1382. Acute Kidney Injury with Piperacillin–tazobactam and Vancomycin in the Intensive Care Unit
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Background. Several recent retrospective studies have suggested that the combination of vancomycin (V) with piperacillin–tazobactam (PTZ) is associated with increased nephrotoxicity. We prospectively evaluated the outcomes of patients admitted to all of our medical and surgical intensive care units (ICU) with a normal baseline creatinine clearance (CrCl) that received vancomycin in combination with either ceftazidime (CEF) or PTZ to determine whether kidney injury occurs using RIFLE criteria.
Methods. ICU patients who received combinations of V with either PTZ or CEF were prospectively evaluated from June 1, 2017 to April 28, 2018 using Theracost. V and PTZ dosing were standardized per ICU policy and monitored by clinical pharmacists. We included patients between ages 18 and 90, and receipt of >72 hours of combination antibiotic therapy. We excluded patients that were pregnant, had a hematologic malignancy, chronic kidney disease, or neuromuscular disease. Data collected included, CrCl, V troughs, dosage and length of all antibiotics used, ICU length of stay (LOS), and co-administered nephrotoxic medications (e.g., NSAIDs and IV contrast). The primary objective was to compare the incidence of AKI in these study groups, as defined by the RIFLE criteria.
Results. Of 233 patients evaluated, 58 (25%) met inclusion criteria, 45 received PTZ-V and 13 CEF-V. Only eight of 58 (14%) MRA-positive criteria.

Table 1: Data Summary

|          | PTZ-V | CEF-V | P-value |
|----------|-------|-------|---------|
| Age (median, range) | 68 (35–84) | 64 (18–79) | 0.54 |
| Gender (male) | 30 (67%) | 7 (84%) | 0.51 |
| Median weight (kg) | 86 (54–136) | 82.4 (51–156) | 0.6 |
| No > 100 kg | 11 (24%) | 3 (23%) | 0.77 |
| Median V trough/24 | 11.4 (5.5–32.7) | 10.6 (6.4–29.5) | 0.695 |
| Median V days (range) | 5 (3–16) | 4 (3–13) | 0.99 |
| Co-admin nephrotoxic agent | 41 (91%) | 85 (7%) | 0.61 |
| ICU LOS | 11 (4–38) | 14 (3–32) | 0.38 |
| Hospital LOS | 15 (4–36) | 20 (6–72) | 0.037 |
| No. AKI by RIFLE | 13 | 0 | 0.028 |

We found no correlation with co-administered nephrotoxic agents, vancomycin troughs, or body weight and AKI.

Conclusion. Our prospective observational study data revealed significant AKI with PTZ-V compared with CEF-V but it did not impact patient long-term outcomes. Caution with PTZ-V may be required when used in ICU settings even in patients with normal baseline CrCl.

Disclosures. J. S. Lewis II, Merck: Consultant, Consulting fee.

1383. In vivo Pharmacokinetic/Pharmacodynamic (PK/PD) Evaluation of NOSO-502, a First-in-Class Odiilorhabdin Antibiotic, Against E. coli (EC) and K. pneumoniae (KPN) in the Murine Neutropenic Thigh Model
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Background. Several recent retrospective studies have suggested that the combination antibiotic therapy. We excluded patients that were pregnant, had a hematologic malignancy, chronic kidney disease, or neuromuscular disease. Data collected included, CrCl, V troughs, dosage and length of all antibiotics used, ICU length of stay (LOS), and co-administered nephrotoxic medications (e.g., NSAIDs and IV contrast). The primary objective was to compare the incidence of AKI in these study groups, as defined by the RIFLE criteria.

Results. Of 233 patients evaluated, 58 (25%) met inclusion criteria, 45 received PTZ-V and 13 CEF-V. Only eight of 58 (14%) MRA-positive criteria.

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We found no correlation with co-administered nephrotoxic agents, vancomycin troughs, or body weight and AKI.

Conclusion. Our prospective observational study data revealed significant AKI with PTZ-V compared with CEF-V but it did not impact patient long-term outcomes. Caution with PTZ-V may be required when used in ICU settings even in patients with normal baseline CrCl.

