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1114. Effectiveness and Safety of Beta-lactam Antibiotics with and without Therapeutic Drug Monitoring in Patients with *Pseudomonas aeruginosa* Pneumonia or Bloodstream Infection

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Session: P-62. PK/PD Studies

Background. *Pseudomonas aeruginosa* (PSAR) is challenging to treat due to its multiple resistance mechanisms, limited anti-PSAR agents, and population pharmacokinetic (PK) variances. Beta-lactam antibiotics (BLA) are commonly used to treat PSAR infections and although they have a wide therapeutic index, suboptimal exposures may lead to treatment failure and antimicrobial resistance while high exposure may result in adverse effects. Certain patient populations may benefit from BLA therapeutic drug monitoring (TDM) due to their significant PK variability. The purpose of this study was to compare clinical outcomes in patients with PSAR pneumonia (PNA) or bloodstream infection (BSI) receiving BLA with and without the guidance of TDM.

Methods. Retrospective, parallel cohort study conducted at UF Shands Gainesville and UF Health Jacksonville evaluating five years of patients with PSAR PNA or BSI. TDM group was defined for routine BLA TDM compared to nonroutine BLA TDM service (non-TDM). Patients were excluded if they died before a culture result, transferred in with a positive PSAR culture, were transplant recipients, cystic fibrosis or burn injury patients. The primary outcome was a composite of presumed clinical cure defined as the absence of the following: all-cause in-hospital mortality, escalation, and/or additional antimicrobial therapy for PSAR infection after 48 hours of treatment with primary susceptible regimen due to worsening clinical status or transfer to a higher level of care.

Results. Two-hundred patients were included (TDM n=95; non-TDM n=105). The overall primary composite outcome of presumed clinical cure occurred in 73% of patients (82% and 75% of the TDM and non-TDM cohorts, respectively; p=0.301). A post-hoc multivariate analysis was conducted to assess predictors of not attaining clinical cure.

Table 1. Patients' demographics and baseline characteristics

Characteristics[b]	Cohort[a] TDM (n=95)	Non-TDM (n=105)	p value
Age (years)	61±11	61±11	0.683
Male	56 (59)	73 (70)	0.005
BMI (kg/m^2)	26 (22-33)	25 (20-31)	0.175
CL_{CR} (mL/min)	69 (36-111)	69 (43-105)	0.589
NH/LTC Resident	7 (7)	15 (14)	0.118
Immunosuppressed	9 (9)	4 (4)	0.105
IVDU	13 (14)	20 (19)	0.308
Charlson Comorbidity Index	4 (2-5)	5 (3-7)	0.081
SOFA score	5 (2-8)	5 (2-8)	0.808
APACHE II score	19 (14-26)	22 (17-28)	0.059
Positive culture source			
Blood	49 (52)	36 (34)	0.013
skin and soft tissue	11 (12)	15 (14)	0.057
urine	17 (18)	11 (10)	0.688
catheter-associated	5 (5)	5 (5)	0.534
intra-abdominal	7 (7)	5 (5)	0.959
other	4 (4)	7 (7)	0.191
Respiratory	46 (48)	69 (66)	0.019
Respiratory and blood	8 (8)	2 (2)	0.035
Hospital acquired infection	41 (43)	49 (47)	0.618
Antibiotic used for PSAR infection			
Cefepime	69 (73)	51 (49)	<0.001
Ceftazidime	0 (0)	1 (1)	0.999
Piperacillin-tazobactam	7 (7)	39 (38)	<0.001
Meropenem	18 (19)	10 (10)	0.055
Aztreonam	1 (1)	0 (0)	0.475
Ceftazidime-avibactam	0 (0)	1 (1)	0.999
Prolonged infusion BLA*	26 (27)	103 (96)	<0.001
Polymicrobial infections	32 (34)	47 (45)	0.109
Gram-positive	7 (7)	13 (12)	0.561
Gram-negative	23 (24)	31 (30)	0.579
both	2 (2)	3 (3)	0.999
Infectious Diseases Consult	66 (69)	29 (28)	<0.001

[a] Data are presented as "mean (standard deviation)", "number (%)" or "median (interquartile range)" as appropriate.
[b] SD, standard deviation; BMI, body mass index; CL_{CR}, creatinine clearance; NH/LTC, nursing home/long-term care; IVDU, intravenous drug use; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; PSAR, *Pseudomonas aeruginosa*.
* BLA administration via infusions of ≥ 3 hours

