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BRIEF REPORT

Management of Drug Toxicity in *Mycobacterium avium* Complex Pulmonary Disease: An Expert Panel Survey

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Adverse events are frequent in nontuberculous mycobacteria pulmonary disease treatment, but evidence to support their management is scarce. An expert panel survey on management of adverse events shows consistent opinions on management of hepatoxicity, ocular toxicity, ototoxicity, tinnitus, and gastrointestinal upset. These opinions can provide assistance in individual patient management decisions.

Keywords. antibiotic treatment; nontuberculous mycobacteria; adverse events; *Mycobacterium avium* complex; azithromycin.

Treatment of *Mycobacterium avium* complex pulmonary disease (MAC-PD) requires prolonged courses of potentially toxic antimicrobials and has suboptimal outcomes, with culture conversion rates of 65% in patients treated for >1 year [1]. Across published cohorts, up to 70% of all treated patients reported a treatment-related adverse event (AE) [2–4] and 30%–70% of patients receiving daily antimicrobial treatment permanently discontinue at least 1 drug in their initial regimen because of AEs [2–4]. These regimen modifications may contribute to development of macrolide resistance [5] or suboptimal outcomes.

There are very limited published data to support management decisions even for the most frequent AEs in MAC-PD treatment, and management of drug toxicity is poorly addressed in current guidelines. To know the opinions of clinicians with expertise treating MAC-PD, we designed a survey on AE management in MAC-PD, using the SurveyMonkey online tool (http://www.surveymonkey.com). The survey presented common AEs in MAC-PD treatment (hepatotoxicity, ocular toxicity, gastrointestinal upset, tinnitus, and ototoxicity) and a choice of management strategies; the AEs were selected by a during a face-to-face meeting at the European Respiratory Society conference (Paris, September 2018). Experts were selected from the Nontuberculous Mycobacteria Network European Trials Group (NTM-NET) (www.ntm-net.org) membership on basis of publication records of cohort studies of MAC-PD management. We sought to include experts from geographically diverse settings to capture the full range of opinions and underlying cultural differences and drug availabilities.

Twenty-three experts were identified and invited; 21 completed the survey. A summary of the questions and answers is presented in Table 1. The full questions and answers of the survey are available in the Supplementary Data.

There was almost unanimous agreement that mild, rifampicin-associated, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations do not require action beyond ongoing surveillance; treatment interruption or a switch to a rifamycin-free regimen was preferred by most respondents only with severe hepatotoxicity (ALT and/or AST concentrations >5 times the upper limit of normal). Hepatotoxicity, which may manifest as AST/ALT elevations or cholestasis [6], occurred in 19% of MAC-PD patients in

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Table 1. Summary of Survey Questions and Responses

Question	Type	Disease Severity	Event	Culprit	Option	Vote, %
1	NB	Moderate-severe	AST/ALT 2 × ULN	Rifampicin	Repeat test	86
					Lower dose	0
					Thrice weekly	0
					Interrupt rifampicin	4
					Interrupt regimen	0
					Switch to rifabutin	0
					Switch to other class	10
2	NB	Moderate-severe	AST/ALT 5 × ULN	Rifampicin	Repeat test	0
					Lower dose	0
					Thrice weekly	5
					Interrupt rifampicin	20
					Interrupt regimen	40
					Switch to rifabutin	5
					Switch to other class	30
3	NB	Moderate-severe	Blurry vision	Ethambutol	Thrice weekly	0
					Lower dose	0
					Stop ethambutol	11
					Interrupt ethambutol	5
					Switch to other class	84
4	FC	Severe	Bloating/diarrhea	?	Rifampicin	0
					Ethambutol	0
					Azithromycin	100
					Amikacin	0
5	FC	Severe	Bloating/diarrhea	Azithromycin	Lower dose	21
					Switch to clarithromycin	47
					Switch to other class	5
					Supportive Rx	26
6	FC	Severe	Slight hearing loss	Amikacin	Lower dosing frequency	70
					Switch to ALIS	0
					Stop amikacin	25
					Switch to other class	5
					Continue IV amikacin	0
7	NB	Moderate	Tinnitus	Azithromycin	Lower dose	65
					Switch to clarithromycin	20
					Switch to other class	0
					Interrupt azithromycin	15
					Continue regimen	0
8	NB/FC	Mild-moderate	Needed class switch	Rifampicin	Clofazimine	4.40[a]
					Amikacin/streptomycin	4.21[a]
					Moxifloxacin/other FQ	2.30[a]
					Linezolid	2.15[a]
					Bedaquiline	2.10[a]
9	NB/FC	Mild-moderate	Needed class switch	Ethambutol	Clofazimine	4.30[a]
					Amikacin/streptomycin	4.05[a]
					Moxifloxacin/other FQ	2.25[a]
					Linezolid	2.25[a]
					Bedaquiline	2.16[a]

Abbreviations: ALIS, amikacin liposome inhalation suspension; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FC, fibrocavitary; FQ, fluoroquinolone antibiotic; IV, intravenous; NB, nodular-bronchiectatic; Rx, treatment; ULN, upper limit of normal.

[a]Mean preference score.

2 recent cohorts [4, 7]. This hepatotoxicity is mostly an idiosyncratic (ie, concentration/dose-independent) event, with spontaneous resolution and no recurrence after rifampicin reintroduction in >90% of MAC-PD patients [7], which mirrors previous experiences and recommendations in tuberculosis treatment [6].

