Background. Aspergillus (ATM) is a monocotablast stable to hydrolysis by metallo-β-lactamases (MBLs). Avibactam (AVI) is a non-β-lactam β-lactamase inhibitor that inhibits serine carbapenemases (CPEs), such as ESBLs, KPCs, AmpC, and some OXAs.

Table 1

| Organism | All | ESI | PHP | SSS |
|----------|-----|-----|-----|-----|
| Candida spp. | 0.00094 ± 0.00009 | 0.00018 ± 0.00005 | 0.00006 ± 0.00005 | 0.00002 ± 0.00003 |
| C. albicans | 0.0044 ± 0.0081 | 0.0090 ± 0.0048 | 0.0050 ± 0.0030 | 0.0060 ± 0.0032 |
| C. auris | 0.0159 ± 0.0053 | 0.0018 ± 0.0016 | 0.0002 ± 0.0001 | 0.0001 ± 0.0001 |
| C. dublinensis | 0.0044 ± 0.0081 | 0.0090 ± 0.0048 | 0.0050 ± 0.0030 | 0.0060 ± 0.0032 |
| C. glabrata | 0.0329 ± 0.0566 | 0.0329 ± 0.0566 | 0.0329 ± 0.0566 | 0.0329 ± 0.0566 |
| C. kefyr | 0.0329 ± 0.0566 | 0.0329 ± 0.0566 | 0.0329 ± 0.0566 | 0.0329 ± 0.0566 |
| C. talaromycetis | 0.0329 ± 0.0566 | 0.0329 ± 0.0566 | 0.0329 ± 0.0566 | 0.0329 ± 0.0566 |
| C. parapsilosis var. grubii | 0.0329 ± 0.0566 | 0.0329 ± 0.0566 | 0.0329 ± 0.0566 | 0.0329 ± 0.0566 |
| Aspergillus spp. | 0.0150 ± 0.0053 | 0.0010 ± 0.0001 | 0.0010 ± 0.0001 | 0.0010 ± 0.0001 |
| Scedosporium spp. | 0.0044 ± 0.0081 | 0.0090 ± 0.0048 | 0.0050 ± 0.0030 | 0.0060 ± 0.0032 |

*ALL includes ESI, PHP, SSS, IA, UI, and other infection types.

Conclusion. MGX demonstrated potent antifungal activity against Candida spp., Aspergillus spp., C. neoformans var. grubii, and non-Aspergillus moulds, including Scedosporium spp. isolates. Notable activity was seen against C. auris, echinocandin-resistant Candida spp., azole-resistant Aspergillus, and Scedosporium spp. isolates. Further clinical development of fosmanogepix in difficult-to-treat resistant fungal infections is warranted.

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126. Antimicrobial Activity of Aztreonam-Avibactam against Gram-negative Bacteria Isolated from Patients Hospitalized with Pneumonia in Europe, Latin America, and Asia in 2019

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Background. Aztreonam (ATM) is a monobactam stable to hydrolysis by metallo-β-lactamases (MBLs). Avibactam (AVI) is a non-β-lactam β-lactamase inhibitor that inhibits serine carbapenemases (CPEs), such as ESBLs, KPCs, AmpC, and some OXAs. ATM-AVI is under clinical development for the treatment of serious infections caused by Gram-negative bacteria (GNB), including MBL-producers.

Methods. 2,582 GNB (1,630 Enterobacteriaceae [ENT] and 952 nonfermentative-GNB) were consecutively collected (1/patient) from 56 medical centers located in Western Europe (W-EU; 22 centers in 10 nations), Eastern Europe (E-EU; 12 centers in 9 nations), Latin America (LATAM; 10 centers 6 nations), and the Asia-Pacific region (APAC; 12 centers in 8 nations) in 2019 and susceptibility (S) tested against ATM-AVI and comparators at a central laboratory by reference broth microdilution methods.

