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1239. Ceftaroline versus Vancomycin as First-Line Therapy for MRSA Bacteremia

Meghan Kamath, PharmD[1]; Ariel Ma, PharmD[2]; Scott T. Johns, PharmD[3]; [1]VA San Diego Healthcare System, San Diego, California; [2]VA San Diego Medical Center, San Diego, California; [3]San Diego VA Healthcare System, San Diego, California

Session: P-72. Resistance Mechanisms

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

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 ceftaroline or vancomycin for MRSAB and less than 72 hours of prior MRSA therapy. Adjunct MRSA therapy was allowed only if routinely indicated for the infection (e.g. rifampin for prosthesis). Patients in the vancomycin group were matched 1:1 to patients in the ceftaroline 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 ceftaroline 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 ceftaroline 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 ceftaroline and vancomycin (4 vs. 3 days, p = 0.806). In addition, 30-day all-cause mortality, in-hospital mortality, 90-day readmission or treatment failure, inpatient length of stay, total duration of bacteremia, and rate of adverse events did not significantly differ between groups.

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

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

Leonard R. Duncan, PhD[1]; Kamal Hamed, MD, MPH[2]; Jennifer Smart, PhD[3]; Michael A Pfaller, MD[1]; Helio S. Sader, MD, PhD, FIDSA[1]; [1]JMI Laboratories, North Liberty, Iowa; [2]Basilea Pharmaceutica International Ltd., Basel, Basel-Stadt, Switzerland; [3]Basilea Pharmaceutica International AG, Basel, Basel-Stadt, Switzerland

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. Ceftobiprole, the active moiety of the prodrug ceftobiprole medocaril, is an advanced cephalosporin approved in many European and other countries for the treatment of adults with community- and hospital-acquired pneumonia, excluding ventilator-associated pneumonia. Ceftobiprole 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 ceftobiprole and comparators was evaluated against recent MDR *S. aureus* and MRSA clinical isolates.

Methods. 13,868 *S. aureus* isolates were collected from patients with various infection types at 34 US medical centers from 2016–2020. Susceptibility to ceftobiprole 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) to ≥3 of the following antimicrobials: clindamycin (CM), daptomycin (DAP), erythromycin (ERY), gentamicin (GM), levofloxacin (LEV), linezolid (LZD), tetracycline (TET), tigecycline (TGC), trimethoprim-sulfamethoxazole (TMP-SMX), or vancomycin (VAN). Isolates displaying oxacillin MIC values ≥4 mg/L were categorized as MRSA.

Results. Ceftobiprole was more active than ceftaroline (CPT) against MRSA (99.2% susceptible [S] versus 94.0% S, respectively) (Table). Ceftobiprole maintained activity against 88.0% of the CPT-NS isolates, but CPT was only active against 6.5% of the ceftobiprole-NS isolates. Ceftobiprole was also highly active (97.7–100.0% S) against isolates NS to CM, DAP, ERY, GM, LEV, LZD, TET, TGC, or TMP-SMX. No VAN-NS isolates were detected. Importantly, ceftobiprole was more active (97.7% S) than CPT (83.0% S) against the subset of MDR-MRSA isolates.

Conclusion. **Conclusions**: Ceftobiprole 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 ceftobiprole to treat *S. aureus* infections in the US.

		% Susceptible [a]	
Group	Number	Ceftobiprole	Ceftaroline
All	13,868	99.7	97.4
MDR	2,013	98.0	85.2
MRSA	5,906	99.2	94.0
MDR-MRSA	1,750	97.7	83.0
Ceftobiprole-NS	46	0.0	6.5
Ceftaroline-NS	357	88.0	0.0

MDR, multidrug-resistant; MRSA, methicillin-resistant *S. aureus*; NS, nonsusceptible
[a] Clinical and Laboratory Standards Institute (CLSI) interpretive criteria were applied for all antimicrobials except ceftobiprole, for which European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria were used.

