comparator agents were S tested by reference broth microdilution methods at a central laboratory. Breakpoints for the following organizations were applied when available: CLSI, EUCAST, USCAST, and US FDA.

Results. PLZ was active against 95.5% and 98.0% of isolates as per US FDA (≤2 mg/L) and USCAST (≤4 mg/L) criteria, respectively. S rates as per US FDA and USCAST criteria were 97.4% and 90.2% for AMK, 86.4% and 85.6% for GEN, and 83.8% and 81.1% for TOB, respectively (Table). CLSI and US FDA breakpoints were identical for these three older aminoglycosides, and EUCAST breakpoints were identical for GEN and TOB and one doubling dilution higher for AMK when compared with USCAST. Per US FDA criteria, carbapenem-resistant ENT (CRE) S rates to PLZ and AMK were 71.5% and 58.3%, respectively. Differences in S rates between PLZ and AMK were higher when applying USCAST for resistant subsets, such as CRE (72.2% versus 38.5%, respectively), ESBL-phenotype (92.7% versus 72.4%, respectively), and multidrug-resistant isolates (n=1,348; 88.6% versus 59.6%, respectively). GEN and TOB exhibited limited activity against ENT resistant subsets.

Conclusion. PLZ retained potent activity against ENT, including resistant subsets. The discrepancies among the S rates for aminoglycosides were greater when applying breakpoints generated using the same stringent contemporary methods applied to determine PLZ breakpoints.

Table 1

Breakpoint setting organization/ organism group (number tested)	% Susceptible			
	Plazomicin	Amikacin	Gentamicin	Tobramycin
All *Enterobacterales* (9,303)				
CLSI	NA[a]	97.4	86.4	83.8
EUCAST	NA	95.5	85.6	81.1
USCAST	98.0	90.2	85.6	81.1
US FDA	95.5	97.4	86.4	83.8
CRE (403)				
CLSI	NA	58.3	42.2	17.4
EUCAST	NA	45.7	40.4	14.6
USCAST	72.2	38.5	40.4	14.6
US FDA	71.5	58.3	42.2	17.4
ESBL-phenotype (1,907)				
CLSI	NA	88.7	52.7	38.7
EUCAST	NA	82.6	51.8	35.0
USCAST	92.7	72.4	81.8	35.0
US FDA	91.7	88.7	52.7	38.7

[a] NA, not available.

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1279. In Vitro Activity of Nacubactam (OP0595) Alone and in Combination with β-Lactams against β-Lactamase-Producing Enterobacterales Isolated in Japan

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Session: P-58. Novel Agents

Background. Nacubactam (NAC) is a novel serine β-lactamase inhibitor in clinical development, and inhibits Ambler class A, class C, and some class D β-lactamases. In addition, it has penicillin-binding protein (PBP) 2-dependent antibacterial activity and an 'enhancer' effect when combined with β-lactams bound to PBP3. This study assessed the in vitro activity of NAC alone and in combination with β-lactams against IMP-type metallo-β-lactamase-producing and ESBL-producing Enterobacterales isolated in Japan.

Methods. The MICs for the clinical isolates in Japan were determined and time kill studies were performed. IMP and ESBL genes were detected by PCR. The MICs were determined by broth microdilution method following CLSI methodology. β-lactams and NAC were tested as a ratio of 1:1. Time kill profiles were also studied according to CLSI methodology.

Results. The MIC_{50}/MIC_{90}s of NAC alone against 112 IMP-producing Enterobacterales and 154 ESBL-producing Enterobacterales were 2/ >32 and 2/8 mg/L, respectively. Regarding the MICs of cefepime (FEP)/NAC and aztreonam (ATM)/NAC against IMP-producing isolates, the MIC_{90}s were 2 and 1 mg/L and the MIC ranges were 0.06 - 32 and 0.06 - 4 mg/L, respectively. The MIC_{90}s of FEP/NAC and ATM/NAC against ESBL-producing isolates were 0.5 and 1 mg/L. These MIC_{90}s of β-lactam/NAC against IMP-producing and ESBL-producing isolates were significantly lower than those of β-lactam alone (>128 mg/L). The highest MIC of ATM/NAC against IMP-producing isolates was lower than that of FEP/NAC. In addition, bactericidal activities of β-lactam/NAC were observed at the lower concentration of β-lactam compared to that of β-lactam alone.

