Results. Of 1,426 studies identified, 18 encompassing 8,966 patients were included. Treatment with vancomycin was associated with significantly increased odds of nephrotoxicity (OR, 2.41; 95% CI, 1.71 to 3.40; P<0.00001) relative to its alternatives. A subgroup analysis grouping studies by reported vancomycin dosing approach revealed a stronger association between vancomycin and nephrotoxicity in studies with fixed-dose vancomycin regimens (OR 5.31; 95% CI 1.93 to 14.56; P=0.001) relative to studies with vancomycin therapeutic drug monitoring (TDM) (OR 2.17; 95% CI 1.51 to 3.13; P<0.0001).

Figure 2. Forest plot indicating the risk of nephrotoxicity associated with vancomycin vs. comparators.

Table 1. Summary of included studies.

| Study | Nephrotoxicity definition | Comparator drug(s) | Infection type | Vancomycin dosing approach | Concurrent gram-negative coverage |
|-------|--------------------------|-------------------|----------------|---------------------------|----------------------------------|
| Reuther 2014 | BCi > 3.1 and/or ID > 8.4 mg/dL | Teicoplanin | BSI, BSI, IE | TDM | None |
| Carver 2017 | Increase in SO to 2.5 mg/dL or > 50% (both unchanged) | Teicoplanin, rifampin, tobramycin | BSI, BSI, IE | TDM | No information |
| Corre 2018 | Increase in SO to 2.5 mg/dL (both unchanged) | Teicoplanin, meropenem | BSI, BSI, IE | TDM | Adenomycin, metronidazole |
| Cordado 2020 | SCr > 2 mg/dL, and/or ID > 8.4 mg/dL | Teicoplanin, ceftriaxone | BSI, BSI, IE | TDM | Adenomycin, metronidazole |
| Faenm 2020 | Discontinued therapy due to renal failure | Teicoplanin, cefuroxime | BSI, BSI, IE | TDM | Adenomycin, metronidazole |
| Holland 2018 | Increase in SO to 3.1 mg/dL or > 50% (both unchanged) for at least 2 consecutive days | Teicoplanin, amikacin | BSI, BSI, IE | TDM | Adenomycin, metronidazole |
| Huang 2017 | Blood creatinine increased | Teicoplanin | BSI, BSI, IE | TDM | Adenomycin, metronidazole |
| Huang 2016 | AV | Teicoplanin | BSI, BSI, IE | TDM | Adenomycin, metronidazole |
| Kallulinin 2018 | Increase in SO of 1.5 mg/dL or > 50% from baseline | Teicoplanin | BSI, BSI, IE | TDM | None |
| Konrath 2015 | Blood creatinine increased | Teicoplanin | BSI, BSI, IE | TDM | None |
| Liu 1996 | >50% increase in baseline SO | Teicoplanin | BSI, BSI, IE | TDM | Meropenem, amikacin, ciprofloxacin, ticarcillin, quinolones, metronidazole |
| O’Hara 2018 | SCr = 2 times the ULN | Teicoplanin | BSI, BSI, IE | TDM | Adenomycin, metronidazole |
| Polman 2017 | Renal failure | Teicoplanin | BSI, BSI, IE | TDM | Adenomycin |
| Reed 2009 | Acute renal failure | Teicoplanin | BSI, BSI, IE | TDM | Adenomycin, metronidazole |
| Van der Awer 2015 | A reversible increase in SO (2.5 mg/dL) | Teicoplanin | BSI, BSI, IE | TDM | Adenomycin, metronidazole |
| Wunderl 2003 | Kidney failure | Teicoplanin | BSI, BSI, IE | TDM | Adenomycin |
| Wunderl 2012 | Increase in SO to 3.1 mg/dL or > 50% from baseline | Teicoplanin | BSI, BSI, IE | TDM | No information on the drugs |

Odds ratios (ORs) and 95% confidence intervals (95% CIs) are shown for each study and the pooled analysis using a random effects model and the Mantel-Haenszel method. OR=1 means that the risk of kidney injury in the vancomycin group is greater than that in the comparator group.

Figure 3. Forest plot indicating a strong association between vancomycin and nephrotoxicity in studies with fixed-dose vancomycin regimens relative to studies with vancomycin therapeutic drug monitoring (TDM).

Odds ratios (ORs) and 95% confidence intervals (95% CIs) are shown for each study and the pooled analysis using a random effects model and the Mantel-Haenszel method. OR=1 means that the risk of kidney injury in the vancomycin group is greater than that in the comparator group.

Conclusion. This analysis shows that intravenous vancomycin is associated with greater odds of renal toxicity relative to alternative antibiotics. This effect was not as pronounced in studies where vancomycin TDM was used potentially indicating benefit of TDM although further study is required to confirm this.

Disclosures. All Authors: No reported disclosures

1113. Oral Tebipenem as Step-Down Therapy Following Intravenous Ertapenem in a 7-day Hollow-Fiber In Vitro Infection Model
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Session: P-62. PK/PD Studies

Background. Intravenous (IV) to oral (PO) antibiotic step-down therapy has many benefits including reducing the length of hospital stay and lowering the risk of nosocomial infections and overall cost. While fluoroquinolones have been utilized as a
down-step therapy for urinary tract infections (UTI) for some time, increases in fluoroquinolone-resistant Escherichia coli makes this an increasingly unsuitable option. Tebipenem (TBP) is an orally bioavailable carbapenem administered as a pro-drug (tebipenem pivoxil hydrobromide) with broad-spectrum activity that is currently in development for the treatment of patients with complicated UTI. Herein we describe the use of a reduction from IV ETP therapy and the need for evaluation as a step-down from other study.

Results. Bacteria grew well in the no-treatment control group, reaching densities >10⁶ CFU/mL. ETP 1g q24h for 1 or 3 days followed by a halting of therapy. Samples were collected for enumeration of bacterial populations and observation of simulated PK profiles throughout.

Conclusion. These data demonstrate the potential utility of TBP as oral step-down from IV ETP therapy and the need for evaluation as a step-down from other IV therapeutics.
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. FK/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 retrospective, 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, extrapulmonary infections, acute kidney injury, reintubation, or invasive ventilator support.

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. A post-hoc multivariate analysis was conducted to assess predictors of not attaining clinical cure.

Disclosures. All Authors: No reported disclosures

Table 1. Patients’ demographics and baseline characteristics

| CharacterISTIC | TDM (n=95) | Non-TDM (n=105) | p value |
|---------------|------------|-----------------|--------|
| Age (years)   | 63±14      | 64±15           | 0.883  |
| Male (%)      | 56 (60)    | 72 (68)         | 0.050  |
| BMI (kg/m²)   | 26±2.9     | 25±2.9          | 0.273  |
| CRP (mg/L)    | 13 (9-39)  | 10 (8-55)       | 0.589  |
| BUN (mg/dL)   | 7 (6-11)   | 5 (4-9)         | 0.518  |
| Creatinine (mg/dL) | 0.7 (0.6-1.4) | 0.7 (0.6-1.1) | 0.108  |
| AST (U/L)     | 15 (14)    | 20 (18)         | 0.103  |
| CHB-C-reactive index | 4.0±1.1    | 5.1±1.7         | 0.881  |
| SODA score    | 5 (4-8)    | 5 (4-8)         | 1.000  |

Table 2. Primary and secondary outcomes

| OUTCOME | TDM (n=95) | Non-TDM (n=105) | p value |
|---------|------------|-----------------|--------|
| Total clinical cure | 75 (80) | 70 (67) | 0.301  |
| All-case mortality | 12 (13) | 21 (20) | 0.589  |
| Antibiotic escalation | 4 (14) | 6 (10) | 0.724  |
| Escalation in level of care | 3 (1) | 0 (0) | 0.497  |
| All-cause in hospital mortality | 15 (16) | 23 (22) | 0.198  |
| Hospital length of stay | 21 (15-31) | 21 (14-29) | 0.337  |
| Intensive care unit length of stay | 19 (11-24) | 14 (8-23) | 0.019  |
| Adverse event during BLA therapy | 31 (32) | 29 (30) | 0.898  |
| Acute kidney injury | 3 (3) | 6 (6) | 0.497  |
| Renal dysfunction | 5 (5) | 3 (3) | 0.483  |

*Data are presented as number (%) or median (interquartile range) as appropriate.

1115. Evaluation of Gepotidacin (GSK2140944) Pharmacokinetics and Food Effect in Japanese Subjects
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Session: P-62. FK/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 single oral doses in the fed state. Part 2, gepotidacin PK was assessed following 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-∞]) and maximum observed concentration (Cmax) 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 dosing.