Methods. Nine subjects with CF were enrolled in the 2 to <18 y old cohort of an ongoing Phase 1 PK study of single-dose intravenous TOL/TAZ in pediatric subjects with suspected or proven Gram-negative infection (NCT02266706). Population PK models for TOL and TAZ were developed using PK data from 12 adult studies and preliminary PK data from pediatric subjects. An exploratory analysis comparing modeled plasma TOL and TAZ PK parameters between CF (N = 9) and non-CF (N = 9) pediatric subjects was conducted.

Results. Mean (range) age and weight of the 9 CF subjects were 11.4 (5.5-17.5) y and 37.4 (17.4-60) kg, respectively. For TOL, the mean (SD) systemic clearance (CL) was normalized by weight was 0.16 (0.03) L/hours/kg in CF and non-CF subjects, respectively, suggesting no difference in CL. Similar observations were made for volume of the central compartment normalized by weight. All subjects achieved the plasma PK/pharmacodynamic (PD) target of %T>MIC of at least 30% for an MIC of 4 µg/mL.

There was a trend towards more patients experiencing nephrotoxicity with such combinations, predominantly with piperacillin-tazobactam. There is a global increase in Gram-negative (GN) pathogens, with an increased interest in the safety, tolerability, and PK of POS IV and POS PFS in pediatric patients (patients) aged 2 to 17 y with documented or expected neutropenia. Methods. This is an ongoing, nonrandomized, multicenter, open-label, sequential dose-escalation study evaluating POS IV and POS PFS. Patients are divided into 2 age groups: 2 to <7 and 7 to 17 y. Each age group includes 2 dose cohorts: 3.5 mg/kg/d and 4.5 mg/kg/d. Patients received 10–28 d of POS initially as IV solution with the option to switch to PFS after 10 d for the remainder of the treatment period. PK sampling was conducted after 7–10 d on each formulation. Target PK exposure was ~90% of patients with C_{\text{T>MIC}} of 500–2,500 ng/mL. C_{\text{T>MIC}} was defined as AUC over a dosing interval.

Results. 57 of 66 patients (86%) who received POS IV were PK evaluable; 35 patients (53%) received POS PFS, of whom 30 (86%) were PK evaluable. Table 1 shows C_{\text{T>MIC}} and proportion in target range of PK-evaluable patients by dose cohort and age group. The safety profiles of POS IV and PFS were similar to those previously reported for adults treated with oral/IV POS.

Table 1. C_{\text{T>MIC}} and proportion in target range of PK-evaluable pts

| Dose, mg/kg | Age, y | Formulation | n | Mean C_{\text{T>MIC}}, ng/mL | n (%) within C_{\text{T>MIC}} range, ng/mL |
|-------------|--------|-------------|---|-----------------------------|-------------------------------------|
| 3.5         | 2-7    | IV          | 11 | 743                        | 2 (18)                             |
|             | 7-17   | PFS         | 5 | 511                        | 3 (60)                             |
| 4.5         | 2-7    | IV          | 13 | 1080                       | 0 (1300)                           |
|             | 7-17   | PFS         | 7 | 976                        | 1 (14)                            |
|             |        |            | 14 | 1310                       | 0 (1303)                           |
|             |        |            | 8 | 1190                       | 0 (1003)                           |

Conclusion. POS PFS resulted in lower POS exposure than IV across age groups at both dose levels. POS exposure was substantially lower in the younger age group for both IV and PFS. At 4.5 mg/kg, the patients in this study achieved the predefined target but did not achieve systemic exposures (mean C_{\text{T>MIC}} comparable to those seen in adults with POS IV or PFS. These results suggest that study of POS IV and PFS dosing >4.5 mg/kg is warranted.

Disclosures. A. H. Groll, Merck: Consultant, Investigator, Biogen: Speaker honorarium, Grant/Research Support for Speaker honorarium. T. L. Lehnlebrecher, Merck: Consultant, Investigator, Biogen: Speaker honorarium. Astellas: Consultant, Investigator, Biogen: Speaker honorarium. Basilica: Consultant, Investigator, Biogen: Speaker honorarium. Pfizer: Consultant, Investigator, Biogen: Speaker honorarium. B. Steinbach, Merck: Consultant, Investigator, Biogen: Speaker honorarium. C. Bruno, Merck: Consultant, Investigator, Biogen: Speaker honorarium.
of Southern Nevada. Treatment was considered empiric when antibiotic was given prior to culture results. Escalation was the additional of an aminoglycoside or colistin after the start of C/T.

**Results.** There were 30 patients in the study. Average age was 57 (SD = 16) and most 19 (63%) were male, Caucasian 22 (73%) and were admitted from the community or home (60%). The most frequent comorbidities were diabetes 13 (43%), heart disease 12 (40%) and chronic pulmonary disease 10 (33%). Previous medical history within 90 days included 15 (50%) hospitalizations, 13 (43%) infections, 6 (20%) Intensive Care Unit stays and 7 (23%) surgeries. All patients received a GN antimicrobial within 30 days prior to C/T. Ninety-three percent of infections were due to P. aeruginosa and 17 (57%) were polymicrobial. All but 4 patients had multidrug-resistant P. aeruginosa. The most frequent source of infection (some multiple sources) was respiratory 20 (67%), cUTI 8 (27%) and sepsis 5 (17%). Empiric C/T therapy was given to 7 (23%) patients. One patient required escalation of therapy after C/T. Average duration of C/T was 10 (SD = 5.4) days. 23 (77%) patients were discharged within 30 days of last dose of therapy. Microbiological eradication was documented for 12 patients. There were 5 (17%) readmissions, but none associated with a GN infection. Six patients died (1 bilateral stroke, 1 cancer, 2 septic shock, 1 pneumonia and 1 complications of burn).

