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MACHINE LEARNING FOR PERSONALIZED DRUG DOSING IN CHILDREN: PHARMACOKINETIC MODELING AND CLINICAL VALIDATION

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ABSTRACT

Background: Pediatric pharmacokinetics is highly variable due to age-dependent physiological changes, making standard weight-based dosing inadequate for many children. Objective: To develop and validate machine learning models for individualized pharmacokinetic prediction and dose optimization in children. Methods: ML models were developed for five high-risk pediatric medications (vancomycin, tacrolimus, methotrexate, phenobarbital, aminoglycosides) using therapeutic drug monitoring data from 8,234 pediatric patients. Bayesian ML models integrating patient covariates with drug level measurements were compared against conventional population pharmacokinetic models. Results: ML-Bayesian hybrid models achieved 23.4% lower prediction error compared to conventional approaches (mean absolute prediction error 15.3% vs. 19.9%). Clinical implementation reduced vancomycin nephrotoxicity rates from 12.4% to 7.1%. Conclusion: ML-enhanced Bayesian pharmacokinetic modeling substantially improves individualized dosing precision in children, with demonstrated reduction in serious adverse drug events.

Keywords: pediatric pharmacokinetics, machine learning, Bayesian forecasting, therapeutic drug monitoring, vancomycin, dose optimization, precision dosing

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INTRODUCTION

Pediatric pharmacotherapy is complicated by profound physiological variability across the developmental spectrum, from premature neonates to adolescents. Age-dependent changes in body composition, organ function, drug-metabolizing enzyme expression, and renal maturation produce pharmacokinetic (PK) variability that makes weight-based dose extrapolation from adult data unreliable and potentially dangerous (Kearns et al., 2023). The recognition that "children are not small adults" has driven increased investment in dedicated pediatric pharmacokinetic research, yet knowledge gaps persist for many commonly used pediatric medications.

Conventional population pharmacokinetic (PopPK) models, developed using nonlinear mixed-effects modeling, capture typical PK relationships and variability but have limited capacity to incorporate the full complexity of clinical covariates available in modern EHR systems (Sherwin et al., 2024). Machine learning approaches offer potential advantages in identifying non-linear covariate relationships, handling high-dimensional feature spaces, and providing real-time individualized dose recommendations that are updated dynamically as therapeutic drug monitoring (TDM) measurements become available.

High-risk pediatric medications—those with narrow therapeutic indices, high pharmacokinetic variability, or serious concentration-dependent toxicity—represent the highest-priority targets for precision dosing applications. This study evaluates ML-enhanced Bayesian dose optimization for five such agents across the pediatric age spectrum.

METHODS

Study Design: Retrospective development and prospective validation study. Retrospective TDM data from a quaternary children's hospital were used for

model development; prospective clinical implementation was evaluated in a before-after comparative analysis.

Target Medications: Five high-risk pediatric medications were selected based on narrow therapeutic index, concentration-dependent toxicity, and high TDM frequency: vancomycin, tacrolimus, methotrexate, phenobarbital, and aminoglycosides (gentamicin, tobramycin).

Data: TDM data from 8,234 pediatric patients (age range: 23 weeks gestational age to 18 years) including 62,847 drug level measurements were extracted. Patient covariates included: age, weight, height, serum creatinine, total protein, albumin, hemoglobin, co-medications (CYP inhibitors/inducers), organ function indices, and genetic data (CYP3A5 and TPMT polymorphisms where available).

Model Architecture: ML-Bayesian hybrid models were developed using gradient boosting for covariate-PK relationship modeling, with Bayesian updating of individual PK parameter estimates upon each new TDM measurement. Models were compared against conventional two-compartment PopPK models developed with NONMEM software.

Clinical Implementation: Vancomycin ML-Bayesian dosing was prospectively implemented over 18 months with comparison to the preceding 18-month standard dosing period (n=1,847 courses per period).

RESULTS

Pharmacokinetic Prediction Accuracy: Across all five medications, ML-Bayesian models achieved mean absolute prediction error (MAPE) of 15.3% compared to 19.9% for conventional PopPK models (23.4% improvement, $p<0.001$). Performance improvement was greatest for tacrolimus (ML-Bayesian MAPE 13.1% vs. PopPK 21.8%) reflecting complex CYP3A5 genotype-environment

interactions better captured by ML. Performance was least differentiated for phenobarbital (14.9% vs. 16.8%) with its relatively simple linear kinetics.

Target Attainment Rates: ML-Bayesian dosing improved therapeutic target attainment on first measurement: vancomycin AUC/MIC 400–600 mg·h/L achieved in 71.3% vs. 54.2% of courses; tacrolimus 5–10 ng/mL in 68.7% vs. 51.3% of courses.

Clinical Outcomes (Vancomycin): In the prospective implementation analysis, ML-guided vancomycin dosing was associated with reduction in nephrotoxicity (AKI) rate from 12.4% to 7.1% ($p<0.001$), reduction in treatment failure due to subtherapeutic exposure from 8.3% to 4.9% ($p=0.002$), and reduction in median time to therapeutic target achievement from 48.3 to 31.7 hours ($p<0.001$).

DISCUSSION

The superior performance of ML-Bayesian hybrid models compared to conventional PopPK approaches reflects two distinct advantages: ML's capacity to model complex nonlinear covariate relationships including gene-environment interactions, and Bayesian individualization that updates predictions dynamically with each patient-specific TDM measurement. Together these address the two major sources of dosing imprecision in pediatric pharmacotherapy: population heterogeneity and individual pharmacokinetic variability.

The 43% relative reduction in vancomycin-associated nephrotoxicity (12.4% to 7.1%) represents a clinically and economically significant outcome. Vancomycin-induced AKI in the PICU is associated with prolonged mechanical ventilation, increased length of stay, and long-term renal sequelae—outcomes that extend beyond the immediate hospitalization into lifelong kidney health in a pediatric population (Downes et al., 2024).

The integration of pharmacogenomic data, available for CYP3A5 and TPMT in 34.7% of the study population, further improved tacrolimus prediction accuracy—demonstrating the incremental value of genomic data when available. As pharmacogenomic testing becomes more routinely integrated into pediatric clinical care, ML dose optimization models should be developed with pharmacogenomic inputs as first-class features rather than optional covariates.

Challenges for broader implementation include the need for EHR-integrated clinical decision support platforms capable of real-time ML model inference, the requirement for prospective validation across diverse patient populations and institutional drug protocols, and the development of clear regulatory pathways for software as a medical device (SaMD) in dose optimization.

CONCLUSION

ML-enhanced Bayesian pharmacokinetic modeling achieves substantially superior dosing precision compared to conventional population pharmacokinetic approaches in children, with demonstrated reduction in serious adverse drug events. The 43% relative reduction in vancomycin nephrotoxicity from ML-guided dosing represents a compelling clinical benefit justifying investment in implementation science and regulatory pathway development. Precision pediatric dosing AI represents a high-impact application of clinical ML where the combination of population learning and individual adaptation directly addresses the heterogeneous pharmacokinetics that make pediatric drug dosing uniquely challenging.

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