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1241. In Vivo Efficacy of Meropenem Against Metallo-ß-Lactamase (MBL)-Harboring *Pseudomonas aeruginosa* and Correlation to In Vitro Susceptibility Upon Addition of EDTA

Abigail K. Kois, PharmD[1]; Tomefa E. Asempa, PharmD[2]; David P. Nicolau, PharmD[1]; [1]Hartford Hospital, Hartford, Connecticut; [2]CAIRD, Hartford Hospital, Hartford, Connecticut

Session: P-72. Resistance Mechanisms

Background. Prior investigations evaluating the predictive value of zinc-depleted media for MBL-susceptibility testing have focused on *Enterobacterales*. Therein, bacterial killing observed with meropenem (MEM) *in vivo* was concordant 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* (PSA) using the murine thigh infection model and zinc-depleted MICs.

Methods. MBL-harboring PSA isolates (VIM n=11; NDM n=10) were tested both *in vivo* (neutropenic murine thigh infection model) and *in vitro* (broth microdilution). The 24h murine thigh study 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-limited media. Time > MIC values (generated in each zinc-depleted media) were then plotted against the change in 24h bacterial density count in an Emax model.

Results. Average 0 h bacterial densities were 5.21 ± 0.40 and 5.13 ± 0.81 $\log_{10}$ CFU/thigh for NDM and VIM isolates, respectively. MEM resulted in -0.09 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. For both NDM- and VIM-harboring PSA, an Emax model with MICs generated in CAMHB+EDTA 30 mg/L (r^2 = 0.88) provided the highest correlation with MEM *in vivo* activity compared with CAMHB (r^2 = 0.55).

Conclusion. Results indicate that MIC values generated in conventional CAMHB do not appropriately characterize the *in vivo* efficacy of meropenem against MBL-harboring PSA, and addition of EDTA (30 mg/L) to CAMHB appears to be a viable option for *in vitro* testing of these organisms.

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

Tasneem Abdallah, MD, MRCP[1]; Reem Elajez, PharmD[2]; Tawheeda Ibrahim, MD[2]; Abeir Alimam, MD[2]; Ali S. Omrani, MBBCh, MSc, FRCP, FRCPath[2]; [1]Hamad medical corporation, Doha, Ad Dawhah, Qatar; [2]Hamad Medical Corporation, Doha, Ad Dawhah, Qatar

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%). *Kelbsiella 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	7	23.3%
Klebsiella pneumoniae	17	56.7%
Pseudomonas aeruginosa	4	13.3%
Other	2	6.7%
MDRO	29	96.7%
Antibiotic resistance		
MERO	22	73.3%
Colistin	6	20%
Cipro	27	90%
AG	7	23.3%
Bacteremia	8	26.7%
Documented clearance		
Yes	12	40%
No	6	20%
Not applicable	12	40%
Fosfomycin resistance within 90 days		
Yes	5	16.7%
No	14	46.6%
Not done	11	36.7%

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

Management outcomes and safety profile

Clinical outcome	22	73.3%
Microbiological outcome	20/22	91%
Treatment success	21	70%
Side effect		
Hypokalemia	13	43.3%
Grade 1	9/13	69.2%
Grade 2	4/13	30.8%
Hypernatremia	7	23.3%
Grade 2	2/7	28.5%
Grade 3	3/7	43%
Grade 4	2/7	28.5%
Neutropenia	2	6.7%
Grade 2	2	
Eosinophilia	2	6.7%
Grade 1	2	
Allergy	1	3.3%
Premature discontinuation	6	20%
30 days Mortality	7	23.3%
ICU admission	11	36.7%

The table describes percentage of primary outcome (clinical success) along with safety profile and mortality rate

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

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1243. Eravacycline in Bacteremia: A Case Series

Justin A. Andrade, PharmD, BCIDP[1]; Robert Kosalka, MD[2]; James Truong, PharmD, BCPS[2]; Joshua R. Rosenberg, MD[3]; [1]The Brooklyn Hospital Center/LIU Pharmacy, Brooklyn, New York; [2]The Brooklyn Hospital Center, Brooklyn, New York; [3]Brooklyn Hospital, Brooklyn, NY

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 ceftazidime-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 finalized to 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 ceftriaxone (CRO) (day 18-26). On day 27, meropenem (MEM) was initiated for gram-negative bacteremia and started on IV trimethoprim/