth, so you—you want to find other—well, definitely an aerobic activity for your lungs.

Dr. Daley:

So now let me summarize. New guidelines are now available for NTM pulmonary disease, and for those who meet diagnostic criteria, initiation of therapy is preferred, especially in those who have higher bacterial load and extensive radiographic disease. MAC should be treated with a 3-drug macrolide-containing regimen and administered for 12 months after culture conversion to negative. You can administer this 3 times a week in people who have nodular bronchiectatic disease, but in cavitary disease, it should be daily, and we would consider the addition of parenteral aminoglycoside for the first 2 to 3 months. And in treatment-refractory MAC pulmonary disease, we would use ALIS as an addition to our guideline-based therapy.

So, thank you for listening today, and I will now pass it over to Dr. Shannon Kasperbauer for the next part of the presentation on mycobacterium abscessus and strategies to manage adverse events and improve adherence.

Dr. Kasperbauer:
Thank you, Dr. Daley. We will now be discussing mycobacterium abscessus.

Mycobacterium abscessus pulmonary disease is a chronic lung condition. These pictures illustrate the progressive destruction in one of my patients that we've been following since 2003. It's important to understand the evolution of taxonomy in this infection. In the 1990s, we regarded this just as mycobacterium abscessus, and in 2006, we understood that there were 3 distinct organisms divided as mycobacterium abscessus, mycobacterium massiliense, and mycobacterium bolletii. In 2011, the mycobacterium massiliense and bolletii were grouped into 1 category of mycobacterium abscessus subspecies bolletii, and since 2013, they are distinct subspecies, so depending on the literature that you're reviewing, it's important to understand that these changes occur. Currently, there's mycobacterium abscessus subspecies abscessus, subspecies massiliense and subspecies bolletii.

And why is this important? I'm going to spend some time on this slide, and it really revolves around the behavior of the organism in the presence of the macrolides. So, mycobacterium massiliense, which is the first row, is an organism that's sensitive to macrolides, and when we tested at 3 days—which most labs will give you a 3-day report—it looks susceptible. If we were to extend the incubation to 14 days, it is again susceptible, so it does not have this feature of inducible macrolide resistance, it has a dysfunctional erm gene, and therefore, if the macrolides are used in this infection, it's working. It is working as an antimicrobial.

That is in contrast to mycobacterium abscessus or mycobacterium bolletii. These organisms have inducible macrolide resistance, so at 3 days the organism will look susceptible, but with extended incubation to 14 days, the inducible macrolide resistance is detected because it has a functional erm gene, and therefore, if you are using a macrolide in these infections, you are not counting it as an active antimicrobial. It's being used as an anti-inflammatory or an immune modulator.

Finally, in the last row, any of these organisms can become resistant and develop mutational resistance. This is picked up on the 3-day susceptibility test and the 14-day susceptibility test. This is due to a point mutation in the 23S ribosomal gene.

The PICO questions that were addressed in the recent guidelines are going to be reviewed here, the first of which was, In mycobacterium abscessus pulmonary disease, should a macrolide-based regimen be used for treatment? And the answer is, in those strains without inducible or mutational resistance, we would recommend a macrolide-containing, multidrug regimen. This was a strong recommendation but low certainty in effect. In mycobacterium abscessus disease caused by those strains that have inducible or mutational resistance, a macrolide can be used as part of the regimen, but it's being used as an immune modulator, and it's not counted as an active drug in the treatment regimen. There are no studies that were identified in this guideline review that compared macrolide-containing regimens to non-macrolide-containing regimens, and therefore, these were graded as having a low certainty in effect.

But understanding the different subspecies is very important, and I'm going to illustrate that here. It has prognostic indications. In 57 patients who received a standardized combination regimen, which was a macrolide-based regimen with 4 weeks of cefoxitin and amikacin, they defined cure rates in abscessus versus those with massiliense, and you can see the outcomes were significantly different. Eighty-eight percent of patients were able to be achieved—were able to achieve cure in mycobacterium massiliense and only 25% in mycobacterium abscessus.