Table 2. Primary and secondary outcomes

Outcomes[b]	Cohort[a] BLA TDM (n=95)	No BLA TDM (n=105)	p value
Composite presumed clinical cure	78 (82)	75 (79)	0.301
All-cause mortality	12 (13)	21 (20)	0.185
Antibiotic escalation/addition	4 (4)	6 (6)	0.724
Escalation in level of care	3 (3)	0 (0)	0.497
All-cause in-hospital mortality	14 (15)	23 (22)	0.198
Hospital length of stay	21 (15-33)	21 (11-29)	0.337
Intensive care unit length of stay	19 (11-28)	14 (8-23)	0.019
Adverse event during BLA therapy			
Acute kidney injury	31 (30)	29 (28)	0.440
Clostridioides difficile	3 (3)	6 (6)	0.497
Neurotoxicity/encephalopathy	5 (5)	3 (3)	0.481
Readmission rates			
30-day	25 (26)	21 (20)	0.289
60-day	12 (13)	14 (13)	0.883
90-day	17 (17)	9 (9)	0.050

[a] Data are presented as "number (%)" or "median (interquartile range)" as appropriate.

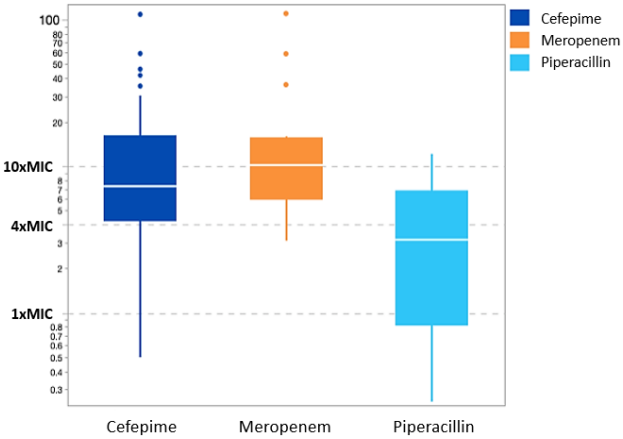
Table 3. Predictors of not attaining presumed clinical cure

Candidate Variables[a,b]	p value	OR	Lower 95%	Upper 95%
Age ≥ 61 years	0.018	1.027	1.001	1.054
SOFA Score ≥ 7	0.008	2.962	1.357	6.469
ICU admission	0.040	3.006	1.008	8.968
RRT during BLA therapy	0.005	3.359	1.313	8.596
MIC ± 1 dilution from CLSI breakpoint	0.042	3.109	1.040	9.294

[a] Candidate variables with univariate p < 0.2.
[b] RRT, renal replacement therapy; MIC, minimum inhibitory concentration; CLSI, Clinical and Laboratory Standards Institute

Conclusion. While there was no difference in the primary composite outcome of presumed clinical cure, future studies can use these data to assess TDM patient selection and whether a bundled care approach of BLA regimens with known clinical benefit, early TDM-guided dose optimization, and continued clinical assessment improves outcomes in patients with PSAR PNA or BSI compared to use of each modality individually.

Figure 1. Boxplot of fC_{min}:MIC ratios for BLA administered



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

1115. Evaluation of Gepotidacin (GSK2140944) Pharmacokinetics and Food Effect in Japanese Subjects

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Session: P-62. PK/PD Studies

Background. Gepotidacin, a novel, first-in-class triazaacenaphthylene antibiotic, inhibits bacterial replication and has *in vitro* and *in vivo* activity against key pathogens, including drug-resistant strains, associated with a range of infections. Gepotidacin is currently in Phase 3 clinical studies for the treatment of uncomplicated urinary tract infections and gonorrhea. This study (NCT02853435) was designed to assess gepotidacin pharmacokinetics (PK) in Japanese subjects (fasted and fed).

Methods. A tablet formulation of 750 mg gepotidacin free base was used in the study, which was conducted in two parts: Part 1, gepotidacin PK was assessed following 1500 and 3000 mg single oral doses in the fasted state; and Part 2, gepotidacin PK was assessed following 1500, 2250, and 3000 mg single oral doses in the fed state. Serial blood and urine samples were collected in both study parts.

Results. Part 1: The area under the plasma drug concentration-time curve from time 0 to infinity ($AUC_{[0-\infty]}$) and maximum observed concentration (C_{max}) were slightly higher in Japanese subjects than in Caucasian subjects at the same dose levels and with the same formulation. Following gepotidacin dosing in the fasted state, the 1500 mg dose was tolerated, while the 3000 mg dose was poorly tolerated with mild or moderate gastro-intestinal adverse effects (GI AEs) reported by most subjects shortly

after being dosed. Part 2: PK was linear with doses in the range of 1500–3000 mg. Administration of gepotidacin 3000 mg tablets in the fed state slightly reduced C_{max} and slightly increased AUC at the 3000 mg dose level. The 1500 and 2250 mg doses were tolerated while the 3000 mg dose was better tolerated compared to the fasted state with fewer and short-lived GI AEs, mostly mild in intensity. After oral administration of 1500–3000 mg, high urine drug concentrations were achieved, remaining above the minimum inhibitory concentration of 4 µg/mL for up to 24 hours.

