SPEAKER: So once the decision has been made to undertake antibiotic therapy for MAC infection, a number of things need to happen. Monitoring is hugely important. And the monitoring needs to include visual field testing for patients on ethambutol, should include monitoring of CBC so that we know that white counts are OK, should include, if and when amikacin is used, renal function testing as well. And since both macrolides and amikacin can cause decrements in hearing, hearing testing would be appropriate to do. So those things need to be considered as important, I would say necessary, adjunctive management steps.

An added feature, which at times slips into the backgrounds and gets less important consideration than it needs to have, is ongoing surveillance of sputum cultures. So the understanding of success in treatment of these diseases comes out of serial sputum cultures that reveal the change from sputum culture positive state to achieving culture negative state. And quite pointedly, if you don't look, you will not know.

The collected guidelines are somewhat imperfect around guidance on how often to obtain sputum cultures. I think in the field, we have evolved a standard and the guidelines suggest a standard around sputum samples being obtained in the range of four-week intervals or four- to six-week intervals. But serial and frequent sampling of sputum is really critically important in managing disease. Hopefully to show that we are clearing the infection, which is obviously the goal, but also allowing us to identify patient populations who are not having success in infection eradication.

And because we can check and because we should be checking serially, we can then, as clinicians, have a sense of who is having success and who is having failure of the current antibiotic regimen. And while we don't want to have failure of these antibiotic regimens, it does happen. And we do indeed have refractory infections, despite antibiotic therapy. And in the consensus view and now that there is an FDA approved product specifically for MAC infections at the FDA level, we have agreement around a six-month interval of persistent positive sputum cultures defining a refractory treatment state.

Stated otherwise, we would want, as clinicians, to track because if we find repeated sputum cultures consistently through a six-month period on treatment, then we are not achieving success in our treatment strategy and we need to consider alternatives for therapy. And that brings us into a more complex treatment circumstance, but it's also critically important that we be able to recognize that because a relatively more data-depauperate and uninformed circumstance leaves the patient not treated well and potentially exposed to greater disease consequences and the unfortunate side effects of medications.

So when we consider therapy in refractory disease patients, historically, the consideration, it has revolved substantively around whether and when to add drugs like amikacin. And historically, what we have used is IV administration of amikacin. And while it's been shown to be substantially affected in patients with refractory disease whose pathogen is susceptible to amikacin, there are, of course, issues. Particularly with parenteral administration of amikacin, there are end organ toxicities, and those are twofold. Number one, hearing toxicity, and the second is renal toxicity.

And what we know is that as the period of IV amikacin therapy extends, the risk for toxicities, either renal or ototoxicity, goes up substantially. That requires ongoing monitoring of hearing and renal function, but also will necessarily result in a cautious end of therapy typically within a space of average two to four months of IV amikacin therapy. So that we historically have this prospect of a good drug for adjunctive therapy in refractory disease, namely IV amikacin, but its side effect profile has limited the duration of use in any one patient and has been associated with these toxicity concerns, which are very understandable.