Ocular toxicity by ethambutol was considered a reason to stop ethambutol or switch to another antibiotic class for 95% of the experts; 5% would interrupt and attempt a rechallenge. This aligns well with the available data. In 2 cohorts of MAC-PD treatment, ophthalmologist-confirmed ocular toxicity occurred in 26 of 364 (8%) and 8 of 229 (3%) patients on daily

ethambutol therapy (15 mg/kg/dose) [7, 8] and 0 of 90 patients on thrice-weekly dosing (25 mg/kg/dose) [8]. Yet, in the Griffith et al cohort, 99 of 229 patients (43%) had symptoms that warranted an ophthalmology consult and 24 (10%) stopped ethambutol at least temporarily [8]. The risk of ethambutol ocular toxicity increases with total drug exposure and thus it typically occurs late, that is, after >6 months, in therapy [7, 8]. Blurred vision and color vision disturbance are the most frequent manifestations, and these are mostly reversible after stopping ethambutol; 4 patients were rechallenged with ethambutol thrice weekly (25 mg/kg/dose) and none developed recurrent ocular toxicity [8]. Stopping ethambutol without adding a third drug to the regimen occurs frequently [3, 5, 7], but is a known risk factor for development of macrolide resistance [5] and should be avoided.

Azithromycin was uniformly considered most likely responsible for bloating and diarrhea. Its management differed in the panel, with switching to clarithromycin, continuing azithromycin with supportive treatment, and lowering the azithromycin dose as the most frequent strategies. These strategies evolve around maintaining macrolide therapy and highlight the key role of macrolides in MAC-PD treatment [1]. Lowering azithromycin dose or offering supportive treatments (eg, nighttime administration, anti-emetics) both proved successful in a previously published cohort [9]. Similarly, lowering the azithromycin dose or switching to clarithromycin were the preferred strategies for azithromycin treatment–emergent tinnitus (65% and 20% of votes). Tinnitus occurred in 18 and 46% of patients in 2 cohorts of high-dose (500–600 mg/day) azithromycin therapy for MAC-PD [4, 9]. One study reported good outcome of lowering azithromycin doses from 600 mg to 300 mg/day [9].

Lowering azithromycin doses may increase the risk of treatment failure in patients with severe or fibrocavitary disease in whom regular doses may already be subtherapeutic [10, 11]. A switch to clarithromycin can be successful, but it is unproven whether this is due to clarithromycin causing less bloating and diarrhea or being less ototoxic [4, 9] or due to lower macrolide exposure because of shorter half-life and greater reduction in serum clarithromycin (68%) than azithromycin (23%) concentrations caused by rifampicin-induced cytochrome P450 metabolism [10].

Ototoxicity with hearing loss is a notorious AE of parenteral aminoglycoside therapy and was observed in 42% (10/24) of patients treated with streptomycin and 27% (3/11) of patients treated with amikacin for macrolide-resistant MAC-PD [12]. Our panel preferred to lower the amikacin dosing frequency to thrice weekly or stop amikacin, as ototoxicity risk is associated with total aminoglycoside exposure. Switching to an alternative drug was not a common strategy, likely because no alternative drugs with proven efficacy in severe MAC-PD exist [5, 9, 12]. Because aminoglycoside antimicrobial activity is exposure dependent [10], lower dosing is likely to negatively impact microbiologic outcomes. Switching to amikacin liposome inhalation suspension (ALIS) or inhalation of conventional amikacin could be a rational strategy; in the CONVERT trial, only 10 of 223 (4.5%) patients receiving ALIS reported hearing loss vs 7 of 112 (6.3%) in the control arm [13]. However, the safety of switching to inhaled formulations of amikacin has not been investigated in the setting of proven amikacin ototoxicity.

The panel was also asked to rank 5 antimicrobials (amikacin, clofazimine, moxifloxacin, linezolid, and bedaquiline) as their preferred replacements for ethambutol and rifamycins; clofazimine and amikacin (or streptomycin) were preferred replacements for both the rifamycins and ethambutol. This selection is in part driven by local availability and patient preferences, particularly for clofazimine [4], but also reflects in vitro activity and in vivo treatment outcomes [4, 5, 9, 12]; the high ranking of the parenteral and toxic amikacin and streptomycin emphasizes the limited options available. The outcome of MAC-PD treatment with regimens in which amikacin replaces rifampicin or ethambutol or in which clofazimine replaces ethambutol has not been addressed in clinical studies.

This survey focused on MAC-PD treatment and only addressed a set number of AEs; several other important AEs (eg, vestibular toxicity, nephrotoxicity, and QTc interval prolongation) may arise during MAC-PD treatment [8, 10, 12]. Toxicities and outcomes are different in treatment of other nontuberculous mycobacterial (NTM) species (eg, *Mycobacterium abscessus*). Also, the members of the panel, while managing large numbers of NTM patients, are in frequent contact as members of numerous committees and projects. As a result, the topics addressed in the survey have likely been discussed previously between the experts, which may explain some of the level of agreement. This level of agreement contrasts with the very limited published data available to support these management decisions and a previous survey of other aspects of MAC-PD treatment where agreement among an expert panel was low [14].

In summary, this survey summarizes the opinions of MAC-PD experts on treatment-related AE management. Hepatoxicity of rifampicin was preferentially managed by watchful waiting or, if severe, interruption and reintroduction of normal doses. Azithromycin-associated diarrhea and tinnitus were preferentially managed by lowering the dose or switching to clarithromycin, with caveats. Ethambutol was discontinued in case of ocular toxicity; with careful monitoring, reintroduction using a thrice-weekly regimen might be safe in selected patients but our panel does not recommend this based on the low level of evidence and the potential associated risk. In the event of amikacin-induced hearing loss, the panel preferred lowering the dosing frequency or discontinuation. If rifampicin or ethambutol needs to be discontinued, clofazimine and amikacin were the favored replacements. These opinions

can provide assistance in clinical decision making, but should not be used as an alternative to expert consultation.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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