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Editorial

What is new in BTS 2017 & ATS/ERS/ESCMID/IDSA 2020 guidelines on treatment of non-tuberculous mycobacterial pulmonary disease?

Non-tuberculous mycobacteria (NTM) are ubiquitous in the environment. Though there are over 190 NTM species and many more are being reported[1], but only a few NTM species are clinically important to produce pulmonary disease in susceptible individuals. These include *Mycobacterium avium* complex (MAC), *M. kansasii*, *M. xenopi*, *M. malmoense* and *M. genavense* among the slowly growing mycobacteria and *M. abscessus* (MAB) and its three subspecies (MAB subsp. *abscessus,* MAB subsp. *massiliense* and MAB subsp. *bolletii*) among the rapidly growing mycobacteria[2]. Because of a large number of species, the diagnosis, treatment and prevention of NTM are challenging.

In 2007 the landmark guidelines of the American Thoracic Society (ATS) for the first time comprehensively described diagnosis, treatment and prevention of both pulmonary and extrapulmonary NTM diseases[3]. Subsequently, two more guidelines, the British Thoracic Society (BTS) 2017[4] and the ATS/European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases/Infectious Diseases Society of America (ATS/ERS/ESCMID/IDSA) 2020[5], were published. Latter two guidelines specifically focus on NTM pulmonary disease (NTM-PD) in adults without HIV/AIDS and cystic fibrosis. Both the guidelines recommend clinical, microbiological and radiographic criteria described by the ATS (2007) guideline[3] for the diagnosis of NTM-PD.

Major changes in these recent guidelines[4,5] include emphasis on (*i*) isolation and identification of the same NTM species or subspecies (in MAC and MAB) in at least two sputum cultures from two sputum specimens submitted over an interval of at least a week; (*ii*) or one positive culture from the bronchoalveolar lavage (BAL) specimen (if the patient is unable to produce sputum); and/or (*iii*) in one or more sputum or bronchial washings specimens when a concurrently obtained transbronchial or other lung biopsy reveals suggestive histopathological features [granulomatous inflammation or acid-fast bacilli (AFB)]. Clinical criteria include the presence of pulmonary or systemic features, radiographic criteria include the presence of nodular or cavitary shadows on a chest radiograph or multiple small nodules with bronchiectasis on a high-resolution computed tomography (HRCT) of the chest and this must be combined with exclusion of other possible diagnoses[3-5].

While the culture of pulmonary samples is done on both solid and liquid media to increase sensitivity of culture for NTM by 15 per cent[6], Lowenstein–Jensen (LJ) medium was found to be most sensitive for NTM detection in some studies[5,7,8]. The Clinical and Laboratory Standards Institute (CLSI)[7] recommends the use of 7H10 and 7H11 solid media and incubation temperatures of 28±2°C and 36±1°C for rapid growers and slow growers, respectively; although higher temperature (42°C) might accelerate growth of *M. xenopi*, lower incubation temperatures have not been proven useful in the diagnosis of NTM-PD[7].

Correct identification of the NTM isolate is essential for predicting its clinical relevance[2,4,5] and planning an appropriate treatment regimen and this can be done by both molecular and mass spectrometry-based methods. Molecular identification of NTM species using either probes or gene sequencing is currently the method of choice[2]. Though probe-based assays are more convenient to use and easy to implement at the field level, these suffer from their limited discriminatory power[2,4,9]. Targeted gene sequencing method has greater discriminatory power than other molecular methods and includes several target genes such as 16S rRNA, *hsp*65, *rpo* B, and the 16S-23S

rRNA internal transcribed spacer (ITS) region[2-5]. While 16S rRNA gene alone has a limited discriminatory power, complementing it with additional target genes *hsp*65, *rpo* B, and the 16S-23S ITS can yield best results including differentiation up to subspecies level in MAC and MAB[2,4,5]. With great improvements in protein extraction protocols and databases, the matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) is supposed to offer better discriminatory power for NTM species and subspecies but it also cannot differentiate all genetically-related NTM species[2,4,5].

