Clinical Compendium / Nontuberculous Mycobacterial Lung Disease: Strategies and Solutions for Real-World Management

OVERVIEW

Nontuberculous mycobacteria (NTM) represent more than 200 species and subspecies, some of which can produce chronic infection in the lungs and other organs. Among the NTM, *Mycobacterium avium* complex (MAC) is the most prominent. Guidelines issued in 2020 are helpful to guide the management of patients with NTM lung disease (NTM-LD). Nonetheless, care is highly individualized through collaboration by an interprofessional team of experienced clinicians. In this case-based activity, Jennifer Faber-Gerling, RN, MS, CNS, NP-BC, David Griffith, MD, and Christina O'Connor, PharmD, BCPS, AAHIVP, provide their insight to address challenges encountered in everyday clinical practice. Their discussion highlights best practices in diagnosis and treatment initiation and modification based on guideline recommendations for MAC-LD, recent scientific and therapeutic advances, strategies for optimizing treatment adherence and completion, and the importance of shared decision-making with interprofessional collaborative care. Join the faculty in this interactive, case-based dialogue about the real-world management of patients with MAC-LD.

CONTENT AREAS

- Diagnostic criteria
- Strategies to optimize treatment
- Interprofessional collaboration
- Macrolide susceptible vs nonsusceptible MAC-LD
- Cavitary vs noncavitary MAC-LD
- Treatment failure
- Treatment monitoring

FACULTY

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Target Audience

This activity was developed for pulmonologists, infectious diseases specialists, nurse practitioners, nurses, pharmacists, and other clinicians who have a role in the diagnosis and treatment of patients with nontuberculous mycobacterial lung disease.

Learning Objectives

- Describe best practices to ensure a timely diagnosis and initiation of guideline-based treatment for nontuberculous mycobacterial lung disease (NTM-LD)
- Explain the clinical impact of recent scientific and therapeutic advances in NTM-LD
- Create individualized treatment plans for patients with NTM-LD that align with the latest guidelines and clinical advances
- Apply strategies for optimal collaboration with patients with NTM-LD, including shared decision-making

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Editor's Note: This is a transcript of a presentation on July 15, 2022. It has been edited and condensed for clarity.

CASE 1

Case Background

AB, a 69-year-old patient, reports several pulmonary infections over the past year. They notice a few weeks after completing each course of antibiotic treatment, cough, shortness of breath, and fatigue return. Over the past year, AB reports losing 30 lb due to poor appetite (current body mass index (BMI): 21.4 kg/m^2). They are currently reporting night sweats and increased mucus production.

Allergies: NKDA

Past Medical History

- Atrial fibrillation
- Chronic obstructive pulmonary disease
- Dyslipidemia
- Hypertension
- Obesity

Social History

- Former smoker (50 pack-year smoking history)
- Retired schoolteacher

Current Medications

- Albuterol 90 mcg 2 inhalations every 4 to 6 hours as needed for shortness of breath
- Atorvastatin 20 mg at bedtime
- Fluticasone 100 mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg 1 inhalation once daily
- Hydrochlorothiazide 25 mg daily
- Lisinopril 20 mg daily
- Metoprolol succinate 100 mg daily

Case 1 Question 1

What factor increases clinical suspicion for *Mycobacterium avium* complex – lung disease (*MAC*-LD) in this patient?

A. Atrial fibrillation
B. Chronic obstructive pulmonary disease
C. Hypertension
D. Former smoker

Answer Rationale

The correct answer is **B**.

- Chronic obstructive pulmonary disease (COPD), bronchiectasis, cystic fibrosis, prior tuberculosis, are a few examples of risk factors for the development of *MAC*-LD due to damaged lungs from underlying pulmonary disease.[1,2]
- Other factors that increase the risk for the development of *MAC*-LD include diseases or medications that weaken the immune system, gastroesophageal reflux disease, women who are postmenopausal, and people ≥ 65 years of age.[2,3]
- There has not been a link between atrial fibrillation, hypertension, or former smoking status and the development of *MAC*-LD. Although current or prior smoking history can increase the risk for developing COPD, and subsequently *MAC*-LD, people who did not have a smoking history also developed *MAC*-LD.[1]

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1. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Clin Infect Dis*. 2020;71(4):905-913. doi:10.1093/cid/ciaa1125
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Faculty Commentary

Christina O'Connor, PharmD: This is a fairly illustrative example of what we would see in the pulmonary *Mycobacterium avium* complex (MAC) clinic and highlights a common risk factor for pulmonary MAC, being underlying pulmonary disease. Specifically, in this case, that is chronic obstructive pulmonary disease (COPD), but others could include bronchiectasis (a condition where the lungs are damaged, making it difficult to clear mucus), cystic fibrosis, and prior tuberculosis. Smoking, here, is a little bit of a red herring. It can increase the risk of COPD, but smoking, in and of itself, is not a specific, direct risk factor for pulmonary MAC.

Jennifer Faber-Gerling, RN: It's really important to optimize the treatment and management of these predisposing risk factors, especially if we're embarking on therapy and treatment for mycobacterial infection.

David E. Griffith, MD: I agree completely, and with particular emphasis on bronchiectasis. I know we spend a great deal of our time educating and managing our patients with bronchiectasis.

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Case 1 Question 2

Aside from clinical and radiologic criteria, which of the following microbiologic criteria is required for a diagnosis of *MAC*-LD?

A. Two positive sputum cultures from at least 3 expectorated sputum samples
B. A positive culture from at least 2 separate bronchial lavages
C. Two positive cultures from monthly bronchial washes
D. A positive sputum culture from a single expectorated sputum sample

Answer Rationale

The correct answer is **A**.

- A diagnosis of *MAC*-LD relies on the exclusion of other diagnoses along with clinical (pulmonary or systemic symptoms), radiologic (chest X-ray with nodular or cavitary lesions, or a chest CT with bronchiectasis and small nodules), and microbiologic criteria (at least 2 positive sputum cultures from $\geq$ 3 expectorated sputum samples, at least 1 positive bronchial wash or lavage culture, or a transbronchial or lung biopsy with histologic features of mycobacterial disease with a positive culture for *MAC* and $\geq$ 1 sputum or bronchial washing that is culture positive).[1]
- Due to the extensive workup and diagnoses of exclusion to achieve a diagnosis of *MAC*-LD, many patients experience a delayed diagnosis[2] or misdiagnosis initially.[3,4]

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1. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Clin Infect Dis*. 2020;71(4):905-913. doi:10.1093/cid/ciaa1125

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Faculty Commentary

David E. Griffith, MD: This question looks at how we diagnose patients with MAC lung disease and there are 3 criteria in general. Symptoms consistent with mycobacterial disease, radiographic abnormalities that are consistent with mycobacterial disease and then microbiologic criteria that include at least 2 positive expectorated sputum cultures for the same mycobacterial species. They can also be induced specimens. Or 1 positive specimen from a bronchoalveolar lavage or a positive culture from a lung biopsy. That, of course, would be the gold standard for diagnosing mycobacterial disease. I would say there's a little bit of a caveat about the bronchoalveolar lavage culture. It's important to know the pathogenicity of the NTM species that you obtain from the bronchoalveolar lavage. One extreme example is a lavage specimen culture-positive for mycobacterium gordonae would not be indicative of mycobacterium gordonae lung disease because that almost never happens. Clinicians still have to be aware of some detail about the microbiology and particularly the pathogenicity of mycobacteria that they obtain.

It's also important to recognize that there are usually delays in diagnosis of nontuberculous mycobacterial disease and one of them that is particularly important from my perspective is that when clinicians are working up cough, they tend to stop after ruling out usual abnormalities, such as asthma or reflux or post-nasal drip. It's important to remember that a chronic cough is defined as 8 weeks or more of cough. If you have someone who has a cough for at least 8 weeks, there's not an obvious reason for that cough, it's okay then to go into the radiographic assessment of that patient which is necessary in order to identify these patients who have bronchiectasis and nontuberculous mycobacterial disease.

Christina O'Connor, PharmD: I'll add from a pharmacist's perspective, not being a diagnostic expert, it is important to get a medication history that's not just the history of what the patient is on right now, but also antibiotics that they have been prescribed, regularly or cyclically, all the way until they reach that diagnosis. So, particularly past exposure to macrolides and quinolones would be something that I would want to get out from their medication history.

Jennifer Faber-Gerling, RN: As I do a lot of clinical education with the patient, they're always wanting to know specifically when do you make the decision to actually initiate that treatment. We just mentioned that 2 positive sputums is 1 of the criteria, but we're looking at the clinical presentation of the patient as well. What symptoms they're actually having, culture and number of cultures, which is important, and then, lastly, the radiographic evidence. And I think it's sometimes helpful to reinforce that with the patient and actually show them their films so that they can appreciate that.

David E. Griffith, MD: I agree completely, Jen. That's invaluable, so the patients have a picture in their mind's eye of what we're talking about when we talk about changes in their scans.

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Case 1 Question 3

Which of the following methods assists in optimizing an accurate diagnosis of *Mycobacterium avium* complex lung disease?

A. Sputum samples should be collected simultaneously
B. Sputum samples should contain 1 mL of sputum per sample
C. Sputum samples should be collected over a 1-week period or longer
D. Sputum samples require induction with nebulized hypertonic saline solution

Answer Rationale

The correct answer is **C**.

