Background. Patients with invasive fungal infections are often critically ill and immunosuppressed with multiple comorbidities that may impact drug absorption and exposure. This study sought to characterize isavuconazole serum concentrations (ISCs) in a cohort of real-world hospitalized patients when administered by intravenous solution (IV), enteral as intact capsules, or tube as opened capsule contents.

Methods. This retrospective cohort analysis included all hospitalized patients who received isavuconazole as prophylaxis or treatment between September 2017 and September 2018 and had therapeutic drug monitoring performed. For patients receiving isavuconazole by tube, the capsules were opened and contents were diluted with 10-30 mL of sterile water. Administration was per package insert for intact capsules and IV solution. ISCs were obtained as part of routine care and were quantified by high-performance liquid chromatography. An appropriate trough was defined as within 4 hours of the next scheduled dose. Currently, there is a lack of correlation between isavuconazole exposure and efficacy or toxicity; thus, ISCs were compared between administration routes.

Results. 93 ISCs were obtained during 65 encounters from 55 unique patients. The majority of patients were post-transplant (69.1%) and death occurred during 12 (18.5%) encounters. ISCs based on different characteristics of the cohort are shown in Table 1. All ISC assessments were detectable, median 2.3 mg/dL (Q1: 1.5 mg/dL, Q3: 3.3 mg/dL). Administration via tube achieved similar ISCs compared with IV therapy (1.6 mg/dL vs. 1.9 mg/dL, respectively). However, administration of intact capsules resulted in higher median ISCs, 3 mg/dL (Q1: 1.9 mg/dL, Q3: 4.1 mg/dL). All 14 patients with administration via tube were post-transplant, which was not shown to have a significant impact on ISCs (median, transplant 2.2 mg/dL vs. non-transplant 2.7 mg/dL).

Table 1. Characterization of Isavuconazole Concentrations

Table 1. Characterization of Isavuconazole Concentrations[a]

Characteristic	Frequency (n=93 serum concentrations)	Isavuconazole Serum Concentration (mg/dL)
Concentration:		
< 4 hours of next dose	80 (86)	2.3 (1.5-3.4)
≥ 4 hours of next dose	13 (14)	3.0 (1.9-3.3)
Duration of therapy at assessment		
Day 5 or less	3 (3.2)	3.3 (3.2-4.5)
Day 6-10	25 (26.9)	2.0 (1.3-2.7)
Day 10-30	35 (37.6)	1.9 (1.4-3)
Primary route of administration		
Intravenous	34 (36.6)	1.9 (1.3-2.8)
By mouth	45 (48.4)	3.0 (1.9-4.1)
Via tube	14 (15.1)	1.6 (1.3-2.5)
Transplant status		
Yes	71 (76.3)	2.2 (1.5-3.5)
No	22 (23.7)	2.7 (1.5-3.3)
Treatment purpose:		
Prophylaxis	26 (28)	3.0 (2.0-5.2)
Treatment	67 (72)	2.0 (1.4-3.2)
Location during assessment:		
Floor	65 (69.9)	2.7 (1.8-3.7)
Intensive care unit	28 (30.1)	1.9 (1.3-2.5)

[a]Data are reported in n (%) or median (IQR)

Conclusion. ISCs were detectable in all patients regardless of transplant status or location at the time of assessment. Administration of isavuconazole via an enteral feeding tube achieved comparable serum concentrations compared with FDA-approved routes of administration and may represent an important alternative for select patients.

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

1304. Characterization of Tebipenem Pivoxil Hydrobromide Pharmacokinetics-Pharmacodynamics (PK-PD) in a Neutropenic Murine Acute Pyelonephritis (AP) Model

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Session: P-59. PK/PD studies

Background. Tebipenem pivoxil hydrobromide (tebipenem HBr), an orally (PO) bioavailable prodrug of tebipenem, is a carbapenem with broad-spectrum activity against Gram-positive and -negative bacteria that is being developed for the treatment of patients with complicated urinary tract infections, including AP. Data from a one-compartment *in vitro* infection model demonstrated that the ratio of free-drug plasma area under the curve (AUC) to MIC with adjustment for dosing interval (τ) (AUC:MIC ratio•$1/\tau$) was the PK-PD index most associated with tebipenem HBr efficacy [VanScoy BD *et al.*, IDWeek 2019, Poster 1565]. Studies were undertaken to characterize the magnitude of tebipenem HBr free-drug plasma AUC:MIC ratio•$1/\tau$ associated with efficacy for Enterobacteriaceae using a neutropenic murine AP model.

