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

Jessica Howard-Anderson, MD[1]; Michelle Earley, MS[2]; Toshimitsu Hamasaki, PhD[3]; Chris W. Bower, MPH[4]; Gillian Smith, MPH[4]; David van Duin, MD, PhD[5]; Scott R. Evans, PhD[3]; Jesse T. Jacob, MD, MSc[1]; [1]Emory University, Decatur, GA; [2]George Washington University, Rockville, Maryland; [3]The George Washington University, Rockville, Maryland; [4]Georgia Emerging Infections Program, Decatur, GA; [5]University of North Carolina, Chapel Hill, North Carolina

Session: P-72. 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 polymyxins.

Methods. The CDC-funded, Georgia Emerging Infections 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, 34 (47%) were alive with no adverse events, 21 (29%) were alive with ≥ 1 adverse event, and 18 (25%) had died. Patients first treated with C/T had a lower 30-day mortality rate than those treated with polymyxins (14% vs 39%, p=0.03). Additionally, those receiving C/T had better overall clinical outcomes, with an adjusted DOOR probability of having an improved outcome of 67% (95% CI 53%–80%) compared to those receiving polymyxins (Figure 1). Partial credit analyses indicated consistent results across different patient values of survival with adverse events (Figure 2).

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

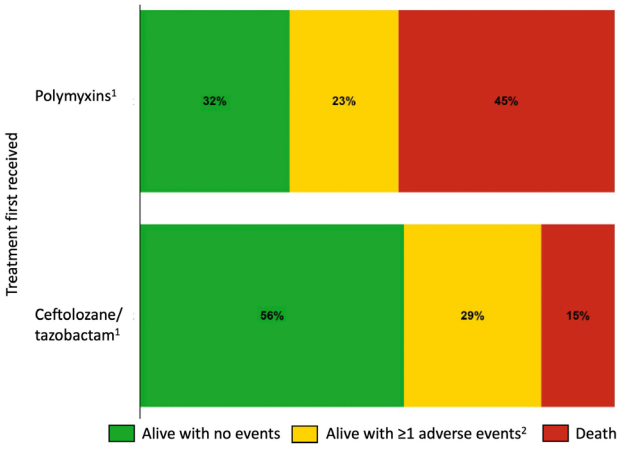
	Polymyxins (n=31)	Ceftolozane/ tazobactam (n=42)	Total (n=73)	P-value[1]
Age category (years)				
19 – 49	8 (26)	11 (26)	19 (26)	
50 – 64	9 (29)	11 (26)	20 (27)	0.95
65 – 79	10 (32)	16 (38)	26 (36)	
>79	4 (13)	4 (10)	8 (11)	
Male	23 (74)	24 (57)	47 (64)	0.13
Race (n=70)				
Black	26 (90)	30 (73)	56 (80)	0.21
White	3 (10)	10 (24)	13 (19)	
Other or multiracial	0	1 (2)	1 (1)	
Charlson comorbidity index >2	19 (61)	24 (57)	43 (59)	0.72
Required dialysis prior to admission	11 (35)	6 (14)	17 (23)	0.03
Residence 3 days prior to culture				
Inpatient	20 (65)	22 (52)	42 (57)	0.54
Long-term facility (LTCF or LTACH)	8 (25)	13 (31)	21 (29)	
Private residence	3 (10)	7 (17)	10 (14)	
Culture source				
Sterile site	2 (6)	10 (24)	12 (16)	
Lower respiratory tract	17 (55)	15 (36)	32 (44)	0.13
Urine	7 (23)	7 (17)	14 (19)	
Wound	5 (16)	10 (24)	15 (21)	
Admitted to ICU in prior week	15 (48)	15 (36)	30 (41)	0.28
ID consult within week of culture	28 (90)	40 (95)	68 (93)	0.65
Days from culture to start of polymyxin or C/T, median (IQR)[2]	4 (3–6)	3 (3–5)	4 (3–6)	0.67
Days from culture to discharge or death, median (IQR)	15 (14–25)	16 (10–23)	16 (10–23)	0.60
Duration of polymyxins or C/T (whichever given first)	8 (4–12)	9 (6–15)	8 (5–13)	0.22

All values are presented as number (%) unless otherwise stated

1. Determined by X^2 or Fisher exact test for categorical variables and Wilcoxon rank-sum test for continuous variables
2. If antibiotics had been started prior to the culture, this was counted as zero days

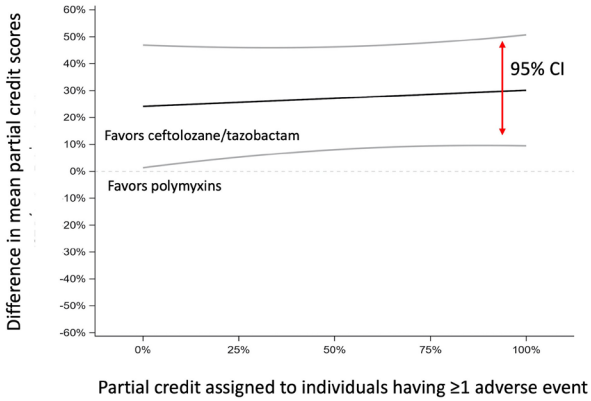
Abbreviations: LTCF, long term care facility; LTACH, long term acute care hospital; ICU, intensive care unit; ID, infectious diseases; IQR, interquartile range

Figure 1: Inverse probability of treatment weighting-adjusted desirability of outcome ranking (DOOR) distributions by treatment group, accounting for adverse events and survival status that occurred up to 30 days after CRPA culture.