- Due to the potential for environmental contaminants (ie, soil, tap water, steam from bathtubs and showers, and certain geographic locations), ≥ 3 sputum samples should be collected over ≥ 1 week period.[1,2] At least 2 positive sputum samples isolating *MAC* indicates persistent disease.[2]

- Simultaneous collection of sputum should be avoided due to airway colonization from environmental contamination.[2]
- Ideally, a sputum sample containing at least 3 mL to 5 mL of volume should be collected to obtain a high-quality sample with minimal saliva content.[3]
- Induction of sputum is not a requirement to collect a sample, but some individuals may require assistance in expectorating an adequate sputum sample. Inhalation of isotonic or hypertonic saline nebulization solution can assist in inducing sputum collection.[4,5]
    - For best results, the saline solution should be delivered over 15 to 20 minutes and a short-acting β2-agonist (ie, albuterol) should be considered to minimize bronchoconstriction[5]
- If there is difficulty obtaining or producing an adequate specimen through noninvasive techniques, a respiratory therapist should be consulted or an invasive sample (ie, bronchoscopy) may be warranted.[6]

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Faculty Commentary

Jennifer Faber-Gerling, RN: In my experience, we want to get those samples on different days, greater than a week's period of time in between them, and part of that is to avoid airway colonization. From the hands-on approach is that when we're billing providers, they will not pay for multiple samples in 1 day. That is significant to the end user, which is the patient, if they receive a bill for that. These don't necessarily need to be induced samples. If the patient can expectorate on their own, that is ideal, however because we're dealing with underlying bronchiectasis, we do teach the patients how to do daily airway clearance twice a day. They're essentially taught how to do their own sputum inductions and I think the yield in those samples are a little bit higher. My experience is we rarely have to go to bronchoscopy in these patients, so you save them an intervention that could have some significant risks. And we help try to facilitate getting these samples by having sputum mailer kits available for the patient that has a requisition and a container in them and then they know where to drop these off. Anything we can do to help obtain those samples is ideal.

Christina O'Connor, PharmD: I like to counsel patients on—and make sure they understand—that mycobacterium is ubiquitous in the environment, soil, and water.

Jennifer Faber-Gerling, RN: If you have access to a respiratory therapist in management of this sort of chronic infection, they're invaluable, but recognizing the fact that not everybody has that as a resource. Investing time to help the patient be able to do effective airway clearance and be able to provide these samples for you is well worth the time.

David E. Griffith, MD: It's always important to emphasize why we want the specimens and it's to monitor their hopefully good response to therapy or the not-so-good response to therapy and, as maybe a trigger later on, for shifting the focus of the antimycobacterial regimen.

CASE 2

Case Background

CD, a 59-year-old patient, comes for an initial visit of acid-fast bacilli (AFB) smear-positive, nodular-bronchiectatic, macrolide-susceptible *Mycobacterium avium* complex (*MAC)*-lung disease. They have various questions regarding treatment initiation and duration.

Case 2 Question 1

Which of the following approaches to care should the patient be educated on to overcome barriers to treatment adherence?

A. Understand that once sputum conversion occurs, treatment will be discontinued
B. Access to pharmacologic and nonpharmacologic treatment will be ensured at each visit
C. The patient should understand up front the need to commit to lifelong treatment
D. Treatment-holidays are allowed on an as needed basis as determined by the patient

Answer Rationale

The correct answer is **B**.

- To promote optimal treatment outcomes, treatment expectations should be discussed up front with the patient. The decision to initiate treatment is dependent on various factors and should take into consideration organism pathogenicity, disease severity, comorbidities, antimicrobial susceptibility testing, benefits and risks of treatment, and patient goals.[1]
- Each visit should, at a minimum, assess response to treatment, if initiated, along with discussions of any barriers to treatment adherence (ie, need for pillboxes, risk of resistance due to nonadherence) continuous access to pharmacologic treatment (ie, ensuring prescription insurance coverage), multidisciplinary team support, and nonpharmacologic treatment (ie, airway clearance devices and methods) to promote successful treatment outcomes.[1]
- The recommended duration of treatment for *MAC*-lung disease is 12 months after culture conversion from positive to negative. The patient should understand that treatment is not discontinued once sputum conversion occurs. They should also understand treatment is not meant to be lifelong.[1]
- Patients should also understand the need to adhere to long-term prescribed therapy whether daily or thrice weekly and should not embark on self-imposed treatment-holidays as it may promote resistance, which is associated with worse outcomes.

Reference

1. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Clin Infect Dis*. 2020;71(4):905-913. doi:10.1093/cid/ciaa1125

Faculty Commentary

Christina O'Connor, PharmD: With this next case, we are presented with a really important time point which is when that patient is coming for their initial visit and they have a lot of questions about when treatment will be initiated and what the duration of that treatment might be. I use that time with the patients to help to set expectations, because setting good expectations helps to set them up for success. First this is going to be more than 1 antibiotic. This is going to be multiple pills per day and then I want you to think in terms of months of treatment and don't think in terms of days of treatment. This is a longer term. I usually talk about that 12 months post-culture conversion, as well, with them, just trying to set them up to get them in that time frame without making a hard commitment to promise, "Okay, it's going to be this specific date." But try to give them a road map of what this treatment is going to look like. And then I also always assess any potential barriers to treatment and those can often be things such as their insurance, do they have insurance coverage for their medications, and how about adherence tools. I ask them what adherence tools they use currently and then I also help to suggest some that may help them in the future, like pill boxes, calendars, and really making it a patient-tailored approach. And speaking with them and trying to understand what are their barriers that they see or foresee, and then what kind of tools that we can use to help them overcome any of those barriers. That's an ongoing process that starts with the first visit, but that's continued throughout their treatment course. We want to make sure they get good support throughout.

Jennifer Faber-Gerling, RN: I definitely agree that utilizing time up-front is a well-worth investment as far as establishing rapport with the patient, letting them know that you're partnering with them throughout this prolonged treatment course and that they can reach out to you with any questions or problems throughout this because it's really important that they know that they have a resource if they're having symptoms or side effects or they didn't hear something correctly. Even though it is a little bit labor-intensive to do that up-front, it saves you a lot of time down the road.

David E. Griffith, MD: It's important to recall, these people come in with almost zero knowledge base related to bronchiectasis and mycobacterial disease. It requires repeated education attempts, and success depends a lot on the rapport you establish and the comfort that the patient feels that they're going to have the support that they need going through this. It's very unusual for someone to sail through this without problems or without questions. I think that physicians in the community lose patients sometimes because the patient doesn't feel that their questions are answered or that they're getting the help that they need with the problems that inevitably arise with this type of treatment.

Christina O'Connor, PharmD: I usually tell people, up-front, expect side effects, but we're here to help you through and manage the side effects. You're not going to be alone if you have side effects. This is our contact and these are the paths that you should follow with the different kinds of side effects you may experience. I try to make it positive, but I also want to be realistic in saying that these are tougher medications to take. This is a commitment, but we're here to help you with that commitment.

David E. Griffith, MD: I think it's very important that the patient understands, and as much as the practitioner understands, that we have a limited armamentarium in managing this disease. The first episode of nausea, you cannot just drop a drug, because you ain't got much to replace it with. People require help and there are plenty of strategies for that, but going through all of the problems that inevitably arise with these MAC regimens.

Jennifer Faber-Gerling, RN: Depending on the individual, we have to overcome some barriers when we talk about mycobacterial disease and treatment. I can't tell you how many times I've heard patients come in with the preconceived notion that the treatment is worse than the disease. And so that education and that time going through that, and letting them know that they're not alone, it's not a treatment failure if you start having side effects, we're going to work through it together. And there's always a plan B and plan C. It might not be the ideal, but we will figure it out together.

David E. Griffith, MD: There is always a plan B and a plan C. Can you think of the last time we had an untreatable patient? Now, with drug resistance, sometimes that is a possibility, but otherwise no. We are usually able to shepherd these people through the worst of it.

Christina O'Connor, PharmD: As a tip for pharmacists, we're always really good at saying what are the side effects, but we should say what are the benefits. They should go hand-in-hand when you counsel on a med. Here's the potential side effects that you may experience and the path that you should take to get the support you need for that, but here's what the benefits that I've seen for my patients. And that kind of helps to balance that discussion.

Case Background

CD, a 59-year-old patient comes to clinic for routine follow-up of smear-positive, noncavitary, nodular-bronchiectatic macrolide-susceptible *MAC*-lung disease. CD reports moderate improvement in their symptoms since starting treatment with daily azithromycin, ethambutol, and rifampin. They are also using a flutter valve to assist in the clearance of their airways. Upon further questioning, they report intermittent adherence to treatment since they have difficulty in keeping track of all the medications they are supposed to take.

Case 2 Question 2

What is the most appropriate recommendation for the management in this patient? [PICO Question VIII]

A. Modify treatment to monotherapy with daily azithromycin
B. Modify treatment to daily azithromycin and ethambutol
C. Modify treatment to daily azithromycin and amikacin liposome inhalation suspension
D. Change azithromycin, ethambutol, and rifampin from daily dosing to thrice weekly dosing

Answer Rationale

The correct answer is **D**.

- Per the clinical practice guidelines for the management of NTM-LD, in patients with nodular/bronchiectatic *MAC*-susceptible-lung disease, intermittent administration of a 3-drug treatment administered thrice weekly remains the standard of care. But, if sputum cultures remain positive after 6 months of treatment, therapy should be switched from intermittent to daily.[1,2]

- Similar rates of sputum conversion and better tolerability when compared to daily treatment are noted benefits of this approach.[1,3,4]
- Thrice weekly treatment should be avoided in patients who received previous treatment or have cavitary, moderate, or severe disease.[1]
- Recommended oral antibiotic treatment includes azithromycin 500 mg, ethambutol 25 mg/kg, and rifampin 600 mg given 3-times weekly.[1]

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Faculty Commentary

David E. Griffith, MD: The next question looks at a patient who is having problems with adherence because of medication burden. The correct answer is to change the MAC regimen from daily dosing to 3-times-weekly dosing and, I want to emphasize as strongly as I can that no patient should ever receive macrolide monotherapy with active MAC disease. That is the most sure way to create macrolide resistance. I hope everyone knows that, but just in case someone forgot, macrolide resistance for active MAC disease is never appropriate.

The 3-times-weekly regimen is the preferred regimen for nodular bronchiectatic MAC disease in the most recent guidelines. There are several case series that show that 3-times-weekly therapy is as effective as daily therapy and actually tolerated better. There are fewer side effects than with daily therapy. For patients who are failing therapy, or have failed therapy in the past, or have severe disease, cavitary disease, 3-times-weekly therapy is not appropriate, and daily therapy should still be used. Also, patients who reach 6 months with positive cultures should be switched from 3-times-weekly therapy to daily therapy. But, by and large, the success rate with 3-times-weekly therapy in nodular bronchiectatic disease is every bit as good as with daily therapy.

