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Drug susceptibility of non-tuberculous mycobacteria in East London:

A four year retrospective review

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Introduction

Non-tuberculous mycobacteria (NTM) can cause a variety of infections, particularly in immunocompromised patients. Barts Health NHS Trust (BHNT) in East London serves a population of more than 2.5 million people, providing tertiary haematology, oncology, cardiothoracic and transplant services. Identification and drug susceptibility testing (DST) of NTM from BHNT is performed by the Public Health England National Mycobacterial Service South (NMRS-S). In this retrospective study we reviewed the NTM resistance patterns from the BHNT population.

Methodology

NMRS-S carries out DST utilising broth microdilution to Clinical and Laboratory Standards Institute (CLSI) standards[1]. Isolates were reported as susceptible, intermediate or resistant depending on measured minimum inhibitory concentration (MIC) to the following agents:

- *M. avium/intracellulare* - clarithromycin
- *M. kansasii* - rifampicin, clarithromycin and ethambutol
- *M. abscessus* and *M. chelonae* - a panel of agents **(Table 1).**

All BHNT samples positive for NTM species between 01/01/11 and 31/07/15 were included in this study.

Table 1. CLSI breakpoints for NTM DST

	MIC by CLSI Criteria - µg/ml		
	Susceptible	Intermediate	Resistant
Amikacin	≤16	32	≥64
Ciprofloxacin	1	2	≥4
Clarithromycin	≤2	4	≥8
Co-trimoxazole	≤38	-	≥76
Doxycycline	≤1	2-4	≥8
Cefoxitin	≤16	32-64	≥128
Linezolid	≤8	16	≥32
Minocycline	≤1	2-4	≥8
Moxifloxacin	≤1	2	≥4
Tobramycin	≤2	4	≥8

Results

196 isolates underwent susceptibility testing – results for the major species were as follows:

M. avium/intracellulare (n = 80) – 1 *M. avium* isolate was resistant to clarithromycin with 1 *M. intracellulare* isolate intermediate; the remainder were susceptible (97.5%).

M. kansasii (n = 26) isolates were all susceptible to first line agents (100%).

M. abscessus (n = 62) susceptibility results are shown in **Figure 1.** Overall, drug resistance was more common than susceptibility, with resistance nearly universal to co-trimoxazole, doxycycline, minocycline, moxifloxacin and tobramycin. The majority of isolates were intermediate to amikacin and cefoxitin.

M. chelonae (n = 12) isolates showed variable drug susceptibility **(Figure 2).** Resistance was universal to co-trimoxazole, cefoxitin and moxifloxacin, with significant rates of resistance to linezolid, amikacin and ciprofloxacin. The majority of isolates were susceptible to clarithromycin.

Figure 1. M. abscessus drug susceptibilities

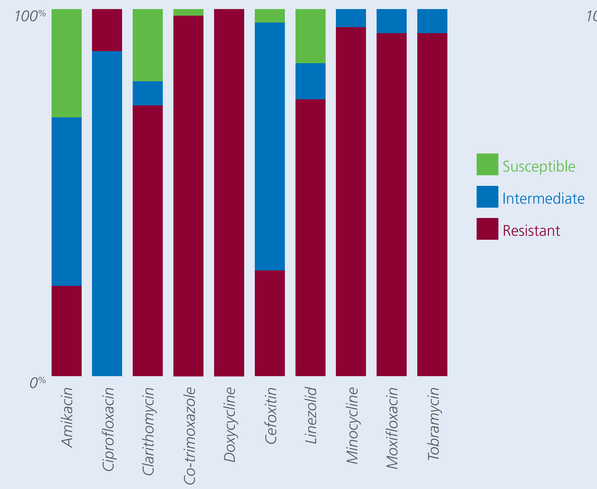
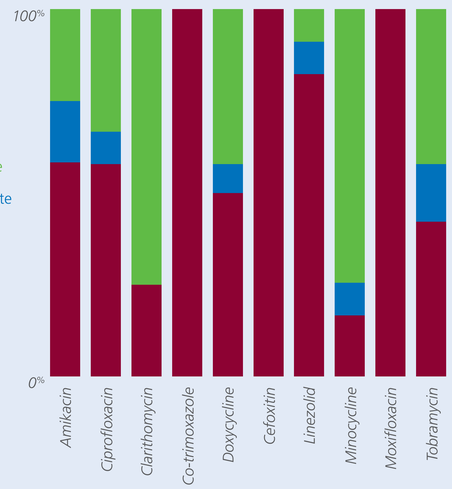


Figure 2. M. chelonae drug susceptibilities



Discussion

The NRMS-S performs DST by broth microdilution[2] on isolates meeting ATS criteria[3]. However, for some species, the impact of these results on clinical practice is not clear. There are limited data linking clinical outcomes to DST results for *M. abscessus*[4], in which inducible macrolide resistance is well recognised[5]; additionally, mycobacteria can have differing drug susceptibilities in their planktonic and biofilm forms[6].

In this study population, *M. avium, M. intracellulare* and *M. kansasii* isolates were susceptible to first line agents almost without exception. Routine DST may not be clinically necessary for these species – it might be reasonable to selectively test isolates from patients who fail to respond to first line therapy.

M. chelonae and *M. abscessus* isolates exhibited variable susceptibility profiles in this population. *In vitro*, *M. abscessus* isolates were nearly universally resistant to fluoroquinolones, tetracyclines, tobramycin and co-trimoxazole. The benefits of routinely testing against these agents therefore seem minimal in this population. For drugs with more variable susceptibility results, testing may yield benefits; however, data linking *in vitro* susceptibility testing with clinical outcomes are lacking.

Conclusions

Consideration should be given to limiting DST to isolates which fail to respond to first line therapy for *M. avium/intracellulare* and *M. kansasii*. For *M. abscessus* and *M. chelonae*, high *in vitro* resistance rates limit the utility of DST for agents such as fluoroquinolones. There may be value in performing DST for agents with more variable resistance patterns; however, there is a paucity of data linking DST data with clinical outcomes. Prospective clinical studies are required to further understanding in this area.

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3 - Griffith et al., An Official ATS/IDSA Statement: Diagnosis, Treatment and Prevention of Nontuberculous Mycobacterial Diseases, *American Journal of Respiratory and Critical Care Medicine* **2007**; 175:367-416
4 - Huang, Y. et al., Clinical Outcome of *Mycobacterium abscessus* Infection and Antimicrobial Susceptibility Testing, *Journal of Microbiology, Immunology and Infection* **2010**; 43: 401-406
5 - Stout, J., Koh, W. and Yew, W., Update on pulmonary disease due to non-tuberculous mycobacteria, *International Journal of Infectious Diseases* **2016**; 45: 123-134
6 - Greendyke, R. and Byrd, T., Differential Antibiotic Susceptibility of *Mycobacterium abscessus* Variants in Biofilms and Macrophages Compared to That of Planktonic Bacteria, *Antimicrobial Agents and Chemotherapy* **2008**; 52: 2019-2026