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MIC Distributions of Routinely Tested Antimicrobials and of Rifabutin, Eravacycline, Delafloxacin, Clofazimine, and Bedaquiline for *Mycobacterium fortuitum*

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Rapid-growing mycobacteria (RGM) are environmental organisms which may cause infections in patients with particular risk factors. While members of the *Mycobacterium abscessus* complex (MabsC) are the most commonly identified RGM from patient samples, *Mycobacterium fortuitum* is the second most commonly identified RGM in our setting in Singapore (1, 2). Although less common, the spectrum of clinical infections is similar (3). Treatment guidelines are not species specific, but it is generally recommended that combination antibiotics be used based on susceptibility testing results (4, 5). Due to the low incidence of infections caused by *M. fortuitum*, clinical evidence is limited, and clinical efficacy of individual antibiotics for treatment is unclear.

The majority of the *M. fortuitum* complex have also been reported to have inducible clarithromycin resistance due to the *erm*(39) gene (6), indicating the need for alternative antibiotics to treat these infections.

We previously described the antibiogram of MabsC isolates, with additional susceptibility testing performed to an extended panel of antimicrobials, including rifabutin, eravacycline, clofazimine, and bedaquiline (7). A review of the antibiogram of *M. fortuitum* isolates was performed to compare against *M. abscessus* complex. Laboratory records were retrospectively reviewed for MabsC and *M. fortuitum* isolated between 1 January 2017 and 31 December 2019. Identification was performed routinely with Bruker matrix-assisted laser desorption ionization (MALDI) Biotyper (Bruker, Billerica, MA, USA). Nonduplicate isolates with susceptibility testing results available were included.

Routine susceptibility testing in our laboratory was performed if the following microbiological criteria were met: there was more than one respiratory sample from a single patient growing *M. fortuitum* or if isolated from bronchoalveolar lavage samples. Testing was performed for all isolates cultured from nonpulmonary samples. Routine susceptibility testing was performed by using broth microdilution (RAPMYCO plates, Sensititre; Thermo Fisher Scientific, MA, USA) as per manufacturer instructions using the Sensititre AIM automated inoculation delivery system. The plates were incubated at 30°C and read after 3 to 5 days of incubation when sufficient growth was seen in the control wells. The plates were then reincubated for up to 14 days to identify inducible clarithromycin resistance. MIC readings for co-trimoxazole and linezolid were interpreted at 80% inhibition and at 100% inhibition for all other antimicrobials. The MIC results were interpreted according to CLSI breakpoints.

A customized plate, SGPNUHS1 (Sensititre; Thermo Fisher Scientific, Waltham, MA, USA), was used to test a subset of isolates (isolates between 1 January 2017 and 31 December 2019) against rifabutin, eravacycline, delafloxacin, clofazimine, and bedaquiline (7). *Mycobacterium peregrinum* ATCC 700686 was used as a quality control strain (8).

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TABLE 1 MIC distribution of antibiotics against *Mycobacterium fortuitum* and MIC_{50} and MIC_{90} of *M. fortuitum* and *M. abscessus* complex

