Background. Oral valganciclovir and intravenous ganciclovir are used for prophylaxis, treatment, and preemptive treatment of cytomegalovirus and human herpesvirus 6. It is important to estimate the exposure to these antivirals, as deviating levels can cause adverse events or induce acquired drug resistance, which can both lead to treatment failure. Therapeutic drug monitoring (TDM) is a good tool to estimate drug exposure in these patients. With this observational study we aimed to evaluate which patients would benefit most from TDM.

Methods. An observational study was performed in adult solid-organ and stem cell transplant recipients on routine (val)ganciclovir (dosed according to renal function, weight and indication). As valganciclovir is a prodrug of ganciclovir, only the latter was measured. Ganciclovir trough ($C_{\text{trough}}$) and peak ($C_{\text{peak}}$) concentrations were measured with a validated LC-MS/MS assay. The target concentrations defined for the study were 1–2 mg/L and 2–4 mg/L for prophylaxis and treatment, respectively, and over 5 mg/L toxic.

Results. From June 2018 to April 2019, 66 patients were included. Within this timeframe, 236 $C_{\text{trough}}$ and 52 $C_{\text{peak}}$ were measured with median of 4 samples per patient. The median $C_{\text{trough}}$ was 1.1 mg/L and 2.3 mg/L for prophylaxis and treatment, respectively. Over 50% of the concentrations were out of the therapeutic window. The median creatinine for all measurements was 100 µmol/L. Observational analysis showed patients with kidney failure and on continuous renal replacement therapy (CVVH) had more concentrations measured out of the predefined range (Figures 1 and 2). For one individual with augmented renal clearance we observed significantly lower concentrations during routine dosing. 6 toxic concentrations were measured (5 subjects); creatinine concentrations ranged 71–527 µmol/L in these individuals. A preliminary linear-mixed model analysis did not show drug formulation, age or gender as a significant predictor for ganciclovir concentrations.

Conclusion. We believe that patients with decreased renal function, on CVVH or showing changes in renal function might benefit from TDM to guide therapy. TDM of ganciclovir for patients without renal failure remains debatable. Further studies with specific patient groups are needed to confirm these results.

Table 1. Patient characteristics (n=66)

| Characteristic                  | No. (%) of patients | median (IQR) |
|--------------------------------|---------------------|--------------|
| Gender                         |                     |              |
| Female                         | 25 (62%)            |              |
| Male                           | 41 (38%)            |              |
| Age (years)                    | 58 (48.5-64)        |              |
| BMI (kg/m²)                    | 23.5 (20.7-26.4)    |              |
| Weight                         | 71.1 (60.9-83.1)    |              |
| Height                         | 176 (169-182)       |              |
| Transplant type                |                     |              |
| Stem cell transplant           | 21 (31)             |              |
| Kidney                         | 9 (14)              |              |
| Lung                           | 13 (20)             |              |
| Liver                          | 9 (14)              |              |
| Heart                          | 8 (12)              |              |
| Other*                         | 6 (9)               |              |

*Small intestine, liver/pancreas/small intestine, kidney/pancreas, lung/liver

Ganciclovir treatment

| Therapeutic issue               | No. (%) of patients | median (IQR) |
|--------------------------------|---------------------|--------------|
| CMV prophylaxis                | 37 (56)             |              |
| CMV treatment                  | 16 (24)             |              |
| HHV 6 treatment                | 13 (20)             |              |

Route of administration

| Dose (mg/kg/day)               | 10 20 30 |
|--------------------------------|----------|

Figure 1. Variability of Ganciclovir concentrations during oral prophylaxis.

Figure 2. Variability of Ganciclovir concentrations during intravenous treatment.

Disclosures. All authors: No reported disclosures.
including vancomycin intermediate susceptible Staphylococcus aureus (VISA) and daptomycin non-susceptible strains (DNS). Lipoglycopeptides, notably dalbavancin (DAL), have been employed due to their ease of administration and enhanced activity against highly resistant S. aureus. As previously demonstrated, the use of β-lactams, specifically ceftazidin (CFZ) in combination with anti-MRSA drug therapy has been effective in eradicating S. aureus complicated by increased resistance. The objective of this study was to evaluate the activity of DAL, VAN, and DAP, alone and in combination with CFZ in a pharmacokinetic/pharmacodynamic (PK/PD) model.

