Antibiotics in tuberculosis treatment: Impacts on the respiratory microbiome and the role of optimal dosing

openaccessgovernment.org/article/antibiotics-in-tuberculosis-treatment-impacts-on-the-respiratory-microbiome-and-the-role-of-optimal-dosing/194632

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The respiratory microbiome plays a crucial role in maintaining immune regulation. In this article, Dr Wilber Sabiiti emphasizes the need for optimized antibiotic dosing strategies to minimize harmful effects on the microbiome and improve treatment outcomes for patients with TB

Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), is a leading infectious disease killer, requiring long-term multidrug antibiotic therapy. While these antibiotics are vital for disease eradication, they can disrupt the respiratory microbiome, a complex community of microbes that contribute to immune defence, inflammation regulation, and mucosal integrity. [1] Increasing evidence shows that disturbances to this microbiome can lead to secondary infections, altered immune responses, and poor recovery. Our study, evaluating seven anti-TB antibiotic regimens, showed a depressing effect on the microbiome early in treatment, characterised by a reduction in microbial abundance and diversity. A regimen containing moxifloxacin and 20mg/kg of rifampicin caused significant depression of the microbiome, followed by recovery to pretreatment levels within three months of treatment. In contrast, microbiome recovery was slow and did not reach pretreatment levels in a regimen containing 35mg/kg by the end of the three-month treatment follow-up. [2,3] This implies that an extra 15mg/kg of rifampicin had a more devastating impact on the microbiome. Therefore, understanding how anti-TB antibiotics affect the respiratory microbiome and how optimized dosing strategies can minimize harm is crucial for improving treatment outcomes and preserving a healthy host-microbiota balance.

The respiratory microbiome: A critical but fragile ecosystem

The human respiratory tract is colonized by diverse microbial populations, primarily bacteria, including members of the Streptococcus, Prevotella, Veillonella, and Haemophilus genera. [4] These commensals play essential roles in maintaining mucosal health and modulating immune responses. They inhibit pathogen colonization through competitive exclusion, produce antimicrobial compounds, and interact with host immune cells to maintain tolerance or stimulate defence mechanisms. [4] A quarter of the world's population lives with latent TB, raising the question of whether the microbiome plays a role in suppressing TB infection. Disruption of this balanced microbial community, known as dysbiosis, can have far-reaching consequences. In respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and pneumonia, dysbiosis is both a symptom and a contributor to disease progression. [5] In the context of TB, anti-tuberculosis therapy (ATT) can severely disrupt this ecosystem.

Standard TB treatment involves a prolonged regimen, typically six months and/or longer for drug susceptible and drug-resistant TB, respectively. [6] While these drugs are targeted against Mtb, they can have broad-spectrum effects, especially rifampicin and moxifloxacin, which affect both Gram-positive and Gram-negative bacteria. [3] Wipperman et al. found that patients undergoing ATT showed significant reductions in microbial diversity, with commensal taxa being depleted and opportunistic pathogens, such as Pseudomonas and Staphylococcus, becoming more prevalent. [7] This reduced diversity weakens colonization resistance and may promote inflammation, airway damage, or secondary infections. Additionally, certain anti-TB drugs reach the upper respiratory tract via the bloodstream or mucosal excretion, directly exposing microbiota to sub-inhibitory concentrations of antibiotics. This exposure can select for resistant organisms and shift microbial communities toward dysbiotic states. [1] These microbiome alterations can persist long after therapy, causing long-term damage to individual health post-TB treatment.

There are several consequences of respiratory dysbiosis. First, dysbiosis may impair mucosal immunity, making patients more susceptible to viral and bacterial co-infections. [8] This is especially dangerous in high-TB-burden regions where HIV and influenza co-circulate. Second, the loss of beneficial microbes can exacerbate inflammation, impair tissue repair, and delay recovery. [8] Furthermore, the respiratory microbiome may influence host responses to Mtb itself. Some commensals modulate alveolar macrophage activity and cytokine production. [9] Disruption of these signals may weaken the immune system's ability to contain TB infection. Conversely, microbial products from a healthy microbiome may enhance vaccine responses or drug efficacy, a synergy that dysbiosis undermines. [10-12]

The role of optimal antibiotic dosing

Given these risks, optimizing antibiotic dosing becomes a critical strategy to mitigate microbiome damage while ensuring therapeutic success. The key is to achieve pharmacokinetic and pharmacodynamic (PK/PD) targets that eradicate Mtb without unnecessarily prolonging or intensifying microbial disruption.

Precision dosing and therapeutic drug monitoring (TDM): Variability in drug absorption, metabolism, and clearance means that standardized doses may lead to suboptimal drug exposure in some patients and excessive exposure in others. TDM can tailor dosages to individual needs, avoiding unnecessarily high concentrations that exacerbate microbiome damage. [13-15]

Shorter regimens: Recent studies have demonstrated that four-month regimens using drugs like moxifloxacin or rifapentine can be as effective as six-month courses in certain patients. [16] Shorter duration reduces the cumulative antibiotic pressure on the microbiome, limiting long-term dysbiosis. However, this needs to be further investigated because shorter regimens contain high doses of broad-spectrum antibiotics.

Narrow-spectrum targeting: Although current TB regimens require broad-acting agents, future research may enable the development of narrower-spectrum therapies or host-directed therapies that limit collateral damage to non-target microbes. Targeted drug delivery (e.g., inhaled formulations) may also reduce systemic exposure and protect microbiota outside the lungs.