Results. Overall, 99.9% of ENT (MIC90p 0.06/0.25 mg/L), including 99.1% of carbapenem-resistant ENT (CRE; MIC90p 0.25/0.05 mg/L), were inhibited at an ATM-AVI MIC of ≤ 8 mg/L (Table). CRE rates were 1.4%, 23.7%, 6.3%, and 9.6% in W-EU, E-EU, LATAM, and APAC, respectively. A CPE was identified in 95 of 113 CRE isolates (84.1%). These CPEs included NDM-like (31.0% of CRE), KPC-like (26.5%), OXA-48-like (24.8%), and VIM-like (7.1%). Six isolates produced 2 CPEs. The highest ATM-AVI MIC value among MBL-producers (n=43; MIC90p 0.12/0.05 mg/L) was observed with Pseudomonas aeruginosa. Among P aeruginosa, MBLs were identified in 8 out of 11 isolates. Following MBL, ATM-AVI was highly active against S to meropenem (75.4%), piperacillin-tazobactam, and ceftazidime were 69.4%, 72.5%, and 75.7%, respectively, and ranged from 64.3% in E-EU to 82.0% in W-EU. MEM non-S. P aeruginosa varied from 22.2% in W-EU to 54.8% in E-EU. ATM-AVI was highly active against S to meropenem, S. maltophilia, inhibiting 95.0%, 100.0%, and 90.0%, and 90.0% of isolates from W-EU, E-EU, LATAM, and APAC, respectively, at ≤ 8 mg/L. S. maltophilia S to cefotimoxazole were 90.0%, 97.7%, 85.7%, and 100.0% in W-EU, E-EU, LATAM, and APAC, respectively. ATM-AVI also was very active against Burkholderia spp. (highest MIC, 8 mg/L).

Conclusion. Our results support clinical development of ATM-AVI to treat pneumonia caused by ENT (including MBL-producers), P. aeruginosa, S. maltophilia, and Burkholderia spp.
activity of gepotidacin and comparator agents when tested against contemporary Escherichia coli (EC) and Staphylococcus saprophyticus (SSAP) clinical isolates collected from patients with UTIs worldwide as part of the SENTRY Antimicrobial Surveillance Program.

**Methods.** A total of 1,467 EC and 92 SSAP isolates were collected from 73 medical centers located in US (38), Europe (27), Asia-Pacific region (4), and Latin America (4). These isolates were tested for susceptibility by reference methods in a central laboratory (JMI Laboratories). MIC results for gepotidacin and comparators were interpreted as per US FDA and EUCAST criteria. Isolates were from UTIs, 70% of which were from ambulatory, outpatient, emergency, and family practice medical services.

**Results.** Gepotidacin (MIC<sub>90</sub> of 2/4 mg/L) displayed activity against 98.2% of all observed MICs ≤ 4 mg/L. Susceptibility rates of trimethoprim-sulfamethoxazole (TSMX; MIC<sub>90</sub> of 8/16 mg/L), ciprofloxacin (MIC<sub>90</sub> of 0.015/ > 4 mg/L), and amoxicillin-clavulenate (MIC<sub>90</sub> of 8/16 mg/L) were 67.1%, 72.9%, and 78.7% (CLSI), respectively. Greater susceptibility against EC isolates was seen for fosfomycin (MIC<sub>90</sub> of 0.51 mg/L; 99.0%), nitrofurantoin (MIC<sub>90</sub> of 16/32 mg/L; 97.4%), and meropenem (<0.015/0.03 mg/L; 100%). An ESBL phenotype was observed in 15.3% of EC isolates; gepotidacin (MIC<sub>90</sub> of 2/4 mg/L) remained active against these isolates. Gepotidacin (MIC<sub>90</sub> of 0.06/0.12 mg/L) also was active against 92 SSAP isolates, with 100% of MICs ≤ 0.5 mg/L. Susceptibility of SSAP isolates to TSMX, ciprofloxacin, or nitrofurantoin was greater than 98.8% (CLSI), while fosfomycin showed little activity (MIC<sub>90</sub> 64/ > 256 mg/L; 98.9% R [EUCAST]).

**Conclusion.** Gepotidacin demonstrated potent activity against contemporary Escherichia coli, including SSAP-producing isolates and S. saprophyticus isolates collected worldwide.

