**SPEAKER:** The next step is to follow how are they doing. So obviously, if they're not tolerating a medicine, you need to switch it out for something else. It's another supportive reason for why we do sequential additions of medications, because it gives me a greater feel for which drug is the culprit.

If they're having nausea, were they having it after the addition of azithromycin or ethambutol, or was it the rifampicin, because that then gives me perhaps a better option of a drug to remove and then replace it with another therapy. That could be amikacin, either systemically delivered or inhaled. Could be something like clofazimine. We do have other options to treat them, and then, of course, we'll have susceptibility testing to come back.

Once we have them on a regimen in which they can tolerate, then we can begin to look at whether it's making a difference. So in terms of discussions with the patient, we, again, have established very clearly what caused us to recommend treatment, and that's what we're focused on. So for example, if it was the cough that was the predominant symptom, we want to know has the cough improved. If it's the fatigue, if it's the weight loss, have those begun to turn the corner and they begin to appreciate that there is some benefit to the therapy.

And then we're looking for a micro biologic response. And what we aim for, our target, is eradication. That would be our number one target.

We will, however, have to think about what do you do when the patient improves, they are clinically better, their symptoms are better, they're feeling pretty good, and yet you have not achieved a microbiological cure. So in those patients who you've got cultures on, in research studies the definition of culture conversion has been three sequential negative cultures. And the guidelines would recommend to treat for one year past the onset of culture conversion, which would be that first negative culture.

So if you adhere to that as your definition of success, which we do, that means you need to be getting monthly cultures. And we do, in fact, see our patients monthly, or if they are coming at enormous distance, work out with a lab that we can get samples to so we can monitor the microbiologic effect, and we are looking for that culture conversion. If they achieve culture conversion, then we tell them we are going to treat for 12 months past this date at which time we can rejoice and stop your medications.

But if you're not having that success, at some point you have to pivot. You have to make a change in your therapeutic options. For us, that target time is six months. And so if a patient has not achieved success at six months, certainly systematically, but if not microbiologically, then we're looking for a therapeutic change.

Now in general, that is an addition to the current regimen. So for us, that might be the addition of clofazimine or inhaled amikacin. And then we would begin the same process, monitoring their cultures over time to see if they have had any additional improvement.

Now what do you do with the patient who can't cough up any sputum? If it's a patient who previously was producing sputum with cough, and you can get tests on cultures, and now they can't produce cough and sputum, then that means we take that as a negative culture. Unless there's some other feature that would make us worry about need the need to re-image and put a bronchial scope down to obtain a specimen from a lower airways.

But then there are those patients in whom you had to make the diagnosis by bronchoscopy. And I'm not advocating that we do monthly bronchoscopy to look for cultures, but at some point you're going to have to make an assessment to see if you've achieved microbiological effects. And again, for us, that time point would be six months. Even if they are symptomatically improved, unless their CT scan has considerably improved, and if it has, I would stay the course, and then we have to decide how long we intent to treat, then it might be prudent to think about repeat bronchoscopy copy to see if you've had any effect on the microbiology.

Now one word of caution in that is, we talk about these patients as if they have MAC lung disease and that's all that we're going to follow. But then there are patients who will have mixed infections, and they add a new wrinkle in terms of your assessment. And in some cases, you know that going into it because those patients will have MAC on one culture, and then they'll grow mycobacterium abscessus on the next culture. But in many patients-- not-- in some of our patients that we treat, what they will then appear to have is-- you actually are having the effect on the MAC.

The MAC is gone. You're not growing it in culture, but you're growing abscessus now. And the decision about whether to pivot and change your therapy to make sure you're covering that to me is very dependent upon the clinical response. Had they had clinical change in symptoms, and then have they had any radiographic changes that would suggest improvement.