Methods. The well-characterized DANS VISA strain, D712, was evaluated in eight different regimens in duplicate via a one-compartment 7-day PK/PD model. The experimental regimens were as follows: D712 growth control, DAL 1500 mg given on day 1, VAN 2 g given every 12 hours, DAP 10 mg/kg once-daily, CFZ 2 g given every 8 hours and DAL, DAP, and VAN in combination with CFZ.

Results. The combinations of DAL+CFZ, VAN+CFZ, and DAP+CFZ demonstrated a significant log CFU/mL reduction (more than 5 log CFU/mL and up to detection limit), compared with each drug used as monotherapy (P < 0.001). Neither DAP nor VAN demonstrated sustained bactericidal activity (represented by a >3-log CFU/mL reduction from baseline) and resulted in significant regrowth, when administered alone. However, the DAP + CFZ, and VAN+CFZ combination models demonstrated bactericidal activity at 4 hours and 24 hours, respectively. While DAL alone did demonstrate bactericidal activity, the DAL+CFZ combination was more rapidly bactericidal, achieving a >3-log reduction from baseline in 8 hours vs. 48 hours (P < 0.05).

Conclusions. The combination of DAL, VAN, or DAP with CFZ demonstrated significantly improved activity against this multiple drug-resistant S. aureus strain. Further research is warranted, both in vivo and in vitro, to explore the synergistic capabilities of anti-MRSA drug therapy in combination with β-lactams.

Disclosures. All authors: No reported disclosures.

1540. A Population Pharmacokinetic Model for Vancomycin in Korean Patients Receiving Extracorporeal Membrane Oxygenation Therapy: A Prospective Study

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Background. There is no literature on population pharmacokinetics (PK) of vancomycin in Korean patients receiving extracorporeal membrane oxygenation (ECMO) therapy. The aim of this study was to develop a population PK model for vancomycin in Korean ECMO patients.

Methods. We prospectively enrolled 14 patients who were undergoing ECMO and receiving vancomycin from July 2018 to April 2019. After initial dose of vancomycin was administered, serial blood samples (seven to nine times per patient) were drawn before the next dose. A population PK model for vancomycin was developed using a nonlinear mixed-effect modeling. Age, sex, creatinine clearance, and body weight were tested as potential covariates in the model. Model selection was based on log-likelihood test, model diagnostic plots, and clinical plausibility.

Results. Fourteen patients were included over the period. Ten received vancomycin for three or more episodes of infections, and one received both type ECMO. Eleven were men and the median age was 54 (interquartile range 45–66.3). Mean estimated glomerular filtration rate (eGFR) was 69 ± 46 mL/minute/1.73m² by the modification of diet in renal disease equation. A total of 123 vancomycin concentrations from the patients were included in the analysis. The population PK of vancomycin was best described by a two-compartment model with a proportional residual error model. The typical value (%between-subject variability) for total clearance was estimated to be 3.43 L/h (21.6%), central volume of distribution was 9.22 L, the intercompartmental clearance was 10.75 L/h (46.9%), and the peripheral volume of distribution was 19.6 L (26.6%). The proportional residual variability was 8.81%. Creatinine clearance significantly influenced vancomycin clearance (CL). The proposed equation to estimate vancomycin clearance in Korean ECMO patients was CL = 4.33 × (eGFR – 56).

Conclusion. A two-compartment population PK model successfully describes vancomycin PK profiles in Korean ECMO patients. The model could be used to optimize the dosing regimen if more data become available from currently ongoing clinical study.

Disclosures. All authors: No reported disclosures.

1541. A Novel and Fast Liquid Chromatography Method for Determination of Fluoroquinolones in Human Plasma

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Background. Fluoroquinolones (FQs) are frequently used antimicrobial agents. Concerning the high concentration-dependent bactericidal activity, concentrations of FQs in the biological fluids must be monitored to ensure treatment success. The literature search revealed that there is no method for the determination of levofloxacin (LEV), ciprofloxacin (CIP), moxifloxacin (MOX), and gemifloxacin (GEM) in plasma up to date. Consequently, the aim of this study was to develop and validate a new high-performance liquid chromatography (HPLC) method for determination of these FQs in plasma and evaluate effects of concomitant drugs on plasma FQ concentrations of patients.