	Data for *Mycobacterium fortuitum*[a]																					Data for *Mycobacterium abscessus* complex		
		No. of isolates with MIC (mg/liter) of:																						
Antibiotic	Total no. of isolates	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	% S	% I	% R	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Clarithromycin	86					0	0	0	0	0	0	0	12	18	56[b]				0.0	0.0	100.0	>16	>16	1	>16
Amikacin	86									59	23	2	2	0	0	0	0[b]		100.0	0.0	0.0	1	2	16	16
Tobramycin	86									0	0	0	1	59	26[b]				0.0	0.0	100.0	16	>16	16	>16
Cefoxitin	86											0	0	0	37	39	9	1[b]	0.0	88.4	11.6	64	128	64	64
Imipenem	86										5	21	43	13	1	3	0[b]		30.2	65.1	4.7	8	16	16	32
Doxycycline	86						4	8	15	0	0	0	2	0	57[b]				31.4	0.0	68.6	>16	>16	>16	>16
Linezolid	86									1	8	20	27	16	6	8[b]			65.1	18.6	16.3	8	32	16	>32
Co-trimoxazole	86							44	15	16	9	0	1	1[b]					97.7	NA	2.3	0.25	2	8	>8
Ciprofloxacin	86						57	19	8	2	0	0	0[b]						100.0	0.0	0.0	0.12	0.5	>4	>4
Moxifloxacin	86							67	15	4	0	0	0	0[b]					100.0	0.0	0.0	0.25	0.5	>8	>8
Delafloxacin	32		0	0	0	1	10	16	5	0	0	0	0	0[b]					NA	NA	NA	0.25	0.5	>8	>8
Eravacycline	32			24	8	0	0	0	0	0	0	0	0	0	0[b]				NA	NA	NA			0.12	0.25
Clofazimine	32	0	0	0	0	0	25	7	0	0	0	0	0[b]						NA	NA	NA	0.12	0.25	0.12	0.25
Bedaquiline	32	5	21	6	0	0	0	0	0	0	0	0	0[b]						NA	NA	NA	0.008	0.015	0.06	0.12
Rifabutin	32				0	0	0	0	0	0	2	13	16	1	0	0[b]			NA	NA	NA	8	8	16	32

[a]S, susceptible; I, intermediate; R, resistant; NA, not applicable. Blank spaces indicate drug concentrations outside the tested range.
[b]Isolates for which there was no inhibition detected, with an MIC was above the tested range.

A total of 86 *M. fortuitum* isolates were included. Extended susceptibility testing (rifabutin, eravacycline, delafloxacin, clofazimine, and bedaquiline) was performed for 32 isolates from 2019. The MIC distributions are summarized in Table 1. MIC_{50} and MIC_{90} values of *M. fortuitum* and MabsC are also presented in Table 1. The data of MabsC have been previously reported (7). A stark contrast in susceptibility between MabsC and *M. fortuitum* is seen for some of the routinely tested antibiotics.

A difference in susceptibility in clarithromycin was seen, which is consistent with previous data (6). All *M. fortuitum* isolates were resistant to clarithromycin compared to approximately 70% susceptibility seen for MabsC (7).

Differences were also seen in tetracyclines and quinolones. MabsC demonstrated high levels of resistance to doxycycline and quinolones akin to intrinsic resistance (7). Conversely, *M. fortuitum* had higher levels of susceptibility to both drugs, particularly ciprofloxacin.

The MIC distributions of *M. fortuitum* and MabsC overlapped closely for cefoxitin, imipenem, linezolid, and trimethoprim-sulfamethoxazole with a trend toward higher susceptibility rates in *M. fortuitum* (7).

All isolates were resistant to tobramycin. While the majority of isolates were susceptible to amikacin, the MICs against amikacin were lower for *M. fortuitum*.

In vitro activity of the additional drugs in the extended panel eravacycline, delafloxacin, rifabutin, clofazimine, and bedaquiline against *M. fortuitum* was demonstrated. Low MICs for delafloxacin indicate a class activity of quinolones against *M. fortuitum*. Despite higher rates of resistance to doxycycline, eravacycline had *in vitro* activity against both *M. fortuitum* and MabsC (7). The MIC_{50} and MIC_{90} of *M. fortuitum* were lower than MabsC for rifabutin, eravacycline, bedaquiline, and delafloxacin (Table 1) (7).

Our data suggest that there are more antibiotic treatment options available for *M. fortuitum* infection than MabsC. The antibiogram data presented may be used for selection of empirical therapy for patients, particularly those with severe disease or disseminated infection requiring early initiation of antimicrobials. Empiric therapy may also be started earlier due to the time required from culture to availability of susceptibility results. The addition of new antibiotics such as clofazimine, bedaquiline, and eravaycline may also be useful for empirical treatment of RGM in light of significant *in vitro* activity. The differences in *in vitro* activity between the two most commonly seen RGM are highlighted. Nonetheless, there are currently limited data on correlation between MIC results and outcomes for RGM, and further clinical data may better define suitable antibiotic regimens for these multidrug-resistant organisms.

Data availability. The data will be available on reasonable request.

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