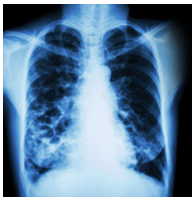

NONTUBERCULOUS MYCOBACTERIAL LUNG DISEASE:
REAL-WORLD APPLICATION OF NEW GUIDELINES AND TREATMENT ADVANCES

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. In the first of this 2-part activity, Drs. Shannon Kasperbauer and Kevin Winthrop discuss the recommendations in the 2020 ATS/ERS/ESCMID/IDSA guidelines, for which Dr. Winthrop was a senior author, and the evidence supporting the recommendations. Extensive discussion focuses on the macrolides and aminoglycosides, including treatment advances.

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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Consultant: AN2 Therapeutics, Insmed, NTMir, Paratek

Kevin Winthrop, MD, MPH

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

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Kevin Winthrop, MD, MPH

Hi, I'm Kevin Winthrop, I'm a professor of Infectious Diseases and Public Health here in Portland, Oregon at Oregon Health and Science University. I'm delighted to be here and joined by my good friend and colleague, Dr. Shannon Kasperbauer.

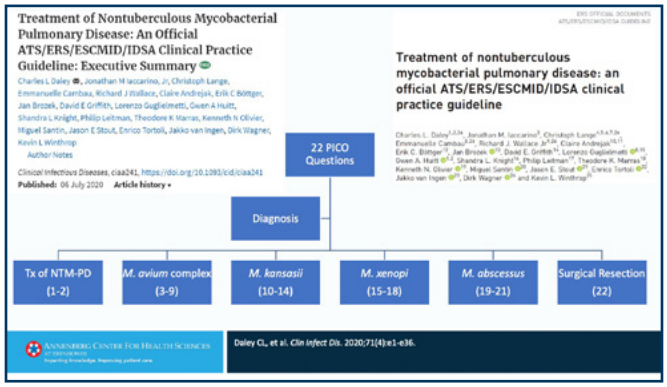
Shannon Kasperbauer, MD

Hi, welcome, thank you. I'm happy to be part of this program, and I am an infectious disease provider at National Jewish and an assistant professor in the Department of Medicine here at the University of Colorado School of Medicine.

Kevin Winthrop, MD, MPH

Shannon and I go back a long way and we're excited to give you an overview today of the recently published and long thought-about guidelines. These are the 2020 nontuberculous mycobacterial guidelines recently published in the *Clinical Infectious Diseases* journal. This was a 3- or 4-year effort among professional societies both from Europe and the United States, including the American Thoracic Society, Infectious Disease Society of America, the European Respiratory Society, and the European Society for Clinical Microbiology and Infectious Diseases.

The 4 groups, we all came together, we shared data. This was a typical guideline as of the last few years where PICO questions are formulated, and there are specific questions on a topic that compare one intervention with another. And this forms a basis for our systematic literature review and then there is a methodologist, who works with us as a group, who conducts that literature review. And then we come together, again as a group, over several years actually, to review the data as it's found, and of course to update our literature searches as new data is published.



This was quite an undertaking. Chuck Daley at National Jewish was the leader of our group. I was a senior author on these guidelines as I was also on the prior guidelines in 2007. We definitely highlighted lots of gaps in literature and there's fewer gaps now than there were 10 years ago.

What Shannon and I would like to do is take you through some of the highlights, specifically in regard to the 2 most common and most important pulmonary NTM pathogens in North America, and that'd be *Mycobacterium avium* complex and *Mycobacterium abscessus*. So, with that, I'll turn to you, Shannon, to start us out talking about MAC.

Shannon Kasperbauer, MD

I am going to begin by discussing the diagnosis of MAC lung disease. As many of you know, these are environmental organisms and they're ubiquitous in the environment, so it requires more rigorous criteria than diagnosing a case, for example, of pulmonary tuberculosis. And so it's required that you have a combination of both clinical and radiologic criteria. Clinical criteria can include pulmonary and/or systemic symptoms. Radiologic criteria include nodular or cavitary opacities on either a chest x-ray or a computed tomography (CT) scan. You'll often see concomitant bronchiectasis, and then appropriate exclusion of other diagnoses should occur.

The microbiologic criteria are listed here to include 2 positive cultures from at least 2 separate sputum samples. If the results are non-diagnostic, consider repeat sputum acid-fast bacillus (AFB) smear and culture. They also include microbiologic criteria from 1 bronchial wash or lavage, or a transbronchial or other biopsy with mycobacteria histological features, and at least 1 positive culture.

I'll comment that a few other issues should be considered when diagnosing MAC lung disease, and that is it's recommended that you culture to the species level. There are at least 12 separate species in the MAC umbrella, and we would like to see consistent reproducible growth of the same species. That also holds true for the diagnosis of *Mycobacterium abscessus* complex, you should identify the organism to the species level. As far as acquiring specimens, we like to obtain at least 3 specimens to increase our yield of a diagnosis, and preferably over a week, or multiple weeks, rather than back-to-back. And if a patient is not expectorating, I would encourage you to introduce them to airway clearance, because in bronchiectasis, sometimes patients are not producing sputum and you add something like a flutter valve and they're much more able to produce or expectorate a sputum on their own. And if they're not able to expectorate, then to consider sputum induction. So, using hypertonic saline methods to acquire a sample, and we actually prefer this to a bronchial lavage.

Kevin Winthrop, MD, MPH

I'll just add that we didn't change these diagnostic criteria compared to the 2007 guidelines, and really—even at that time—we had quite a bit of debate that the way we constructed the guidelines was to err more on the side of specificity rather than sensitivity. And so we required that second positive sputum, for example. Even in the right person, you know, their CT looks like they've got bronchiectasis, or cavitary, or whatever. One sputum we just thought wasn't good enough.

There has been data published since then, and we've done some studies as part of that, showing that if the person has radiographic findings that are characteristic and they have 1 positive sputum, then they really truly have disease. It would be more sensitive, I would just add, if we just used 1 positive sputum.

