1219. Unfavorable Clinical Outcomes with Polymyxins Compared to Ceftolozane/Tazobactam for the Treatment of Carbenapenem-Resistant Pseudomonas aeruginosa

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Session: P-7.2. Resistance Mechanisms

Background. Patients with carbapenem-resistant Pseudomonas aeruginosa (CRPA) have high in-hospital mortality rates. It is unknown if patients with CRPA treated with ceftolozane/tazobactam (C/T) have improved clinical outcomes compared to those treated with polymyxin.

Methods. The CDC-funded, Georgia Emerging Infectious Program performed active population- and laboratory-based surveillance for CRPA isolated from sterile sites, urine, lower respiratory tract and wounds in metropolitan Atlanta, GA from 8/1/2016–7/31/2018. We reviewed charts of adults without cystic fibrosis who were hospitalized within 1 week of CRPA culture. Using a desirability of outcome ranking (DOOR) analysis which incorporates both benefits and risks into a single outcome, we estimated the probability that a patient treated first with C/T would have a more desirable clinical outcome at 30 days than a patient treated with polymyxins (polymyxin B or colistin). We adjusted for confounding using inverse probability of treatment weighting (IPTW) based on culture source and need for dialysis at baseline. A partial credit analysis allowed for variable weighting of DOOR ranks and calculation of differences in mean partial credit scores.

Results. Among 710 cases from 18 different hospitals, we identified 73 patients treated for CRPA infections with polymyxins (n=31) or C/T (n=42). Most patients were male (64%) and Black (80%), and those receiving polymyxins were more likely to have required dialysis at baseline (35% vs. 14%, p=0.03) (Table 1). At 30 days after culture, 82% of patients received polymyxins (polymyxin B or colistin). We adjusted for confounding using inverse probability of treatment weighting (IPTW) based on culture source and need for dialysis at baseline. A partial credit analysis allowed for variable weighting of DOOR ranks and calculation of differences in mean partial credit scores.

Table 1: Characteristics of hospitalized patients with carbapenem-resistant Pseudomonas aeruginosa in metropolitan Atlanta, GA, stratified by treatment regimen

| Treatment | Polymyxins (n=31) | Ceftolozane/tazobactam (n=42) | Total (n=73) | P-value |
|-----------|-------------------|-----------------------------|-------------|---------|
| Age category (years) | | | | |
| 19 – 49 | 8 (26) | 11 (26) | 19 (26) | 0.93 |
| 50 – 64 | 9 (29) | 11 (26) | 20 (27) | 0.95 |
| 65 – 79 | 10 (32) | 16 (38) | 26 (36) | 0.79 |
| ≥80 | 4 (13) | 13 (31) | 17 (23) | 0.11 |
| Male | 22 (74) | 24 (57) | 47 (64) | 0.13 |

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1. Percentages are adjusted using inverse probability of treatment weighting, controlling for culture source and need for dialysis at baseline. 2. Adverse events measured included: acute kidney injury, discharge to higher acuity location than previous residence, or being hospitalized 30 days after culture.
This displays the difference (ceftriazone/tazobactam minus polymyxin) in mean partial credit scores (black line) and associated 95% confidence bands (gray lines) as a function of the partial credit score assigned to an individual having at least one adverse event (range 0 – 100%). A score of 100% is assigned to patients alive with no adverse events and a score of 0% is assigned to patients who die. A difference in mean partial credit scores of approximately zero suggests there was no difference observed between treatment groups.

Conclusion. These findings support the recent Infectious Diseases Society of America guidance favoring C/T over polymyxins for treatment of CRPA infections.

Disclosures. David van Duin, MD, PhD, Entasis (Advisor or Review Panel member); genentech (Advisor or Review Panel member); karina (Advisor or Review Panel member); Merck (Grant/Research Support, Advisor or Review Panel member); Pfizer (Consultant, Advisor or Review Panel member); Qpex (Advisor or Review Panel member); Shionogi (Research Support, Scientific Research Study Investigator, Advisor or Review Panel member); utility (Advisor or Review Panel member) Scott R. Evans, PhD, Abbvie (Consultant); Advantagene (Consultant); Alexion (Consultant); Amgen (Consultant); AstraZeneca (Consultant); Attractive (Consultant); Best International Group (Consultant); Cardinal Health (Consultant); Clever (Consultant); FHI Clinical (Consultant); genentech (Consultant); Gilead (Consultant); Horizon (Consultant); International Drug Development Institute (Consultant); Lung Biotech (Consultant); Microbiotix (Consultant); Neovasc (Consultant); nobel Pharma (Consultant); Novartis (Consultant); Novolution (Consultant); Pfizer (Consultant); Rakuten (Consultant); Roche (Consultant); Roivant (Consultant); SAB Biopharm (Consultant); Shire (Consultant); Stryker (Consultant); SVB Leerink (Consultant); Takeda (Consultant); Teva (Consultant); Tracsa (Consultant); Vir (Consultant).

1220. Is MIC all that matters? MIC Distributions of Ceftazidime and Cefepime in Ceftriaxone-Resistant E. coli and Klebsiella spp.