This was also illustrated in a systematic review, the data of which is in this table, and you can see here in the second column sustained culture conversion without relapse was only seen in 23% of those patients with mycobacterium abscessus versus 84% with mycobacterium massiliense. Importantly, they also saw higher recurrence rates in those patients that had mycobacterium abscessus. So understanding which subspecies is very important.

Now, this was also examined, this distinction in subspecies, to understand whether or not it was a predictor for progression, and in fact, it wasn't. In this study of 113 patients who were followed for 3 ½ years, about a third of the patients in the abscessus group progressed, and 38% in the massiliense group progressed requiring treatment, so knowing your subspecies does not necessarily help you with whether or not a patient is going to progress requiring treatment, but they did find 3 characteristics that were important predictors of progression, and that included being underweight, having bilateral lung disease and having cavitary lung disease.

The second question that was addressed in the guidelines statement related to how many antibiotics should be included in a regimen, and the recommendation was that a multidrug regimen include at least 3 active drugs guided by in vitro susceptibility in the initial phase of treatment. This was a conditional recommendation, again with very low certainty in the estimates of effect, and the reason for that is that there are no studies that have directly compared the efficacy or safety of different multidrug regimens. However, the few case series that have described treatment outcomes all used regimens that included at least 3 or more drugs. The authors of the guidelines statement at this time recommended that a 3-drug regimen be included.

The next question is, How long should we treat patients? Should shorter durations or longer durations be used? And their recommendation was that either a shorter or a longer treatment regimen be used with expert consultation. Unfortunately, there is a paucity of data in this area. There was 1 observational retrospective study that identified a very small sample size and only indirectly addressed this question. Therefore, it was felt to be of too low quality to form a basis of a recommendation.

I'm going to describe to you our approach at National Jewish when we're treating pulmonary mycobacterium abscessus. When we have a patient with abscessus, the first question we ask is, How does it behave in the presence of a macrolide? In other words, does it have a functional erm gene or a dysfunctional erm gene? I'm going to go down the right side of this slide first. In mycobacterium massiliense, which has a dysfunctional erm gene, we would use a macrolide-based regimen, and again, we are counting that macrolide as an active drug. The other drugs that are chosen could be IV amikacin and a second IV agent, such as imipenem, cefoxitin or tigecycline. We would recommend using those agents for 1 to 2 months and then transitioning to a macrolide plus 2 additional drugs. Often times in our hands that includes inhaled amikacin and clofazimine. If you are treating a more drug-resistant strain, such as mycobacterium abscessus or bolletii, again we would recommend at least 3 active drugs. If you use the macrolide, you're not counting it, but you may use it as an anti-inflammatory or an immune modulator. And then typically we treat patients with 3 drugs, including 2 IV agents for 2 months and step down to, again, 3 active drugs. This is going to be more difficult in that second phase because these are drug-resistant organisms, and the likelihood of having active oral drugs is low. We would recommend surgery for patients that have focal disease, and our usual approach is to try to achieve culture conversion and then treat a patient for 12 months of negative cultures.

The final PICO question that I'll review in this talk was about surgery. Should surgery plus medical therapy or medical therapy alone be used to treat NTM pulmonary disease? In select patients with NTM pulmonary disease, the authors suggested surgical resection as an adjuvant to medical therapy after expert consultation. Again, this was rated as a conditional recommendation with very low certainty in the estimates of effect. I'm going to highlight one study that was published in 2011. This was a review of our patients at National Jewish with mycobacterium abscessus pulmonary disease. One hundred and seven patients were included, and there were significantly more surgical patients than medical patients whose cultures converted and remained negative for at least 1 year, and that was statistically significant.

So the key points to summarize my talk are that mycobacterium abscessus complex is comprised of 3 subspecies with different degrees of susceptibility to the macrolides. Differentiation of these subspecies is critical to the management and the prognosis of your patient. Macrolides should be used in the treatment of macrolide-susceptible infection. At least 3 active drugs should be used to treat mycobacterium abscessus infection. And the optimal duration of therapy is unknown, and we would recommend expert consultation.