Adjunctive probiotics or microbiome support: Administering probiotics or prebiotics during ATT could help maintain or restore microbial balance. While evidence in TB-specific settings is limited, this approach has shown promise in other antibiotic-associated dysbiosis cases. [17] More research is needed to identify suitable strains and assess interactions with TB drugs. It is important to note that in our study, we observed a quantitative microbiome recovery without administering probiotics. However, the quality of such recovery needs further investigation. [3] Targeted anti-TB phage therapy may be another avenue to explore regarding TB elimination while preserving a healthy microbiome.

Balancing eradication and preservation

Successful TB treatment while preserving the respiratory microbiome is a complex challenge. On one hand, incomplete or suboptimal treatment can lead to drug resistance and relapse. On the other hand, overly aggressive or prolonged regimens can cause lasting harm to the host microbiota. Optimal antibiotic dosing serves as a bridge between these competing demands. A more nuanced approach that recognizes the respiratory microbiome as a key player in recovery can help reshape TB therapy. This involves not just refining drug dosages, but also considering the timing, route, and microbial consequences of treatment. As more evidence becomes available about the microbiome's role in health and disease, this balance will become increasingly central to precision medicine in TB care. This also calls for a paradigm shift in antibiotic drug trials to consider the microbiome as one of the parameters to assess drug safety.

1. Naidoo, C. C. et al. The microbiome and tuberculosis: state of the art, potential applications, and defining the clinical research agenda. The Lancet Respiratory Medicine vol. 7 892–906 Preprint at https://doi.org/10.1016/S2213-2600(18)30501-0 (2019).
2. Sabiiti, W. Battling Tuberculosis whilst Maintaining the Respiratory Microbiome. Scientia (2025) doi:https://doi.org10.33548/SCIENTIA1181.
3. Musisi, E. et al. Effect of seven anti-tuberculosis treatment regimens on sputum microbiome: a retrospective analysis of the HIGHRIF study 2 and PanACEA MAMS-TB clinical trials. Lancet Microbe 4, e913 e922 (2023).
4. Man, W. H., De Steenhuijsen Piters, W. A. A. & Bogaert, D. The microbiota of the respiratory tract: Gatekeeper to respiratory health. Nature Reviews Microbiology vol. 15 259–270 Preprint at https://doi.org/10.1038/nrmicro.2017.14 (2017).
5. Dickson, R. P., Erb-Downward, J. R. & Huffnagle, G. B. Towards an ecology of the lung: New conceptual models of pulmonary microbiology and pneumonia pathogenesis. The Lancet Respiratory Medicine vol. 2 238–246 Preprint at https://doi.org/10.1016/S2213-2600(14)70028-1 (2014).

6. World Health Organization. Global Tuberculosis Report 2023. https://iris.who.int/bitstream/handle/10665/373828/9789240083851-eng.pdf?sequence=1 (2023).
7. Wipperman, M. F. et al. Antibiotic treatment for Tuberculosis induces a profound dysbiosis of the microbiome that persists long after therapy is completed. Sci Rep 7, (2017).
8. Segal, L. N. et al. Enrichment of the lung microbiome with oral taxa is associated with lung inflammation of a Th17 phenotype. Nat Microbiol 1, (2016).
9. Chen, Z., Liu, Y. & Huang, W. Alveolar macrophage modulation via the gut–lung axis in lung diseases. Frontiers in Immunology vol. 14 Preprint at https://doi.org/10.3389/fimmu.2023.1279677 (2023).
10. Hong, S. H. Influence of Microbiota on Vaccine Effectiveness: “Is the Microbiota the Key to Vaccine-induced Responses?” Journal of Microbiology vol. 61 483–494 Preprint at https://doi.org/10.1007/s12275-023-00044-6 (2023).
11. Weersma, R. K., Zhernakova, A. & Fu, J. Interaction between drugs and the gut microbiome. Gut vol. 69 1510–1519 Preprint at https://doi.org/10.1136/gutjnl-2019-320204 (2020).
12. Zhao, Q., Chen, Y., Huang, W., Zhou, H. & Zhang, W. Drug-microbiota interactions: an emerging priority for precision medicine. Signal Transduction and Targeted Therapy vol. 8 Preprint at https://doi.org/10.1038/s41392-023-01619-w (2023).
13. Alffenaar, J. W. C., Tiberi, S., Verbeeck, R. K., Heysell, S. K. & Grobusch, M. P. Therapeutic drug monitoring in tuberculosis: practical application for physicians. Clinical Infectious Diseases, vol. 64, 104–105. Preprint at https://doi.org/10.1093/cid/ciw677 (2017).
14. de la Cuesta-Zuluaga, J., Müller, P. & Maier, L. Balancing act: counteracting adverse drug effects on the microbiome. Trends in Microbiology Preprint at https://doi.org/10.1016/j.tim.2024.09.011 (2024).
15. Brasier, N. et al. A three-level model for therapeutic drug monitoring of antimicrobials at the site of infection. The Lancet Infectious Diseases vol. 23 e445–e453 Preprint at https://doi.org/10.1016/S1473-3099(23)00215-3 (2023).
16. Dorman, S. E. et al. Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis. New England Journal of Medicine 384, 1705–1718 (2021).
17. McFarland, L. V. From yaks to yogurt: The history, development, and current use of probiotics. Clinical Infectious Diseases 60, S85–S90 (2015).

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