about the ability to implement this recommendation in a real-world setting. At UMass Memorial Medical Center (UMMMC), an AUC pharmacy to dose protocol was created to manage infectious diseases (ID) consult patients on vancomycin. The service was piloted by the pharmacy residents and 2 clinical pharmacists. The purpose of this study was to determine if a pharmacy to dose AUC protocol can safely and effectively be implemented.

Methods. A first-order kinetics calculator was built into the electronic medical record and live education was provided to pharmacists. Pharmacists ordered levels, wrote progress notes, and communicated to teams regarding dose adjustments. Patients were included based upon ID consult and need for vancomycin. After a 3-month implementation period, a retrospective chart review was completed. Patients in the pre-implementation group were admitted 3 months prior to AUC pharmacy to dose, had an ID consult and were monitored by trough (TR) levels. The AUC group was monitored with a steady state peak and trough level to calculate AUC. The primary outcome evaluated time to goal AUC vs. time to goal TR. Secondary outcomes included number of dose adjustments made, total daily dose of vancomycin, and incidence of nephrotoxicity.

Results. A total of 64 patients met inclusion criteria, with 37 patients monitored by TR and 27 patients monitored by AUC. Baseline characteristics were similar except for weight in kilograms (TR 80.0 ±25.4 vs AUC 92.0 ±26.7; p=0.049). The average time to goal AUC was 4.13 (±2.08) days, and the average time to goal TR was 4.19 (±2.30) days (p=0.982). More dose adjustments occurred in the TR group compared to the AUC (1 vs 2; p=0.037). There was no difference between the two groups in dosing (TR 15.8 mg/kg vs AUC 16.4 mg/kg; p=0.788). Acute kidney injury occurred in 5 patients in the AUC group and 11 patients in the TR group (p=0.765).

Conclusion. Fewer dose adjustments and less nephrotoxicity was seen utilizing an AUC based protocol. Our small pilot has shown that AUC pharmacy to dose can be safely implemented. Larger studies are needed to evaluate reduction in time to therapeutic goals.

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1311. Intrapulmonary Pharmacokinetics of Cefiderocol in Hospitalized and Ventilated Patients Receiving Standard of Care Antibiotics for Bacterial Pneumonia

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Session: P-59. PK/PD studies

Background. Cefiderocol (CFDC), a novel siderophore cephalosporin, has potent *in vitro* activity against Gram-negative bacteria causing nosocomial pneumonia (NP). The non-inferiority of CFDC to meropenem in Day 14 all-cause mortality in NP was previously demonstrated. In this study, we assessed the intrapulmonary pharmacokinetics of CFDC in hospitalized and ventilated patients with bacterial pneumonia receiving standard of care (SOC) antibiotics.

Methods. A multicenter, single-arm, open-label study was conducted to assess epithelial lining fluid (ELF) and plasma concentrations of CFDC at steady state in mechanically ventilated patients with bacterial pneumonia receiving SOC antibiotics (NCT03862040). Seven patients received 2 g doses of CFDC (or renally adjusted doses), infused over 3 hours, q8h, or q6h for patients with augmented renal function (creatinine clearance estimated by Cockcroft-Gault equation >120 mL/min). One bronchoalveolar lavage (BAL) sample per patient was collected to determine ELF concentration at 3 or 5 hours after at least 3 CFDC doses (or ≥6 doses in patients with severe renal impairment). Four blood samples were collected per patient for plasma concentrations at 1, 3, 5, and 7 hours after the start of the infusion used for BAL sampling. Urea concentrations in blood and BAL were measured to calculate CFDC concentrations in ELF.

Results. Geometric mean (minimum, maximum) ELF concentration of CFDC was 7.63 (3.10, 20.7) µg/mL at the end of infusion (3 h after the start of infusion) (N=4) and 10.4 (7.19, 15.9) µg/mL at 2 hours after the end of infusion (5 h after the start of infusion) (N=3). ELF/free plasma concentration ratios were estimated to be 0.212 at the end of infusion and 0.547 at 2 hours after the end of infusion based on the *in vitro* unbound fraction of 0.422.

Conclusion. The individual ELF concentrations of CFDC were close to, or higher than, 4 µg/mL in pneumonia patients. Compared with the ELF/free plasma area under the curve ratio in healthy subjects (0.239), the ELF/free plasma concentration ratio at the end of infusion (0.212) was comparable, and at 2 hours after the end of infusion (0.422) was higher in pneumonia patients. These findings suggest delayed distribution and sustained exposure of CFDC in the ELF of pneumonia patients.

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1312. Metallo-β-lactamase-Producing Enterobacterales (MBL-EB): Is it Time to Rethink Our Assessment Tools?

