SPEAKER: So the Clinical Laboratory Standard Institute is the governing institute that gives us guidelines on drug susceptibility testing in mycobacteria. And drug susceptibility testing for these organisms, and particularly for MAC, are clinically relevant really for only two antibiotics, or two classes. And that includes the macrolides and the aminoglycosides.

So, what I'm trying to say here, is that the reports that you're getting on your in vitro MICs matter for those two drugs. And particularly, when you get a report back, which will say clarithromycin resistance, or intermediate, or susceptible, that's a class effect. So that allows you to understand the likelihood of that patient responding to either clarithromycin or azithromycin. The second important class is the aminoglycosides. And the MIC report is going to reflect amikacin sensitivity or resistance.

Now, in the last iteration of the CLSI guidelines that came out in November of last year, the breakpoints for interpreting sensitivity or resistance changed. And the reason why they changed was because of data that showed that greater than 64 mattered. Greater than 64 on the MIC means that there's been mutational resistance within the organism, and that confers a conformational change in the binding site for that antibiotic, and therefore that antibiotic will not work.

So again, the two important drugs on that test are the macrolides and amikacin. For the macrolides, the MIC that confers resistance is greater than 32 micrograms per ml. And the MIC that's important to remember for amikacin is greater than 64.

In general, in a treatment-naive patient, a patient that's not been exposed to these antibiotics before, for other reasons, the vast majority of those patients will have a sensitive strain to the macrolides and the aminoglycosides. It's when patients have been exposed to these agents, either because of NTM lung disease, or because of other chronic conditions, that they have a risk of developing drug resistance. Now, the likelihood of seeing drug resistance in a treatment-experienced patient is probably still low. But we know that there are certain discrete risk factors for developing drug resistance.

The first of which is being on monotherapy of either of those agents. So more data exists in the setting of macrolide resistance. We know that patients that have been exposed to macrolide monotherapy are at greater risk of developing resistance to the macrolides. We don't know exactly when that occurs, and I can tell you in clinical experience, it's very different for each patient.

The other important risk factor to be aware of, is using a macrolide with a quinolone. The quinolones do not protect against developing macrolide resistance. And I think that makes sense, because we know that the likelihood of MAC being sensitive to the quinolones is very low-- about 10% of our MAC isolates in our experience are sensitive to quinolones. So therefore, you're effectively using macrolide monotherapy when you put a patient on a cocktail including azithromycin and moxifloxacin, for example. We use ethambutol as part of our three-drug standard cocktail because we believe that it protects against developing macrolide resistance.

And why is all of this important? Well, particularly for macrolide resistance, if a patient's been macrolide-sensitive, and you tell them that their likelihood of cure is somewhere between 65% and 85%, and then they become macrolide resistant, their cure rates drop to about 10%. And now you have to entertain ideas such as-- or therapy such as prolonged, injectable aminoglycosides, such as six months of IV amikacin and surgery for that particular patient. So those are heroic interventions in a disease that we largely consider incurable.

As far as when to try-- check drug susceptibility testing, I recommend it in all patients who are going to initiate antibiotic treatments, in patients who are persistently culture-positive at six months of treatment, and in patients that are culture-converters but go on to have a relapse or a reinfection after they've completed treatment.