Methods. A single dose pharmacokinetic study was completed in neutropenic mice infected via intra-renal injection with 10^4 CFU/kidney of *Escherichia coli* NCTC 13441. Following PO administration of 4 tebipenem HBr doses (1, 15, 45 and 100 mg/kg), plasma samples were collected at 0.25, 0.5, 1, 2, 4, 6 and 8 hours post-treatment initiation and drug concentrations were determined using LC/MS/MS. Dose-ranging studies were completed using a panel of 7 Enterobacteriaceae isolates (tebipenem HBr MIC values of 0.015 to 0.5 mg/L). Mice were infected with 10^4 CFU/kidney via

intra-renal injection. Two hours post-incubation, 8 total daily tebipenem HBr doses (0.3 to 135 mg/kg) were fractionated into regimens given every 8 hours. The relationship between change in $\log_{10}$ CFU/g from baseline at 24 hours and free-drug plasma AUC:MIC ratio•$1/\tau$ was fit using a Hill-type model. Free-drug plasma AUC:MIC ratio•$1/\tau$ values associated with net bacterial stasis and 1- and 2-$\log_{10}$ CFU/g reductions from baseline at 24 hours were determined.

Results. The relationship between change in $\log_{10}$ CFU/g from baseline at 24 hours and tebipenem HBr free-drug plasma AUC:MIC ratio•$1/\tau$ described the data well ($r^2 = 0.833$). Free-drug plasma AUC:MIC ratio•$1/\tau$ values associated with net bacterial stasis and a 1-$\log_{10}$ CFU/g reduction from baseline were 26.2 and 54.1, respectively. A 2-$\log_{10}$ CFU/g reduction was not achieved.

Relationship between change in log10 CFU/g from baseline at 24 hours and tebipenem HBr free-drug plasma AUC:MIC ratio•$1/\tau$ based on data for a panel of Enterobacteriaceae isolates evaluated in the dose-ranging studies conducted using a neutropenic murine acute pyelonephritis model
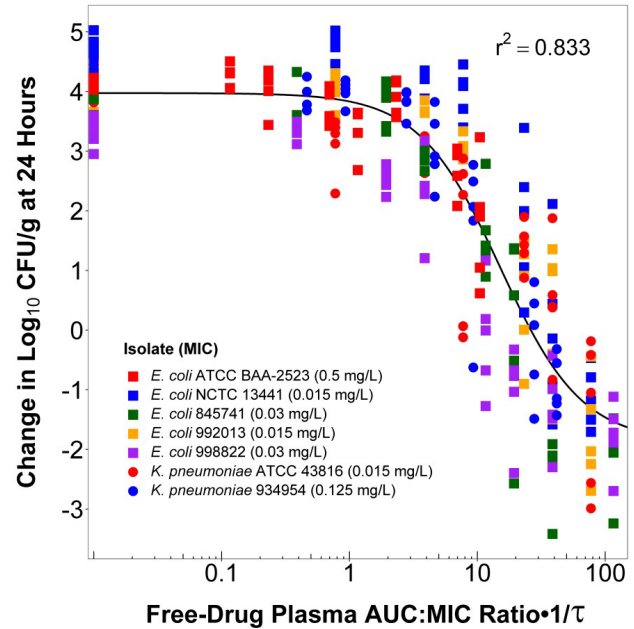
Conclusion: These data will be useful to support tebipenem HBr dose selection for clinical studies in patients with AP.

