

**SPEAKER:** So when one considers therapy for NTM disease, there are some specific recommendations. And I'd like to it to focus on the MAC organisms-- not just that they are most numerous, but that there are concrete guidelines and recommendations regarding the treatment management. And clinicians should be familiar with and comfortable with that management plan. So what those consensus guidelines ask of clinicians is that for all treatment including multi-drug regimen, that monotherapy is a frighteningly bad idea.

The risk for acquisition of resistance is great, and there are no data showing utility in monotherapy circumstances of single drug for NTM infection. So for the nodular bronchiectasis MAC infected population, the ATS-IDSA guidelines and the more recent European guidelines argue that we should be using a three-drug regimen. That being a macrolide-- either Clarithromycin or Azithromycin-- plus Ethambutol plus a rifamycin, either Rifampin or Rifabutin.

For the mild disease population with nodular bronchiectasis, the recommendations state that three times weekly therapy would be appropriate. That would include Clarithromycin, or probably more likely Azithromycin is the predominant choice now at 500 milligrams thrice weekly. It can be downward adjusted for small people or intolerance. Plus Ethambutol at a three times weekly dose of 25 milligrams per kilo. Plus Rifampin typically 600 milligrams, three times weekly. Or alternative, Rifabutin 300 milligrams three times weekly.

There are still I think some uncertainties whether thrice weekly or daily should be the preferred choice, but in more active or a substantial disease, the guidelines argue for upscaling the antibiotics to daily, which would be still as Azithromycin-- which could be thrice weekly, or a lower dose daily-- or alternative Clarithromycin, plus Ethambutol at 12 to 15 milligrams a day, and Erythromycin, specifically or more commonly Rifampin, 600 milligrams daily.

The next consideration is whether you have a more severe disease circumstance. And that would either be the radiographic presence of severe bronchiectasis, and specifically directly cavitory disease. So for cavitory disease, the recommendations strongly state that one should really consider and probably add an IV agent. And Amikacin is the commonly and very strongly preferred agent because of its greater activity against these mycobacteria.

And so the regimen then would be in addition to the standard oral regimen that IV Amikacin would be added. There-- we can touch on this later-- but there are now data showing some utility of inhaled Amikacin, specialty a liposomal formulation Amikacin, though that was developed after these consensus documents were developed, so that the consensus guidelines don't really address that yet.

A hugely important underlying consideration for the decision making process around antibiotic administration is that the clinician should obtain drug susceptibility testing. And the two agents for which we have strong data showing that there is an outcome determination that accords to drug susceptibility testing are for macrolide antibiotics and for Amikacin. So while it's not perhaps commonplace for clinicians to consider this, they really should strongly undertake this aspect as well, which is to obtain on the recovered pathogen antibiotic susceptibility testing. And specifically for macrolides and for IV Amikacin.

That will be incredibly important to know because the presence of resistance to either those antibiotics associates with a much riskier treatment course and a poor prognosis regarding treatment management. So those are critically important things that need to be included as well.