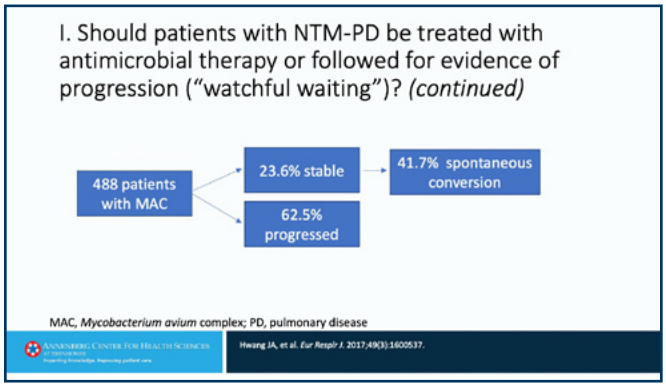
Note, we do accept the 1 bronchial wash because it's a deeper respiratory tract sample. We're more convinced that it's real. But

suffice it to say we rigged it up to be somewhat specific because ... for a couple of reasons. One, as you know, some people don't have disease, particularly ones that have clean CT scans, they look normal and they have 1 positive MAC. And I don't know what to make of that, it might have been transient, it might just be in and out of the airway, or maybe they have super early disease and they are going to have radiographic findings in 3 months or 6 months. I've seen that happen, but obviously the more you find, it intuitively makes sense to be more likely that it's real.

The more likely it's truly there on a consistent basis, then probably it's more likely this is associated with disease. And I guess that kind of plays into the first question, what do you do when you find it? And should you treat people right away, or should you wait? What do you do when you find 1 positive sputum? That kind of thing. I don't know, what do you do?

Shannon Kasperbauer, MD

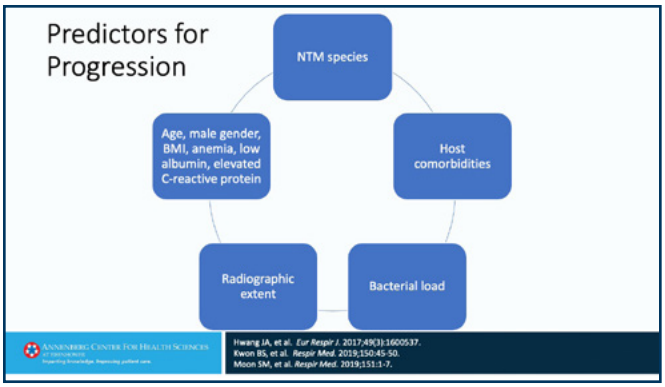
That is a great segue, Kevin, into the first PICO question which is, what do you do when you find it and you absolutely do meet microbiologic criteria? Do you pursue antimicrobial therapy or do you just watch for evidence of progression? And, as you know, as part of the expert panel, the recommendation was suggesting initiation of treatment rather than watchful waiting, especially in the context of those that have predictors for progression, which include those that are smear-positive or those that have cavitary lung disease.



This is a study out of Korea, in Seoul, that was looking at a cohort of individuals, both patients with bronchiectatic nodular and cavitary disease, and following them for at least 3 years. And they recognized that approximately 63% of patients progressed in that 3-year timeframe, so the majority of individuals. And there were certainly predictors for progression, including things like being smear positive, or having cavitary lung disease, but in the 23% or so that they had over 3 years of data, I think it's interesting to see here that 40%, almost 42%, had spontaneous culture conversion.

Perhaps those were patients with milder disease. We don't know a lot about them to understand the predictors for those that were able to spontaneously convert, but it just really speaks to the heterogeneous nature of our patients.

I wanted to just point out some predictors for progression. It's a complex environment. We know that not all NTM species are the same, and some are clearly more clinically relevant, and I'll just put as an example here, *Mycobacterium abscessus*.



If you had *Mycobacterium abscessus* in a patient recovered multiple times, that's going to be more likely to be a pathogen than isolating something like *Mycobacterium lentiflavum*, or *Mycobacterium gordonae*. So, the NTM species matters. Host comorbidities can play a role in progression. As an example, those individuals that may be immune compromised, or have genetic disorders, such as cystic fibrosis. The bacterial load is important. And that's been consistent in multiple studies that those individuals that are smear positive are more likely to progress, and the extent of radiographic abnormalities. Having cavitary disease, that is not a patient who you would ever put on a watchful waiting protocol, you would really want to try to treat that individual aggressively.

And then finally, there's other characteristics about the individual. The older the age, in some studies having male gender was a predictor for progression, which may be related to the COPD phenotype, and upper lobe emphysema, and cavitary disease, having a low BMI and less than 18.5 kg/m^2, and this has been shown in both MAC and *M. abscessus* to be a predictor for progression. Being anemic, having a low albumin, or having elevated inflammatory markers. Kevin, did you have any thoughts on ...

Kevin Winthrop, MD, MPH

I totally agree with this, and I think a lot of us consider these risk factors for progression, and obviously, if the patient's sick or not sick, do they feel poorly or not, and that's a big trigger. If they feel poorly and they want to be treated, it's going to push you to initiate therapy, or if you see evidence of progression already. Let's face it, a lot of times we see patients, they're on their third or fourth CT scan, at least at our centers, and we can see that. "Oh, there's quite a bit of progression in the last 12 months or 6 months," and so that's what will push you to therapy. Even maybe if they're feeling fine, you're concerned about the progression.

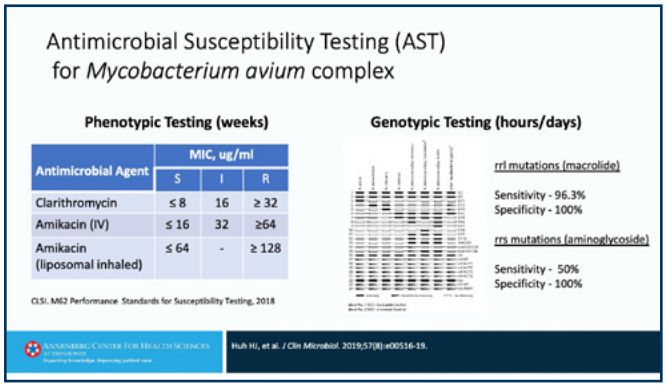
And that would be in the absence of these risk factors, but certainly, I consider these things enough if I think they're more likely to progress more quickly because of these things. I'd also add just emphysema or other underlying lung diseases. You mentioned a couple of them, but I'm convinced emphysematous patients progress more quickly with MAC than non-emphysematous patients. I guess the other thing, too, is you think about whether you can get rid of it or not. I mean, I always think of that as well, and I know we debated that during the guidelines and there's no real firm way to define whether something looks "get ridable" or not, but obviously it's a dual-edged sword. Because when there's not a lot there you think, "Well, let's just

leave this alone, we don't need to treat it yet." On the other hand, the patient might say, "Well, why don't we just try to get rid of it if there's not a lot there?" Which is a really valid concept. We don't really know. Obviously there is no randomized clinical trial (RCT) comparing watchful waiting with initiation of therapy.

