A PK/PD modelling workflow for evaluating empirical antibiotic combination therapies: application to neonatal sepsis in the BARNARDS study

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Introduction

Empirical antibiotic combination therapy is a cornerstone of sepsis treatment. There is an urgent need to optimise empirical treatment of neonatal sepsis in low- and middle-income countries (LMICs) due to high rates of antimicrobial resistance (AMR) and treatment failures. This study presents a pharmacokinetic/pharmacodynamic (PK/PD) modelling workflow to assess empirical antibiotic combinations, applied to data from the BARNARDS study, which evaluated the use and efficacy of empirical therapies for neonatal sepsis in LMICs.

Methods

Data from 290 neonates across six countries in sub-Saharan Africa and South Asia were included. Each neonate was treated with one of four antibiotic combinations: ampicillin–gentamicin, amoxicillin clavulanate–amikacin, ceftazidime–amikacin, or piperacillin–tazobactam–amikacin. For each neonate, 1000 PK profiles were simulated using published neonatal population PK models, incorporating patient characteristics and site-specific dosing schedules. PK/PD target attainment, defined as achieving at least one PK/PD target in a combination, was determined considering the minimum inhibitory concentration (MIC) of the infecting pathogen. The percentage of target attainment (PTA) was calculated for each patient, and the proportion of patients achieving PTA >80% was compared to observed survival rates for each combination.

Results

The workflow integrates patient characteristics, pathogen susceptibility and PK/PD data to evaluate empirical antibiotic treatments. It can inform empirical treatment selection tailored to specific regions based on local AMR patterns, dosing regimens, and antibiotic availability and costs. In this analysis, PTA >80% was achieved in 34% of neonates treated with ampicillin-gentamicin, 68% with amoxicillin clavulanate–amikacin, 93% with ceftazidime–amikacin, and 85% with piperacillin–tazobactam–amikacin. PTA results generally aligned with survival rates, demonstrating the potential of this approach to predict the efficacy of currently used and alternative empirical treatments.

Conclusions

We developed a PK/PD modelling workflow to evaluate empirical antibiotic therapies for neonatal sepsis in LMICs, aiming to inform treatment guidelines and mitigate the impact of AMR on treatment outcomes. A follow-up trial is currently underway, with plans to incorporate dried blood spot sampling. These data will provide insights into the PK of key antibiotics in neonates from LMICs, how PK relates to outcomes, and guide the design of optimal dosing regimens.