Disclosures. Brian D. VanScoy, B.S., Institute for Clinical Pharmacodynamics, Inc. (Employee)Spero Therapeutics (Grant/Research Support) Steven Fikes, BA, Institute for Clinical Pharmacodynamics, Inc. (Employee)Spero Therapeutics (Grant/Research Support) Christopher M. Rubino, PharMD, Institute for Clinical Pharmacodynamics, Inc. (Employee)Spero Therapeutics (Grant/Research Support) Sujata M. Bhavnani, PharMD, MS, FIDSA, Institute for Clinical Pharmacodynamics, Inc. (Employee)Spero Therapeutics (Grant/Research Support) Nicole S. Cotroneo, BS, Spero Therapeutics (Employee, Shareholder) Ian A. Critchley, PhD, Spero Therapeutics (Employee, Shareholder) Thomas R. Parr, PhD, Spero Therapeutics (Employee, Shareholder) Paul G. Ambrose, PharMD, FIDSA, Institute for Clinical Pharmacodynamics, Inc. (Employee)Spero Therapeutics (Grant/Research Support)

1305. Comparison of Pharmacokinetics of DSTA4637S, a novel THIOMAB[TM] Antibody-Antibiotic Conjugate, in Patients with Staphylococcus aureus Bacteremia Receiving Standard-of-Care Antibiotics with Pharmacokinetics in Healthy Volunteers

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Session: P-59. PK/PD studies

Background. DSTA4637S, a THIOMAB[TM] antibody-antibiotic conjugate against *Staphylococcus aureus,* is a potential therapy for complicated *S. aureus* bacteremia. Single doses showed favorable safety and pharmacokinetics (PK) in healthy volunteers (HVs). This study compares HV PK results to PK from a Phase 1b study evaluating multiple doses in patients with bacteremia.

Methods. In a Phase 1a study, HVs received single intravenous (IV) doses (5, 15, 50, 100, or 150 mg/kg) of DSTA4637S. The Phase 1b, randomized, double-blind, placebo-controlled, multiple ascending-dose study enrolled patients with MRSA or MSSA bacteremia receiving ≥ 4 weeks of standard-of-care (SOC) antibiotics in combination with IV DSTA4637S (15, 45, or 100 mg/kg) weekly (4-6 doses). Intensive PK serum and plasma sampling was performed after first and last doses of DSTA4637S. Total antibody (TAb) was measured in serum by ELISA. DSTA4637S conjugate (ac-dmDNA31)

and unconjugated dmDNA31 were measured in plasma with IA-LC-MS/MS and LC-MS/MS, respectively. DSTA4637S PK was analyzed using a non-compartmental approach using WinNonlin.

Results. DSTA4637S PK data were evaluated in 20 HVs in the Phase 1a study and 19 patients with *S. aureus* bacteremia in the Phase 1b study. In both HVs and patients, systemic exposures of TAb and ac-dmDNA were generally dose proportional over the dose ranges tested. In patients compared to HVs, $C_{max, cycle 1}$ for ac-dmDNA31 and TAb were reduced 26.7-51.3% and 32.4-44.1%, respectively, contributing to lower patient AUC_{0-7}. Unconjugated dmDNA31 concentrations were low (< 11 ng/mL), peaking 1-2 days after dosing, in both studies. There was no clear association between DSTA4637S exposure (ac-dmDNA31) and demographic factors (age, weight, sex), clinical status (bacteremia at dosing, infection site), adverse events (infusion-related reactions), or exploratory biomarkers (CRP, procalcitonin, inflammatory cytokines).

Conclusion. DSTA4637S PK analysis demonstrated lower exposures in patients with *S. aureus* bacteremia compared to HVs. Potential explanations for reduced exposures include factors related to disease status, non-specific organ uptake, and target-mediated clearance.

Disclosures. Sharon M. Rymut, PhD, Genentech (Employee, Shareholder) Rong Deng, PhD, Roche (Consultant, Employee, Shareholder) Ryan Owen, PhD, Genentech (Employee, Shareholder) Ola Saad, PhD, Genentech - Roche (Employee) Aklile Berhanu, PhD, Genentech, Inc. (Employee, Equity interest (Stock/Stock Options)) Jeremy Lim, PharmD, Roche (Employee, Shareholder) Montserrat Carrasco-Triguero, PhD, Genentech (Employee) Jessica A. Couch, PhD, Genentech (Employee, Shareholder) Melicent C. Peck, MD, PhD, Genentech (Employee)

1306. Comparison of the Use of Extended and Intermittent Infusion Cefepime and Piperacillin/tazobactam in Non-critically Ill, Obese Patients

