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1241. In Vivo Efficacy of Meropenem Against Metallo-β-Lactamase (MBL)-Harboring Pseudomonas aeruginosa and Correlation to In Vitro Susceptibility Upon Addition of EDTA
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Session: P-72. Resistance Mechanisms

Background. Prior investigations evaluating the predictive value of zinc-depleted media for MBL susceptibility testing have focused on Enterobacteriaceae. In particular, bacteremia involving organisms identified in vitro as meropenem (MEM) resistant has been correlated with their 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 vitro (neutropenic murine thigh infection model) and in vitro (broth microdilution). The 24 h 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 24 h bacterial density count in an Emax model.

Results. Average 0 h bacterial densities were 5.12 ± 0.49 and 5.13 ± 0.81 log CFU/ml 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. For both NDM- and VIM-harboring PSA, an Emax model with MICs generated in CAMHB-EDTA (r² = 0.88) provided the highest correlation with MEM in vitro activity compared with CAMHB (r² = 0.65).

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
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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). K. pneumoniae (17, 56.7%), E. 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 |
|---------------------------------|---------|----------------------|------------------------|-------|
| Efficacy (MDRO)                 | 29      | 56.7                 | 13.3                   | 8.7   |

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 | 28.6%
Grade 3 | 3/7 | 43%
Neutropenia | 2 | 6.7%
Eosinophilia | 2 | 6.7%
Grade 1 | 2 | 
Grade 2 | 1 | 3.3%
Premature discontinuation | 6 | 20%
30 days Mortality | 7 | 23%
IU admission | 11 | 38.7%

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
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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 ceftriaxone-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 V AN was added. BC finalized to VRE faecium and regimen was modified to ERV on day 12. Repeat BC on day 15 was sent 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 ceftiraxone (CRO) (day 18-26). On day 27, meropenem (MEM) was initiated for gram-negative bacteremia and started on IV trimethoprim/
sulamethoxazole (TMP/SMX) the following day for pneumonia caused by TMP/SMX-susceptible S. multilinosa. BC finalized on day 29 to S. multilinosa resistant to TMP/SMX, regimen modified to ERV. Repeat BC on day 30 finalized to no growth and ERV was continued until day 42 with no recurrence of bacteremia; however, patient died on day 45. Patient 3 with renal failure and on day 1, CRO started for SBP prophylaxis. On day 13, BC was negative for daptomycin and ceftazidime (CAZ-AVI) as patient was febrile and BC repeated. BC finalized to VRE faecium and was started on ERV on day 17 and completed a 7-day course with no recurrence of bacteremia; however, patient died on day 34. Patient 4 initially treated for bacterial superinfection with CRO and azithromycin, and subsequent history of pneumonia treated with VAN and MEM (day 10-17). On day 19, patient was febrile and treated with VAN and FEP until day 27. Repeat BC on day 29 finalized to VRE species and modified to ERV on day 32. ERV continued for a 7-day course and was discharged with no repeat BC obtained to confirm clearance. Patient in SS started on VAN and MEM. On day 1, BC on admission finalized to VRE faecium and therapy switched to ERV. Repeat BC taken on day 3 after ERV initiation were negative. Discharged to complete two-week course of ERV.

Conclusion. ERV may be an option for bacteremia as demonstrated by clearance in four of five cases. More studies must be conducted as these reports show variable clinical outcomes.

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1244. In Vitro Activity of Ceftaroline-Avibactam and Comparator Agents Against MDR Enterobacterales and Pseudomonas aeruginosa Collected in Latin America During the ATLAS Global Surveillance Program 2018-2019

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Session: P-72. Resistance Mechanisms

Background. Ceftaroline-avibactam (CAZ-AVI) is a β-lactam/β-lactamase inhibitor combination that can inhibit class A, C, and some class D β-lactamases. Resistance caused by β-lactamases often results in multidrug-reistance (MDR). This study evaluated the in vitro activity of CAZ-AVI and comparators against MDR Enterobacterales and Pseudomonas aeruginosa isolates collected from patients in Latin America.

Methods. Non-duplicate clinical isolates were collected in 2018-2019 in 10 countries in Latin America. Susceptibility testing was performed using CLSI broth microdilution and interpreted using CLSI 2021 and FDA (ticycline) breakpoints. MDR was defined as resistant (R) to ≥3 of 7 sentinel drugs: amikacin (AMK), aztreonam (ATM), ceftazidime (CAZ), cefepime (FEP), colistin (CST), levofloxacin (LVX), meropenem (MEM), and piperacillin-tazobactam (TZP).

Results. The activity of CAZ-AVI and comparators against all isolates and MDR subsets is shown in the table. MDR rates for the studied species ranged from 16.3% among E. cloacae to 35.7% among K. pneumoniae: CAZ-AVI was active against 98% of Enterobacterales isolates and maintained activity against 74-98% of MDR isolates of the examined Enterobacterales species. Only ticyccline showed higher activity among P. aeruginosa: CAZ-AVI was active against 87% of all isolates and 47% of MDR isolates; no other studied drug was more active. The three most common MDR phenotypes among Enterobacterales were: 1) R to all sentinel drugs except CST (n=145, 11.9% of all MDR isolates; 78.6% S to CAZ-AVI), and 3) R to all sentinel drugs except AMK and CST (n=50, 4.1% of all MDR isolates; 100% S to CAZ-AVI). The three most common MDR phenotypes among P. aeruginosa were: 1) R to all sentinel drugs except CST (n=75, 19.2% of all MDR isolates; 24.7% S to CAZ-AVI), 2) R to all sentinel drugs except AMK and CST (n=72, 19.1% of all MDR isolates; 96.7% S to CAZ-AVI); and 3) R to AMK, LVX, and MEM (n=74, 8.6% of all MDR isolates; 24.3% S to CAZ-AVI).