Shannon Kasperbauer, MD

The next question, question number 2, is whether or not patients should be treated empirically or based on in vitro drug susceptibility test results. And I point out, in this table, the 3 organisms and the related antibiotics that matter. For MAC, susceptibility-based treatment should be macrolides and amikacin over empiric therapy. For *Mycobacterium kansasii*, we recommend using rifampicin or rifampin susceptibility testing to guide treatment. In *Mycobacterium abscessus*, we recommend getting susceptibility tests on macrolides and amikacin.

And I know Kevin's going to talk about this in a little bit more detail later, but you should really strive to understand what flavor of abscessus you're treating, because the outcomes are incredibly different, and this is all based on this one characteristic of macrolide susceptibility. And that can occur by 2 mechanisms. Patients can have organisms that have what we call constitutive resistance, meaning that you look at it 3 days and it looks resistant, or they can have a feature called inducible macrolide resistance, and that is only known by testing either a 14-day incubation, or extended incubation, or sequencing for this *erm*(41) gene.

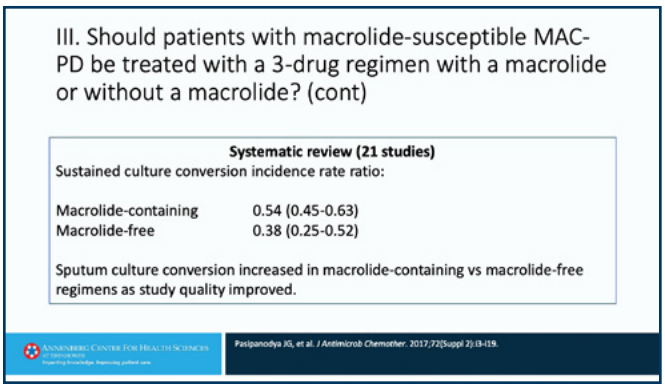


What does this look like? Well, I just introduced you to these 2 different concepts. The first is phenotypic testing, which is the method that we've been using for several decades to test drug susceptibility testing in MAC, and this is done through broth microdilution. So, you basically are using the broth to see if the organism grows in a certain concentration of the drug. And I've listed here the cut points for the minimum inhibitory concentration for the macrolides, parenteral amikacin, and inhaled liposomal amikacin. On the right, I'm introducing genetic testing, so the advantage here is that using a molecular-based assay to probe for these mutations is very sensitive and specific in the case of macrolides, not as sensitive for the aminoglycosides, but the turnaround time is incredible compared to what you're waiting on with the phenotypic testing.

We can get these results if we grew up an isolated MAC in a week, by day 8 I have the genotypic testing results, and so, it's quite helpful information. The other point that I will comment on here is that sometimes patients that have had a lot of treatment experience actually have what we call heteroresistance. So they have a mixed population where some of their strains are actually sensitive and others have developed resistance. We wouldn't know that necessarily with phenotypic testing, but we can pick that up on genotypic testing.

The information clinicians are getting today compared to 2 years ago, it's quite a bit different. And that was part of the guideline to us, too, that there was this hope that we could move the labs along with some of the lab aspects of the guidelines in terms of really pushing for this kind of testing and reporting.

The next question is, should patients with macrolide-susceptible MAC be treated with a 3-drug regimen with or without a macrolide? And I would just emphasize here that macrolides are important. They are the most important drug in our regimen. So, the expert panel recommended that a 3-drug regimen, in fact, include a macrolide, and the strength was strong.



I'm showing you data here from a systematic review looking at the rates of sustained culture conversion with a macrolide-containing regimen vs macrolide-free. And you can see there's a significant difference, although these are not ideal rates. 54% sustained culture conversion with a macrolide-containing regimen. I would comment that the sputum culture conversion increased in these studies as the study quality improved. So, it's probably closer to around 74% culture conversion in those individuals that can tolerate at least 12 months of medication.

Kevin Winthrop, MD, MPH

I just agree with you 100% that I don't know that any of the other drugs do a whole lot, they're just there to protect the macrolide. At least that's what I think about rifampin and ethambutol, anyway. The only reason not to use a macrolide is really macrolide resistance, but you know sometimes I use it anyway because I think of mixed populations being there, like you mentioned. How, how about you? What's your thought about that?

Shannon Kasperbauer, MD

I think about this a lot in the context of *Mycobacterium abscessus* subspecies and abscessus, that where we have evidence of inducible macrolide resistance, should we use the macrolide or not? I try to, if I can. It gets a little complicated when you have 5 antimicrobials on board, and multiple QT-prolonging agents, in an elderly patient.

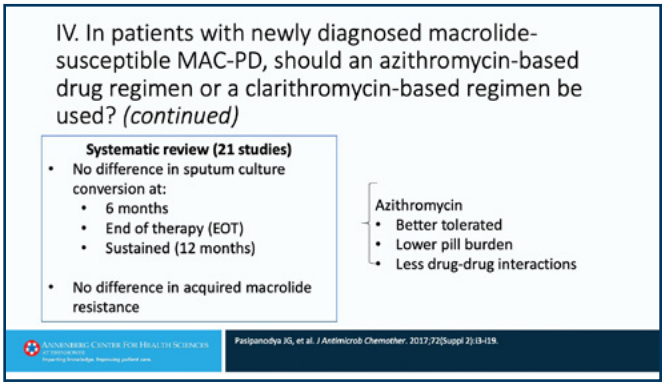
I think the individuals that I really strive to continue it for are those frequent exacerbators with bronchiectasis; and certainly if they have co-infection with pseudomonas, simply because of the data that say that macrolides are helpful—in 3 randomized studies—in those patients with bronchiectasis. So, those are my reasons for using it, but I have a low threshold to stop it in a macrolide-resistant MAC patient if they're having any issues with drug-drug interactions or intolerance, because I think that's where your prognosis is so poor and you're trying to use parenteral aminoglycosides for 6 months, and you're getting that patient to surgery if they can tolerate it and I just don't know that it's worth it in those patients.

Kevin Winthrop, MD, MPH

I agree. I've had some patients, as you have, that they all of a sudden have macrolide resistance, but then the next isolate I get from them they don't, and I see the amikacin MIC is bouncing around, and it just speaks to the fact that these are probably usually polyclonal infections. I mean, certainly the environmental presence of these bugs is polyclonal, so it would make sense to me if patients are often infected by more than 1 strain. I always think about those things, too, but I think that the macrolide is really important.