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Session: P-59. PK/PD studies

Background. Obesity rates have dramatically increased over the last several decades, however, there is limited data to guide how antibiotics should be adjusted in obese patients. Physiologic differences including an increased volume of distribution and increased renal clearance may alter their pharmacokinetics and pharmacodynamics and subsequently, their efficacy. For beta-lactams like piperacillin/tazobactam (pip/tazo) and cefepime, extended infusion (EI) maximizes the time above the minimum inhibitory concentration (MIC) for optimal bactericidal activity. This dosing strategy may help decrease variability in achieving the target time above MIC in this patient population and lead to more favorable outcomes.

Methods. This single-center, retrospective, pre-/post- analysis included patients with a body mass index (BMI) > 30 that received EI (infused over 4 hours) or intermittent infusion (II) (infused over 30 minutes) pip/tazo or cefepime between 2/1/2020-4/30/2020 and 2/1/2019-4/30/2019, respectively. The primary outcome was in-hospital, all-cause mortality. Secondary outcomes included clinical success rate and hospital length of stay (LOS).

Results. During the evaluation periods, 98 patients met inclusion criteria (EI, N=53; II, N=45). Mean BMI was not statistically different between groups (EI, 36.0 kg/m2 [30.1-46.3]; II, 36.5 kg/m2 [30-48]). There were no cases of mortality in either group. The mean LOS in the II group was 13 days compared to 11.5 days in the EI group [95% CI -4.14-7.04; p=0.606]. After excluding one outlier of 104 days in the EI group, the average LOS was 9.5 days [95% CI: -0.87-7.33; p=0.121]. Markers of clinical success including time to resolution of fever (II: 47 hours; EI: 34 hours; p=0.216) and time to resolution of leukocytosis (II: 2 days; EI: 3.8 days; p=0.089) were not significantly different between groups.

Conclusion. The use of EI pip/tazo and cefepime was not associated with any differences in in-hospital, all-cause mortality, hospital LOS, or clinical success when compared to the use of II pip/tazo and cefepime. The lack of significant differences between groups may be attributable to the small sample size limiting the ability to detect a difference, especially regarding hospital LOS.

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

1308. Ex vivo Impact of Autologous Blood Transfusion (ABT) on Concentrations of Antibiotics used for Surgical Prophylaxis

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Session: P-59. PK/PD studies

Background. ABT is widely employed during surgical procedures involving high blood loss, such as liver transplantation and open heart surgery. While ABT mitigates the need for allogeneic blood transfusions, an unintended consequence may be removal of drugs, including antimicrobials. Herein, we determined the ex vivo loss of antimicrobials utilized for surgical prophylaxis through an ABT system.

Methods. Experiments were conducted in duplicate to simulate processing of ABT blood during surgery. Packed red blood cells and fresh frozen plasma (300ml) were acquired from banked blood and inoculated to achieve clinically-relevant plasma concentrations of vancomycin (VAN), the piperacillin (PIP) component of piperacillin/tazobactam, and the ampicillin (AMP) component of ampicillin/sulbactam.

Inoculated blood was processed through a Cell Saver® Elite™ ABT system to fill a 125mL Latham bowl and washed with 500mL of normal saline. Processed fluid was directed to a reinfusion or waste bag; additional blood samples were collected from each. Drug concentrations were measured in all samples. The amount of VAN, PIP, and AMP infused through the Cell Saver (initial), and resulting in the reinfusion and waste bags was calculated.

Results. A range of 193-265mL of combined blood containing drug were processed in each experiment through the ABT system. Initial average plasma concentrations were 61, 107, and 172 mg/L for VAN, PIP, and AMP, respectively. When corrected for volume and hematocrit, plasma concentrations translated to a mean ± SD of 3 ± 1% of VAN in the reinfusion bag and 93 ± 2% in the waste bag. For PIP, plasma concentrations translated to 2 ± 1% of PIP in the reinfusion bag and 84 ± 13% in waste, while 2 ± 1% and 120 ± 5% of AMP was found in the reinfusion and waste bags, respectively. Unaccounted drug (0-14%) was considered sequestered in the device.