Conclusion. NAC in combination with β-lactams showed excellent in vitro activities against not only ESBL-producing Enterobacterales but also IMP-producing Enterobacterales isolated in Japan. ATM/NAC tended to show higher antimicrobial effect against IMP-producing isolates by the enzyme stability of ATM. These results support the complex activities of NAC which works as a β-lactamase inhibitor, an antibacterial agent and also an enhancer when combined with β-lactams. Furthermore, these will be useful for selecting a partner β-lactam for NAC.

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1280. In-Vitro Activity of Cefiderocol, Imipenem/Relebactam, & Ceftazidime/Avibactam in Ceftolozane/Tazobactam Resistant Strains of Multidrug Resistant Pseudomonas aeruginosa

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Session: P-58. Novel Agents

Background. The activity of imipenem/relebactam (I/R), ceftazidime/avibactam (CZA) and cefiderocol (FDC) were evaluated against clinical isolates of multidrug resistant (MDR) strains of *P. aeruginosa* which was resistant to ceftolozane/tazobactam (C/T). The recent increase of MDR *P. aeruginosa* strains isolated from clinical samples has prompted research and development of new antimicrobials that can withstand its multiple resistance mechanisms. C/T is an effective option for treatment of MDR *P. aeruginosa* in our facility with only 10% of resistance in MDR strains, but the emergence of resistance may occur due to the presence of a carbapenemase gene or an ampC mutation.

Methods. Antimicrobial susceptibility testing for C/T Etest® (bioMérieux, Inc.) were performed on all MDR strains initially screened by the VITEK2® (bioMérieux, Inc.). 10% (n=20) of all MDR isolates were resistant to C/T by the CLSI 2019 breakpoints. These resistant isolates were tested for presence of a carbapenemase gene using the GeneXpert CARBA-R (Cepheid®) PCR and against CZA Etest® (bioMérieux, Inc.) I/R gradient strips (Liofilchem®) and FDC broth microdilution (Thermo Scientific™ Sensititre™).

Results. A total of 20 clinical isolates of MDR *P. aeruginosa* resistant to C/T were tested following standardized CLSI protocols and techniques. All 20 isolates were screened for the presence of a carbapenemase gene (*bla*VIM, *bla*NDM, *bla*KPC, *bla*OXA-48, *bla*IMP). A *bla*VIM gene was detected in 6 (30%) out of 20 isolates. FDC demonstrated the greatest activity with 85% (n=17) of susceptible isolates (CLSI MIC <4μg/dL). CZA (CLSI MIC <8μg/dL) and I/R (FDA MIC <2μg/dL) showed 15% (n=3) and 10% (n=2) of susceptible isolates respectively. FDC was active against all 6 *bla*VIM isolates, where all 6 strains were resistant to CZA and I/R as expected. 3 isolates tested non-susceptible against FDC; additional characterization was not performed at this time.

Conclusion. Based on these results, FDC demonstrated the greatest in-vitro activity against C/T resistant strains of MDR *P. aeruginosa*. FDC also demonstrated activity against all 6 MDR *P. aeruginosa* carrying *bla*VIM gene. FDC is a strong option to consider on MDR *P. aeruginosa* strains based on a resistance testing algorithm and a cost/effective protocol.

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1281. Longitudinal and Spatial Variation in the Human Microbiome in a Phase 2a Clinical Study of Gepotidacin in Adult Females with Uncomplicated Urinary Tract Infection

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Background. Gepotidacin (GSK2140944) is a first in class novel oral triazaacenaphthylene bacterial topoisomerase inhibitor. In this study, we evaluated the potential