Shannon Kasperbauer, MD

In a newly diagnosed, macrolide-susceptible individual, should an azithromycin-based regimen or clarithromycin-based regimen be used? And I think 20 years ago, there was really an emphasis to use clarithromycin. I think that was the first thing mentioned in the guidelines, and, in fact, it was clarithromycin and rifabutin, which we almost never use together any longer because of drug-drug interactions.



The recommendation that came out in 2020 from the expert panel was to suggest azithromycin over clarithromycin. Again, this is a conditional recommendation with low certainty and effect, but in the systematic review that's shown here there was no difference in sputum culture conversion at 6 months, or at end of treatment, or sustained culture conversion. And there was no difference in macrolide resistance developing between azithromycin and clarithromycin. But my personal bias is that azithromycin is better tolerated. It just is!

I see so many side effects from clarithromycin, including dysgeusia, and anorexia, and weight loss. That's one of the things that I've mentioned in the beginning of this talk that we know having an underweight individual, that individual is not going to do as well and they're going to progress more quickly. So, if there's anything that we can do to help them tolerate the most important drug, and allow them to gain some weight, I think it's worthwhile switching them off the clarithromycin to azithromycin. It's a lower pill burden, too, and less drug-drug interactions.

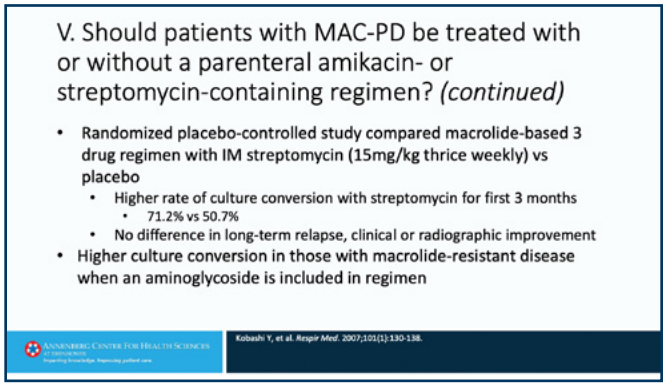
Kevin Winthrop, MD, MPH

Yes, I agree. I think, also, that MICs to clarithromycin are usually lower, and I think it's been, for years, that the infectious disease clinician will pick up the susceptibility report, like we normally do, and look, and see better MICs and probably pick clarithromycin. I think historically that's been a lot of what's also driven that as a choice, but I see less of it now, probably because of the guidelines, but also just learning, over time, collectively. And I agree, there's no question, azithromycin is better tolerated.

A nice study you guys did, too, a few years ago, just showing that macrolide levels are higher when you're on azithromycin because of that drug-drug interaction with clarithromycin and rifampin, for example, where rifampin cuts down clarithromycin. So, it probably makes sense on an efficacy side to favor azithromycin, too. Of course, we don't need data to say that other than the data I just mentioned. There's no head-to-head data, but I think our experience, at least observationally, personally anecdotally, is that there's probably no difference in outcome between the 2 drugs other than that one is probably better tolerated than the other.

Shannon Kasperbauer, MD

Should patients with MAC be treated with or without parenteral amikacin or streptomycin? There is really a couple of considerations where I would strongly recommend it, and one is in an individual with cavitary disease, advanced or severe bronchiectatic disease, or macrolide-resistant pulmonary disease.



And I'll tell you that there's really 1 randomized placebo-controlled study that compared a macrolide-based regimen with or without intramuscular streptomycin. And they did see 1 outcome that was statistically significant. It was that there was a higher rate of culture conversion in the patients on the treatment arm in the first 3 months.

That was seen in 71% that received the streptomycin, vs about 50% in the placebo group. But in the long-term outcomes, so long-

term relapse, or clinical or radiographic improvement, there was no difference between the 2 arms. We know that in macrolide-resistant disease, there's a higher culture conversion rate, and certainly a higher sustained culture conversion in what we call cure in those individuals that receive long durations of intravenous aminoglycoside, and that's on the order of 6 months. And that data came, again, retrospective data, from Tyler, Texas. So, do you use vitamin A much, Kevin, in your practice?

Kevin Winthrop, MD, MPH

My answer would be is I would use it in every single patient if I could, if it was easy, and not toxic, and my belief is it kills mycobacterium better than any of the drugs we have. And obviously, that's why we use it in people who are really sick, like with cavitary disease, as you mentioned, I think amikacin really works. I have to admit, I've never used streptomycin in my life. I don't know why.

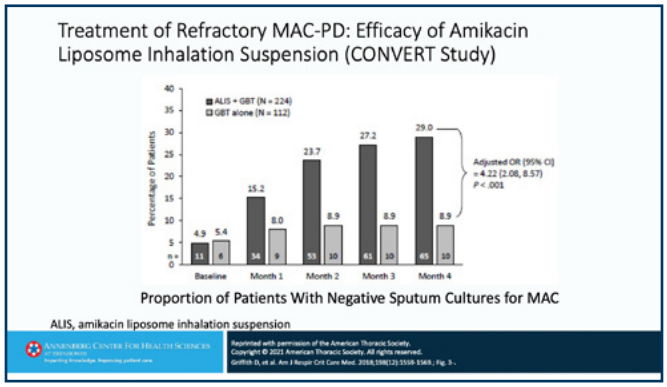
I guess my 2-cents about amikacin—and I don't think we address this in the guideline—I think most of us use it intermittently, 3 times a week. I think there are still a few people that use it daily. There's still some controversy about that. My feeling is it's tolerated better, at least longer term, if you use it in intermittent fashion.

I think there's some data to back that up, but efficacy-wise, it kind of makes sense to me that you just would need to use it intermittently based on the growth characteristics of mycobacterium. I've never really seen a head-to-head study of daily vs thrice-weekly for a few months where you look at outcomes. I definitely favor intermittent.

Shannon Kasperbauer, MD

I use twice-weekly therapy for any patient who needs to receive parenteral aminoglycosides.

Moving on to inhaled amikacin. In patients with macrolide susceptible MAC, should a regimen with or without inhaled amikacin be used? And there's really 2 groups of patients we're going to consider. The first is in newly diagnosed individuals. It is not recommended in those individuals to use inhaled amikacin parenteral formulation, or the recently FDA-approved product, amikacin liposome inhalation suspension (ALIS). And so that is based on the fact that the studies of the liposomal preparation did not include newly diagnosed MAC patients.