Conclusion. These *ex vivo* assessments of antibiotic removal during ABT are the first to demonstrate significant loss of antibiotics (>95%) when processed through the ABT system. Further studies measuring impact of ABT on drug concentrations in patients undergoing surgery are warranted.

Disclosures. **David P. Nicolau, PharmD**, **Cepheid** (Other Financial or Material Support, Consultant, speaker bureau member or has received research support.)**Merck & Co., Inc.** (Consultant, Grant/Research Support, Speaker's Bureau)**Wockhardt** (Grant/Research Support) **Joseph L. Kuti, PharmD**, **Allergan** (Speaker's Bureau)**bioMérieux** (Research Grant or Support, Other Financial or Material Support, Speaker Honorarium)**Melinta** (Research Grant or Support)**Merck & Co., Inc.** (Research Grant or Support)**Paratek** (Speaker's Bureau)**Summit** (Other Financial or Material Support, Research funding (clinical trials))

1309. Imipenem/Cilastatin/Relebactam (I/R) Alone and in Combination against Pseudomonas aeruginosa (PSA) in the In Vitro Pharmacodynamic Model

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Session: P-59. PK/PD studies

Background. I/R, a carbapenem-beta-lactamase inhibitor antibiotic, is active against most imipenem-resistant PSA, including MDR isolates. Combination therapy may enhance activity against MDR pathogens and suppress resistance. This study's objective was to assess the efficacy of I/R compared with combinations including colistin (CST) or amikacin (AMK) against PSA in an IVPD model.

Methods. Human-simulated concentrations of I/R 500/250 mg every six hours, a total daily dose of CST 360 mg, and AMK 25 mg/kg daily were reproduced alone and in combination against 6 imipenem-non-susceptible PSA with I/R MICs of 1/4 to 8/4 mg/L in an IVPD over 24h. The primary endpoint was the difference in 24h colony forming units (CFU) between each combination regimen and its components alone. The log ratio differences of the area under the CFU curve were also calculated to compare the overall bacterial burden resulting from exposure to I/R alone with those treated by combination regimens. Emergence of resistance was tested at 24h using drug-containing plates at 3xMIC.

Results. I/R, CST, and AMK alone produced 24hCFU changes consistent with isolate MICs. One isolate (already I/R non-susceptible) developed I/R resistance, and 4 and 3 developed CST and AMK resistance, respectively. I/R plus CST suppressed all resistance and resulted in synergistic or additive interactions against three of six isolates with 24h CFU reductions ranging from -2.62 to -4.67 $\log_{10}$CFU/mL. This combination further reduced overall bacterial burden by 79-81% compared with I/R alone against two I/R-non-susceptible strains. I/R plus AMK also prevented resistance emergence but exhibited indifferent interactions against all isolates at 24h with the combined drugs achieving -0.51 to -3.33 $\log_{10}$CFU/mL reductions. Minor overall reductions in bacterial burden were observed relative to I/R alone.

Conclusion. I/R plus CST resulted in additivity or synergy against three of six PSA and prevented I/R and CST resistance, whereas the addition of AMK only suppressed resistance. The greatest overall reductions in bacterial burden, however, were observed with I/R plus CST against I/R-non-susceptible isolates, supporting targeted use of this combination against this phenotype when alternatives are unavailable.

Disclosures. **David P. Nicolau, PharmD**, **Cepheid** (Other Financial or Material Support, Consultant, speaker bureau member or has received research support.)**Merck & Co., Inc.** (Consultant, Grant/Research Support, Speaker's Bureau)**Wockhardt** (Grant/Research Support) **Joseph L. Kuti, PharmD**, **Allergan** (Speaker's Bureau)**bioMérieux** (Research Grant or Support, Other Financial or Material Support, Speaker Honorarium)**Melinta** (Research Grant or Support)**Merck & Co., Inc.** (Research Grant or Support)**Paratek** (Speaker's Bureau)**Summit** (Other Financial or Material Support, Research funding (clinical trials))

1310. Implementation of AUC:MIC Pharmacy to Dose in an Academic Medical Center: A Pilot Study

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Session: P-59. PK/PD studies

Background. The new ASHP/IDSA consensus guidelines recommend area under the curve (AUC) monitoring to optimize vancomycin therapy. Little is known