The recommended doses are azithromycin 500 mg, ethambutol 25 mg per kg and rifampin 600 mg. 10 mg per kg you might come across in some of our older female patients, someone under 50 kg, in which case you might need to change the rifampin dose. But I hope there's no reluctance to use the 3-times-weekly therapy. I think the most important part of it is you're less likely to have to modify 1 of the drugs, either dosing or eliminating it, by using the 3-times-weekly regimen.

Jennifer Faber-Gerling, RN: This particular patient is having difficulty adhering to the regimen and we get anxious about that because of drug resistance, but this is talking about medication administration and trying to tailor it to that individual. What works for 1 patient, I've found, doesn't work for every patient. Some patients can take a handful of pills all at the same time, and if that's the case and their stomach tolerates that, I say take it right before you go to bed, and keep it consistent so it's the same time every day. If they are unable to tolerate all those medications at the same time, I go in alphabetical order. Most people tolerate a Z-pack (azithromycin) and I'll have them take the macrolide in the morning, ethambutol maybe 2 hours after lunch, and then target the rifampin for closer to bedtime, because if they do have side effects, that's usually the culprit, not always. But it's just talk them through it, and see if they can come to a schedule that they can remember to take these every day, and they're not dividing doses, that they're taking all of their azithromycin at one time, all of their ethambutol at one time, and all of their rifampin at one time.

Christina O'Connor, PharmD: An additional tool we utilize in our practice to start folks off is a written calendar that has the days of the week, so it's real clear, especially with that 3-times-a-week regimen. Typically, we do Monday, Wednesday, Friday, but again we do tailor it to the patient's needs. It says the number of pills that they'll be taking, here's the total number Monday, on Wednesday and on Friday. Patients tend to like that and have that visual in front of them so they get that idea stamped into their heads. That's 1 thing we typically give them at their visit with us. The other thing that pharmacists can really add here, too, is making sure that dosing correlates well, and make sure if someone is transitioning from a once-daily to 3-times-a-week that the dose is also transitioned appropriately.

Case Background

CD leaves a message for the medical staff reporting continued difficulty in adhering to treatment for *MAC*-LD. On the days they are instructed to take treatment, they report taking azithromycin in the morning, ethambutol in the afternoon, and rifampin in the evening, due to fear of side effects. At times, they forget to take some of the medications because they forget to bring them along.

Case 2 Question 3

How would you advise the patient to take azithromycin, ethambutol, and rifampin, to promote adherence to treatment?

A. Take all medications together at the same time
B. Split the dose of each agent in half and take it twice daily
C. Take azithromycin and ethambutol on the same day and rifampin the next day
D. Change the patient from thrice weekly dosing to daily dosing

Answer Rationale

The correct answer is **A**.

- Although sequential therapy upon initiation of *MAC*-LD may be of benefit in some patients, ultimately, the goal is to take all drugs at the same time in order to achieve peak concentration against the *MAC* organism. If the patient is not able to tolerate all 3 medications at once, azithromycin may be taken in the morning with rifampin, and ethambutol in the evening, but they should not be split into dosing on alternative days.[1,2]
- Splitting doses of the medications in half is 1 way to promote the development of resistance and should be avoided due to the lack of achieving therapeutic concentrations of the medications.[2]

- If treatment were changed from thrice weekly dosing to daily dosing, the potential for side effects to develop would increase, which may cause further concern for medication nonadherence in this patient.[1]

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Faculty Commentary

Jennifer Faber-Gerling, RN: This next question ties into how to increase adherence. One is to take all the medications at the same time. When we initiate treatment, a lot of the times if the patient is treatment-naive or they had a history of intolerance to medications, we'll do what we call a staggered start, or a sequential addition of each of these medications. And typically, what I've seen in our practice, is we'll introduce, say, azithromycin and then 3 to 5 days later, we'll add the ethambutol, so then they're taking azithromycin and ethambutol. And then the additional 3 to 5 days, we add rifampin, and then they'll be on full therapy in under 2 weeks.

You don't want to prolong that too long because we don't want them on monotherapy for any extended period of time, and we worry about drug resistance. I tell patients, during that staggered start, it might be ideal to start each of the meds at a different time, so if they did have side effects, we may be able to link it to the newest medication that was started, as opposed to taking them all at once. But when they're on the full regimen, it may be helpful for adherence for them to transition to taking them all at the same time so that they have consistency with that. We don't encourage splitting doses or halving doses, and sometimes patients do that independently because they're not tolerating the drugs. I encourage them, if they're having side effects, to reach out to their provider to discuss that so we can strategize a way for that medication administration and tolerance to happen. I encourage patients. My statement is, "I don't want you to feel any different on the meds than you feel off the meds and, if you do, you need to talk to someone about that."

Christina O'Connor, PharmD: When we do the staggered start, we'll also put the staggered start into the calendar, so usually the calendar is the first full 3 weeks, and then phase them in, 1 at a time, and then it'll say, this is the regimen completed and onwards. When we do those, we also lay that all out to help them, to guide them so they're not trying to figure out how many and often.-We'll start, if there's multiple pills, the first day is 1 pill, we'll actually titrate them out a little bit, but, again, no longer than 2 to 3 days for the titration, or the phase-in, because you don't want it to be monotherapy periods.

I'll also have a common question from patients, or a common misconception is they think, when we say these medications have a lot of drug interactions, they automatically think of administration. If I take them together, they interact. Not that, necessarily, interactions can happen independent of the time that you take a medication. I will counsel the patients that they don't have to—it's not required to spread them all out because of drug interactions for all these medications.

Jennifer Faber-Gerling, RN: I think just individualizing it to that patient. Some patients are just taking their antibiotics for mycobacteria but then we have some very complicated patients that have a lot of comorbidities and they may need assistance to how to … what time of day to take their antibiotics as opposed to some of the other therapies that they're already on.

Christina O'Connor, PharmD: Sometimes I'll recommend 2 separate pill boxes so 1 pill box for their typical medications, and then a separate, individual pill box for their MAC meds. So that if a patient is on another medical regimen, then it's less confusing for them to get them all mixed up. If the patient's only on 1 other medication, or just a few, I don't always recommend that.

CASE 3

Case Background

EF was recently diagnosed with *MAC* -LD after more than 3 years of experiencing symptoms (ie, weight loss of 14.2 kg, excessive sputum production, and shortness of breath reducing their exercise capacity) and seeking medical treatment from various providers. The medical team, together with the patient, decide to initiate medical management.

Case 3 Question 1

Which 1 of the following is recommended to optimize patient management?

A. Assign a dietitian to address the patient's weight loss since a BMI < 20 kg/m^2 now meets the criteria for referral
B. Recommend an interprofessional approach with communication among team members
C. Schedule follow-up visits at least every 2 to 4 weeks to evaluate sputum culture conversion
D. Provide the patient with educational pamphlets and resources

Answer Rationale

The correct answer is **B**.

- The provision of comprehensive care and the promotion of effective communication amongst various members of the medical team, and the patient, is essential in achieving positive clinical outcomes due to the various complexities associated with *MAC* management.[1]
- EF has experienced significant weight loss since manifesting symptoms of *MAC*-LD. The patient should be referred to a dietitian to identify techniques to reduce weight loss since there is no threshold for a referral based on weight loss or BMI. Additionally, low BMI and poor nutrition is associated with poor disease outcomes.[2]
- Ongoing sputum evaluation, in consultation with microbiology, should be performed every 1 to 2 months while on treatment to assess treatment response and, ultimately, to determine treatment duration. For patients with sputum cultures that remain positive beyond 6 months of treatment, their potential for disease progression and decline in lung function remains greater. Ideally, sputum conversion should occur within 3 to 6 months of treatment and continued for 12 months after culture conversion.[2-4]
- Although patient pamphlets may assist in providing education for the patient, core principles of shared decision-making occurs when members of the healthcare team engage in an active and open discussion about the options, benefits, outcomes, and risks of treatment. The decision to

implement a treatment plan is based on medical evidence, the patient's values and goals, and the provider's advice.

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Faculty Commentary

Christina O'Connor, PharmD: The care of patients with mycobacterial infection takes a village. It's many people that are really needed to help support these patients and it ranges across professions, includes, of course, physicians, advanced practice providers (APPs), also nurses, clinical microbiologists, dietitians, pulmonary respiratory therapists. It's really a team effort.

Jennifer Faber-Gerling, RN: Comprehensive care is really what it takes to make this a successful endeavor for patients. I would highlight the value of a dietitian because we know that a low BMI has a poorer outcome in these patients and they need all the help they can get in that nutritional arena. The other thing, too, that some patients find helpful—and they don't always think about this—is a psychiatric provider to help them manage and navigate chronic disease. My experience was with a psychiatrist that really focused on more the global health of the patient and even about sleep hygiene and worrying about different things that could affect their sleep hygiene. Patients would come back and they were really invested in establishing care with a local provider to be able to access that. They just didn't realize that that was part of this whole picture for them.

David E. Griffith, MD: I would like to harken back to some of our previous discussion about the dual nature of disease for these people, the bronchiectasis and their mycobacterial disease. One of the things I've been most impressed with here at National Jewish is how incredibly grateful the patients are for the time that the respiratory therapy people and the nutritionists spend with them because they come from an environment where there's very little known about what they have. All of a sudden, they're in the deep end of the pool with people who can tell them everything they want to know and can give them advice

about what to do. As far as what we do for patients, this team approach and the education that's provided is as valuable as anything else.

Christina O'Connor, PharmD: We have a dedicated visit with the patient that's a referral from pulmonology or infectious disease and we meet with the folks in the clinic, typically anywhere between 30 to 60 minutes. As some of the other non-direct patient care, we'll do e-consults where we'll review therapeutic drug monitoring results or drug interactions, say, if a patient that doesn't need a direct visit that day to sit down with us. And then also we'll take phone calls for those issues that arise, like side effects that come up. We'll do that often in an initial triage type of call to see if it's something that we can mitigate through counseling, and then we'll also partner with our physician and advanced practice colleagues when it's something more, that we may need to change the medication or something really concerning we need to do now.