That brings us to the second category, in patients who have failed treatment. We call these treatment refractory patients, who've had at least 6 months of guideline-based therapy. There is a strong recommendation to add ALIS to the treatment regimen rather than just continuing the oral regimen alone, and the outcomes from the CONVERT study are listed on this next slide.

This was a 2:1 randomization of patients who were in this treatment-refractory group to receive the treatment arm, which is the ALIS, or amikacin liposome inhalation suspension, with guideline-based therapy, or guideline-based therapy alone. What you are seeing here is the percentage of patients or the proportion of patients who ultimately achieved negative sputum cultures for MAC based on the baseline vs month 1, 2, 3, and 4. And even by month 1, you see a difference in these columns, where 15% of those on ALIS were beginning to convert their cultures, and that goes up steadily out to month 4.

I will stop and just say that the methods that were used in this study were quite rigorous. They had all patients hold their treatment while they were collecting sputum cultures, and they collected 3 separate days of sputum cultures on a monthly basis. So, you had to have 3 days each month of negative cultures to label you or, or fall into the culture conversion, or negative sputum culture category. And now to month 4, you see a significant difference in those that were on ALIS vs those on the guideline-based therapy alone, with a *P*-value that was less than 0.001. Any comments, Kevin, on that study?

Kevin Winthrop, MD, MPH

I would just comment, too, that we subsequently published follow-up data for these people, and the people that convert are very likely to stay negative while they're on this therapy. And then even after they stop all treatment, at least at the 3-month time period when we measured them, most were still culture negative. I'd love to look 1 year later or 2 years later. I don't know that it'll be any different than with any other of our therapies where we think we've converted someone, or maybe cured them. Obviously people can get reinfected. I always tell my patients, 50% of people who complete therapy will be culture-positive again in the next few years, and that's based off institutional case series. I think this data shows that the drug is active, and it works, and the sustainability data is impressive, and it was good to see.

Shannon Kasperbauer, MD

Yes, and definitely it's important to emphasize how treatment refractory these patients were. A lot of those folks had been on treatment for years, and so our goals for discussion with them were if you've been on treatment for 2 years and you haven't converted, you're not going to convert, in most cases, unless you went to surgery, for example. So, you know, when patients came back to me and they said, "Gosh, it was only 30% conversion." I look at the glass half full and say, "Yes, but these were people that we were never expecting would convert," and yet a third of them went on to convert and have, as you've described, durable culture conversion. So, I think that's really valuable.

Kevin Winthrop, MD, MPH

Yes, and it allowed us to stop the treatment, right? I mean that someone said, "Well, who cares about my sputum? I mean, what's the big deal?" So, this is 30% of people that basically, for almost all of them, we stopped their treatment eventually because they met treatment stoppage criteria, they were negative for 12 months. That's the time point at which we try to stop treatment. So, you know, if you can convert some of the negative it puts them on the pathway to potentially completing therapy and going off therapy, which is nice because I think you agree that with the refractory disease folks, it's tough to take them off treatment if they're still culture-positive.

Shannon Kasperbauer, MD

Now we're going to shift gears and talk about more of the mild phenotype of patients. In macrolide-susceptible MAC, should we use a 3-drug regimen or could we get away with maybe a 2-drug regimen for treatment? And the recommendation was, in fact, that a treatment regimen at this time should contain a total of 3 drugs. And why is that? Most of the studies have evaluated 3-drug regimens. There is 1 study that was a randomized study comparing 2 vs 3, but, unfortunately, the study was underpowered and had several methodologic weaknesses.

Providers are concerned about acquired macrolide resistance with 2 drugs, and so there is an ongoing 2 vs 3 multicenter study (2v3) to evaluate this question, and in which I'm involved, but not as intimately as Kevin. So will you comment on that study, Kevin?

Kevin Winthrop, MD, MPH

It really grew out of working very intimately with patient and patient advocacy groups in our patient panel, trying to understand what was important to them, and developing a research roadmap that was very patient-driven, and patient-centered.

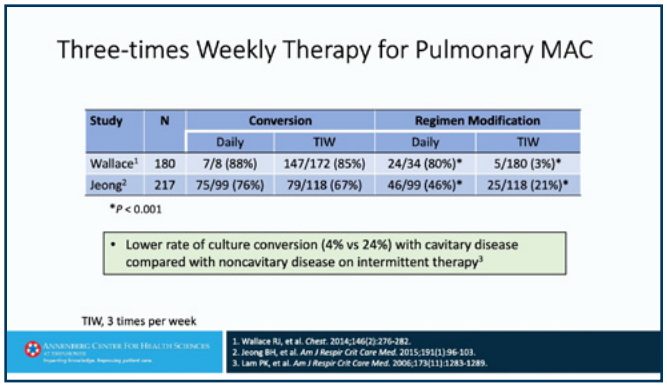
And, one of the primary questions was the question you just posed, can we use less drugs? Do we really need 3? Can't we just use 2? There is some data out there, not much, as you were mentioning. There was 1 RCT, I think, that suggested 2 drugs look just as good as 1 drugs, but it was a really small trial.

We have about 30 centers around the country doing the trial together, so it's really helped us establish an NTM trials network, which has been nice. The partcipants in the trial are mostly mild to moderate patients. They're not cavitary patients. We're measuring effectiveness really. So, our patient is just as likely to clear their sputum on the 2-drug regimen. And then also tolerability. Are the 2 regimens equally tolerable or is there a difference between them? Obviously, our hypothesis is fewer drugs equals higher tolerability.

Shannon Kasperbauer, MD

As you were just alluding to, this is a rare infectious disease where we're telling our patients that they have to take 3 different antimicrobials for 12 to 24 months. And most people just stop listening when they hear that. It's quite overwhelming. So, we've all been looking for ways to make that more successful, and one of the ways is addressed in PICO question number 8. Should you use a daily regimen or can you use a 3-times weekly macrolide-based regimen for treatment?

And in patients with non-cavitary bronchiectatic nodular macrolide-susceptible MAC, we do suggest a 3-times weekly macrolide-based regimen be used. In patients that have cavitary disease, or advanced disease, we would not recommend using thrice-weekly therapy, And here's the data that supports that recommendation. So, these were 2 studies out of Texas and Korea, looking at culture conversion rates in individuals that were treated either with a daily or 3-times weekly regimen.