The second portion of my talk is going to address strategies to manage adverse events and improve adherence. When patients are surveyed about their most bothersome symptoms, in multiple surveys fatigue is at the top of the list. This is followed by respiratory complaints, medication adverse events, and concerns related to mental health, including depression and anxiety.

I'm going to begin with the adverse events to the drugs, beginning with the macrolides. Azithromycin and clarithromycin, as you have heard, are essential drugs in the treatment of patients with NTM disease and MAC disease, and experience suggests that azithromycin is better tolerated. And the most common adverse events include gastrointestinal complaints, tinnitus and hearing loss, hepatotoxicity and a prolonged QT interval.

In this table I have strategies to manage these adverse events. Specifically for gastrointestinal complaints, I recommend changing clarithromycin to azithromycin, moving administration to bedtime, and consider taking this medication with a small starch. If patients are describing that metallic taste in their mouth, that is unique to clarithromycin; therefore, switch to azithromycin. If patients begin complaining of tinnitus or hearing loss, I would certainly interrupt medication for a period of time, look for other agents on their medication list that could be contributing to these symptoms and consider changing to thrice-weekly therapy. For hepatotoxicity—again, if mild—hold the medication and consider rechallenging to determine the etiology. If patients have a prolonged QT interval, again, stopping other medications before starting the macrolide, that would also prolong the QT interval, but this can certainly be a rate-limiting side effect.

The second drug is ethambutol. This is a relatively well-tolerated medication, and when paired with a macrolide, it decreases the risk of acquired macrolide resistance, so it's very important. We also know that treatment failure is significantly higher in those patients that

discontinue ethambutol versus those that are able to continue it as part of their regimen. The most common adverse events include ocular toxicity and neuropathy.

In this study of 229 patients with MAC pulmonary disease who were receiving ethambutol as part of their regimen, 40% of patients had ocular symptoms at some time of their treatment that were not at all related to the ethambutol. In the 8 patients who did develop optic neuritis, all of those were in the patients receiving daily treatment versus those patients that were receiving 3 times weekly treatment. Fortunately, all patients returned to their baseline vision, and importantly, all patients developed symptoms in between their appointments, so we counsel patients to see an ophthalmologist every 3 to 6 months, but you have to counsel your patients to read fine print every day and let you know if they are having any changes in their vision. If a patient complains of changes in their vision, you need to stop the medication immediately and have them see an ophthalmologist and consider a neuro-ophthalmologist if the first exam is unrevealing. This can be a rate-limiting toxicity. Neuropathy is also something that we see in our patients on chronic ethambutol therapy. It can be progressive and irreversible and, again, can be a rate-limiting toxicity.

The rifamycins are the third drug used in a standard MAC drug regimen. Both rifampin and rifabutin induce the cytochrome P450 system, but rifabutin also acts as a substrate. The most common adverse reactions here include hepatotoxicity, cytopenias, hypersensitivity, orange discoloration of secretions, and unique to rifabutin is uveitis.

If a patient develops hepatotoxicity, I would stop the medication and only consider rechallenging with mild elevations in liver function studies. Cytopenias are common. In fact, we often see a decrease in someone's white blood cell count when they are on rifampin or rifabutin, and most of the time that stabilizes and does not drop to severe levels, so I typically continue the rifampin or rifabutin as long as the white count remains above 2.0.

Thrombocytopenias can also be seen, and if the platelet count drops significantly, you need to stop this medication because it has been associated with the development of ITP. Again, with hypersensitivity reactions, this can be a rate-limiting reaction. Now, orange discoloration is common, it's expected, and so I would reassure the patient if they notice this in their urine or in their sweat. That is to be expected on this medication. Uveitis— again, unique to rifabutin—can be a rate-limiting toxicity, but I would consider rechallenging the patient with rifampin after the rifabutin is stopped and the uveitis resolves.

The final class includes the aminoglycosides. These are potent drugs against MAC organisms, and they are most... Amikacin is the most commonly used aminoglycoside and comes in both parenteral and inhaled formulations. The most common reactions include ototoxicity or vestibular toxicity, nephrotoxicity and electrolyte disturbances in the parenteral form. I'll cover the inhaled-related adverse events in a moment.