As compared to the previous guidelines[3], the recent guidelines[4,5] recommend performing baseline drug susceptibility testing (DST) and estimating minimum inhibitory concentrations (MICs) for drugs which demonstrate better correlations between *in vitro* activity and *in vivo* treatment outcome of the various NTM pulmonary diseases. Broth microdilution method of diluting antibiotics in serial two-fold dilutions indexed to base 2 (*e.g.*, 1, 2, 4, 8, 16 and 32 µg/ml) is currently recommended by the CLSI as the standard method for DST of clinically significant primary NTM isolates as well as relapse/failure isolates[7]. Current guidelines recommend baseline DST for MAC and MAB to macrolides and amikacin and DST to rifampicin and macrolides for *M. kansasii* [4,5]. Clarithromycin is recommended as the class agent to perform DST for macrolides as clarithromycin and azithromycin share cross-resistance and have similar microbial susceptibility patterns[4,5]. Point mutations (A2058G and A2059C) in the 23S rRNA (*rrl*)[5,10,11] gene result in acquired resistance to clarithromycin (defined as an MIC ≥32 µg/ml). Amikacin-acquired resistance is related to specific mutations (A1408G) in the 16S rRNA (*rrs*) gene and corresponds to a MIC ≥64 µg/ml for parenteral amikacin and ≥128 µg/ml for amikacin liposome inhalation suspension (ALIS)[5,7]. In MAB pulmonary disease, there is also a good correlation between *in vitro* activity and the *in vivo* treatment outcome for macrolides and amikacin[12]. Other parenteral drugs with *in vitro* activity include imipenem, cefoxitin and tigecycline (a glycylcycline derivative of minocycline that binds to the 30S ribosomal subunit of susceptible organism)[13] and oral drugs with some activity include oxazolidinones - an adenosine triphosphate synthase inhibitor (linezolid, tedizolid) and clofazimine, a riminophenazine antibiotic; the latter acts synergistically with macrolides and amikacin and prevents the emergence of amikacin-resistant MAB *in vitro*[14]. Strains of MAB subspecies *abscessus* and MAB subspecies *bolletii* have erythromycin-resistant methylase (*erm*) gene, *erm*(41) which is responsible for inducible resistance to macrolides and can be measured *in vitro* by prolonged (up to 14 days) incubation of microdilution (clarithromycin ≥8 µg/ml) or detection and characterization of the *erm*(41) gene by molecular method. MAB subspecies *massiliense* is susceptible to macrolide (MIC <4 µg/ml) due to the presence of nonfunctional *erm*(41) gene[4,5]. A nonfunctional *erm*(41) gene also occurs in MAB subspecies *abscessus* (C28 sequevar isolate) as a result of a C instead of a T at the nucleotide position 28 (Arg10 instead of Trp10)[5]. All of the three MAB subspecies can develop constitutive macrolide resistance owing to the 23S rRNA (*rrl*) gene mutations (A2058C, A2058G, A2058T, A2059C, A2059G and A2059T)[5,11].

For *M. kansasii*, the DST is done with rifampicin (MIC ≥2 µg/ml) and clarithromycin (MIC ≥32 µg/ml) although resistance to rifampicin is rare[7]. For *M. xenopi,* there is insufficient evidence to make a recommendation for or against susceptibility-based treatment[5].

Following isolation and identification of NTM species and subspecies, its clinical relevance should be carefully ascertained. Any patient meeting all diagnostic criteria does not automatically qualify for the treatment initiation. Recent guidelines strongly recommend a careful assessment of the patient's clinical status, radiological features and pathogenic potential of the isolated NTM species and subspecies after carefully ruling out environmental and laboratory contamination[4,5]. The decision to initiate treatment should be made carefully by considering the presence of comorbid conditions, severity of NTM-PD, the risk of progression and the goals of treatment[4,5]. Before starting the treatment, the following points should be discussed with the patient: the cost of the treatment, goals of treatment and its impact on the quality of life, potential benefits and risks of treatment, chances of developing non-compliance due to side effects, increased potential of progression of NTM-PD in advanced cavitary and severe nodular bronchiectasis, low cure rates for some NTM infections and an issue of recurrence and re-infection[4,5].