David E. Griffith, MD: Physicians should embrace this approach for selfish reasons in that when people call in, there are plenty of questions that can be answered by the team that don't have to go to the physician to answer.

Jennifer Faber-Gerling, RN: As an NP in our group practice, I spend a lot of time one-on-one with the patient or with them and their family members, just providing educational reinforcement. It is important for them to understand this disease process. It's their body and they own that, but spending time reviewing their imaging, their pulmonary function tests, the kind of diving deep, and we've talked about this, about the side effect profiles of these medications and what to do if you experience those side effects. Up-front, talking about surveillance and the duration of therapy, and even introducing some additional things that may come up along the way when we're altering their treatment plans and things like that.

Case Background

Despite an interprofessional approach to optimizing treatment of *MAC*-LD, EF remains symptomatic and is concerned about the possibility of developing drug-resistant disease over time due to experiencing side effects (profound diarrhea and occasional vomiting). Ultimately, the patient voices they would like to achieve a cure and is willing to do whatever it takes, even if it requires surgical intervention.

Case 3 Question 2

Based on the patient's preference, and in collaboration with the medical team, which of the following factors may warrant surgical intervention to assist in achieving a cure in EF? [PICO Question XXII]

A. Noncavitary disease
B. Macrolide-susceptible isolates
C. Development of hemoptysis
D. Persistence of positive sputum sample at 3 months

Answer Rationale

The correct answer is **C**.

- Surgical resection can be considered as adjuvant to medication therapy. Prior to surgery consideration, antimycobacterial therapy should be optimized.[1,2]

- Surgical resection is especially important in patients who have drug-resistant isolates. Additionally, individuals with unresponsive disease, large cavities, hemoptysis, severe bronchiectasis, lung damage, and uncontrolled symptoms, may benefit from surgery.[1,2]
- Yet, potential surgical complications should also be weighed when considering surgical resection. These can include postoperative infections, bleeding, pain (acute and chronic), prolonged drainage of chest tube(s), and death.[2]
- The decision to pursue surgery should be done in collaboration with expert consultation, the medical care team, and the patient.

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Faculty Commentary

David E. Griffith, MD: The next question has to do with surgery for our mycobacterial disease patients. The correct answer here is development of hemoptysis. Surgery is a very important adjunct to any mycobacterial therapy for these patients. There's never been, to my knowledge, a controlled prospective trial looking at surgery vs non-surgery, but in all of the case series, those patients who are able to have surgery do better microbiologically than the patients who don't, just comparing those with and without surgery. Again, these are not prospective randomized trials, they're retrospective case-controlled studies and it's important to remember, patients who get surgery are always carefully selected. They generally have fairly focal disease and they have to have adequate cardiopulmonary reserve to be able to undergo at least a partial lung resection. Square 1 for these patients is that they have to be on adequate antimycobacterial therapy. There's no bigger disaster than the patient who undergoes surgery for mycobacterial disease who's not got adequate control of the infection with their antibiotics. Those are the patients who develop the terrible air leaks and bronchopleural and bronchopleural cutaneous fistulas. Unfortunately, surgery doesn't take the place of medicine in any sense. It is an adjunct.

The indications, there are several. Probably the most important is what I'll refer to as drug-resistant disease. Now, for MAC, what that translates to is macrolide resistance, and there are at least 2 good studies that have shown that if surgery's not included in the management of those patients, that the chances of microbiologic success are very poor. Patients with large cavities who tend not to convert their sputum to negative with medicines alone, recurrent hemoptysis, or severe hemoptysis, such as the patient in this question, patients with destroyed lung segments due to bronchiectasis or anything else, and patients with uncontrolled symptoms. A few times in my career I've seen people with just terribly refractory cough who have a destroyed lung segment taken out with remarkable improvement in their symptoms.

It is important to remember that surgical procedures in the chest are associated with side effects and complications. Probably the 1 we fear the most is air leak and persistent air leak, but also bronchopleural fistulas, and even sometimes bronchopleural cutaneous fistulas. It should not be forgotten that even as advanced as the surgery has become with robotic techniques, minimally-invasive techniques, that postoperative pain is real and can affect people for long periods of time. Lastly, I would say this is always

added in any discussion of surgery, you have to have a competent surgeon. And actually I wouldn't say just competent. You have to have an experienced surgeon. Thoracic surgery is a little bit of a lost art. Most of the surgeons went to cardiothoracic with an emphasis on cardio, but it is extremely important to have a surgeon who knows something about this, who's done it before.
It should not be left to someone who maybe does 1 or 2 of these, every year or so.

Jennifer Faber-Gerling, RN: Surgical resection is a good adjuvant for lots of reasons, which you just outlined for some of these patients. What I am so surprised by, and maybe it's because community providers don't have good resources for a surgeon, that they don't discuss surgery with the patient. A lot of times, I'm the first person that has even said that this is a possibility and those patients are floored. The best thing, I mean especially when you're embarking on treatment, is to lay all the options out there, whether surgery is a possibility or not. I think that patients will do much better if they know what to expect down the road.

The other thing in this particular case, with the hemoptysis, I always counsel patients going for surgical resection that we suspect that potentially that bleeding is coming from the area that we're going to remove, but sometimes that's not always the case. And to set that expectation up-front, because they're going to undergo this procedure and they're going to have a recovery and then they may experience hemoptysis again and they're going to come back to you and say, "I thought we fixed this problem." Bleeding can come from even microscopic areas of the lung, and I think that has to be presented up-front to the patient, as well, so that they know how to manage those expectations.

David E. Griffith, MD: For every patient you see, it's important to, at some point, consciously ask, "Is surgery appropriate for this patient?" For most, it's not, but at least bring it to the surface. Is there an area that would benefit from surgical resection and is the patient a surgical candidate or is their emphysema so bad that we can't do it? At least it is valuable enough to consciously think about it at least at some point.

Jennifer Faber-Gerling, RN: I reinforce that when I'm reviewing their CT scans and I let them know that the thoracic surgeon cannot go in and cherry-pick your lungs. At some point, if you are a surgical candidate, it gives us another option. I try to spin it in a positive light because there are some people that just have extensive diffuse disease, they will never be a surgical candidate. And if we run into treatment failure, drug resistance or symptoms, we still have another option here.

Christina O'Connor, PharmD: As a pharmacist, I usually just touch on this very lightly, but it is part of the education brochure that we share with all the patients and we go through it. It's nice to have that just to highlight the educational brochure as a tool for clinicians as steps through all of these elements. Here's some things about mycobacterial etiology, here's the tests that you would expect to get, here's some of the treatment options which may include possibly surgery. And then I spend the most time on the drug part, and we have a table in there that has the main treatment options, and that's what I really spend time with.

CASE 4

Case Background

GH, a 72-year-old patient splits their time between Illinois and Arizona since retiring and spends much of their time gardening. They are diagnosed with smear-positive, cavitary, macrolide-susceptible *MAC*-lung disease. Patient is very anxious to start treatment soon

Case 4 Question 1

What is the most appropriate treatment recommendation for GH? [PICO Questions I, II, III, IV, and VII]

A. Employ watchful waiting before initiating medication treatment to see if clinical, microbiologic, and radiologic signs/symptoms improve
B. Begin empiric treatment with clarithromycin, isoniazid, and rifampin
C. Initiate treatment with azithromycin, ethambutol, and rifampin based on antimicrobial susceptibility testing
D. Initiate treatment with azithromycin and ethambutol to minimize the development of side effects

Answer Rationale

The correct answer is **C**.

- Treatment initiation with antimycobacterial treatment should occur, as opposed to watchful waiting, especially when the patient is diagnosed with positive acid-fast bacilli (AFB)-smears or cavitary lung disease.[1]
- In patients diagnosed with *MAC*-LD, susceptibility-based antimicrobial testing using broth microdilution should be used to assess macrolide and amikacin susceptibilities compared to initiating treatment empirically.[1,2] It is important to initiate treatment to which the patient's disease is susceptible to minimize the development of resistance.
- Baseline susceptibility testing should be performed in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines for *MAC* isolates.[1]
- For individuals with macrolide-susceptible disease, a macrolide should be included as part of the 3-drug regimen since susceptibility to a macrolide is a predictor of treatment success.[1,3-5]
- Additionally, a 3-drug regimen (azithromycin, ethambutol, and rifampin) is recommended over a 2-drug regimen (azithromycin and ethambutol) for individuals with macrolide-susceptible disease in order to prevent the development of macrolide-resistance.[1,6] Although there may be fewer side effects with a 2-drug regimen, a 3-drug regimen, especially in cavitary disease, remains the treatment of choice.
- The macrolide of choice in patients with macrolide-susceptible MAC-LD is azithromycin due to better tolerability, lower pill burden, once-daily treatment, comparable efficacy, and lower drug interaction potential as compared to clarithromycin.[1]
- The optimal treatment for this patient would be an all-oral daily regimen of azithromycin 250 mg, ethambutol 15 mg/kg, and rifampin 10 mg/kg (maximum dose = 600 mg).[1]

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Faculty Commentary

Jennifer Faber-Gerling, RN: This next question has a patient with a little more severe disease, that's smear-positive, cavitary in nature and the patient is anxious to start therapy. First of all, I want to make sure that everybody knows that we want microbiologic confirmation of the organism and resistance markers, if possible, because this patient is going to need to be on a macrolide, probably, and possibly intravenous aminoglycosides. Having that information up-front, you can assure the patient that this isn't going to go downhill quickly and we have that tincture of time, but we want to make the right treatment decisions up-front. Guidelines do reinforce that they don't want watchful waiting, especially in a person that has a cavity. This is early treatment initiation. I just spoke a little bit about macrolide and amikacin susceptibilities and if you have that ability to get those resistance markers up-front, that's helpful. And just that baseline susceptibility testing to direct your treatment in this patient.

Christina O'Connor, PharmD: We do also have susceptibility testing at our institution, as well, and I use that as a learning point for the patients and pharmacy learners especially that it's interpreted a little differently than the traditional bacteria. Everything you see on the panel there, for susceptibility or minimum inhibitory concentration (MIC), may not correlate to outcomes, and it needs to be in the context of that species. So, for MAC, the macrolide and the amikacin, but for other species, it could be a different drug. I want both patients and other learners to understand that the interpretation of what you see on that panel is more nuanced than with general bacteria where you just go Susceptible-Intermediate-Resistant exactly, for everything you may see.