Conclusion. These in vitro data suggest that CAZ-AVI can be an effective treatment option for infections caused by MDR Enterobacterales and P. aeruginosa collected in Latin America.

Disclosures. Sibylle Lob, PhD, IHMA (Employee)/Pfizer, Inc. (Independent Contractor) Meredith Hackel, PhD MPH, IHMA (Employee)/Pfizer, Inc. (Independent Contractor) Gregory Stone, PhD, AztraZeneca (Shareholder, Former Employee)/Pfizer, Inc. (Employee) Daniel F. Sahm, PhD, IHMA (Employee)/Pfizer, Inc. (Independent Contractor)

1245. In Vitro Activities of Ceftaroline and Comparator Agents Against Bacterial Pathogens Collected from Patients with Skin and Skin Structure Infections: Results of the ATLAS Global Surveillance Program 2012-2019

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Session: P-72. Resistance Mechanisms

Background. Ceftaroline fosamil, the prodrug of ceftaroline, is a central cephalosporin approved for the treatment of patients with skin and skin structure infections (SSSI) caused by S. aureus (both methicillin-susceptible [MSSA] and methicillin-resistant [MRSA] isolates), β-hemolytic streptococci (Streptococcus pyogenes, S. agalactiae, S. dysgalactiae), and select species of Enterobacterales (Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca). The current study is part of the ATLAS (Antimicrobial Surveillance and Leadership and Surveillance) program and evaluated the current activities of ceftaroline and comparator agents against commonly encountered bacterial isolates associated with SSSIs.

Methods. From 2012 to 2019 the ATLAS program received 124,694 bacterial isolates that had been cultured by 493 clinical laboratories in 71 countries from samples of patients diagnosed with SSSIs. All isolates were transported to IHMA, (Schaumburg, IL, USA) where their identities were confirmed using MALDI-TOF mass spectrometry and antimicrobial susceptibility testing performed following standardized CLSI broth microdilution methodology (M07). Patient susceptibilities were determined using 2021 CLSI MIC breakpoints. Phenotypic extended-spectrum β-lactamase (ESBL) screening and confirmatory testing were performed using the CLSI M100 method.

Results. The in vitro activity of ceftaroline is summarized in the following table. Overall, 99.9% of MSSA and 92.8% of MRSA from SSSI were susceptible to ceftaroline (MIC ≤4 µg/ml); 7.1% of MRSA isolates were ceftaroline-susceptible dose-dependent (MIC 2-4 µg/ml) with greatest proportion being from Chile (53.3% of 392 isolates), South Korea (29.3% of 321 isolates), and China (24.7% of 652 isolates). Twelve ceftaroline-resistant MRSA were observed, consisting of 11 of 109 isolates from Thailand (10.1%) and 1 of 161 from China (0.6%). All S. pyogenes and 88.0% of ESBL-negative Enterobacterales were susceptible to ceftaroline.

Results Table

| Organism (n) | Ceftaroline (µg/ml) | MIC (%) | S | SD |
|-------------|--------------------|---------|---|---|
| Staphylococcus aureus, MSSA (3,497) | 0-1.0 | 92.6 | 7.3 | 0.1 |
| Staphylococcus aureus, MRSA (1,035) | 0-1.0 | >99.9 | 0.1 | 0 |
| Staphylococcus pyogenes (5,295) | 0-0.05 | 99.4 | 0.0 | 0 |
| Enterobacterales, ESBL Sensitive (17,933) | 0.125 | 88.0 | 5.1 | 5.9 |

Conclusion. Ceftaroline demonstrates potent in vitro activity against clinically relevant pathogens associated with SSSIs.

Disclosures. Meredith Hackel, PhD MPH, IHMA (Employee)/Pfizer, Inc. (Independent Contractor) Gregory Stone, PhD, AztraZeneca (Shareholder, Former Employee)/Pfizer, Inc. (Employee) Daniel F. Sahm, PhD, IHMA (Employee)/Pfizer, Inc. (Independent Contractor)

1246. Clinical isolates of Pseudomonas aeruginosa Harbor Preexisting Changes in TonB-dependent Receptors Associated with Decreased Susceptibility to Cefiderocol

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Session: P-72. Resistance Mechanisms

Background. Cefiderocol (FDC) is a novel siderophore cephalosporin that retains activity against MDR gram-negative bacteria. In P. aeruginosa (PA), FDC utilizes TonB-dependent receptors (TDRB) PfuA, PiuA, or PiuD to enter the periplasmic space. Previously, we reported a clinical isolate that developed elevated MICs to FDC associated with mutations in genes encoding TBDRs in the absence of prior exposure to FDC. In this study, we investigated the frequency of TBDR mutations not associated with cefiderocol exposure among clinical strains of PA recovered from 1999 to 2018 in a large hospital system in Houston, TX.

Methods. A total of 212 clinical isolates of PA were screened for mutations in TBDR pathways (pirAlp/risk and piaUAd) via whole genome sequencing. Strains with gene mutations predicted to significantly alter protein function (insertion, deletion, or frameshift) were selected for whole genome sequencing. PA01 and 4 clinical PA strains lacking changes in the TBDR genes served as controls. FDC susceptibility testing was performed on Mueller-Hinton agar by Kirby-Bauer disc diffusion (DD). Diapers were measured at 18 and 48 h to assess for the emergence of colonies.

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