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Session: P-72. Resistance Mechanisms

Background. The Clinical and Laboratory Standards Institute (CLSI) lowered MIC breakpoints for many beta-lactam antibiotics to enhance detection of resistance among Enterobacteriales. This shift was also meant to eliminate the need for routine testing for extended-spectrum beta-lactamases (ESBLs). The recommended treatment for ESBL-producing Enterobacteriales is carbapenems. The IDSA guidelines for MDR-GN organisms recommend using ceftriaxone (CRO) resistance as a proxy for ESBL production and thus carbapenem treatment. Under CLSI guidelines, alternative beta-lactams such as ceftazidime (CAZ) and cefepime (FEP) may still be reported as susceptible and thus used by clinicians even in light of IDSA recommendations. The aim of this project was to characterize the MIC distributions of CAZ and FEP stratified by CRO susceptibility.

Methods. Clinical E. coli, K. pneumoniae, and K. oxytoca isolates from blood cultures in adult patients from Nov 2016-Dec 2018 that had MICs tested by the Vitek-2 automated susceptibility testing system for CRO, FEP and CAZ were identified. Descriptive statistics were used to compare MIC distributions across the antibiotics of interest (SPSS). 573 isolates were included, of these, 17.3% were CRO resistant. Most (53%) CRO-R isolates had FEP MICs ≤2 which is considered susceptible per CLSI and CAZ MICs ≤4 which would be considered susceptible by CLSI. Using the EUCAST breakpoint of ≤1, only 12% of CRO-R isolates would be reported as CAZ-S (Figure 1B).

Cefepime MIC Distribution for Ceftriaxone Resistant Isolates

Distribution of MICs for cefepime for ceftriaxone resistant isolates with the breakpoints for EUCAST and CLSI noted with a dashed line

Ceftriazone MIC Distribution for Ceftriaxone Resistant Isolates

Distribution of MICs for ceftriazone for ceftriaxone resistant isolates with the breakpoints for EUCAST and CLSI noted with a dashed line

Conclusion. Half of CRO-R. coli, K. pneumoniae and K. oxytoca have FEP and CAZ MICs at or below the current CLSI breakpoints. This may lead to their use for ESBL infections where a carbapenem is preferred. To prevent unnecessary use, laboratories should consider suppressing FEP and CAZ susceptibilities when CRO-R or adopting more the aggressive EUCAST breakpoints for these agents.

Disclosures. Emily Heil, PharmD, MS, BCIDP. Nothing to disclose Kimberly C. Claes, PharmD, GenMark (Speaker’s Bureau).

1221. Genomic Factors Affecting the Efficacy of Antimicrobial Therapy in Dartpomycin-, Linezolid-, Vancomycin-Resistant Enterococcus faecium (DLEVRE)

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Session: P-72. Resistance Mechanisms

Background. Nosocomial acquisition of vancomycin-resistant Enterococcus (VRE) is one of the most challenging problems in healthcare. As Enterococcus isolates are increasingly resistant to vancomycin, clinicians now rely on alternative antimicrobial therapies including linezolid and daptomycin (DAP) to treat infections. For multidrug-resistant (MDR) VRE, combination therapy with beta-lactams and daptomycin has been shown to be effective.

Methods. Following initiation of empiric DAP and ceftazidime (CPT) for an MDR E. faecium bloodstream infection (VRE_001), we aimed to determine if there existed in vitro synergy between both agents that supported their clinical use. Combination synergy testing was performed using E-test strips and minimal inhibitory concentration (MIC) for both agents were read at 24 hours. For whole genome sequence-based analysis (WGS), genomic DNA from VRE_001 was used for both short read (Illumina MiSeq) and long read sequencing (MinION, Nanopore). The complete genome was assembled and the NCBI AMRFinderplus program used to identify known resistance mechanisms.

Results. Original MICs of VRE_001 from the clinical microbiology laboratory at Northwestern Memorial revealed an MDR E. faecium (Table 1). Combination synergy testing in the experimental laboratory revealed only modest amounts of synergy between CPT and DAP (Table 2). Following WGS, VRE_001 was identified as an ST-584 E. faecium with a 3.2 Mbp genome, including a single chromosome and five plasmids. WGS analysis revealed several mechanisms of antimicrobial resistance (Table 3) genetically supporting the observed MDR-DLEVRE phenotype.

Table 1: Minimal Inhibitory Concentrations (MIC) from the Northwestern Memorial Hospital Clinical Microbiology Laboratory

| Antibiotic | MIC (μg/mL) | CLSI Interpretation |
|------------|-------------|---------------------|
| Ampicillin  | ≥12          | Resistant           |
| Daptomycin | ≤2           | Sensitive           |
| Linezolid  | ≤2           | Sensitive           |
| Vancomycin | ≥32          | Resistant           |
| Ceftazidime| ≤2           | Sensitive           |

Table 2: Synergistic MIC Investigational Laboratory E-testing

| Antibiotic | Daptomycin E-test | CLSI Interpretation |
|------------|-------------------|---------------------|
| Daptomycin | ≥16               | Resistant           |
| Ceftazidime| ≥12               | Resistant           |

Table 3: Genomic mechanisms of antimicrobial resistance identified in VRE_001 using NCBI AMRFinderPlus

| Antibiotic | GenBank Accession | Point Mutations | Resistance Mechanism |
|------------|-------------------|-----------------|---------------------|
| Daptomycin | 584                  | ΔrpoC          | Daptomycin resistance |
| Vancomycin | 584                  | ΔmecA, ΔmecC   | Vancomycin resistance |
| Fluoroquinolones | 584              | ΔcatB          | Fluoroquinolones resistance |
| Aminoglycosides | 584          | Δaph-2.2, 340  | Aminoglycosides resistance |
| Tetracyclines  | 584                   | ΔtetM           | Tetracyclines resistance |