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PHARMACOLOGY

Amikacin Combined with Fosfomycin for Treatment of Neonatal Sepsis in the Setting of Highly Prevalent Antimicrobial Resistance

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ABSTRACT Antimicrobial resistance (particularly through extended-spectrum β-lactamase and aminoglycoside-modifying enzyme production) in neonatal sepsis is a global problem, particularly in low- and middle-income countries, with significant mortality rates. High rates of resistance are reported for the current WHO-recommended first-line antibiotic regimen for neonatal sepsis, i.e., ampicillin and gentamicin. We assessed the utility of fosfomycin and amikacin as a potential alternative regimen to be used in settings of increasingly prevalent antimicrobial resistance. The combination was studied in a 16-arm dose-ranged hollow-fiber infection model (HFIM) experiment. The combination of amikacin and fosfomycin enhanced bactericidal activity and prevented the emergence of resistance, compared to monotherapy with either antibiotic. Modeling of the experimental quantitative outputs and data from checkerboard assays indicated synergy. We further assessed the combination regimen at clinically relevant doses in the HFIM with nine *Enterobacterales* strains with high fosfomycin and amikacin MICs and demonstrated successful kill to sterilization for 6/9 strains. From these data, we propose a novel combination breakpoint threshold for microbiological success for this antimicrobial combination against *Enterobacterales* strains, i.e., $MIC_F \times MIC_A < 256$ (where MIC_F and MIC_A are the fosfomycin and amikacin MICs, respectively). Monte Carlo simulations predict that a standard fosfomycin-amikacin neonatal regimen would achieve >99% probability of pharmacodynamic success for strains with MICs below this threshold. We conclude that the combination of fosfomycin with amikacin is a viable regimen for the empirical treatment of neonatal sepsis and is suitable for further clinical assessment in a randomized controlled trial.

KEYWORDS amikacin, combination antibiotics, fosfomycin, hollow fiber, mathematical modelling, neonatal sepsis, synergy, aminoglycosides, antimicrobial resistance, pharmacodynamics

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