1543. Ceftaroline Model-based Dose Individualization in an Infant with Kidney Disease and Mediastinitis

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Background. Options for the treatment of infections caused by resistant gram-positive bacteria are limited in children with kidney disease. Ceftaroline (CFD) may be an attractive option but dosing recommendations are not available for children with renal dysfunction. We present a case of pharmacokinetics (PK) model-based individualization of CFD in an infant with kidney disease and mediastinitis. A 5-week-old infant with a hypoplastic left side of the heart developed mediastinitis following a Norwood and BT shunt. Blood and chest washout cultures grew *S. epidermidis*. Vancomycin therapy led to acute kidney injury (AKI) (eGFR ~15mL/minute) and therefore, CFD was initiated at 8 mg/kg every 12 hours. The model-based clinical service was consulted to assist with dosing.

Methods. Plasma levels were drawn on day 2 and 10 of CFD. CFD concentrations were determined by HPLC. The pharmacodynamic (PD) target used the MIC of the isolate, 1 μg/mL, and assumed drug diffusion into the mediastinum at 20% of plasma. The PD target was fT>MIC at 100%. Individual PK parameters were estimated using Bayesian estimation with MWPharm++ (Mediware, the Netherlands).

Results. CFD dosing of 8 mg/kg every 12 hours resulted in concentrations well above the target. The trough level was 10 times higher than levels seen in clinical trials. Repeat levels were checked on day 10 due to improved renal function (eGFR 30 mL/minute) and changes in volume status. Changes in both clearance and volume were noted. fT>MIC was maintained 100% during dosing intervals. We dose optimized CFD to achieve the target while minimizing potential toxicity with long-term use. A new dosing regimen, 5.4 mg/kg every 8 hours, was started on day 12 and continued for 6 weeks.

Conclusion. This is the first case report of CFD use in a child with AKI. Though initial dosing resulted in high concentrations, no adverse effects were noted. Successful treatment was completed with a final dosing regimen of 5.3 mg/kg every 8 hours, below the recommended 8 mg/kg every 8 hours. Lower dosing was needed to decrease high drug exposure due to the decreased clearance. This case also demonstrated the feasibility of PK model-based precision dosing within 48 hours, and documented utility in the setting of changes in renal function. Further PK/PD studies are needed in children with renal dysfunction.

Disclosures. **All authors:** No reported disclosures.

1544. Efficacy of Human-Simulated Cefiderocol Exposure Against Gram-Negative Bacteria in an Iron-Overloaded Murine Thigh Infection Model

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Background. Cefiderocol (CFDC) is a siderophore-cephalosporin conjugate which exploits bacterial iron scavenging in reaction to the hypoferremic response of host immunity and achieves potent *in vivo* activity against various Gram-negative bacteria (GNB). In patients with hereditary or iatrogenic hemochromatosis, the hypoferremic response may be altered by iron overload, which could hypothetically suppress the bacterial iron scavenging that bolsters CFDC efficacy. We compared CFDC efficacy between iron-overloaded (Fe+) and normal iron (NFe) murine thigh infection models.

Methods. Female CD-1 mice received iron dextran 100 mg/kg/d for 14 d to induce iron overload (Fe+) (ASM Microbe 2019 abstract HMB-373); an equal number of same-age mice were not dosed (NFe). On day 15, both thighs of mice rendered neutropenic were inoculated with GNB suspensions of 10^7 CFU/mL. Twenty CFDC-susceptible isolates with previously determined CFDC MIC from 0.25 to 4 mg/L, including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacteriales, were used. Two hours after inoculation, treatment mice were dosed with a CFDC regimen simulating the human plasma PK profile after doses of 2g q8h (3 h infusion), while control mice were sacrificed (0 h) or dosed with saline placebo on the same schedule as the CFDC regimen (24 h). All procedures were simultaneously performed in Fe+ and NFe mice. Efficacy was defined as a change in $\log_{10}$ CFU/thigh at 24 h vs. 0 h and was compared between Fe+ and NFe mice for individual isolates using Student's t-test.

Results. Mean (SD) bacterial burdens at 0 h in Fe+ and NFe control mice were 5.77 (0.52) and 5.76 (0.52) and $\log_{10}$ CFU/thigh, respectively, and, at 24 h, increased by 3.49 (0.73) and 3.42 (0.96) $\log_{10}$ CFU/thigh, respectively. Mean (SD) efficacies of CFDC in Fe+ and NFe mice were -1.98 (0.83) and -1.98 (0.72) $\log_{10}$ CFU/thigh, respectively. For 17 of 20 individual isolates, no significant differences in efficacy between Fe+ and NFe mice were observed ($P > 0.05$); 2 of the 3 isolates with a difference had greater efficacy in Fe+ mice.

Conclusion. Human-simulated exposure of CFDC is equally efficacious in iron-overloaded and normal hosts against a variety of GNB susceptible to CFDC. The potential clinical use of CFDC to treat GNB infections in patients with iron overload is supported.