David E. Griffith, MD: That cannot be over-emphasized. That is the least well-understood aspect of MAC that I am aware of and, unfortunately, after all these years doing it, it doesn't seem to change in terms of penetration to clinicians in general. Macrolide, amikacin and that's it for MAC, and with particular emphasis on ignoring fluoroquinolones. However much we can do to educate people about that, unfortunately it's not intuitive. You're not born with that information. You've just got to know it and it's our job to try to help people understand that. It's a very destructive misunderstanding, unfortunately.

Case Background

GH reports being overwhelmed by the number of medications necessary to treat their disease. They picked up their medications from the pharmacy but have not started them yet and are wondering if you have any suggestions of how to ease into treatment.

Case 4 Question 2

Which of the following strategies may improve GH's success in completing treatment?

A. Introduce treatment sequentially by adding a drug 1 at a time every month over a 3-month period
B. Educate that all of the medications must be initiated at the same time to improve treatment response
C. Introduce treatment sequentially by adding a drug every few days until the desired regimen is achieved
D. Recommend GH take their medications every other day until they know the effects of the drugs and whether they will have any side effects

Answer Rationale

The correct Answer is **C**.

- For some people initiating treatment, a full-dose, multiple-drug regimen started all at once may affect tolerability. Therefore, starting treatment sequentially by adding a drug *every few days* until the desired regimen is achieved, is recommended. Sequential therapy with accompanying dose titration is recommended to improve tolerability of this complex regimen. Additionally, it can assist in identifying the drug causing the side effect if introduced in this manner. This approach may be used in mild, moderate, or severe disease and would not promote the development of resistance since *MAC*-LD is associated with slow replication of the isolate.[1,2]
- Dosage titration is recommended every few days over a 1 to 2-week period and not over 3 months since the goal of treatment is to achieve sputum conversion by 3 to 6 months, when possible.[3]
- Since a daily regimen is recommended based on GH's diagnosis, every other day dosing would be suboptimal and would likely promote the development of antimycobacterial resistance.

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Faculty Commentary

Christina O'Connor, PharmD: The patient is asking about being able to ease into treatment which would not be something that would be uncommon to hear in clinic. Or often patients may offer that medications or antibiotics don't sit well with them or they tend to have a lot of side effects and are wondering if there's a way that they can kind of ease into these medications. A great strategy to do that is the sequential start where a new medication would be added about every several days or 3 days or so. Not only does that help folks to gain a bit of tolerance to it, but also to identify potentially which side effects may be linked

to what medication. If it was something started new, potentially a rash would be something common where it would cross antibiotic classes and it may be harder to figure out if somebody just tried to jump into taking a handful of pills all in 1 day, at 1 time.

Jennifer Faber-Gerling, RN: Christina, what are your thoughts about probiotics with the administration of these mycobacterial antibiotics?

Christina O'Connor, PharmD: That's one of the most common things that patients ask me about is either should I take a probiotic or what probiotic should I take. There's a lot of different opinions on that topic and it depends who you talk with. What I usually tell folks, as long as they're immunocompetent, that it tends not to be harmful to them and that it can be helpful for some people for preventing diarrhea, but there's not really strong evidence or consistent evidence that it always prevents what's called *Clostridioides difficile (c.diff.)*, I also encourage folks that it is another pill to take, so they're going to be taking a lot of pills and the probiotic isn't the priority. The antibiotics and the treatment are the priority. And that if they don't see any benefit, especially if it doesn't help settle their stomach or it's not preventing them from any GI side effects, that they don't have to be married to it. In my opinion, they don't have to take it the whole time. But again, I think that opinions are variable, so I'd be interested to hear other's thoughts.

Jennifer Faber-Gerling, RN: We counsel patients that they may be helpful and if you are immunocompetent, that it won't be harmful to you. Sometimes they're already used to taking a high pill burden anyway that they'll add that in with the thought that antibiotics kill off all the good and the bad bacteria, so maybe a little more good bacteria won't hurt.

Case Background

GH was on treatment for 6 months (sputum conversion at month 3) and stopped coming back to clinic. They also self-discontinued *MAC* treatment. Now, more than 1 year after their last visit, they report their symptoms have returned with subsequent macrolide resistance (no other resistance noted), worsening radiograph, and sputum positive.

Case 4 Question 3

Which of the following treatment options should be considered for this patient? [PICO Question V]

A. Surgery
B. Ethambutol + rifampin
C. Ethambutol + moxifloxacin + rifampin
D. IV amikacin + clofazimine + ethambutol + rifampin

Answer Rationale

The correct answer is **D**.

- Sputum culture conversion occurred at 3 months, but the patient stopped taking treatment and the patient developed macrolide resistance. In this case, the macrolide should be removed from their treatment regimen and IV amikacin (15 to 25 mg/kg/day with therapeutic drug monitoring goals of Trough < 5 mg/L; Peak with intermittent dosing 65 to 80 µg/mL) and clofazimine (100 mg daily)

should be added to ethambutol and rifampin therapy.[1] Therefore, ethambutol and rifampin are not an adequate treatment option for GH.

- One study evaluated lung disease in 154 patients with MAC for < 15 months after sputum conversion compared to ≥ 15 months. Those treated < 15 months after sputum conversion were twice as likely to experience recurrence of MAC compared to patients treated for ≥ 15 months of after sputum conversion.[1,2]
- Clofazimine is available through an expanded access program where an investigational new drug application must be completed.[3]
- Although surgery may be considered in patients who develop macrolide-resistant disease, medication treatment should be optimized prior to surgical resection.[1,4]
- A fluoroquinolone alone should not replace a macrolide when macrolide-resistant MAC is identified as data have not proven them to be effective in the management of MAC.[1]

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Faculty Commentary

David E. Griffith, MD: The next question has to do with macrolide resistance which is an extremely important topic. When we talk about setting expectations and what we want to accomplish with therapy, yes, we want patients to feel better. Yes, we want to convert their sputum. But we don't want to make things worse and the worst thing that can happen with standard MAC therapy is that a patient develops macrolide resistance. In this question, the answer is IV amikacin, clofazimine, ethambutol and rifampin, but the patient, by history, was on medicine, converted sputum, and then shows back up with macrolide resistance. So, how did that happen?

If the patient has stopped taking all the medicine, there would be no risk for macrolide resistance. The patient had to have either taken macrolide as monotherapy or taken macrolide with inadequate companion medicines. For instance, in standard MAC therapy, ethambutol, regardless of the MIC, is the most important drug for protecting macrolide. There is 1 good study, at least 1, from Japan that shows if ethambutol is not included in a treatment regimen for MAC, there is an increased risk for macrolide resistance. For instance, if the patient were on azithromycin, ethambutol, rifampin, if ethambutol was dropped, let's say an ophthalmologist told the guy to stop the ethambutol, and you just kept taking azithromycin/rifampin, well rifampin is a terrible drug for protecting macrolide, and that would be a

reason that the patient might have developed macrolide resistance. But something happened and the patient took macrolide inappropriately in order to have developed macrolide resistance.

There is no benefit of continuing macrolide in a regimen of a macrolide-resistant case other than macrolide has some immunomodulatory effects and might be beneficial for their bronchiectasis, but in terms of microbiology, it is not appropriate.

The cornerstone is intravenous amikacin if the isolate has an MIC that is susceptible for amikacin. In terms of dosing amikacin, I think we can just say nobody knows. I will tell you how I approach it. The peak amikacin level has to exceed the amikacin MIC of the organism. After that, I think all bets are off and my approach to it is once I exceed that MIC, let's say it's 32 mcg/mL, once I get a peak level up above 32 mcg/mL, I'm not going to push it a lot more because if I lose amikacin in this patient to toxicity, I haven't got much I can treat the patient with.

As far as I'm aware, there are no data to say whether a peak amikacin level of 38 mcg/mL is as good as a peak amikacin level of 80 mcg/mL in this type of patient, but I do know that the toxicity associated with amikacin is going to be significantly less with that lower amikacin dose. Maybe you'll be lucky and they've got an amikacin MIC of 8 mcg/mL where you can exceed the MIC by 3-fold with your amikacin level in the mid-30s. I don't generally check trough levels because I usually use 3-times-weekly amikacin and the trough levels are almost always undetectable.

There are 2 good studies I know of that have looked at treatment outcome for macrolide resistance and both came to the same conclusion. The chances of treatment success are optimal or best if you can use a parenteral drug like amikacin and you can combine it with surgery. But without that combination, outcomes are poor in general for these patients and, in fact, for patients with advanced disease, this is a terminal illness.

In terms of how long to treat patients, our treatment goal is 12 months of sputum culture negativity while on therapy, but there is at least 1 study that suggests that disease recurrence can be minimized with at least 15 months of therapy. But usually, in order to attain 12 months of sputum culture negativity, the patient is going to have at least 15 months of treatment, usually a little bit longer than that.

Clofazimine is available in an expanded access program through Novartis and the Centers for Disease Control. It's given to the patient at no charge. It does require a consent form from the patient and a little education about it. And, as I mentioned, surgery is a very valuable tool for macrolide resistance, but, as with our previous discussion about surgery, it depends entirely on the focal nature of disease, the patient's cardiopulmonary reserve and the competence of the thoracic surgeon.

I want to take 1 final hit at the fluoroquinolones. The fluoroquinolones offer nothing in this setting. I know people add them perhaps as a kitchen sink drug, but there is no data anywhere that fluoroquinolones, in macrolide-resistant disease, are helpful. But just going back to the initial comments, this is a preventable process. In my opinion, it's as bad or worse than creating a drug-resistant tuberculosis patient. It should not happen. Physicians must be very careful to manage macrolide and companion drugs in these patients to avoid macrolide resistance.