Disclosures. J. S. Lewis II, Merck: Consultant, Consulting fee.

1384. RSV Monoclonal Antibody (MK-1654) Phase 1 Pharmacokinetics (PK) in Healthy Adults and Population PK Modeling to Support Pediatric Development
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Background. Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection and hospitalization in infants. MK-1654 is a monoclonal antibody (mAb) being developed to prevent RSV infection in infants and is undergoing evaluation in a Phase 1 study. Incorporation of YTE mutations extends its half-life to allow for dosing once every RSV season. Preliminary Phase 1 PK results and the development of a population PK model that characterizes adult PK to predict pediatric exposures are presented here.

Methods. In this double-blinded Phase 1 study, 152 healthy males and females of nonchilbearing potential aged 19–59 years were randomized in a 3:1 ratio to receive a single dose of MK-1654 or placebo as a bolus intramuscular injection (IM) or an intravenous infusion (IV) over 2.5 hours. Dose levels included 100 mg IM, 300 mg IM, 300 mg IV, 1,000 mg IV and 3,000 mg IV. Serial serum samples were collected to measure MK-1654 PK via a validated LC/MS assay. A noncompartmental PK analysis was conducted using preliminary data from 60 subjects up to Day 150 (900 observations). A population PK model was developed to simultaneously characterize the IM and IV adult PK data and to predict pediatric PK through allometric scaling. Pediatric MK-1654 PK was predicted for several IM doses for a typical sized infant (35 weeks gestational age at birth; 4 months chronological age at dosing; 50 percentile weight).

Results. In adults, the median time to maximum concentration observed was 6–10 days following IM injection. The apparent half-life of MK-1654 ranged from ~70–85 days after either IM or IV doses. The estimated IM bioavailability was ~71%. Cmax and AUCinf increased dose proportionally following IV administration. MK-1654 adult PK was best characterized using a two-compartment model with first-order elimination. IM absorption was described using a first-order rate constant with lag time. Inter-individual variability was included for clearance (CL and Q), central volume (V2) and absorption rate (Ka). The pediatric model suggested apparent terminal half-life in a typical infant is shorter than adults, likely being driven by infant growth during treatment.

Conclusion. Predicted infant PK profiles support further development of MK-1654 in children.
1385. Efficacy of Cefazidime–Avibactam in Combination with Aztreonam (COMBINE): Solutions for Metallo-β-Lactamase Producing-Enterobacteriaceae (MBL)

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Background. Novel antibiotics will not be available to combat the threat of MBLs until 2021. One strategy to overcome MBLs is to combine CAZ-AVI + ATM. ATM is not hydrolyzed by MBL and AVI offers protection for ATM and CAZ vs. ESBLs and AmpCs. The combination also offers a theoretical advantage to inactivating multiple PBP’s by using dual β-lactam therapy. Our objective was to define optimal dosing profiles for clinical use of ATM to add to CAZ-AVI in the hollow fiber infection model (HFIM).

Methods. 15 subjects were enrolled in each of four groups: CAZ-AVI q6h + ATM q12h; CAZ-AVI q12h + ATM q6h; ATM q6h + CAZ-AVI q12h. These dosing regimens were studied at a 7.5 g, CFU/mL in the HFIM. Human dosing regimens of CAZ-AVI 2 g/0.5 g q8h (2 hours infusion) and ATM 2 g q8h (2 hours infusion) were simulated in alone and in combination. Continuous infusion (CI) regimens of CAZ-AVI 6.5 g/1.5 g per day CI + ATM 6 g/day CI and q8h regimens were given simultaneously and sequentially (ATM given 2 hours after CAZ-AVI). Resistant subpopulations were profiled on single (ATM), double (CAZ-AVI) and triple (ATM/CAZ-AVI) drug plates containing 2/24/4, 8/8/4, or 32/32/4 mg/L over 7 days.

