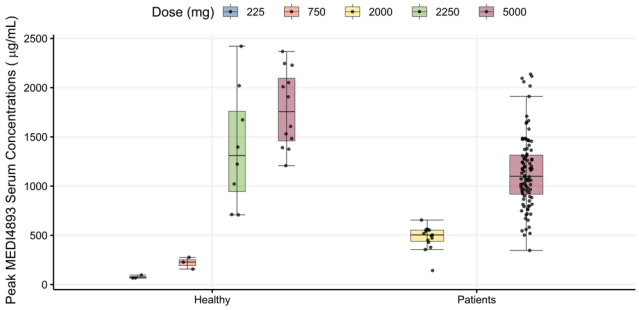

Disclosures. **All authors:** No reported disclosures.

1558. A Population Pharmacokinetic Model for Posaconazole Intravenous Solution and Oral Powder for Suspension Formulations in Pediatric Patients With Neutropenia

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Background. Posaconazole is approved in adults for prophylaxis and treatment of invasive fungal disease. Two formulations that offer weight-based dosing—intravenous (IV) and oral powder for suspension (PFS)—are being evaluated in children. A population pharmacokinetic (popPK) approach was used to characterize and predict the PK exposure of posaconazole PFS and IV formulations in children to identify dosages associated with achieving a target PK of 1200 ng/mL as the mean C_{avg} and individual C_{avg} ≥500 ng/mL and <2500 ng/mL in ~90% of patients.

Methods. A popPK model was developed through nonlinear mixed-effects modeling using data obtained from a trial in children with neutropenia (ClinicalTrials.gov, NCT02452034; Merck protocol, MK-5592-097). Three dose cohorts (3.5, 4.5, and 6 mg/kg/day [≤300 mg/day]) were studied in two age groups (2–<7 years and 7–17 years). Posaconazole IV was administered twice on day 1 then once daily through at least day 10, followed by PFS once daily through day 28 at clinician discretion. A compartmental model, including both formulations, was fit to the data. Model selection was based on the Log-Likelihood Criterion, goodness-of-fit plots, and scientific plausibility. Significance of the covariates was assessed in a stepwise forward inclusion/backward procedure. An additional assessment characterized the impact of different food covariates on bioavailability.

Results. An open one-compartmental PK model with first-order absorption and estimated bioavailability, as well as allometrically scaled effects of body weight on clearance and volume, adequately described the PK of posaconazole IV and PFS formulations. Model predictions are shown in the Table. Effects of the different food covariates were not statistically significant. Simulations indicated that for the 6-mg/kg/d dose, model-predicted C_{avg} generally met PK targets. Model-predicted C_{avg} was ≥500 ng/mL in >90% of subjects in all cohorts. The 1200-ng/mL target geometric mean C_{avg} was achieved for all but the 2–<7 years cohort receiving the PFS formulation.

Conclusion. This popPK-based analysis demonstrated that the 6-mg/kg/d dose of IV or PFS posaconazole formulation (≤300 mg/days) is appropriate for children (2–17 years) and that PFS can be administered without regard to food.

Table. Model-predicted geometric mean C_{avg}, percentage of patients in prespecified posaconazole steady state C_{avg} target range, and percentage of patients achieving C_{min} ≥500 ng/mL after IV and oral PFS administration of posaconazole 4.5, 6.0, or 7.5 mg/kg/d (to ≤300 mg/d) in children

Dose Cohort, mg/kg/d	Age Group, y	Formulation	Model-Predicted Percentage of Patients With C_{avg}			Model-Predicted Geometric Mean C_{avg}, ng/mL (%GCV)	Model-Predicted Percentage of Patients With C_{min} ≥500 ng/mL, %
			<500 ng/mL, %	500-2500 ng/mL, %	>2500 ng/mL, %		
4.5	2 to <7	IV	2.8	95.6	1.6	1045 (40)	55
		PFS	17.2	82.1	0.7	796 (51)	52
	7 to 17	IV	0.8	93.4	5.8	1361 (42)	79
		PFS	7.6	89.9	2.5	1042 (52)	76
6.0	2 to <7	IV	0.2	94.4	5.4	1365 (39)	70
		PFS	6.8	91.2	2.0	1050 (50)	69
	7 to 17	IV	0.1	82.2	17.7	1748 (41)	90
		PFS	3.1	89.1	7.8	1332 (51)	86
7.5	2 to <7	IV	0	83.2	16.8	1714 (40)	79
		PFS	2.9	89.3	7.8	1321 (51)	80
	7 to 17	IV	0	70.2	29.8	2001 (42)	94
		PFS	1.9	82.1	16.0	1547 (53)	90

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

1559. Ertapenem Plus Ceftriaxone or Ceftaroline Dual B-Lactam Combination for *Enterococcus faecalis*

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Background. Ampicillin-ceftriaxone β-lactam therapy has become the standard of care for treating serious *Enterococcus faecalis* infections. Alternative regimens are of interest due to ceftriaxone's association with *C. difficile* infections and VRE colonization, and ampicillin's instability and inconvenient dosing schedule.