Jennifer Faber-Gerling, RN: One point I wanted to highlight in regards to macrolide resistance is I do have a candid conversation with patients about symptom management and not always reaching for that antibiotic and doing some antibiotic stewardship. We want to work off of data and this is a chronically ill patient that's going to have recurrent exacerbations which may or may not be mycobacteria-related. I think primary care physicians, when azithromycin came on the market, they used it like water and what I encourage patients to do is always have a sputum container on hand, advocate or contract with their provider and say, if I am having symptoms, can I have a requisition to drop my sputum sample off because if this is something other than mycobacteria, we want those susceptibility results so we can target that particular bacteria with the antibiotic that's appropriate. And so, pretend you have an allergy to a macrolide and you cannot get that because we want that for your mycobacterial treatment.

Christina O'Connor, PharmD: I'll speak to the amikacin. I consider it to be more of an art than a science when you use it for mycobacteria. And I always encourage, I use 2- and 6-hour levels. The protocol that we use, just the nuts and bolts of how to get the peak to extrapolate it from the 2- and the 6-hour post-dose. I always encourage the inpatient pharmacist we need this amikacin to last. We're in it for the long run with the amikacin. You do not have to be ultra-aggressive with it. You don't always have to hit 80 mcg/mL with it and so that's how I work with my inpatient colleagues to kind of tell them we need to set this person up so that this drug can be tolerated and hit that sweet spot between tolerable and effective for as long as possible.

Jennifer Faber-Gerling, RN: With aminoglycoside, I really feel like educating the patient about potential side effects, mainly the hearing issues, that we need to hear about that because we do want to preserve that and be able to maintain adequate treatment for their mycobacterial infection. But you're almost kind of getting informed consent when you're putting somebody on intravenous amikacin because it can go south quickly and I think the patient needs to understand the potential ramifications of it.

CASE 5

Case Background

IJ, reports significant clinical symptoms and positive microbiologic cultures consistent with *MAC*-lung disease. On chest radiograph, cavitary lesions in the middle lobes of the lungs measuring between 2.5 and 3 cm are present.

Case 5 Question 1

Which of the following statements is true regarding noncavitary and cavitary *MAC*-LD management? [PICO Question I, VIII]

A. Cavitary disease is more likely to be associated with worse outcomes
B. Optimal management for cavitary disease is thrice weekly treatment
C. Treatment for noncavitary and cavitary disease is the same
D. Watchful waiting is reasonable for patients with noncavitary but not cavitary *MAC*-LD

Answer Rationale

The correct answer is **A**.

- Individuals with cavitary disease have a worse prognosis compared to those with noncavitary disease.[1,2]

- Furthermore, the size of the cavitary lesion has a profound effect on clinical outcomes where cavities > 2 cm were associated with both worse treatment outcomes and higher mortality.[3]
- Active antimycobacterial treatment is recommended in both cavitary and noncavitary *MAC*-LD compared to watchful waiting. Although antimycobacterial medication management is typically the same, depending on isolate susceptibility, the 1 aspect of treatment that differs is the frequency of administration. For individuals diagnosed with cavitary disease, daily treatment should be initiated as opposed to thrice weekly.

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Faculty Commentary

Jennifer Faber-Gerling, RN: This next question is looking at cavitary lesions in the lungs and we highlighted the fact that cavitary disease is more likely to be associated with worse outcomes in patients. The presence of cavitary lung disease ups the ante as far as the severity of lung disease and these cavities are really difficult to treat. To get antibiotic delivery to areas of the lung, you need blood flow, and we know that we don't have the ability to measure the blood flow to those areas, but it's probably likely that there isn't great blood flow to those areas. There are innumerable amounts of bacteria within those cavities that could actually spill into healthy areas of lung tissue, so the goal with that is to try to resolve these cavities in whatever way we can. Amikacin is the big gun to be able to attempt to do that, but then, as we've discussed previously, the adjuvant of surgery sometimes is needed to eradicate these cavities.

David E. Griffith, MD: Unfortunately, we don't have just an objective decision analysis for this sort of thing. We sort of gestalt the cavity, is it little, is it big, what are the chances we think it's going to resolve? We're uncomfortable with what I'll call larger cavities, let's say 3, 4 cm and larger, that don't close while we're treating the patient. There's not prospective data I'm aware of, but I think we're all very uncomfortable about leaving those cavities because of the 2 things you said, recurrence and spillage.

Christina O'Connor, PharmD: When I hear cavitary disease, I'm thinking daily therapy with the orals. Not only do you have to understand the organism and the way the susceptibilities work, but you also have to have a basic understanding about the disease state itself, because that informs the build of the regimen. It's not as simple as, "I know a simple source and a bug, and I come up with a regimen." You have to know about the disease severity of the patient. If this is first treatment vs recurrence vs relapse, to be able to get that actual pharmacotherapy regimen built correctly. I think it's a great place for us to partner with our colleagues and then, for folks that don't feel like they're super-specialists in this area, that's where you have to be really diligent about using the guidelines and really trying to make sure that you can

understand and match up that regimen, and checking it to make sure that it matches with guideline-concordant treatment.

Jennifer Faber-Gerling, RN: Christina, I know you just commented on the fact of cavitary disease and daily therapy. Can you outline the approach, though, with the intravenous aminoglycoside in regards to that?

Christina O'Connor, PharmD: For the orals, we use the 3 times a week for amikacin. Using a higher dose, again more of an art than a science, more of the 20 to 25 mg/kg 3-times-a-week type of dosing, 3 times a week, instead of every single day, for the intravenous therapy. That's generally better tolerated, and I have been able to get patients to tolerate that regimen for months, shooting for an undetectable trough, is really 1 of the keys to making that successfully durable.

Case Background

The following susceptibilities are reported for IJ's *M. avium* isolates.

	MIC (mcg/mL)	Susceptibility
Amikacin (intravenous (IV))	32	Intermediate
Amikacin (liposomal, inhaled)	≤ 64	Susceptible
Clarithromycin	16	Intermediate
Clofazimine	0.12	---*
Ethambutol	2	---*
Linezolid	16	Intermediate
Moxifloxacin	2	Intermediate
Rifabutin	0.5	---*
Rifampin	1	---*
* CLSI without established breakpoints for *MAC* organisms		

Case 5 Question 2

Which of the following treatment recommendations is correct based on IJ's susceptibilities?

A. Dual macrolide therapy should be used to overcome resistance
B. A macrolide should remain part of the multidrug treatment
C. Azithromycin susceptibility should be tested
D. IV amikacin should replace the macrolide component of treatment

Answer Rationale

The correct answer is **B**.

- Based on the susceptibility report, IJ's isolate exhibits an intermediate MIC to clarithromycin (as well as azithromycin).[1,2] Based on this information, a macrolide should be retained in treatment.[1]
- Intermediate MICs are rare and require further confirmation since this could represent a mixed population of MAC organisms. Close monitoring with repeat cultures should be closely monitored for the emergence of macrolide resistance in individuals with confirmed intermediate MICs.[3]

- There are no data to support that dual macrolide therapy would overcome resistance. Additionally, since azithromycin is also representative of the macrolide class, there is no benefit to assessing susceptibility patterns since clarithromycin susceptibility has already been reported.
- IV amikacin demonstrated intermediate susceptibility to IJ's isolates but full susceptibility to amikacin liposomal inhalation suspension (ALIS). Therefore, ALIS may be a potential option for this patient if true macrolide resistance is identified. But at this time, the macrolide can remain a part of the patient's treatment.[4]

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Faculty Commentary

David E. Griffith, MD: The next question is about in vitro susceptibility testing. There is a table with in vitro susceptibility results with minimum inhibitory concentrations and their interpretation. The answer to the question has to do with the macrolide MIC of 16 mcg/mL which is labeled as intermediate by the CLSI and that it should remain part of the multidrug treatment regimen.

We have to make some comments here about the table. The first, and perhaps most important, is that the MICs for linezolid and moxifloxacin have not been validated. The term intermediate for both of those is meaningless. We have no idea what they mean. I know what they mean for moxifloxacin. I think there is actually a possibility that linezolid may have some activity, but they should not be reported, number 1. I know laboratories, including our own, do, but they're always followed by caveats that basically say ignore this number.

Just a couple of quick thoughts about amikacin that are worth remembering. There is a 2-fold amikacin susceptibility, 32 mcg/mL or less is susceptible for intravenous amikacin, 64 mcg/mL or less is susceptible for inhaled liposomal amikacin and that simply has to do with the fact that if you have an isolate with 64 mcg/mL MIC, it is impractical to treat that isolate intravenously. You would have to use IV amikacin doses so high that severe toxicity would be inevitable. It's not that the liposomal amikacin has some magic activity in vitro that generic amikacin doesn't have. It's just a practical matter. I think that laboratories are more savvy these day about reporting this dual activity and clarithromycin isolates with an MIC of 16 mcg/mL are active against MAC. So, I would definitely would use that.

It's important to repeat those. You can have 1 dilution wiggle in these MICs so that an MIC of 16 mcg/mL, the next time might be 32 mcg/mL. Conversely, it might be 8 mcg/mL. It is important that if you have that

intermediate MIC, that you report it. Combining clarithromycin and azithromycin has no value for these patients.

So, based on these numbers, you could use intravenous amikacin or inhaled liposomal amikacin for this particular isolate.

Christina O'Connor, PharmD: I would say few centers do have a microbiology lab that's capable of mycobacterial susceptibility testing. Other places, this may be a send-out test for them, so that's a practical matter to keep in mind and then we will see the amikacin intravenous and inhaled broken out on the micro report with the 2 separate break points. I usually tell them, especially the susceptibility, can take a little bit of time. It may not be that it's back the next day after you did the test.

David E. Griffith, MD: When patients have true acquired mutational resistance to macrolide and amikacin, their MICs go sky high. This MIC of 16 mcg/mL for clarithromycin would not be consistent with the 23S mRNA mutation that's associated with mutational resistance. Similarly, that 32 mcg/mL and 64 mcg/mL MIC would not be consistent with the 16S rRNA mutation. When they're in this level, you can be pretty confident they don't have mutational resistance.

CASE 6

Case Background

KL, a 66-year-old patient, has been receiving treatment for pulmonary MAC disease. They are fearful of failing treatment and want to know how this will be determined.