'Watchful waiting' with periodic clinical review, sputum cultures and imaging may sometimes be preferred to treatment in a few patients with non-severe or non-progressive lung disease and some patients

might achieve spontaneous sputum culture conversion (especially with younger age, higher body mass index and negative AFB at initial diagnosis) or in some patients with more chances of developing drug intolerance and side effects, and some NTM species (MAB) being less responsive to treatment[5]. This clinical decision should be made carefully preferably by a multispecialty team involving patient and requires follow up over time[5]. Nonetheless, the guidelines do suggest initiation of treatment instead of 'watchful waiting' in the context of positive AFB sputum smears, indicating high bacillary load, pathogenic species (*M. kansasii* and *M. xenopi*), cavitary lung disease and a rapid course of the disease impacting on the patient's quality of life and performance status[5].

The recent guidelines[5] recommend adjunctive surgery in addition to medical treatment in carefully selected patients having localized disease and adequate cardiopulmonary reserve and nutrition[2,4,5]. The thoracic surgeon should have good expertise in surgery of mycobacterial diseases[2,4,5]. Presence of NTM-PD *per se* is not a contraindication for lung transplantation. Before listing for lung transplantation, patients with NTM-PD should be able to tolerate optimal antibiotic therapy and should not have progressive disease[4].

About the treatment and drug dosages, there is a paucity of randomized clinical trials in NTM-PD[2]. Based on consensus expert opinion, patients are treated with a three-drug regimen consisting of macrolide, ethambutol and rifampicin/rifabutin on a daily basis in cavitary or severe bronchiectatic disease and parenteral amikacin is added as a fourth drug for the initial 2-3 months for MAC-PD. Patients with non-cavitary, non-severe nodular/bronchiectatic MAC-PD disease should be treated with a three-drug regimen administered intermittently (thrice weekly)[5].

Importance of macrolide in the drug regimen is illustrated by the fact that the success of sputum culture conversion rate falls from about 80 per cent[15] to only 5-36 per cent[16,17] in patients without a macrolide in the drug regimen in MAC-PD. A four-drug regimen with addition of parenteral intravenous amikacin or streptomycin (thrice weekly) for initial 2-3 months is administered in patients with severe or macrolide-resistant or refractory MAC pulmonary disease (persistence of sputum culture positivity six months after guideline-based treatment), ALIS is specifically proven useful for refractory MAC pulmonary disease. Treatment should be continued for at least 12 months beyond sputum culture conversion[5]. The guidelines emphasize on taking an expert consultation while treating macrolide-resistant or refractory MAC disease. MAC-related microbiologic recurrences occur after completion of therapy in 25-28 per cent of patients whereas new infections occur in 46-75 per cent of patients[15,18].

In patients with rifampicin-susceptible *M. kansasii* pulmonary disease, a three-drug regimen of rifampicin, ethambutol and either macrolide or isoniazid, is administered[4,5]. While isoniazid-containing regimen is used daily irrespective of the disease severity, macrolide-containing regimen can be used thrice weekly in non-severe disease[5]. Rifampicin resistance should be suspected if the respiratory specimen culture remains positive at the end of the fourth month[5,19]. In patients with rifampicin-resistant *M. kansasii* disease or patient intolerant to one of the first-line drugs, the guidelines recommend addition of a fluoroquinolone (moxifloxacin)[5]. The guidelines also suggest that rifampicin-susceptible *M. kansasii* pulmonary disease be treated for at least 12 months (including culture conversion period)[5].