And you can see that those conversion rates are very similar, but the regimen modification is drastically different. In the Tyler, Texas group with Dr. Wallace, from those individuals that were on daily treatment, initially 80% of them had to have some sort of regimen modification for intolerance. The same was true in Korea, but not as high, 46% had to have regimen modification vs 3% and 21% in those that were on 3-times weekly. We also know from Dr. Lam's study that there was a very low culture conversion rate in patients that had cavitary disease and who were receiving intermittent or thrice-weekly treatment. That was 4%. So, we would not recommend approaching this for patients with more severe or cavitary disease.

In this slide, I break it down based on the phenotype of disease and the preferred regimen. So, in those patients with mild to moderate forms, or what we call nodular bronchiectatic disease without cavities, we'd recommend 3 oral agents, and administering that thrice-weekly. In those that have cavitary disease you're going to be using those same 3 oral agents, but you're going to be administering them daily, and then using IV amikacin, or streptomycin. As we mentioned earlier, we would recommend using a parenteral aminoglycoside thrice weekly because you're going to have much better tolerance and be able to use it for longer durations of time.

The toxicities that we see with the parenteral aminoglycosides are usually a cumulative exposure, and so the longer you use this, the more likely you're going to start to see some ototoxicity, and less likely nephrotoxicity, when using it 3 times weekly. And in refractory disease, as I said, there's a strong recommendation to add ALIS, and I would recommend using the oral agents daily in those individuals.

Shannon Kasperbauer, MD

The next and final PICO question that I'll be reviewing, is how long do you treat? And I can't tell you how many patients I've seen over

the years that come to me and say, "I was diagnosed years ago, I got my year of treatment, and then 2 or 3 years later, I'm back to where I started." And unfortunately, I think some things get lost in translation and their provider just said, you know, "Here's scripts for these 3 drugs, and you're going to be in a year of treatment, and then you'll be done." But in fact, the recommendation is a year of negative cultures, so that only is understood if you're checking cultures.

That is such an important concept, it's so simple, but it really gets down to the nuts and bolts of managing MAC, that number 1, you need to teach your patients how important it is to follow cultures and then give them tools to get you cultures. That's things like the airway clearance modalities, and hypertonic saline at home, so that you can feel like you have reliable data to follow. So, this recommendation to treat for at least 12 months after culture conversion was a conditional recommendation, and really the bottom line is that there are no randomized studies that have evaluated the optimal duration in patients.

We know that success rates are generally better in observational studies and those that get 12 months of macrolide-based regimen vs less than 12 months. In the Japanese study published in 2017, the relapse rates were about 5% of individuals who had less than 15 months of negative cultures, vs none that had over 15 months of negative cultures. So, I think a good benchmark is 12 months of negative cultures. I don't know, Kevin, are there any individuals for whom you would extend that longer?

Kevin Winthrop, MD, MPH

Sometimes—because of the things you said—sometimes you don't really know when they went negative because they're either not giving you sputum frequently, or someone's not trying to check it frequently, or the quality of their sputum is really poor, and you don't feel like you can trust it. People who are immunocompromised, I might feel less assured about stopping, and I might want to do more.

There is no hard and fast answers here, and as you mentioned, maybe this is even the wrong strategy in some patients, maybe we should be treating for 6 months and giving them a break, and doing it again. I don't know, the cystic fibrosis (CF) flair kind of idea or model, rather than treating pseudomonas for 2 weeks, you treat MAC for 2 months, take a break. I don't know. No one studied these kind of alternative ideas before, and I'll also say that pretty much all the studies we've talked about, other than the 2v3 study, which is an RCT, a lot of the data we have is observational.

The 12 months, I can just tell you, my personal feeling is if you really want to make a dent in the MAC, you have to treat for at least 12 months. That is my feeling from not just personal experience, but also the data, in which shorter time periods are associated with greater chance of relapse or greater and sooner relapse. I don't know if there are patients we should be treating for 24 months, or 18. All I know is that sometimes I drift. I would say my usual is about 18 months because it usually takes 3 or 4 months to convert. You add 12 to that and you're kind of at 16-ish. Do you have other thoughts based on your experience?

Shannon Kasperbauer, MD

No, I just, I think that there are going to be that small group of folks who you just are having a hard time getting cultures, and it's rare though. I really do think that when you give the patients the tools to produce sputum, even if they don't have that feature of what we call wet bronchiectasis, they can at least give you something valuable that on our initial evaluation we can get a positive culture and if they take those methods home with the 7% or 10% saline at home and they're taught how to do it. I think that that's probably the most valuable data that we have, and the best information that we can get. I had a patient actually today ask me, "Well, what do we do if I just can't get anything up?" You know, "Are we going to have to do a bronchoscopy every 6 months?" And my answer was, "No, you know we almost never do that." I do a bronchoscopy to prove that they've culture converted. As long as they're clinically improving, their radiographs are improving … I think if something's moving in the wrong direction, and I just don't have data, and I'm worried about co-infection with something else, maybe I would do a bronchoscopy at that time.

Kevin Winthrop, MD, MPH

Totally agree. It speaks to the fact that we need other biomarkers, and obviously we're all working on that together.

I'll move this to *Mycobacterium kansasii*, and there's 3 or 4 questions on kansasii. The first question was whether or not we ought to use isoniazid-containing regimens or macrolide-containing regimens for treating kansasii.

For those of you who don't know this bug, it's not just in Kansas. It is more common in the south of the United States. It causes similar disease to MAC, and maybe more similar to tuberculosis (TB), but basically what's great about it is that it's curable, and it's even curable with TB drugs.

A lot of kansasii around the world gets treated like TB because they don't know what it is, they think it's just TB and it goes away. South Africa would be a good example. They have a lot of kansasii and a lot of it is just treated as presumed TB, but it does respond to TB drugs. So, rifampin is the cornerstone of therapy against this organism, similar to how Shannon was talking about the macrolide being the cornerstone of therapy against MAC, rifampin would be so here.

The first PICO question was really just asking what regimen should be used for rifampin-susceptible kansasii. So really the question is what other drugs, besides rifampin? And so, specifically, we were asked to look at isoniazid and macrolides, and we reviewed that literature.

There's data supporting either of them, both in vitro, as well as clinical data. Do you have anything more to add about rifampin-susceptible kansasii?

Shannon Kasperbauer, MD

This is the thing about kansasii, as you said, we almost never see it here in Colorado as a referral center because it's curable. It's so easy to treat, it's so drug susceptible. So, I think that you could use either

drug, so it's going to be based on patient tolerance, other drug-drug interactions, things like that.

Kevin Winthrop, MD, MPH

And I'll just say the next question had to do with whether we should be using parenteral aminoglycosides, and the answer was no. Unless it was cavitary disease, we wouldn't consider it. And even with some cavitary disease, I don't use it. How about you?