Case 6 Question 1

What definition is associated with treatment failure in KL?

A. Previous conversion of sputum cultures to negative followed by positive sputum cultures 6 months after the completion of antibiotic treatment
B. Previous conversion of sputum cultures to negative followed by positive sputum cultures 18 months after the completion of antibiotic treatment
C. Inability to convert sputum cultures to negative by 6-months of antimycobacterial therapy
D. Continuation of antibiotic treatment for 12 months after conversion of sputum cultures to negative

Answer Rationale

The correct answer is **C**.

- Treatment failure is defined as the inability to convert sputum cultures to negative by 6 months of antimycobacterial therapy.[1-3]
- Treatment recurrence occurs in patients whose sputum cultures converted to negative while on treatment. Although sputum conversion occurs, sputum cultures are monitored every 6 months after treatment. In patients who experience recurrent growth of *MAC* in the sputum, it can be either relapse/recurrent infection or reinfection.
- Recurrence has been reported in 10% to 48% people successfully completing treatment for *MAC*-LD.[4-6] Nodular bronchiectatic disease, old age, low BMI and *M. avium* isolates are associated with recurrent disease.[3]

- Relapse tends to occur after a shorter duration of time between treatment and symptoms reappearing (ie, ~6 months) compared to reinfection having a significantly longer period of time between treatment and recurrence of symptoms (ie, ~18 months).[7]
- Retreatment is the same for both relapse and reinfection. It is also the same initial treatment but should be based on isolate susceptibility. Resistance to a macrolide is more common with relapse infection. Environmental sources should be assessed in cases of reinfection.[4]

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Faculty Commentary

Christina O'Connor, PharmD: This next question is about differentiating relapsed infection from reinfection or inability to convert sputum cultures due to initial treatment failure. The answer on this one is that it's an inability to convert the sputum cultures to negative by 6 months is defined as failing treatment. The other 2 situations are referring more to relapsed or reinfection. Having that previous conversion of cultures to negative and then after 6 months of completing, then turning positive, would be relapse; whereas having a previous conversion to negative, followed by sputum cultures after 18 months, would be more indicative of reinfection.

Jennifer Faber-Gerling, RN: This is a really important time in the trajectory of the treatment of their MAC because if they remain culture-positive at 6 months, we may be considering the addition of ALIS at this point in time because the ultimate goal of treatment is culture conversion. This is a really important time, especially if they're on guideline-based therapy and we get a CT scan and it's showing progression of disease at that time.

David E. Griffith, MD: Also, important still to emphasize routine collection of sputum for AFB analysis. Without that, you just can't make this kind of determination. You don't know whether they're succeeding or failing and if they have recurrent or disease or relapse. But it cannot be overemphasized, we have to collect sputum from the patient routinely.

Case Background

The decision to add amikacin liposomal inhalation suspension (ALIS) to guideline-based therapy (GBT) is made based on KL's treatment-refractory disease.

Case 6 Question 2

What is the role of amikacin liposomal inhalation suspension (ALIS) in the management of patients with *MAC*-LD?

A. As monotherapy in patients experiencing treatment-refractory disease to reduce disease progression
B. As monotherapy in patients initiating treatment to reduce the risk of side effects
C. As part of combination therapy in patients with treatment-refractory disease to promote the likelihood of sputum culture conversion
D. As combination therapy in patients initiating treatment to reduce the development of drug-resistance

Answer Rationale

The correct answer is **C**.

- ALIS (590 mg of amikacin administered via nebulizer), in combination with a GBT multidrug regimen, assists in increasing sputum culture conversion in patients diagnosed with treatment-refractory disease (persistently positive sputum cultures for more than 6 months).[1-4]
- ALIS should be used as part of combination treatment and never as monotherapy, regardless of disease stage and severity, due to the risk of developing treatment resistance.
- The multinational phase 3 CONVERT trial showed the addition of ALIS to a multidrug regimen yielded significant improvement in microbiologic and clinical outcomes.[2] The primary endpoint of culture conversion was achieved by 29% of patients treated with ALIS added to guideline-recommended therapy at 6 months. Comparable results were observed in an extension phase in patients treated with guideline-recommended therapy alone who did not convert at 6 months. Furthermore, culture conversion rates were more durable at 3 months with the addition of ALIS.
- The sustainability and durability of culture conversion with ALIS was investigated in the cohort of patients who achieved culture conversion by month 6 in the CONVERT study. Results showed that among patients who achieved culture conversion by month 6, 55% of those receiving ALIS plus guideline-based therapy (GBT) vs 0% of those who received GBT alone sustained culture conversion

for up to 12 months of treatment. This finding has implications for the treatment of patients with refractory MAC lung disease.[4]

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Faculty Commentary

David E. Griffith, MD: The next question has to do with the addition of amikacin liposomal inhalation suspension or ALIS to guideline-based therapy. The correct answer is as part of combination therapy in patients with treatment-refractory disease. ALIS should be added to promote the likelihood of sputum culture conversion. A couple of real important observations about ALIS. One of the big failings that we have, in general, in treating NTM disease is we have very little prospective data on the efficacy of the drugs that we use. With ALIS, we have 2 large, controlled, prospective trials of ALIS in addition to guideline-based therapy. There is no other drug that we use for MAC with that kind of database. And 2, it's the only FDA-approved drug for MAC. Nothing else that we use has FDA approval for pulmonary MAC.

In a patient who has refractory MAC lung disease, defined as positive sputum culture after 6 months of guideline-based therapy, ALIS, which is 590 mg of liposomal amikacin, is administered by inhalation daily, in addition to the oral regimen. There are so many important things not to forget. And 1 of them is, remember, of the 2 drugs that we have where MICs matter, 1 is macrolide and 1 is amikacin. We know not to use macrolide as monotherapy due to the emergence of resistance. The same holds true for ALIS. ALIS must be protected in the same manner that you would protect macrolide to prevent the emergence of acquired mutational amikacin resistance. If you've got a macrolide-resistant patient and you make them amikacin resistant, that is bordering on untreatable.

In the pivotal phase 3 trial for ALIS, the addition of ALIS to guideline-based therapy was significantly more associated with sputum conversion for these treatment-refractory patients than was continued guideline-based therapy alone. And that was with a highly-significant *P* value. It was approximately 30% of the patients who received ALIS plus guideline-based therapy vs approximately 9% of the patients who had guideline-based therapy alone. Additionally, when patients were followed on their treatment, patients significantly remained culture-negative longer on treatment with ALIS than with guideline-based therapy alone and then, after stopping therapy, the patients who received ALIS stayed culture-negative significantly longer than the patients who got guideline-based therapy alone. In the trial where those numbers were generated, essentially 0% of the guideline-based therapy people who had initially

converted stayed converted through the duration of treatment and then after treatment was discontinued, whereas about 55% of the patients who had ALIS plus guideline-based therapy stayed culture negative, both during the time they were on therapy and then in the period they were followed off of therapy.

The data are actually rather robust. ALIS is quite effective in patients with treatment-refractory MAC in converting their sputum and in keeping the sputum negative while they're on treatment and after treatment is discontinued.

Christina O'Connor, PharmD: While initiating ALIS, the dose not being the same as when using the non-FDA-approved IV formulation through a nebulizer. ALIS has a specific dose, the 590 daily and making sure they get that dose right and it's not the same if you were using a nonliposomal form. I like to also tell patients that the ALIS has its own specific nebulizer and patients will also get really wonderful education on how to use it. We do have a model kit in our clinic where myself and my colleagues will sit down and go through how to use the ALIS and the nebulizer that goes with it. That's also reinforced through ALIS educators as well.

Jennifer Faber-Gerling, RN: When you're prescribing ALIS, you can't just send the prescription to a specialty pharmacy. There is an enrollment form and then, through the company, there's a support group called Arikares that will help navigate getting that drug to the patient.

David E. Griffith, MD: We can't talk about ALIS without talking about side effects because patients will be very unhappy with you if you don't. And in particular, dysphonia and hoarseness. About half the people who take ALIS are going to get hoarse and, fortunately, it usually goes away and you can continue ALIS, but you can't discuss ALIS with a patient without telling them pretty explicitly what to expect in terms of side effects.

Jennifer Faber-Gerling, RN: We do have strategies to help with dysphonia. Premedicating with a bronchodilator, doing their dose in the evening so they get voice rest overnight. There are some strategies that we can use to help with that, but typically it happens within the first month of administration and if you modify the frequency and then get back up to the daily therapy, they usually can tolerate it after that. It's just preparing them ahead of time so they know what to expect.

David E. Griffith, MD: It's critically important, if you give them a brief interruption, their hoarseness gets better. 90% of the time you can restart it and the patient will not have the same degree of hoarseness, if at all.

Case Background

The decision to add amikacin liposomal inhalation suspension (ALIS) to guideline-based therapy (GBT) is made based on KL's treatment-refractory disease.

Case 6 Question 3

How does amikacin liposomal inhalation suspension (ALIS) work improve drug efficacy in patients with *MAC*-LD?

A. Decreases systemic exposure of amikacin

B. Increases uptake of amikacin into alveolar macrophages
C. Serves as a carrier for other antibacterials to enhance their penetration into the biofilm
D. Reduces enzymatic metabolism in the lung

Answer Rationale

The correct answer is **B**.

- ALIS works by disrupting and inhibiting protein synthesis in the target bacteria (ie, *MAC*) by binding to the 30S ribosomal subunit.[1]
- ALIS also works against MAC-LD by promoting biofilm penetration and increasing the uptake of amikacin into alveolar macrophages.[2]
- Additionally, the ALIS formulation is associated with low systemic exposure to amikacin following administration compared to the intravenous formulation. Therefore, ALIS can provide more localized treatment for the management of *MAC*-LD.[1] Although this is true, this is not how it works in *MAC*-LD.

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Faculty Commentary

Christina O'Connor, PharmD: This is a pharmacology question and the mechanism of action for ALIS is the same as aminoglycosides in general. It binds to the ribosomal subunit and inhibits protein synthesis. It can also promote biofilm penetration and the amikacin uptake can be increased into the alveolar macrophage with the ALIS formulation. In comparison to the intravenous form, you don't have all the other things with the IV form, such as the peripherally inserted central catheter (PICC) line or the intravenous access line, the higher risk of toxicity and, again, not to say that ALIS has zero risk of toxicity, but there's also the benefit of being able to use an inhaled form of the drug.