Disclosures. **All authors:** No reported disclosures.

1545. Development of a Linear Mixed-Effect Pharmacodynamic Model to Quantify the Effects of Frequently Prescribed Antimicrobials on QT Interval Prolongation in Hospitalized Patients

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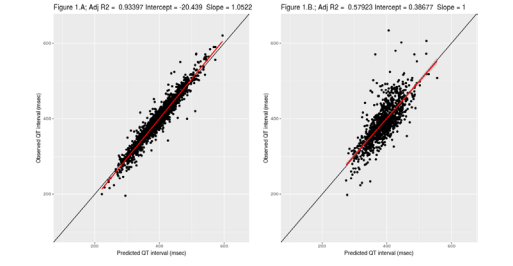
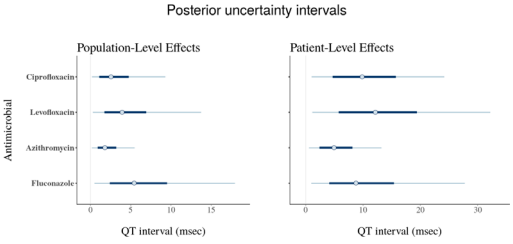
Background. Torsades de pointes is a life-threatening ventricular tachycardia associated with prolongation of the QT interval. Many diseases and medications have been implicated as potentially prolonging the QT interval, but little data exists regarding the means of quantifying this risk. The aim of this study was to describe the impact of commonly used antimicrobials on the QT interval in hospitalized patients.

Methods. Demographic, diseases, laboratory, medication administration history and ECG recording data were collected from the electronic records of adult patients admitted, from July 2018 to December 2018, to two urban hospitals. A model for the QT interval comprised of four sub-models: gender, heart rate, circadian rhythm, and the drug and disease effects. Fixed and random effects with between occasion variability were estimated for the parameters. A Bayesian approach using the NUTS in STAN was used via the brms package in the R® software.

Results. Data from 1,353 patients were used with baseline characteristics shown in Table 1. Observed vs. predicted plots based on the training (Figure 1A) and validation data set (Figure 1B) showed a great fit. The parameters for QT_{cD}, α, gender, and circadian rhythm were accurately identified (Table 2). Similarly, the model correctly described the expected impact of acute or chronic diseases on the QT interval. Uncertainty interval estimates (Figure 2) show that patients treated with fluconazole and levofloxacin are likely to present with a QT interval [mean (95% CI) of 6.84 (0.22,21.45) and 5.05 (0.15, 16.70), respectively], that is > 5 ms longer vs. no treatment, the minimum cutoff that should evoke further risk assessment of QT interval prolongation.

Conclusion. The model developed correctly describes the impact baseline risk factors have on the QT interval. Point estimates of QT interval prolongation show that patients treated with fluconazole and levofloxacin may be at considerable risk; while those treated with azithromycin or ciprofloxacin are more likely to be at an insignificant risk for QT interval prolongation during hospital admission. Further workup to quantify the impact of concomitant treatment with these and other at-risk medications is underway.





Baseline Parameters	Training set (n=948)	Validation set (n=405)	P value
Age (years)	60.65 (19.4)	61.2 (18.7)	0.51
Sex, male (%)	52.2	54.9	0.38
QT (ms)	389 (55.6)	391 (55.5)	0.54
QTc (ms)	453 (39.6)	452 (46.9)	0.87
Serum K (mEq/L)	4.3 (0.69)	4.3 (0.6)	0.24
Serum Ca (mEq/L)	9.1 (0.8)	9.0 (0.7)	0.50
Serum Mg (mEq/L)	2.1 (0.5)	2.1 (0.6)	0.82
Disease states (%)			
Bradycardia	9.4	9.1	0.94
Age >65 years	43.5	43.4	1.00
Sepsis	11.0	9.6	0.48
COPD	10.2	10.3	1.00
CKD	17.1	16.4	0.82
Liver disease	1.8	2.5	0.71
Cardiac arrest	0.1	0.7	0.08
Long QTc syndrome	4.4	6.1	0.24
Atrial fibrillation	14.9	16.4	0.51
Ventricular fibrillation	0.1	0.5	0.21
Bradycardia	1.9	1.6	0.82
Heart block	2.8	4.2	0.25
Hypertension	45.1	43.1	0.52
CAD	16.5	19.2	0.23
Heart failure	17.9	20.9	0.20
Acute MI	11.1	11.3	1.00
ICH	2.6	2.1	0.65
Stroke	0.6	0.9	0.49
Antimicrobial treatment (%)			
Azithromycin	7.4	8.9	0.40
Fluconazole	0.1	0.9	0.06
Levofloxacin	0.5	1.2	0.17
Ciprofloxacin	1.5	0.9	0.56

Data presented as mean (SD) unless otherwise indicated; COPD, chronic obstructive pulmonary disease; CDK, chronic kidney disease; CAD, coronary artery disease; MI, myocardial infarction; ICH, intracranial hemorrhage