**Conclusion.** In this study, C/T was used in patients with serious infections primarily due to P. aeruginosa, with most patients discharged within 30 days and no patients readmitted due to GN infection. This study provides important insights on how C/T is used in clinical practice.

**Disclosures.** R. Kullar, Merck & Co., Inc.: Employee, Salary. B. Jayakumar, Merck: Grant Investigator, Research grant. L. Puzniak, Merck: Employee, Salary.

### 8.29. Therapeutic Drug Monitoring (TDM) of Suspension (SUS), Extended-Release (ER), and Intravenous (IV) Posaconazole (POS) at a Large Transplant Center

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**Session:** Use of PK/PD to optimize existing antibiotics and antifungals

**Thursday, October 5, 2017: 12:30 PM**

**Data on ER and IV POS among organ transplant recipients (OTRs) are limited, and the role of TDM is unclear.**

**Methods.** Retrospective study of patients (pt) receiving any formulation of POS who had serum troughs checked. Therapeutic was defined as 1 mcg/mL.

**Results.** We analyzed 88 pt and 340 levels (SUS: 88, ER: 197, IV: 55). Eighty-five pt were OTRs (97%), 73 were lung transplant recipients (LT) (83%), 17 had cystic fibrosis (CF) (19%), POS was used for treatment (70%) (probable aspergillosis (38%), possible aspergillosis (10%), maoerocytosis (16%), other mycoses (6%), prophylaxis (19%), and pre-emptive therapy (14%). POS was given for intolerance of or contraindication to other azoles (47%), salvage therapy (10%), (P = 0.51) (Figure). There was no difference in serum levels between pt receiving ER vs. IV POS at 300 mg once daily (median 1.2 vs. 1.3 mcg/mL, therapeutic 70% vs. 73%, P = 0.57 and >0.99, respectively). 3 pt had levels £ 0.2 mcg/mL on 300 mg ER: 2 had CF and had undergone LT (0.2 and 0 mcg/mL) and 1 had short-gut syndrome (0.1 mcg/mL). Sixty-six percent and 67% of pt receiving ER or IV POS (300 mg once daily) achieved initial therapeutic levels, respectively; of these, 87% and 83% had median therapeutic follow-up levels, respectively. Serial levels were available for 7 pt whose dose was increased from 300 to 400 mg ER once daily for subtherapeutic levels. 4/7 pt achieved therapeutic levels on 400 vs. 0.7 on 300 mg ER once daily (P = 0.069). Metoclopramide use and CF were associated with subtherapeutic vs. therapeutic levels (25% vs. 4% and 37% vs. 13%, respectively, P = 0.05). When pt with CF were excluded, neither age nor body mass index were associated with POS levels. CF pt had lower levels than non-CF pt on a dose of 300 mg ER once daily (median 0.8 vs. 1.3 mcg/mL, P = 0.018).

**Conclusion.** Therapeutic levels are more reliably achieved with ER & IV POS compared with SUS POS. Serial TDM is unnecessary for most, but is recommended for pt with CF or those on metoclopramide. Dose increases may effectively increase levels. Novel dosing strategies are needed for CF.

**Disclosures.** R. K. Shields, Astellas: Received research funding, Research support.

Merck: Received research funding, Research support. C. J. Clancy, Merck: Received research funding, Research support. Astellas: Received research funding, Research support. Cidara: Received research funding, Research support. Astellas: Scientific Advisor, Advisory board. Merck: Scientific Advisor, Advisory board. Cidara: Scientific Advisor, Advisory board. Medicines Company: Scientific Advisor, Advisory board.

### 8.30. Clinical Manifestations and Outcome of Fluoroquinolone Associated Acute Intestinal Nephritis

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**Session:** Use of PK/PD to optimize existing antibiotics and antifungals

**Thursday, October 5, 2017: 12:30 PM**

**Background.** Fluoroquinolones (FQ) are among the most commonly prescribed antibiotics. Nephrotoxicity related to FQ use is infrequently reported and the mechanism of renal injury is incompletely elucidated. We describe clinical manifestations and outcome of patients with biopsy proven acute intestinal nephritis (AIN) associated with FQ use at our institution.

**Methods.** We conducted a retrospective review of biopsy-proven AIN attributed to FQ use at Mayo Clinic Rochester from 1993 to 2016. Cases were reviewed by a renal pathologist and attributed to FQ use by an expert nephrologist. We also reviewed and summarized all published case reports of biopsy proven AIN that were attributed to FQ use.

**Results.** We identified 24 patients with FQ-related biopsy-proven AIN. The most commonly used FQ was ciprofloxacin (71%) with median antibiotic treatment duration of 7 days (Figure 1). The median duration between starting FQ and the diagnosis of AIN was 8.5 (IQR: 17). Common clinical manifestations included fever (50%), flank pain (8%), and skin rash (21%). However, 17% of the patients were asymptomatic at the time of diagnosis (Figure 2). Majority (58%) of the patients recovered following discontinuation of antibiotics and returned to baseline renal function at a median of 20.5 (IQR: 15.5). Six patients required temporary hemodialysis and 9 patients received steroids.

**Conclusion.** Onset of FQ-related AIN can be delayed and a high index of suspicion is needed by physicians prescribing these agents. Overall outcomes are favorable with recovery to baseline renal function within 3 weeks of discontinuing the offending drug.

**Figure 1:** Therapeutic Drug Monitoring (TDM) of Suspension (SUS), Extended-Release (ER), and Intravenous (IV) Posaconazole (POS) at a Large Transplant Center

**Figure 2:** Presenting clinical features

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