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Session: P-59. PK/PD studies

Background. We previously reported the potent *in vivo* activity of ceftazidime/avibactam human-simulated regimen (HSR) against MBL-EB despite the observed resistance *in vitro* and the lack of avibactam MBL-inhibitory activity (AAC 2014 Nov;58(11):7007-9). Similar to avibactam, relebactam (REL) is a diazabicyclooctane that inhibits serine β-lactamases belonging to Classes A - C but not MBLs. In the current study, we examined the *in vivo* activity of cefepime (FEP)/REL combination HSR against MBL-EB in a murine thigh infection model.

Methods. Six clinical MBL-EB isolates expressing VIM, IMP or NDM and co-expressing at least one β-lactamase of Classes A - C (KPC, CTX-M, TEM, SHV, ACT, CMY) were utilized. MICs of FEP and FEP/REL combination (at fixed REL concentration of 4 mg/L) were determined using broth microdilution. FEP HSR (2 g q12h as 0.5 h infusion) alone and in combination with REL HSR (250 mg q6h as 0.5 h infusion) were established in the infection model. Thighs of neutropenic ICR mice were inoculated with bacterial suspensions of 10^7 CFU/ml. Two hours later, mice were administered the FEP HSR or the FEP/REL HSR. Efficacy was measured as the change in $\log_{10}$CFU/thigh at 24 h compared with 0 h controls.

Results. All isolates were FEP resistant (MIC ≥ 32 mg/L). Addition of REL had no impact on the MIC of the isolates. In *in vivo* studies, the average bacterial burden at 0 h was 5.84 ± 0.41 $\log_{10}$CFU/thigh. In accordance with the *in vitro* susceptibility, administration of FEP HSR was associated with net bacterial growth among all isolates ranging from 0.46 ± 0.60 to 2.97 ± 0.53 $\log_{10}$CFU/thigh. In contrast, FEP/REL combination HSR resulted in substantial bacterial reductions among all isolates ranging from -0.73 ± 0.13 to -1.72 ± 0.14 $\log_{10}$CFU/thigh, indicating that REL enhanced the FEP activity *in vivo*.

Conclusion. Despite the powerful β-lactam hydrolytic capability of MBLs *in vitro*, FEP inactivation in the murine model was attributed predominantly to the expression of the serine β-lactamases. The *in vitro*/*in vivo* discordance in β-lactam/β-lactamase activity against MBL-EB reveals a potential flaw in the currently utilized *in vitro* susceptibility testing methodologies and highlights a challenge encountered during the development of new agents against these isolates.

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1313. MIC Profiling of Ceftazidime-Avibactam (CAZ/AVI) Against Two Carbapenemase producing Klebsiella pneumoniae Isolates

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Session: P-59. PK/PD studies

Background. Carbapenemases confer resistance against a broad range of beta-lactams with a prevalence of 40-60% among CRE (carbapenem-resistant Enterobacteriaceae). CAZ-AVI is commonly used to treat infections due to CPE (carbapenemase-producing Enterobacteriaceae), typically guided by susceptibility testing with a single AVI concentration. This methodology does not take into consideration varying AVI concentration observed in vivo, and may not reliably predict positive clinical outcomes. Our objective was to investigate a novel susceptibility testing method to guide CAZ-AVI therapy.

Methods. Two bloodstream *K. pneumoniae* isolates (CAZ/AVI susceptible) from an abdominal source were recovered from 2 unrelated patients. Both patients were treated with CAZ/AVI, but had discordant outcomes: KP118 (eradication within 24h) and KP286 (persistent bacteremia for over 30 days). Carbapenemase production in the 2 isolates was confirmed via Carba NP test, and CAZ susceptibility was determined in a clinically relevant range of AVI concentration (0 - 16 mg/L). The concentration-response was characterized by the sigmoid inhibitory maximum effect (Emax) model. The best-fit parameter values were used to predict %T > MICi associated with CAZ/AVI exposures expected in peritoneal fluid after standard dosing (2.5g q8h). These CAZ/AVI exposures were simulated in the hollow-fiber infection model (HFIM), and the bacterial responses were correlated to observed clinical outcomes.

Results. The AVI-dependent reduction in CAZ MIC was well characterized in both strains ($R^2 > 0.98$). In HFIM, sustained suppression of KP118 (T > MICi = 100%) was observed over 5 days, but not with KP286 (T > MICi < 100%). These observations are consistent with the clinical courses of the patients.

Conclusion. The discordant patient outcomes could be explained by MIC profiling of CAZ/AVI. This method appears to be more robust than conventional susceptibility testing, and the clinical utility of this approach should be further investigated.

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