Methods. Blank plasma samples spiked with FQs were employed for method validation studies. Validation studies were conducted in accordance with the recommendations of the US FDA. In order to demonstrate feasibility of method, 5 patients with polypharmacy, receiving orally CIP, LEV, or MOX as part of their treatment were included in the study. Blood samples were collected at two different times, just before and 2 hours after the second drug administration.

Results. The separation of FQs was accomplished within 7.5 minutes. The method was linear in the range of 0.1–10 µg/mL with the correlation coefficient >0.99. The RSD at four concentration levels (0.1, 0.3, 4, and 8 µg/mL) was less than 7% with accuracy in the range of 91.1–111.9%. The method was applied to the determination of CIP, LEV, and MOX levels in plasma samples of 5 patients of polypharmacy. Determined CIP and LEV levels were in accordance with literature. On the other hand, MOX concentration 2 hours after administration in plasma of one patient was found to be 6.1 ± 0.1 µg/mL which was 10 times greater than previously reported maximum plasma concentration of MOX (4.5 µg/mL). The patient had hypoaemia and MOX is approximately 50% bound to serum proteins. Due to low level of albumin, the level of free MOX in plasma may be increased.

Conclusion. A simple, fast, and reliable HPLC method was developed and validated for the determination of CIP, LEV, MOX, and GEM in plasma. It is suitable for therapeutic drug monitoring of these FQs and can be applied to other pharmacokinetic and toxicological studies.

Disclosures. All authors: No reported disclosures.

1542. The Evaluation of the In Vitro Synergy of Colistin in Combination with Meropenem and Tigecycline against 50 Multi-Drug Resistant Acinetobacter baumannii strains

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Background. Acinetobacter baumannii possess inherent and acquired antibiotic resistance mechanisms that have rendered most antibiotics, including carbapenems, inactive. Colistin (COL) has risen as salvage therapy against these organisms due to its retained activity against multi-drug-resistant Acinetobacter baumannii (VISA) and dapto- mycin non-susceptible strains (DNS). Lipoglycopeptides; notably dalbavancin (DAL), telavancin (TEL), and dalbavancin plus tigecycline (DAL+CFZ) are currently in clinical trial to evaluate the activity of DAL, V AN, and DAP, alone and in combination with CFZ in a pharmacokinetic/pharmacodynamic (PK/PD) model.

Methods. The well-characterized DANS VISA strain, D712, was evaluated in eight different regimens in duplicate via a one-compartment 7-day PK/PD model. The experimental regimens were as follows: D712 growth control, DAL 1500 mg given on day 1, VAN 2 g given every 12 hours, DAP 10 mg/kg once-daily, CFZ 2 g given every 8 hours and DAL, DAP, and VAN in combination with CFZ.

Results. The combinations of DAL+CFZ, VAN+CFZ, and DAP+CFZ demonstrated a significant log CFU/mL reduction (more than 5 log CFU/mL and up to detection limit), compared with each drug used as monotherapy (P < 0.001). Neither DAP nor VAN demonstrated sustained bactericidal activity (represented by a >3-log CFU/mL reduction from baseline) and resulted in significant regrowth, when administered alone. However, the DAP + CFZ, and VAN+CFZ combination models demonstrated bactericidal activity at 4 hours and 24 hours, respectively. While DAL alone did demonstrate bactericidal activity, the DAL+CFZ combination was more rapidly bactericidal, achieving a >3-log reduction from baseline in 8 hours vs. 48 hours (P < 0.05).

Conclusions. The combination of DAL, VAN, or DAP with CFZ demonstrated significantly improved activity against this multiple drug-resistant S. aureus strain. Further research is warranted, both in vivo and in vitro, to explore the synergistic capabilities of anti-MRSA drug therapy in combination with β-lactams.

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