Recommended Approaches for Integration of Population Pharmacokinetic Modelling with Precision Antibiotic Dosing in Clinical Practice

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Background: Imprecise, 'one-size-fits-all' antibiotic dosing can cause severe side effects (e.g. nephrotoxicity), when overdosed, and increased AMR incidence, when underdosed. Model-Informed Precision Dosing (MIPD), supported by population pharmacokinetic (popPK) models, aims to personalise therapy by accounting for interpatient variability and drug-specific pharmacokinetic properties. Despite its potential, MIPD and PK-informed precision dosing remain underutilised in clinical practice due to challenges in model development, validation, and clinical workflow integration.

Aims: Provide recommendations for integrating popPK models into MIPD software to optimise therapeutic outcomes, specifically addressing implementation barriers and providing a framework for incorporating MIPD tools into healthcare systems, to facilitate antimicrobial dose individualisation as standard-of-care.

Methods: The literature review focussed on best practices for popPK model development and validation. Guidelines from regulatory and advisory bodies were assessed to ensure model quality and robustness when incorporated into MIPD software. Technical requirements for integrating MIPD tools into clinical workflows and electronic health records (EHR) were explored.

Results: We identified steps for developing and integrating popPK models into MIPD software, and provided best practice recommendations for each stage:

- Data considerations: regulatory compliance, reproducibility, and accuracy requires standardised data collection, formatting, exploration, and cleaning.
- Model building: summarised the process of planning, software selection, and developing nonlinear mixed-effects models, along with validation techniques.
- Adaptation of literature models: provided guidelines for sourcing, transcribing, verifying, and evaluating published models to ensure their fit for clinical application.
- Healthcare applications: discussed strategies for model selection, a priori and a posteriori predictions, uncertainty quantification, treatment regimen optimisation, and continuous integration of patient data.
- Software integration: emphasised the need for EHR interoperability, regulatory standard adherence, and quality control measures for clinical deployment.

Conclusion: This review considers popPK model integration into precision dosing software, with recommended approaches consolidated into standardised guidelines covering the workflow from data handling to clinical application. Enhancing EHR interoperability and stakeholder communication are crucial for MIPD tool adoption. By establishing best practices and implementation pathways, we can leverage the clinical utility of MIPD for antimicrobial dose optimisation and enhance patient care.

Figure: Recommended steps for pharmacokinetic model development. Adapted from Byon et al.