As *M. xenopi* pulmonary disease is difficult to treat and is frequently associated with high all-cause mortality, an expert consultation should be obtained[2,4,5]. The guidelines recommend daily treatment with ≥3 drugs, consisting of rifampicin, ethambutol and either a macrolide and/or a fluoroquinolone (moxifloxacin) for the treatment of *M. xenopi* pulmonary disease[4,5]. Three times weekly parenteral amikacin should be added in patients with severe pulmonary disease. Treatment should be continued for ≥12 months after culture conversion[4,5].

Suggested antibiotics regimens for adults with MAB-pulmonary disease have been adequately described previously in the guidelines[4,5,9]. Expert consultation should be obtained while treating MAB[4,5]. Treatment for clarithromycin-sensitive MAB-pulmonary disease includes a combination of 1-2 intravenous drugs [amikacin (3 times weekly), imipenem (or cefoxitin) and tigecycline] and two oral drugs (azithromycin and clofazimine or linezolid) for ≥one month in the initial phase. In the continuation phase 2-3 drugs from azithromycin, clofazimine, linezolid and inhaled amikacin should be administered[4,5]. Inducible or constitutive macrolide resistant MAB-pulmonary disease should be treated with 2-3 intravenous drugs [consisting of amikacin (3 times wkly), imipenem (or cefoxitin) and tigecycline] and 2-3 oral drugs (azithromycin, clofazimine and linezolid) for ≥one

Table. Summary of current research into future treatments

Treatment	Examples	Use/advantages
Novel beta-lactamase inhibitor/lactam combinations	Avibactam-ceftazidime Relebactam-imipenem Vaborbactam-meropenem	Active against broad-spectrum beta-lactamase (BlaMab) of *M. abscessus* (against which traditional beta-lactamases are ineffective)
Dual-lactam combinations	Relebactam-imipenem + amoxicillin Imipenem + various beta-lactams Biapenem + avibactam	*M. abscessus*
Efflux pump inhibitors	Verapamil Plant-derived flavonoids NUNL02 (novel efflux inhibitor)	*M. abscessus*
Novel antibiotics	Tedizolid Omadacycline Thiostrepton	Alternatives to current *M. abscessus*/MAC treatments with fewer side effects and oral options
Disulfiram	-	Rapidly growing mycobacteria
Inhaled clofazimine suspension	-	Increased lung concentrations with improved MIC and tolerability
Bacteriophages	Engineered bacteriophages	*M. abscessus*

Reproduced with permission from reference 22. MAC, *M. avium* complex; MIC, minimum inhibitory concentration

month in the initial phase and followed by 2-3 drugs from azithromycin, clofazimine, linezolid and inhaled amikacin in the continuation phase depending on the DST report[4,5]. In the last two situations, macrolide is not counted as an active drug, but its addition may exert an immunomodulatory effect[4,5]. Intravenous amikacin during the initial phase and inhaled amikacin during the continuation phase may be substituted appropriately with an alternative intravenous/oral antibiotic when the DST reveals the presence of amikacin resistance. Sputum culture conversion [MAB (25-42%) *vs*. *M. massiliense* (82-96%)], failure to convert [MAB (17-55%) vs. *M. massiliense* (0-9%)] and relapse rates [MAB (27-74%) vs. *M. massiliense* (0-18%)] vary according to sub-species[2,4,20,21].

Clinical examination, radiographic and microbiologic investigations should be done periodically to monitor treatment response during the follow up. Sputum culture conversion should be done every 1-2 months. Hypertonic saline should be used to induce sputum if there is no sputum production. Adverse events and serious adverse events monitoring may be done as the treatment is long and patients tend to become less compliant with time. Therapeutic drug monitoring is not done routinely except in patients suspected to have malabsorption or drug–drug interaction[2,4,5].

Since there is a paucity of randomized clinical trials in NTM-PD, future efforts should be focussed on discovery of novel drugs and multicentre and multicountry collaborative research and randomized clinical trials for this disease. Some of the promising novel drugs are listed in the Table.

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