Conclusion. The PK of gepotidacin following administration of a single oral dose to Japanese subjects was linear from 1500–3000 mg and food decreased C_{max} without impact on exposure (AUC). Administration of gepotidacin with food resulted in an improved GI tolerability profile at the higher dose tested in Japanese subjects.

Disclosures. **Mohammad Hossain, PhD**, **GlaxoSmithKline plc.** (Employee, Shareholder, Former employee of and past/current shareholder in GlaxoSmithKline plc.) **Courtney Tiffany, BSc**, **GlaxoSmithKline plc.** (Employee, Shareholder, Former employee of and past/current shareholder in GlaxoSmithKline plc.) **Aline Barth, MSC;PHD**, **GlaxoSmithKline plc.** (Employee, Shareholder, Employee of and shareholder in GlaxoSmithKline plc.) **Aparna Raychaudhuri, Ph.D.**, **GlaxoSmithKline plc.** (Employee, Shareholder, Former employee of and past/current shareholder in GlaxoSmithKline plc.) **Etienne F. Dumont, MD**, **GlaxoSmithKline plc.** (Employee, Shareholder, Former employee of and shareholder in GlaxoSmithKline plc.)

1117. Tazobactam Pharmacokinetic/Pharmacodynamic Target Attainment in Healthy Volunteers and Critically-Ill Hospitalized Patients

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Session: P-62. PK/PD Studies

Background. Pharmacokinetic/pharmacodynamic (PK/PD) targets and attainment are well described for beta-lactams; however, are rarely considered for beta-lactamase inhibitors. Recent evidence suggests that tazobactam (TAZ) target exposures to restore piperacillin bacteriostatic and 1 log 10 bactericidal activity against Enterobacterales are fT> the piperacillin/tazobactam (TZP) MIC of 64% and 77%, respectively. The aim of this study was to evaluate TAZ probability of target attainment (PTA) of a 500 mg every 6-hour dose of tazobactam using population PK data in both healthy volunteers and hospitalized patients.

Methods. PK exposures in 1,000 patients with varying degrees of renal function were simulated using a previously described TAZ PK model developed with data from critically ill infected patients. An identical one-compartment structural model describing TAZ PK using mean population parameters observed in phase 1 PK studies was also used to simulate exposures in healthy volunteers. All simulated patients received 500 mg of TAZ as an intravenous infusion over 30 minutes or as a 3-hour extended-infusion.

Results. The table displays PTA results for patients with an estimated creatinine clearance of 60 mL/min. Based on healthy volunteer data, the highest TZP MIC where ~90% PTA was achieved for bacteriostasis was 1 mg/L and was 0.25 mg/L for bactericidal activity. These were only achieved with extended infusion administration of TAZ. In the cohort of hospitalized patients, >90% PTA of TAZ exposures associated with both bacteriostasis and 1 log kill were achieved up to a MIC of 2 for intermittent infusion and up to 4 mg/L for extended infusion, due to decreased TAZ clearance in hospitalized patients. These values are significantly lower than the CLSI TZP susceptibility breakpoint of 16 mg/L, and PTA rates were lower at increased creatinine clearances.

Table: Percent Target Attainment of Tazobactam exposures associated with restoring bacteriostasis (fT> MIC of 64%) and bactericidal activity (fT> MIC of 77%) of piperacillin in simulated patients receiving 500 mg every six hours of tazobactam with a creatinine clearance of 60 mL/min

TZP MIC	Healthy Volunteer		Critically-Ill Hospitalized Patients	
fT>MIC of 64%	30-min infusion	3-hour infusion	30-min infusion	3-hour infusion
0.25	82	98	100	100
0.5	78	96	99	100
1	71	93	98	100
2	60	87	94	99
4	41	72	84	96
8	14	37	51	79
16	1	6	<1	6
fT>MIC of 77%				
0.25	77	92	99	100
0.5	71	89	97	100
1	63	83	95	99
2	50	73	90	97
4	30	51	77	90
8	8	21	41	62
16	0.5	3	0	0

Conclusion. fT>TZP MIC target attainment is poor with maximal package insert tazobactam doses given with piperacillin, even when administered as an extended infusion. These findings have serious implications for the role of TZP in beta-lactamase producing Enterobacterales, including ESBLs, and suggest the current susceptibility breakpoints are 4-32 fold higher than those supported by PK/PD data.

