

***Mycobacterium abscessus* treatment: From empiricism to mechanism**

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Singapore has reached an inflection point in mycobacterial disease epidemiology, where nontuberculous mycobacterial (NTM) lung infections now nearly surpass tuberculosis (TB) in both incidence and prevalence.¹ Of the >180 known NTM subspecies, members of the *Mycobacterium abscessus* complex (MABC), comprising 3 phylogenetic subspecies—*abscessus*, *bolletii* and *massiliense*—are disproportionately represented in Singapore, accounting for an estimated 30% of incident NTM lung infections.^{1,2} The trend in “replacement” of TB with pulmonary NTM infection is reflected in other industrialised settings, where better control of TB and better NTM awareness and diagnostics have driven a relative decline in TB and a rise in NTM disease. At the same time, the predominance of MABC over *Mycobacterium avium* complex (MAC) in Singapore appears to reflect environmental and climatic determinants; unlike many temperate settings where MAC is dominant, our tropical climate favours MABC as the major pathogen.³ Together, these indicators suggest we will continue to encounter more MABC infections for the foreseeable future.

The clinical and public health implications for this transition are substantial.⁴ When appropriately treated, drug-susceptible TB is usually curable within a defined treatment course and is not typically characterised by long-term relapse. In contrast, NTM lung infections are often chronic, progressive and prone to relapse despite prolonged and toxic multidrug regimens. The result is cumulative morbidity, reduced quality of life and escalating healthcare utilisation. For MABC in particular, outcomes are frequently poor; refractory, relapsing infection can culminate in respiratory failure and death.⁵

One major driver of this gap is pharmacologic: we have spent decades optimising TB regimens for both drug-susceptible and even multi-drug-resistant TB. No equivalent therapeutic certainty exists for MABC. MABC is intrinsically resistant to most antibiotics⁴; current regimens are largely empiric,

assembled around drug susceptibility testing (DST) results.^{6,7} However, DST for MABC is technically challenging and slow. At present, macrolides are the only oral agents for which in vitro susceptibility consistently correlates with clinical response in MABC pulmonary disease. For most other agents, correlations between the minimum inhibitory concentration and outcomes remain weak or unvalidated.⁸

Two major genetic mechanisms govern macrolide resistance in MABC.⁴ Inducible macrolide resistance is mediated by *erm*(41) (a common resistance mechanism in *M. abscessus* subspecies *abscessus* and *bolletii*). This resistance may not be immediately apparent and can develop over the course of treatment. This is incompletely captured by conventional DST unless prolonged incubation is performed, and molecular testing of *erm*(41) is not yet routine locally. In contrast, *M. massiliense* lacks functional *erm*(41), so macrolides remain predictably active. However, high-level macrolide resistance via *rrl* mutations (in the 23S ribosomal RNA gene) can still be acquired during long-term macrolide therapy. Infections with macrolide-resistant MABC subspecies are especially difficult to control and are associated with persistently culture-positive disease, functional decline and excess mortality.

The systematic review by Lim et al. in this issue of the *Annals* highlights the lack of evidence-based combinations that improve clinically meaningful outcomes, the uncertainty around optimal treatment duration, and a lack of harmonised outcome measures.⁹ This therapeutic uncertainty raises a central question: can we realistically design robust, prospective clinical trials to identify antibiotic regimens that work in different MABC subspecies or genotypes, or is MABC lung disease fundamentally an “unwinnable” disease due to underlying host factors or the pathogen’s environmental ubiquity and high mutability? Singapore is engaged in new efforts to answer this. We are participating in the observational arm of the FORMaT trial, an international prospective study evaluating

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treatment strategies in MABC,¹⁰ and in the Singapore MALADY study (manuscript under preparation), a prospective observational study which tracks host responses and MABC genotypes across treatment and watchful waiting.

The authors further highlight the importance of assessing patient-centric outcomes beyond microbiological sputum conversion or radiological changes.⁹ Quality-of-life questionnaires that capture symptom burden and functional status have been endorsed by the US Food and Drug Administration as the primary endpoint for NTM-pulmonary disease drug trials. In addition, lung function testing can provide objective, complementary measures of clinical response. Preclinical animal models of MABC and TB pathology have demonstrated the central role of immunopathology in mycobacterial disease, highlighting opportunities to develop non-antibiotic, host-directed therapies. Developing strategies to reduce host tissue damage during infection and support post-infection functional recovery will be increasingly important as the burden of NTM lung disease continues to rise.

Singapore stands at the forefront of a shifting mycobacterial disease landscape, one that demands re-examination of diagnostic, therapeutic and research paradigms of disease caused by NTM. Moving forward, the field must pivot from empiricism to mechanism: integrating pathogen genomics, host immune profiling and prospective clinical data. Parallel development biomarker-guided strategies may enable more precise definitions of treatment success and development of personalised therapy. Singapore's confluence of high MABC prevalence, established microbiological infrastructure and translational research capacity positions it uniquely to keep pace with this transition.

Ethics statement

Not applicable as there are no study participants.

Declaration

The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

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