Beginning with the parenteral form, again, if ototoxicity develops, this may be rate-limiting. In tinnitus I would certainly think about other medications on the problem list that can also lead to tinnitus, but this may be rate-limiting in the patient. Vestibular toxicity is important to monitor, and again, if someone develops vestibular toxicity, we stop this medication and have them see a vestibular specialist. For nephrotoxicity, I would suggest that you follow renal function weekly in someone on parenteral aminoglycosides, make sure they are maintaining their hydration, and stop other medications that may also affect their renal function, and try to detect electrolyte abnormalities early and correct them before you begin this medication.

In the CONVERT study, which was the study that evaluated the use of ALIS, or amikacin in liposome inhalation solution, versus guideline-based therapy alone, there were often respiratory-related adverse events with this nebulized therapy, and you can see here that almost half of the patients described dysphonia, 37% described cough, 21% described dyspnea, and a fewer proportion described hemoptysis or oropharyngeal pain. The audiologic adverse events are shown here as well. Discontinuation of ALIS occurred in 17.5% of patients in the treatment arm.

I show this slide because it's important to understand that these respiratory adverse events decrease significantly by 2 months of treatment, so it appears there's a conditioning effect that occurs, and if your patient is able to continue the drug either daily or consider decreasing the administration to 3 times weekly, often times these resolve by week 8.

Here are some strategies to improve the adherence to this particular medication. We'll start with dysphonia. You could offer them warm water gargling or glycerin gargle, change the administration to the evening, use lozenge therapy; or finally, if those strategies do not work, consider a brief interruption for 1 to 2 weeks and restarting at a 3-times-weekly administration before working your way back up to daily. Those strategies also work for patients that are describing dyspnea or cough, as well as the use of bronchodilators, and then lozenge therapy in patients that have a cough.

When patients are asked, "If your treatment could change one thing about your NTM lung infection, what would that be?" the top 3 responses include a culture conversion, less coughing and less fatigue.

In order to treat patients with NTM lung disease effectively, it really requires a village. We use a multidisciplinary team here, including respiratory therapy, nutrition, psychotherapy, and our physical therapist and occupational therapist for rehabilitation.

I suggest the following tips for effective communication strategies. When I have a patient and I'm diagnosing this disease, I schedule 2 visits, one to discuss bronchiectasis, to introduce airway clearance and the NTM infection. The second visit is to discuss the results of their bronchiectasis evaluation, talk about airway clearance adherence and whether or not NTM treatment is needed and what will that look like. I recommend you follow up with patients frequently. I typically see people a month after I start them on treatment and then every 3 months thereafter. In the meantime they are getting monthly labs for monitoring and monthly sputum cultures. I use this opportunity for nurses to call them back with results and to check in on their adherence to therapy. I would suggest accessing an airway clearance action plan from the IMPACT website listed here and then introduce other resources to your patients for connectivity, of which 3 references are listed here. This is helpful not only for the patient but for their family members.

And the key points to summarize this portion of the talk are that adverse drug reactions occur in the majority of patients during the course of treatment. It's important to detect these early, manage them appropriately, and try to keep patients on the most effective treatment regimen possible. Management strategies include aggressive treatment of side effects, short drug "holidays" and intermittent administration where appropriate.

NTM lung disease is a chronic condition that affects individuals on multiple levels, both physical and emotional. Fatigue is the highest reported symptom, which is likely multifactorial. And treatment of the whole individual requires a multidisciplinary team. Set up regular follow-up with patients and encourage the use of online resources that I referenced.

Thank you for joining us for this presentation, and please remember to complete the posttest and the evaluation.

Narrator:
You've been listening to a replay of a live broadcast about NTM. This activity was provided by National Jewish Health and supported by an educational grant from Insmed. To receive your free CME credit or to download this activity, go to ReachMD.com/CME. This is CME on ReachMD. Be Part of the Knowledge.