Table 1. Characterization of strains assessed in the HFIM; minimum inhibitory concentration (MIC) values for treatments not assessed are included in parentheses.

| Organism (No. of isolates) | Antimicrobial agent | MIC (µg/mL) | % R | % S |
|----------------------------|---------------------|-------------|-----|-----|
| E. coli (1,487)            | Gepotidacin         | 2/4         | 98.2| 2.8|
|                            | Ciprofloxacin       | 0.015/ > 4  | 97.9| 2.1|
|                            | Amoxicillin-clavulenate | ≤0.12/ > 16 | 97.9| 2.1|
|                            | Nitrofurantoin      | 16-32       | 98.8| 1.2|
|                            | Fosfomycin          | 0.1-1       | 98.9| 1.1|
|                            | Meropenem           | 0.015/0.15  | 100.0| 0.0|

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1263. Assessment of Cefepime (CEF)-Tobramycin (TAM) Human Exposures to Suppression the Emergence of Resistance among Serine (SBL)- and Metallo-Ô-beta-Lactamase (MBL)-Producing Gram-Negative Bacteria (GNB) in a Hollow Fiber Infection Model (HFIM)

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**Background.** CEF-TAM (FTB) efficacy and safety are currently being evaluated in a Phase 3 trial (NCT03840148). TAM, a boric acid-based Ô-lactamase inhibitor, restores susceptibility to CEF when resistance is driven by SBL or MBL (ie, NDM, VIM). This in vitro study assessed whether clinical FTB exposures suppress treatment-emergent resistance in pathogenic Enterobacteriaceae and Pseudomonas aeruginosa.

**Methods.** Bioreactors (C2011, FiberCell) were inoculated with clinical GNB strains (N=6) using highly concentrated log phase cultures (10<sup>6</sup> CFU). Syringe pumps supplied humanized exposures of CEF (2 g), TAM (2 g/0.5 g), cefazidine-avibactam (CZA, 2 g/0.5 g), each as 2 h infusions q6h, or meropenem-vaborbactam (MEV, 2 g/2 g or 0.5 g)) for 7 days. Exposures were confirmed by UPLC/MS/MS for all agents. Subpopulations with elevated FTB MICs (4x) were monitored with drug-supplemented agar. CZA or MEV served as positive or negative controls for selected strains. Samples, serially removed from bioreactors, were saline-washed prior to quantitation of culture to prevent drug carryover.

**Results.** All strains grew rapidly in the presence of CEF (Figure 1), consistent with resistance by broth microdilution (BMD, Table 1). With the addition of TAM, there was extensive killing of the total bacterial populations by FTB, and subpopulations with elevated FTB MICs were never recovered. Like FTB against Klebsiella pneumoniae (KP) BAA-1705, CZA initially decreased the inoculum to the lower limit of detection, but unlike FTB, allowed regrowth to 3.7 log<sub>10</sub> CFU/mL by day 7. The first dose of FTB was bactericidal against VIM+ and NDM+ KP strains while regrowth occurred prior to 8 h of MEV and CZA challenge, respectively. Notably, early failure of MEV is discordant with susceptibility by BMD (MIC= 4 µg/mL). By day 7, FTB sterilized an OXA-48+ KP strain that when challenged by MEV, grew to 9.8 log<sub>10</sub> CFU/mL at 24 h.

Figure 1. Bacterial burdens observed in the HFIM when treated with CEF alone or CEF+TAM (FTB)

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1264. Assessment of In Vivo Efficacy of Cef-Cf-296 in addition to Vancomycin (VAN) and Daptomycin (DAP) against Staphylococcus aureus in the Neutropenic Murine Thigh Infection Model

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Session: P-58. Novel Agents

**Background.** CFC-296 is a novel lysin in pre-clinical development for the treatment of methicillin-susceptible and methicillin-resistant Staphylococcus aureus infections, used in addition to standard of care antibiotics including VAN and DAP. We evaluated the in vivo efficacy of CFC-296 alone and in addition to VAN and DAP against S. aureus.