Shannon Kasperbauer, MD

I think it's really rare to need to use it.

Kevin Winthrop, MD, MPH

I agree. I can't think of a case. Well, I've had a couple of bad ones—bad cavitary disease—that I decided to do it, but may not have needed it. I mean, it is more like TB and tends to respond to therapy. There's a nice meta-analysis and you can see that the culture conversion rates are somewhere north of 75%, 80%, and these are the success rates or the cure rates.

The last thing about kansasii, 2 questions: Should you use a fluoroquinolone? And then, how about 3 times a week or daily? There's not a lot of difference here to MAC. The answer with fluoroquinolones is with MAC, no, you should almost never use a fluoroquinolone for MAC, but for kansasii, certainly you can. Kansasii is very susceptible. I always use it if it's rifampin-resistant because you need another good drug. But in the absence of rifampin-resistance, rarely do we use it. And then, kind of similar to MAC, daily or 3 times a week? You can probably do either. I tend to stick to daily with kansasii. Shannon, thoughts on those concepts?

Shannon Kasperbauer, MD

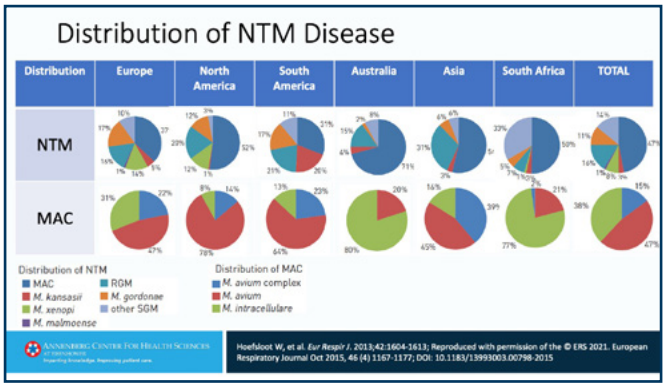
I would say that I don't know that there's data supporting an isoniazid-based regimen thrice-weekly, so if you were going to choose an isoniazid-based regimen, it should be daily. If it were a macrolide-based regimen, I think you can choose either in the milder cases. In any cavitary case, I would only use daily.

Kevin Winthrop, MD, MPH

That goes back to your MAC discussion before—the data around cavitary disease or really recurrent disease. Second or third episodes of treatment really favors—and again, it's observational data—but it does favor daily therapy vs intermittent therapy.

Let's move on to *Mycobacterium abscessus*. So, this is a good update in the guideline. We did review a lot of the recent publications around abscessus. There's a lot more now than just a few years ago.

This is really a convenience sample done by the Dutch group. They just showed that these different countries with different percentages of NTM, of either MAC or rapidly growing mycobacterium like abscessus. You can see abscessus is important, and more important in certain parts of the world, but it's quite important here in the United States. Our pulmonary NTM is due to *Mycobacterium abscessus*, with a few percent being *M. kansasii*, and the rest being MAC.



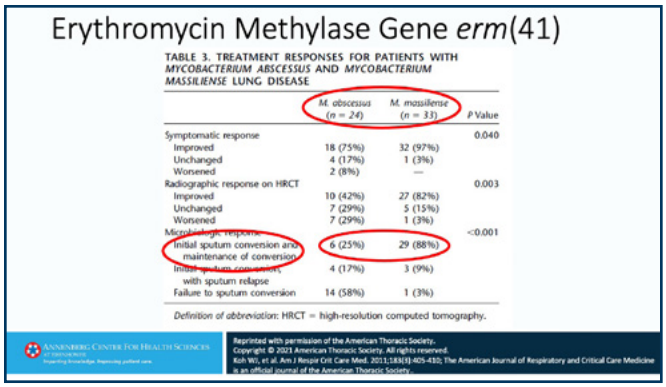
Somewhere 85%, 90% is MAC, 8% to 10% abscessus, 2% to 3% kansasii, and then there's xenopi, and malmoense, a few other things that come in as a couple percent. Abscessus is a big deal.

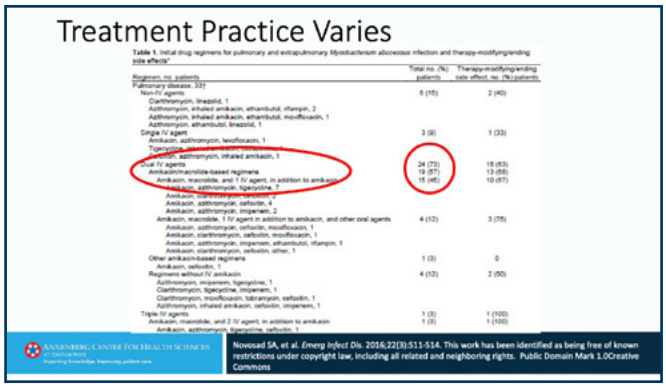
There's a number of North American and particularly Asian studies showing increases in *Mycobacterium abscessus* the last few years, particularly the last 10 years.

You have the issue with cystic fibrosis. It's been well studied in the CF registry in North America where pulmonary NTM has been a reasonably large problem, I'd say, for the cystic fibrosis population. And historically, it was more MAC. But the last 5 or 10 years we've seen kind of a flattening of NTM, but within that flattening, I guess that means MAC rates must have gone down a bit, because abscessus has really gone up, and it's gone up quite a bit the last 5 or 10 years. It has become a very important problem in that group. Overall prevalence of abscessus has risen throughout the US and Asia, where most epidemiology data for that organism are coming from.

Shannon mentioned this earlier about subspecies and how it impacts treatment choice. And really this boils down to the macrolide resistance, or inducible macrolide resistance, as Shannon mentioned previously. And that's caused by this *erm*(41) gene, whether it's present or not. If it's present, it's usually active. Although 10% or 15% of the time it's not active, so it's important you get that information that Shannon was showing you before about whether that *erm* gene is present and active, and whether there is inducible macrolide resistance. Because you can see from this treatment experience here from Won-Jung Koh in South Korea that the presence of macrolide-inducible resistance really, really diminishes your chance of converting someone's sputum.

On the left-hand column, you have *Mycobacterium abscessus*. On the right-hand column, you have the subspecies of abscessus, massiliense. Massiliense does not have an *erm* gene. It does not produce inducible macrolide resistance. So, you can see 88% culture conversion in that group, and only 25% in the abscessus, subspecies abscessus, where presumably, most, if not all, of those have inducible macrolide resistance. So, it does harken back to Shannon's point about diagnostics and lab data. You need this information from your lab because if you have macrolide susceptibility, true susceptibility, it will be very important in terms of your likelihood of curing the patient.