Results. Against E. coli AR10-103, ATM alone mirrored growth control (+3.14 at 168 hours) (All units Log CFU/mL change vs. baseline). CAZ-AVI alone showed some intrinsic activity (+1.19 at 168 hours). CAZ-AVI 2g/0.5g q8h (2 hours infusion) + ATM 2 g q8h showed limited regrowth and stasis (+0.34 at 168 hours) vs. the simultaneous combination resulted initial bactericidal activity (-3.53 killing within 28 hours) which regrew at ~90.9 at 168 hours. All CI regimens were effective. CAZ-AVI 6g/1.5g per day CI + ATM 6 g/day CI resulted in dramatic killing (up to -5.78 killing within 50 hours) which was sustained (up to -3.90 killing at 168 hours). Comparing the infusion time of CAZ-AVI + ATM on bacterial killing, CI + CI > 2 hours > 30 minutes + 30 minutes. CI + CI resulted in complete suppression of resistance over 7 days. Against K. pneumoniae AR100-102, CAZ-AVI (CI) + ATM (CI) resulted in early synergy (5-log killing within 24 hours) and suppression of resistance for more than 168 hours.

Conclusion. The combination of CAZ-AVI + ATM was highly synergistic and suppressed resistance against MBL Enterobacteriaceae in HFIM. ATM efficacy in combination was driven by S.7’s MIC. A Phase 1 study will assess safety to provide patients a critically important solution against ‘untreatable’ Gram negatives.

Disclosures. T. P. Lodise, Consultant and Scientific Advisor, Consulting fee. B. T. Tsuji, Nabriva: Consultant, Consulting fee. Achaogen: Grant Investigator, Educational grant. ARLG, DCRI: Grant Investigator, Grant recipient. NIH/NIADD: Grant Investigator, Grant recipient.

1386. Efficacy of Repeat Dosing of Oral Fosfomycin in a Dynamic Bladder Infection In Vivo Model

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Background. Oral fosfomycin is indicated for uncomplicated urinary tract infections with activity against MDR uropathogens. Despite off-label use of giving three doses every 2–3 days, limited supporting data are available. We performed pharmacodynamic profiling using a dynamic bladder infection in vivo model to assess adequacy of repeat doses of fosfomycin.

Methods. A bladder infection in vivo model simulating urinary infection concentrations after 3 g q (equiv.) oral doses was used with Mueller–Hinton broth (MHB) with 25 mg/L glucose-6-phosphate. Fosfomycin exposures were validated by LC–MS/MS measurements. Pharmacodynamic response of clinical Enterobacteriaceae isolates were examined (eight E. coli, four E. cloacae, four K. pneumoniae; agar dilution MIC 0.25–64 mg/L) following three doses of fosfomycin given every 72, 48 or 24 hours, compared with single dose therapy; Pathogen kill and resistance was assessed by quantitatively cultures on drug-free and fosfomycin-containing Mueller–Hinton agar (MHA +64 mg/L + 512 mg/L).

Results. Fosfomycin exposure following single and multiple doses were accurately reproduced (mean deviation from target 5.0 ± 3.4%, max 11.8%) with minimal variability (relative standard deviation 2.7 ± 3.1%, max 6.8%). Fosfomycin resistance was detected prior to drug exposure in 8/16 isolates (proportion 0.00002–0.001% of total population). All isolates with high-level heteroresistance regrew following single dose fosfomycin. Following three doses given every 72 hours, one additional K. pneumoniae isolate was killed. All other isolates regrew with amplification of HLR subpopulation (median proportion: 71.4%, IQR 57.5–100%). Despite dosing 48 and 24 hours, the same isolates regrew, although HLR subpopulation amplification was reduced (48 hours dosing: 32.0%, IQR 0.005–83.3%: 24 hours dosing: 6.3%, IQR 0.0004–81.3%).

Conclusion. Dynamic in vitro modeling of multiple doses of oral fosfomycin fails to additionally suppress regrowth in the majority of isolates compared with single dose therapy. Baseline high-level heteroresistance is an important predictor for regrowth. These results suggest that giving multiple doses of fosfomycin is not necessarily better than standard single dose therapy. Earlier timing of repeat doses may help suppress the emergence of resistance.

Disclosures. All authors: No reported disclosures.