CASE 7

Case Background

MN is a 62-year-old patient diagnosed with *MAC*-LD. He will be started on antimicrobial treatment along with a chest vest to promote airway clearance. Since he lives 2 hours away, he wants to know how his treatment response will be monitored.

Case 7 Question 1

What information will assist in determining treatment response?

A. Monthly chest X-ray at his local hospital
B. Annual sputum collection at the nontuberculous mycobacterial (NTM) clinic
C. Sputum collection every 1 to 2 months after treatment initiation at his local clinic
D. Reduced use of airway clearance devices

Answer Rationale

The correct answer is **C**.

- *Clinical* (improvement in pulmonary and systemic symptoms), radiologic (chest radiograph or chest CT recommended at baseline, during treatment, and at the end of treatment. Chest radiography can also be considered every 6 months or if any concerns arise for clinical or microbiologic failure of treatment or disease progression) and *microbiologic* (sputum evaluated every 1 to 2 months after treatment is initiated for conversion. Once sputum conversion is sustained (ie, on repeat culture), less frequent monitoring is needed (ie, every 6 months) to assess treatment response and duration.[1]
- Factors associated with poor prognosis and MAC-related progression may include[2]:
    - Fibrocavitary lung-disease
    - Disease involvement on CT scan (ie, ≥ 4 lobes, large cavitary lesions)
    - Low BMI and/or albumin
    - Elevated inflammatory markers (ie, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP))
    - Symptoms that reduce quality of life
    - AFB smear positivity
    - Inhaled corticosteroid use
    - Male gender
- Various airway clearance techniques exist and should be considered in patients with copious amounts of mucus and problems with clearing mucus. These techniques can include flutter valves (oscillating positive expiratory pressure), chest vest (high-frequency oscillation of the chest wall), physiotherapy of the chest, and pharmacologic agents (ie, hypertonic saline, mucolytics, etc) that can promote expectoration of mucus.[4]
- Since MN lives quite a distance from this specialty clinic, it will be especially important to identify strategies to promote follow-up. This can include engagement of the patient's local primary care provider, the use of telehealth, and continued collaboration with the interprofessional care team.

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Faculty Commentary

Jennifer Faber-Gerling, RN: The patient is wanting to know how his treatment response will be monitored. The correct answer is sputum collection every 1 to 2 months after treatment initiation. That's really important because it is going to direct the duration of therapy, but you also want to be assessing your patient for any systemic symptoms, radiographic reimaging to see where they're at. We recommend at baseline and then probably 6 months in, and then, at the end of treatment, trying to get sputum from patients. Sometimes it's very difficult. Try to make that as easy as possible. We use a sputum mailer kit so that the patient just needs to drop it off.

We've also talked about factors that are associated with a poor prognosis. This is cavitary lung disease, multiple lobes that are involved on radiographic imaging, low BMI or albumins, elevated inflammatory markers, and we have a tendency to use the C-reactive protein to monitor that. Symptoms that can reduce the quality of life. And that's hard, too, because patients may not want—if it's side effects from meds—they may not want to stay on their regimen. AFB smear positivity, inhaled corticosteroid use and male gender specifically.

We talk a lot about maintenance and what patients can do to proactively manage their disease, and airway clearance is a way to do that. We typically start with some kind of flutter device with hypertonic saline or a mucolytic and then, in certain cases, we may layer on oscillating vest therapy. In our patients, we preface that's the foundation of their care. We also want to make sure we're partnering with the patients and any other providers that are active with their care, that everybody knows the importance of follow-up and that's clearly defined and the monitoring that's required on these intense regimens as far as symptom management. And then the need for collecting sputum.

Case Background

MN is prescribed a daily regimen of azithromycin 500 mg, ethambutol 1200 mg, and rifampin 600 mg, based on antimicrobial susceptibility testing.

Case 7 Question 2

Prior to initiating treatment for *MAC*-LD, which of the following tests should be performed at baseline?

A. TSH
B. Electrocardiogram
C. G6PD
D. Monofilament

Answer Rationale

The correct answer is **B.**

- Treatment-emergent adverse effects have been reported in more than 90% of patients initiating treatment for nontuberculous mycobacterial lung infections.[1] Therefore, it is essential to have an accurate baseline assessment of the patient prior to initiating treatment.
- All patients should have a complete blood count (CBC) and comprehensive metabolic panel (CMP) drawn prior to the start of treatment.[2]
- Patients receiving medications that can cause QTc prolongation (ie, macrolides, fluoroquinolones, or clofazimine) should have an electrocardiogram performed to assess for QTc prolongation.[2]
- For those receiving treatment with a macrolide and/or aminoglycoside, an audiogram should be assessed prior to initiating treatment with either of these agents.[2]

- Similarly, in patients starting ethambutol, a visual acuity and color discrimination test should be conducted prior to initiation of this medication.[2]

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Faculty Commentary

David E. Griffith, MD: The next question has to do with monitoring for toxicity.

The answer to the question is electrocardiogram and I think most are familiar with the fact that the macrolides can prolong the QTC interval. By themselves, the macrolides are very safe. There's really not much evidence out there that macrolides are associated with even maybe a detectable level of ventricular tachycardia. However, there are those patients who have baseline elevated QTC intervals and I think that's the reason to do the EKG is to make sure you're not about to give azithromycin to someone with a QTC interval of 500 milliseconds. If it's 450 milliseconds, obviously it's a risk-benefit decision, but without macrolide, the success of MAC treatment is extremely poor. We get complete blood count (CBC) and comprehensive metabolic panel (CMP). The CBC is important particularly for following rifampin. Again, the CMP also for rifampin and renal insufficiency and, for azithromycin and rifampin, for hepatotoxicity.

We recommend an audiogram because azithromycin can affect hearing. Also later, if ALIS is chosen for a refractory patient, that is important for knowing the baseline hearing acuity of patients. And then visual acuity and color vision testing. You know, we use a wall chart and the little blue Ishihara book. What's even more important is educating patients about ocular symptoms, because it's not likely a patient is going to walk into your office the same day that they develop ethambutol ocular toxicity. They have to be able to know what to look for, stop the drug, and then contact you.

There is controversy about how often you do these tests. For instance, once I have a baseline electrocardiogram (EKG), I generally don't repeat it unless I change drugs that might alter the QTC interval. In terms of CMP and CBC, I think every few months is adequate. I'm a little more aggressive than some about the visual acuity, color vision testing. I like to do it monthly for the first several months and then every 2 or 3 months after that. But again, as we've said, symptoms trump the monitoring in terms of ethambutol ocular toxicity. Patients have to be confident and comfortable that we are monitoring them for safety. That we are watching out for them while they are taking these medications for their MAC disease.

Christina O'Connor, PharmD: We use a collaborative practice agreement with our pharmacists where we are the first line to review all the labs for the patients and the ECGs. So, as long as the electrocardiogram (ECG) is normal, we can review that independently. Same with the lab results. And then we reach out to physicians and APPs if there's something concerning on the labs.

Case Background

MN also mentions persistent ringing in their ears that developed within the past year. The only new medications they started within this period are listed below.

Medication List

- Azithromycin 500 mg daily
- Ethambutol 1200 mg daily
- Rifampin 600 mg daily
- Tiotropium inhaler 2 inhalations of 2.5 mcg daily

Case 7 Question 3

Which of the following medications is responsible for causing MN's symptoms?

A. Azithromycin
B. Ethambutol
C. Rifampin
D. Tiotropium

Answer Rationale

The correct answer is **A**.

- The development of tinnitus secondary to azithromycin occurred in 18% to 46% of patients receiving high doses (ie, 500 to 600 mg/day) for the treatment of *Mycobacterium avium* complex pulmonary disease.[1-4]
- Ethambutol is associated with both ocular toxicity and neuropathy while rifampin can cause hepatotoxicity, orange secretions, cytopenias, and hypersensitivity.[1]
- Although tiotropium is used for symptomatic support it is not associated with the development of tinnitus or hearing loss.

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Faculty Commentary

Christina O'Connor, PharmD: This question relates to suspected drug toxicity. I think most are familiar with the aminoglycosides causing ototoxicity, but also the macrolides have been linked to ototoxicity.-I

counsel patients when they're starting a macrolide that ototoxicity is a possibility and something that I want them to call and let us know about if it does occur. I also give patients mnemonics to help them remember what some of the side effects are. For the other ones that don't correlate with the ototoxicity, I tell patients that R, red, is for rifampin. It will turn your urine red color and your body fluids a red color and also R is for rash which is common with the others as well. And then E is for eyes. Ocular toxicity with ethambutol. That is something that is simple, that they can take away with them, hopefully, and remember.

Jennifer Faber-Gerling, RN: In these complex patients, that have underlying bronchiectasis, they may be using aminoglycosides either for acute treatment of pseudomonas or suppression of pseudomonas, so not only is the macrolide a risk with the NTM treatment, but also with aminoglycosides and that ongoing tinnitus.

David E. Griffith, MD: This is tough because it's largely subjective. What do you do? We've talked through this. You can't just throw away drugs, particularly a drug like azithromycin. Clarithromycin may be a little less ototoxic, but still potentially ototoxic. I find that one particularly challenging because the patient is not happy, but I may not have much else to offer.

Christina O'Connor, PharmD: I find the most common is really the diarrhea and upset stomach with the macrolide to start, and that typically gets better. If you can get through the first couple of weeks on your macrolide, take it with food can help with the diarrhea, we can see you through it. Again, trying to preserve that macrolide every way we can. Sometimes they'll get that metallic taste and, again, most people can tolerate that as long as we can stick with it. It's not harmful to you. Accentuating the things that I call the green light side effects or the yellow light where we can still proceed with the treatment. You may need some support. These are things oftentimes that patients are able to tolerate. But those, especially the diarrhea, initial diarrhea, seem to be much more common than the tinnitus or any kind of ototoxicity with a macrolide.