The first couple of questions here … How many antibiotics should we include within a multi-drug regimen against abscessus? So, Shannon, how many do you include, and what do you think?

Shannon Kasperbauer, MD

I recommend at least 3. I agree with the expert panel's recommendation. I think what you just touched on, this issue of the macrolide susceptibility, not only does it change how you would treat the patient, but take a step back and it changes your initial conversation with the patient, and it really frames your goals completely differently. Because if I have a patient that has a massiliense strain, we are going to be full-court-press to try and get rid of it and cure them of that infection, vs someone that may have whatever stage of abscessus. You're going to be thinking about your goals differently if you know that only a quarter of those patients are going to achieve microbiologic cure.

When you have that subset of folks that have macrolide resistance, I think one of the greatest challenges is just to find 3 active drugs. And upfront, that's easier when you can choose 2 parenteral agents, for example, and maybe 1 oral agent. But after you're done with that couple of months of intravenous (IV) medications, then what do you step down to? That's where I think we really struggle to find a complementary regimen that's going to have activity and not induce resistance in patients.

Kevin Winthrop, MD, MPH

That plays into a couple things.

This was an Emerging Infections Network (EIN) survey we did years ago of infectious disease physicians around the country treating abscessus. You can see a huge variety of regimens. Most of them were built around at least 2 IV agents. Which is within what we recommend for the guidelines, 3 agents, at least 2 being IV. But as you know, abscessus is generally resistant to pretty much all oral antibiotics unless you have that macrolide, and then unless you have access to clofazimine (no longer available in the US) where there's at least in vitro susceptibility.

There is great heterogeneity out there in terms of how people are started. Some of this reflects the fact that we just don't know the best way to treat this, some of it also reflects the heterogeneity and the susceptibility reports, and people trying to use those to guide therapy.

In the document, we do have some recommended treatment regimens for macrolide-susceptible abscessus. We talk about whether or not to use the macrolide when there's resistance, which you and I just talked about. There may be a rationale for using it.

It plays into the next PICO question which is, "What is the duration of therapy and how do we construct this therapy?" It's obviously tough to use 2 or 3 IV drugs for 12 months or 18 months. It's impossible! So, it raised this question. I have to say, there was a lot of debate around the table. I mean this whole idea of this aggressive parenteral phase upfront, and then stepping down, like you mentioned, to something more suppressive, or something that's not IV-based. Whether that works, whether the suppressive strategy works people just end up back on IVs, some people do and some people don't, you don't really know who's going to end up back on IV.

These were our debates. Unfortunately, we don't have a ton of data and I'll just say on question 21, in patients with *M. abscessus*, should shorter or longer durations of therapy be used for treatment? And our expert opinion was we thought the data favored a shorter or longer treatment regimen. Either one. I mean, we don't know!

The nice meta-analysis by Diel in *Chest* from 2017, showing a variety of treatment outcomes in terms of looking at culture conversion. That line there is at 35% or something. Often studies are kind of better than that half or less than that. When you really look at the studies, it's really dictated by subspecies and whether or not there's macrolide susceptibility. The ones that are more successful in terms of higher proportions of culture conversion are ones where macrolide susceptibility exists. So, it's a tough question. I don't know where you sit with it. Obviously, the panel is open to studying alternative durations of therapy in the future, and we acknowledge that it may not be a one-size-fits-all solution. After constructing this 3- or 4-drug regimen to start for a few months, where do we go from here? So, I think it's case-by-case. What are your thoughts in general?

Shannon Kasperbauer, MD

I think this is one of the most challenging infections we all manage. When I say that, I mean the macrolide-resistant abscessus because of its propensity for drug resistance, the toxicity of the agents that we have to use, those incredibly abysmal cure rates. I think training and working here for the last 14 or 15 years, I have a low threshold, especially in individuals that are younger or with more focal disease, to think about surgery. We showed this again with a retrospective

analysis of our patients that Julie Jarand published, that adding surgery to these individuals significantly changed the outcomes.

I think that there is a huge potential for research in this area, and I think we really need to come up with some novel ideas for abscessus because this can be such a terrible prognosis for a susceptible individual, especially the CF population. I think that combination of CF and abscessus is incredibly difficult to treat because by the time they get to us, they are densely resistant to most of the routine drugs we would use because they've been on them for so many years.

Kevin Winthrop, MD, MPH

I'm glad you mentioned the surgery. That was one of the papers that formed the evidence base around the answer to question 22, which was really whether surgery should be employed alongside medical therapy. We all thought that, yes, there was data to support it. We also mentioned that expert consultation should be sought.

This is like treating multi-drug resistant (MDR) or really extensively drug-resistant (XDR) TB. I mean it's not easy. You have a ton of drug resistance and tolerability issues and you're constantly second guessing yourself. It's very difficult to treat this infection. I do think that this is one where expert consultation is really, really helpful.

I do want to mention one thing that you also mentioned, and that was resistance. By the time people end up at your place, or my place, or others, they may have been through a lot and they've developed resistance. We didn't hit on the amikacin resistance. If you've got an MIC greater than 64 mcg/mL to MAC, or abscessus, or whatever, it is uniformly resistant from the data we've seen. So, if it's 64 mcg/mL below, there's susceptibility at least if you can get a level high enough to get at the bug.

In inhaled forms, you're probably able to still have some activity even with an MIC of 64 mcg/mL. But if it's above 64 mcg/mL it's fully resistant. There's no real rationale in using amikacin. And I will say that stinks, because with abscessus, amikacin is probably your best friend, and you really don't want to lose the ability to use it. Even when I'm having patients inhale amikacin, I'm really careful about having other drugs on board to make sure that I diminish—well, I think I'm diminishing—the probability that they'll develop resistance, by providing multi-drug coverage.

The 2020 guidelines provided recommendations for real-world treatment of patients with NTM lung disease, mostly around the organisms we mentioned, MAC, kansasii, and abscessus, but there's a few other organisms covered in that document. Refractory disease, recurrent disease, we've talked about cavitary, non-cavitary, daily vs intermittent, we mentioned the liposomal amikacin, and amikacin in general.

There are some good data out there, and the RCTs that have been done recently with the liposomal amikacin, the 2 vs 3 RCT, there's a number of things happening out there that are going to give us kind of good or better head-to-head data to help us answer some of these questions.

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