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Title: Characterization of the Effect of Biofilm Formation on the Antimicrobial Activity of Tigecycline against Mycobacterium abscessus using a Hollow Fiber Infection Model and Pharmacokinetic/Pharmacodynamic Modeling.

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Objectives: *Mycobacterium abscessus* (Mab) infections have been associated with high fatality rates in cystic fibrosis patients, due to its inherent drug-resistance mechanisms and biofilm (BF) formation attenuating drug sensitivity. Therefore, it is crucial to characterize the impact of drug resistance and BF formation on the pharmacological profile of antibiotics to improve therapeutic outcomes.

Methods: Dynamic time-kill assays were conducted using HFIM under the diverse exposure scenarios mimicking in vivo lung distribution obtained after intrapulmonary aerosol (IPA) administration of TGC in mice. MIC value to non-drug-exposed Mab was incorporated into a PK/PD model to describe potency against less susceptible species. To assess BF formation and its effect on TGC permeability, Transwell™-based system was utilized. Based on the data, a mathematical model was developed to reflect TGC's effect on bacterial growth and transition to less susceptible populations. The model was utilized to simulate the lowest effective dosing regimen, followed by a global sensitivity analysis to assess the importance of model parameters.

Results: High exposure to TGC effectively eradicated Mab, but the pattern and time course of bacterial resistance development depended on the dosage regimen when exposure was insufficient for complete bacterial killing. The PK/PD model based on the *in vitro* dynamic time-kill assay captured multiple factors influencing antibacterial activity of TGC. Model-based simulations suggested 3,300 μg would be required to eradicate Mab in HFIM without regrowth, which is comparable to 55 mg/kg TGC once daily by IPA *in vivo* in mice. GSA highlighted that factors associated with BF were critical determinants of bacterial burden following TGC treatment.

Conclusions: A quantitative assessment of the impact of factors modulating the pathophysiological properties of Mab is expected to enhance our understanding of how Mab undermines antibacterial killing as well as TGC concentrations required to eliminate Mab from the infection site, contributing to the development of more efficacious treatment strategies.

References: