Session: P-72. Resistance Mechanisms

Background. Beta-lactams have demonstrated superior outcomes over vancomycin for MRSA bacteremia. Clinical studies of the anti-MRSA beta-lactam ceftriaxone in MRSA bacteremia (MRSab) are largely limited in size or focus on combination or salvage regimens. This study sought to further examine ceftriaxone as first-line therapy for MRSA.

Methods. This was a retrospective matched cohort study at the San Diego VA Medical Center between November 2010 and June 2020. Patients had to have received at least 72 hours of ceftriaxone or vancomycin for MRSab and less than 72 hours of prior MRSA therapy. Adjunct MRSA therapy was allowed if only routinely indicated (e.g., rifampin in prophylaxis). Patients in the vancomycin group were matched 1:1 to patients in the ceftriaxone group by age ( +/- 10 years) and Pitt bacteremia score (+/- 1 point). The primary outcome was duration of bacteremia after initiation of MRSA therapy, including time on prior MRSA therapy.

Results. Fifteen patients were included in each group, with a median age of 65 years and Pitt bacteremia score of 0. Patients in the ceftriaxone group were more likely to have CKD; to have been on a different MRSA agent prior to initiation of the study drug, with a median of 1 day of prior treatment; and to have been on adjunctive rifampin or clindamycin. Though not significant, more patients in the ceftriaxone group also had endovascular sources, uncontrolled sources, and longer durations of therapy. The median duration of bacteremia after initiation of MRSA therapy did not significantly differ between ceftriaxone and vancomycin (4 vs. 3 days, p = 0.806). In addition, 30-day all-cause mortality, in-hospital mortality, and day-7 hospital mortality did not significantly differ between groups.

Conclusion. This study suggests ceftriaxone may be an appropriate first-line agent for the treatment of MRSA bacteremia with similar outcomes between groups despite the ceftriaxone group likely experiencing more difficult-to-treat infections. However, it was not powered to detect differences between groups, and further research has the potential to introduce bias. Prospective comparative studies are needed to corroborate these findings.

Disclosures. All Authors: No reported disclosures

1240. Ceftriaxone Activity against Drug-Resistant *Staphylococcus aureus* Clinical Isolates Collected in the United States from 2016 through 2020

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Session: P-72. Resistance Mechanisms

Background. Multidrug-resistant (MDR) and methicillin-resistant *Staphylococcus aureus* (MRSA) present significant treatment challenges and can cause serious morbidity and mortality. Ceftriaxone, the active moiety of the prodrug cefotribime medocaril, is an advanced cephapirin approved in many European and other countries for the treatment of adults with community- and hospital-acquired pneumonia, excluding ventilator-associated pneumonia. Ceftriaxone is currently in phase 3 clinical development to support a New Drug Application in the United States for acute bacterial skin and skin structure infections and *S. aureus* bacteremia. Here, the activity of ceftriaxone and comparators was evaluated against recent MDR *S. aureus* and MRSA clinical isolates.

Methods. 13,668 *S. aureus* isolates were collected from patients with various infection types at 34 US medical centers from 2016–2020. Susceptibility to ceftriaxone and comparator agents was tested by CLSI methods. Current CLSI and EUCAST interpretive criteria were applied (Table). Isolates were categorized as MDR if they were non-susceptible (NS): CLSI criteria (group B) to ≥2 of the following antimicrobials: clindamycin (CM), daptomycin (DAP), erthromycin (ERY), gentamicin (GM), levofloxacin (LEV), linezolid (LZD), tetracycline (TET), tigecycline (TGC), trimethoprim-sulfamethoxazole (TMP-SMX), or vancomycin (VAN). Isolates displaying oxacillin MIC values ≥4 μg/mL were categorized as MRSA.

Results. *C. difficile* was more active than ceftriaxone (CPT) against MRSA (99.2% susceptible [S] versus 94.0% S, respectively) (Table). Ceftriaxone maintained activity against 88.0% of the CPT-NS isolates, but CPT was only active against 6.5% of the ceftriaxone-NS isolates. Ceftriaxone was also highly active (97.7–100.0% S) against isolates to CM, DAP, ERY, GM, LEV, LZD, TET, TGC, or TMP-SMX. No VAN-NS isolates were detected. Importantly, ceftriaxone was more active (97.7% S) than CPT (93.0% S) against the subset of MDR-MRSA isolates.

Conclusion. *C. difficile* was highly active in vitro against MRSA and MDR *S. aureus* collected at US medical centers during 2016–2020. These results support the further development of ceftriaxone to treat *S. aureus* infections in the US.
1241. In Vivo Efficacy of Meropenem Against Metallo-β-Lactamase (MBL)-Harboring Pseudomonas aeruginosa and Correlation to In Vitro Susceptibility to Ertapenem

Background. Prior investigations evaluating the predictive value of zinc-depleted media for MBL susceptibility testing have focused on Enterobacteriaceae. In this study, we evaluated a bacterial killing observed with meropenem (MEM) in vivo with its pharmacodynamic profile using MIC values determined in zinc-depleted media compared with conventional cation-adjusted Mueller-Hinton broth (CAMHB). This study aims to evaluate the exposure-response relationship of MEM against VIM- and NDM-harboring P. aeruginosa (PA) using the murine thigh infection model and zinc-depleted MICs.

Methods. MBL-harboring PA isolates (VIM n=11; NDM n=10) were tested in vivo (neutropenic murine thigh infection model) and in vitro (broth microdilution). The 24h murine thigh was conducted with treatment groups receiving a humanized MEM 2g q8h (3h infusion) dose. Six different zinc-limited media were prepared by the addition of EDTA at concentrations ranging from 3 to 300 mg/L to CAMHB. MEM MICs were determined in triplicate in conventional CAMHB and zinc-depleted media. The primary end point was plotted against the change in 24h bacterial density count in an Emax model.

Results. Average 0 h bacterial densities were 5.31 ± 0.40 and 5.13 ± 0.81 log CFU/g for NDM and VIM isolates, respectively. MEM resulted in -0.89 CFU reduction to +3.69 CFU growth against NDM isolates. MEM resulted in -2.59 CFU reduction to +4.81 CFU growth against VIM isolates. All MEM MICs in conventional CAMHB were >64 µg/mL for NDM and ranged from 8 to >64 µg/mL for VIM isolates. Increasing EDTA concentrations resulted in several-fold MIC reductions and on average, a larger magnitude of reduction was observed among VIM (6-fold) compared with NDM-harboring PSA (4-fold) in CAMHB-EDTA 300 mg/L relative to CAMHB. Therein, MBL-harboring PA isolates harboring PSA, and addition of EDTA (30 mg/L) to CAMHB appears to be a viable option for in vitro testing of these organisms.

Disclosures. David P. Nicolaou, PharmD, Abbvie, Cepheid, Merck, Paratek, Pfizer, Wockhardt, Shionogi, Tetraphase (Other Financial or Material Support, I have been a consultant, speakers bureau member, or have received research funding from the above listed companies.)

1242. Efficacy and Safety of Intravenous Fosfomycin for the Treatment of Multi-resistant Gram Negative Infections

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Session: P-72. Resistance Mechanisms

Background. To describe the clinical use, efficacy and safety of intravenous (IV) fosfomycin in the treatment of infections caused by Gram-negative bacteria (GNB).

Methods. Hospitalized patients who received ≥48 hours of IV fosfomycin therapy during September 27, 2017 thru January 31, 2020 were included. The primary outcome was the proportion of subjects with clinical improvement at the end of IV fosfomycin therapy; defined as resolution of baseline signs and symptoms of infection.

Results. Thirty patients were included, of which 19 (63.3%) were males, and the median age was 63.5 years (interquartile range 46–73). Frequent risk factors for GNB infection included hospitalization (23, 76%), receipt of broad-spectrum antibiotics (15, 50%), and surgery (10, 33.3%), all within the preceding 90 days. Urinary tract infection (17, 56.7%) was the most common indication for use of IV fosfomycin, followed by bacteremia (4, 13.3%), and skin and soft tissue infections (4, 13.3%). Klebsiella pneumoniae (17, 56.7%), Escherichia coli (7, 23.3%) and Pseudomonas species (4, 13.3%) were the most common target pathogens. Almost all target pathogens (29, 96.7%) were resistant in vitro to ≥1 agent from ≥3 different antimicrobial classes. The primary outcome was achieved in 22 (73.3%) patients. The most frequently observed adverse events were hypokalemia (13, 43.3%) and hypernatremia (7, 23.3%). However, the majority of adverse events were classified as Grade 1 or Grade 2 severity.

Microbiological characteristics

| Organism                  | E. Coli | Klebsiella pneumoniae | Pseudomonas aeruginosa | Other |
|---------------------------|---------|----------------------|------------------------|-------|
|                           | 7       | 17                   | 4                      | 2     |
| MDRO                      | 29      | 96.7%                | 33.3%                  | 68.7% |

The table describes microbiological characteristics of the isolated organism species, resistance pattern, development of fosfomycin resistance.

Management outcomes and safety profile

Clinical outcome

| Clinical outcome | 22 | 73.3%
|-----------------|----|------------------|
| Microbiological outcome | 20/22 | 91%
| Treatment success | 21 | 70%

Side effect

| Side effect | 13 | 43.3% |
|-------------|----|-------|
| Hypokalemia | 13 | 43.3% |
| Grade 1     | 13 | 43.3% |
| Grade 2     | 13 | 43.3% |
| Hypernatremia | 7 | 23.3% |
| Grade 3     | 20/27 | 77.8% |
| Grade 4     | 20/27 | 77.8% |
| Neutropenia | 2 | 6.7% |
| Eosinophilia | 2 | 6.7% |
| Grade 1     | 2 | 6.7% |
| Grade 2     | 2 | 6.7% |
| Allergy     | 1 | 3.3% |
| Premature discontinuation | 6 | 20% |
| 30 days Mortality | 7 | 23.3% |
| ICU admission | 11 | 38.7% |

Conclusion. IV fosfomycin is a potentially effective and safe option for the treatment of patient with GNB infections.

Disclosures. All Authors: No reported disclosures

1243. Eravacycline in Bacteremia: A Case Series

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Session: P-72. Resistance Mechanisms

Background. Eravacycline (ERV) is FDA-approved for the treatment of complicated intra-abdominal infections, but there is limited experience for non-FDA approved indications.

Methods. We present five cases that utilized ERV for treatment of bacteremia. Results. Patient 1 in septic shock (SS) started on vancomycin (VAN) and cefazidine-avibactam (CZA). Blood culture (BC) finalized to E. coli and regimen narrowed to CZA. On day 9, gram-positive cocci in chains in BC grew and VAN was added. BC finalized to VRE faecium and regimen was modified to ERV on day 12. Repeat BC on day 15 showed no growth with no recurrence of bacteremia until discharged (day 78). Patient 2 treated for MSSA bacteremia with cefazolin and subsequent K. pneumoniae VAP treated with ceftiazonde (CZO) (day 18–26). On day 27, meropenem (MEM) was initiated for gram-negative bacteremia and started on IV trimethoprim/