Disclosures. **Jason M Pogue, PharmD, BCPS, BCIDP**, **Merck** (Consultant)**QPex** (Consultant)**Shionogi** (Consultant)**Utility Therapeutics** (Consultant)**VenatoRX** (Consultant) **Emily Heil, PharmD, MS, BCIDP**, Nothing to disclose

1118. Population Pharmacokinetics of Contezolid Acefosamil and Contezolid – Rationale for a Safe and Effective Loading Dose Regimen

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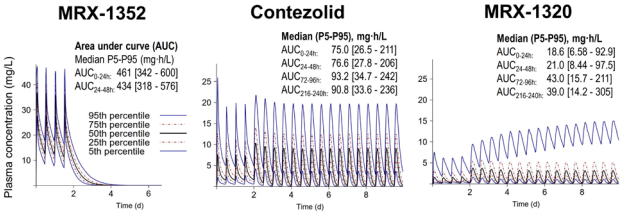
Session: P-62. PK/PD Studies

Background. Contezolid (CZD) is a novel oral oxazolidnone with comparable activity and potentially improved safety compared to current oxazolidinones. The intravenous (IV) double prodrug contezolid acefosamil (CZDa) is converted via MRX-1352 to active CZD. CZDa paired with CZD holds promise as a safe and effective treatment for serious Gram-positive infections such as those caused by methicillin-resistant *Staphylococcus aureus*. Sequential therapy with CZDa IV followed by CZD oral (PO) offers flexible treatment options in hospital and outpatient settings for conditions such as diabetic foot infections. We aimed to design a CZDa/CZD dosage regimen leveraging population pharmacokinetic modeling (PopPK).

Methods. PopPK simultaneously fit data from 184 adult subjects. These were 1) plasma concentrations (by LC-MS/MS) of MRX-1352, CZD, and its metabolite MRX-1320 from 66 healthy subjects receiving CZDa (150-2400 mg IV) for up to 10 days, 2) CZD and MRX-1320 concentrations from 44 healthy subjects receiving single CZD PO doses of 400, 800, or 1200 mg with and without food or multiple doses Q12h for up to 28 days, and 3) CZD concentrations from 74 Phase 2 patients receiving CZD 800 mg PO Q12h. PopPK and Monte Carlo simulations were used to optimize CZD exposures.

Results. CZDa was rapidly converted to MRX-1352, which was converted less rapidly to CZD. CZD was well absorbed and food enhanced its bioavailability. For CZD 800 mg PO with food, apparent total clearance of CZD was 13.1 L/h (22% coefficient of variation) in healthy subjects and 14.5 L/h (53% CV) in patients. The apparent volume of distribution at steady-state was 20.5 L. A loading dose of CZDa 2000 mg IV, then CZDa 1000 mg IV Q12h, and followed by CZD 800 mg PO Q12h achieved areas under the curve (AUC) between 75 and 100 mg*h/L (medians; Figure) on all study days. Compared to CZD AUCs, the MRX-1352 AUCs during IV dosing were higher. While the median MRX-1320 AUCs were lower (18 to 48 mg*h/L), some accumulation was predicted in ~5% of subjects.

Figure: Monte Carlo simulation of contezolid acefosamil 2000 mg IV at 0 h, then 1000 mg IV at 12, 24 & 36 h, followed by 800 mg oral contezolid Q12h



Conclusion. A loading dose of CZDa 2000 mg IV followed by either CZDa 1000 mg IV or CZD 800 mg PO Q12h was predicted to reliably achieve efficacious CZD exposures on day 1 and maintain those exposures throughout therapy. This regimen will be evaluated in Phase 3 studies in complicated skin infections and diabetic foot infections.

Disclosures. **Jürgen B. Bulitta, PhD**, **MicuRx Pharmaceuticals, Inc.** (Consultant) **Barry HAFKIN, MD**, **MicuRx Pharmaceuticals Inc.** (Consultant)

1119. Assessment of Vancomycin Pharmacokinetic Parameters in Pediatric Patients After Liver Transplantation

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Session: P-62. PK/PD Studies

Background. Vancomycin is largely prescribed to treat gram-positive bacterial infections in pediatric patients after liver transplantation with the same empirical doses prescribed in other critical conditions due to the absence of pharmacokinetic studies in this population. The objective of this investigation was to describe the vancomycin pharmacokinetic parameters and to assess the vancomycin percentage of target attainment with empirical regimen.

Methods. Prospective and longitudinal study with pediatric post-liver transplantation patients who received at least 48 hours of vancomycin between January 2020 and May 2021. Patients with acute or chronic renal failure or receiving renal replacement therapy were excluded. Vancomycin therapy started with 40-60mg/kg daily, one-hour infusion. The pharmacokinetic parameters were determined by one-compartment model with first-order kinetics using near steady-state postdistributional peak and trough within the same dosing interval. Therapeutic target was defined as vancomycin 24-hour area under the curve/minimum inhibitory concentration (AUC^{ss}_{0-24}/MIC) ≥ 400 and < 600. The study protocol was approved by the local ethics committee.

Results. We included 18 sets of peak/trough serum concentrations obtained from 12 patients. The patients had median age of 11 (interquartile range [IQ] 8-16) months. The found vancomycin clearance, volume of distribution and half-life values were,