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

Figure 2: Inverse probability of treatment weighting-adjusted partial credit analysis.



This displays the difference (ceftolozane/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)**Karius** (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** (Grant/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)**Atricure** (Consultant)**Breast International Group** (Consultant)**Cardinal Health** (Consultant)**Clover** (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)**Nuvelution** (Consultant)**Pfizer** (Consultant)**Rakuten** (Consultant)**Roche** (Consultant)**Roivant** (Consultant)**SAB Biopharm** (Consultant)**Shire** (Consultant)**Stryker** (Consultant)**SVB Leerink** (Consultant)**Takeda** (Consultant)**Teva** (Consultant)**Tracon** (Consultant)**Vir** (Consultant)

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

Emily Heil, PharmD, MS, BCIDP[1]; Emily Heil, PharmD, MS, BCIDP[1];
Kimberly C. Claeys, PharmD[2]; Paul Luethy, PhD[3]; [1]University of Maryland School of Pharmacy; University of Maryland Medical Center, Baltimore, MD; [2]University of Maryland School of Pharmacy, Baltimore, Maryland; [3]University of Maryland School of Medicine, Baltimore, Maryland

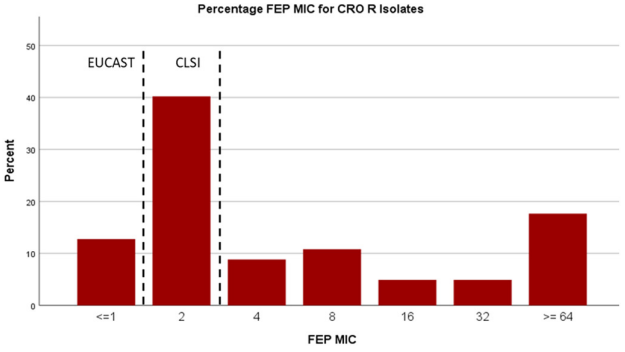
Session: P-72. Resistance Mechanisms

Background. The Clinical and Laboratory Standards Institute (CLSI) lowered MIC breakpoints for many beta-lactam antibiotics to enhance detection of resistance among *Enterobacterales*. This shift was also meant to eliminate the need for routine testing for extended-spectrum beta-lactamases (ESBLs). The recommended treatment for ESBL-producing *Enterobacterales* 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).

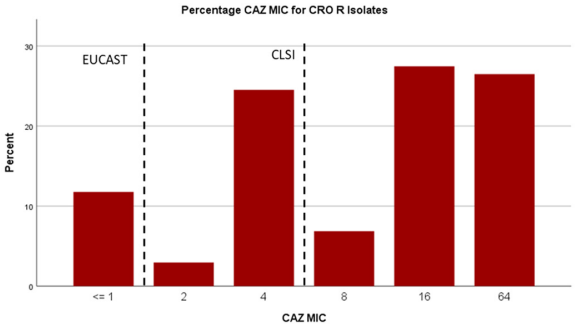
Results. 573 isolates were included, of these, 17.3% were CRO resistant. Most (53%) CRO-R isolates had FEP MICs ≤2 which is considered susceptible per CLSI; 19% had FEP MICs of 4-8 which would be considered S-DD by CLSI (Figure 1A; breakpoints noted by dashed lines). Using the EUCAST breakpoint of ≤1, only 11% of CRO-R isolates would be reported as FEP-S. For CAZ, 40% of CRO-R isolates had CAZ MICs ≤4, which is considered S 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

Ceftazidime MIC Distribution for Ceftriaxone Resistant Isolates



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

Conclusion. Half of CRO-R *E. 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 serious 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. Claeys, PharmD**, **GenMark** (Speaker's Bureau)

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

Samuel W. Gatesy, M.S.[1]; Nathan B. Pincus, BS[1];
William Justin Moore, PharmD[2]; Omar Al-Heeti, MD[1]; Tejas Joshi, MS[3];
Kelly E. R Bachta, MD PhD[1]; [1]Northwestern University, Libertyville, Illinois; [2]Northwestern Medicine, Chicago, IL; [3]Northwestern Feinberg School of Medicine, Chicago, Illinois

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 ceftaroline (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 concentrations (MICs) 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-DLVRE phenotype.

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

Antibiotic	MIC	CLSI Interpretation
Ampicillin	32 µg/mL	R
Daptomycin	12 µg/mL	R
Linezolid	>256 µg/mL	R
Vancomycin	32 µg/mL	R
Ceftaroline	32 µg/mL	n/a

Table 2: Synergistic MIC Investigational Laboratory E-testing

Antibiotic	Daptomycin E-test	CLSI Interpretation
Daptomycin	16 µg/mL	R
Ceftaroline + Daptomycin Combination	12 µg/mL	R

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

Antibiotic	Gene(s)	Point Mutations
Daptomycin	liaS	T120A
	liaR	W73C
	cls	N13I
Vancomycin	vanH-A-X	
	vanS-R	
	vanZ-Y	
Fluoroquinolones	gyrA	S83Y
	parC	S80R
Aminoglycosides	aac(6')-I	
	aph(3')-IIIa	
	ant(6)-Ia	
Trimethoprim	dfrF	
	dfrG	
Tetracyclines	tetL	
	tetM	