Methods. *E. faecalis* wild-type strain JH2-2 was utilized in a 48-hour in vitro pharmacodynamic model with a starting inoculum of 10^6 colony-forming units (CFU)/mL. Models were performed in duplicate to triplicate. Simulated doses of ertapenem 1g every 24 hours (fCmax 12.2 µg/mL; half-life 4 hours; MIC 4 µg/mL), ceftriaxone 2 g every 12 hours (fCmax 28.5 µg/mL; half-life 6.5 hours; MIC 512 µg/mL), and ceftaroline 600 mg every 8 hours (fCmax 27.1 µg/mL; half-life 2.7 hours; MIC 2 µg/mL) were tested. Ertapenem was also combined with ceftriaxone or ceftaroline. Bacterial counts were obtained at 0, 4, 8, 24, 32, and 48 hours. Bactericidal activity was defined as ≥ 3-log10 CFU/mL reduction from the initial inoculum. MICs were assessed at 0, 24, and 48 hours using E-tests in accordance with CLSI.

Results. Ertapenem plus ceftriaxone, and ertapenem plus ceftaroline demonstrated bactericidal activity at 24 hours, but bacterial regrowth was observed at 48 hours (Table 1). An ertapenem MIC increase was only noted in one set of the ertapenem plus ceftriaxone models to 16mcg/mL at 48 hours, from 4mcg/mL at 0 hours. All other models did not have an increase in MIC.

Conclusion. Bactericidal activity of ertapenem-based dual β-lactam combinations may prove to be an alternative treatment for severe *E. faecalis* infections. Mechanistic understanding of penicillin-binding protein (PBP) saturation and optimization of antimicrobial pharmacodynamics must be explored.

Table 1. Average Bacterial log_{10} CFU/mL ± Standard Deviation (SD)		
Antibiotics	**24 Hours**	**48 Hours**
Ertapenem Alone	7.35 ± 0.46	7.21 ± 0.6
Ceftriaxone Alone	6.67 ± 0.18	7.46 ± 0.03
Ceftaroline Alone	4.65 ± 0.67	5.97 ± 0.18
Ertapenem + Ceftriaxone	1.79 ± 0.91*	4.72 ± 0.52
Ertapenem + Ceftaroline	2.29 ± 1.0*	5.05 ± 0.25

*bactericidal activity

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

1560. Pharmacokinetics–Pharmacodynamics (PK-PD) of Gepotidacin (GEP) Against *Escherichia coli* in Murine Pyelonephritis and Thigh Infection Models

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Background. GEP, a first in class novel triazaacenaphthylene bacterial topoisomerase inhibitor, inhibits bacterial replication and has in vitro activity against key pathogens implicated in a range of infections, including drug-resistant strains of *E. coli* associated with acute cystitis.

Methods. PK and PD studies were conducted in murine (male CD-1 mice) thigh and kidney infections. The administered doses ranged from 1 to 200 mg/kg SC every 6 hours starting 1-hour post-infection. Infected tissues were evaluated for bacterial burden at 24-h post-infection (baseline controls at 1-hour post-infection). Plasma and tissue samples (kidney or thigh homogenates) were collected at 15, 30, 60, 120, 240 and 360 minutes. A population PK (PopPK) model was built in NONMEM using plasma exposures. Efficacy was determined against *E. coli* ALL, 997577, ATCC25922, IR5 and NCTC13441 (MICs of 1 to 4 µg/mL) in thigh-infected neutropenic (I-) mice and against *E. coli* ALL in kidney-infected immunocompetent (I+) and I- mice. The PopPK model was used to determine GEP exposures associated with efficacy. PK-PD analyses were conducted using Phoenix WinNonLin 6.3 (Pharsight). The change in log_{10} colony-forming units (CFU) from baseline were correlated with free drug (f) AUC:MIC using an inhibitory model from the Phoenix library, and model parameter values for each isolate were used to calculate the plasma fAUC:MIC associated with stasis, 1- or 2-log_{10} reductions in CFU.

Results. Plasma PK data were best fit by a 1-compartment IV model with first-order elimination and were similar in I+ vs. I- and thigh- vs. kidney-infected mice. The AUC_{0-6} of GEP in kidney was approximately 4- to 5-fold higher than in plasma while the AUC_{0-6} in thigh was approximately half of plasma. In the I- thigh model, median plasma fAUC:MIC ratios for stasis, 1- or 2-log_{10} reductions in CFU were 11, 16, and 25 (ranges 3–17, 4–25 and 7–40), respectively. Efficacy vs. *E. coli* ALL was similar in I- mice infected in thigh or kidney. In I+ mice, the PK-PD target was reduced by half.

Conclusion. Median plasma fAUC:MIC targets ranged from 11 to 25. Higher drug levels in kidney vs. plasma or thigh did not translate into improved efficacy in pyelonephritis vs. thigh-infection models.

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

1561. Omadacycline Pharmacokinetics: Influence of Mortality Risk Score Among Patients with Community-Acquired Bacterial Pneumonia

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