Table 1. Characteristics of clinical heteroresistant mother E. faecalis strains and heteroresistance-derived E. faecalis clones.

| NO. | TGC MIC (mg/L) | NO. | TGC+MIC (mg/L) | TGC+CCP | TGC+PABN |
|-----|---------------|-----|---------------|---------|----------|
| EFSC186 | 0.0025 | Tig-1 | TGC+CCP 1-2 | Tig+CCP 1-2 | TGC+PABN 1-2 |
| NEFA53 | 0.125 | Tig-1 | TGC+CCP 1-2 | Tig+CCP 1-2 | TGC+PABN 1-2 |
| NEFA5 | 0.25 | Tig-1 | TGC+CCP 1-2 | Tig+CCP 1-2 | TGC+PABN 1-2 |
| NEFA27 | 0.25 | Tig-1 | TGC+CCP 1-2 | Tig+CCP 1-2 | TGC+PABN 1-2 |
| NEFA26 | 0.5 | Tig-1 | TGC+CCP 1-2 | Tig+CCP 1-2 | TGC+PABN 1-2 |
| NEFA27 | 0.5 | Tig-1 | TGC+CCP 1-2 | Tig+CCP 1-2 | TGC+PABN 1-2 |

Table 3. List of mutation-related genes, amino acids and proteins by comparison of whole genome between the parental isolate and the TGC-induced resistant strains.

**Conclusion:** Our data indicated that the main mechanism of TGC heteroresistance in E. faecalis might be associated with the efflux pumps. TGC resistance in E. faecalis was associated with mutations in the 16sRNA site or 30S ribosome protein S10. The genetic mutations in several enzymes and transfer systems might also participate in the resistance development to TGC in E. faecalis.

**Disclosures.** All Authors: No reported disclosures

1457. Serial Passage of Enterobacteriaceae to Explore Development of Carbapenem Resistance
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**Session:** P-66. Resistance Mechanisms

**Background.** Carbapenems are broad-spectrum antibacterials that have seen increased usage for the Enterobacteriaceae family in recent years. While carbapenem usage has been associated with increased antibiotic resistance, there is currently a lack of data comparing the risk of reduced susceptibility selection by the two most commonly used carbapenems in the US, ertapenem (ERT) and meropenem (MER). We conducted a novel serial passage experiment with clinical isolates of Enterobacteriaceae to assess the impact of repeated exposure to ERT or MER on phenotypic susceptibility patterns.

**Methods.** Non-duplicate clinical Enterobacteriaceae isolates were selected randomly for inclusion. Antimicrobial susceptibility testing was performed by CLSI disc diffusion methods. Standardized suspensions of isolates were plated on Mueller-Hinton agar, and ERT (10mcg) and MER (10mcg) discs applied. Zones of inhibition were measured and recorded after 16-18 hours incubation. Growth from the innermost zone of inhibition around each disc was used to prepare subsequent suspensions for serial susceptibility testing. This process would be repeated daily for 10 days. Each subsequent serially-passaged isolate was tested against both ERT and MER. Daily zones of inhibition were measured and interpreted. Baseline & final susceptibilities were determined by automated methods (Vitek2).

**Results.** Seventeen Enterobacteriaceae isolates were selected, including: Klebsiella pneumoniae (n=11), Klebsiella oxytoca (n=2), Escherichia coli (n=1), Morganella morganii (n=1), and Enterobacter cloacae (n=2). Despite a greater degree of reductions in zones of inhibition with repeated ERT exposure (vs MER), the overall 10 day trends were not found to be significant different (P=0.529). Resistance developed to ERT in six isolates compared to one MER-resistant isolate (P = 0.053). E. cloacaes was the only species to show a significant change between drugs (P=0.013). Two of these isolates that developed reduced zone changes > 10mm to MER were initially exposed to ERT on an earlier plate.

**Conclusion.** This novel experiment identified the development of some nonsignificant reductions in susceptibility with ERT after serial exposure. Results from this pilot study should encourage larger well-designed studies in this area.

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1458. Uncharted territories: applying "precision medicine" to understand the treacherous landscape of extensively and multidrug resistant (XDR and MDR) Pseudomonas aeruginosa in a patient with cystic fibrosis and lung transplantation
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**Session:** P-66. Resistance Mechanisms

**Background.** Pseudomonas aeruginosa is a persistent and difficult-to-treat pathogen in many patients, especially those with cystic fibrosis (CF). Herein, we describe our experience managing a young woman suffering from CF with XDR P. aeruginosa who underwent lung transplantation. We highlight the contemporary difficulties reconciling the clinical, microbiological, and genetic information.

**Methods.** Mechanism-based susceptibility disk diffusion synergy testing with double and triple antibiotic combinations aided in choosing tailored antimicrobial combinations to control the infection in the pre-transplant period, creating an effective prophylactic and regimen, and managing recurrent infections in the post-transplant period. Thirty-six sequential XDR and PDR P. aeruginosa isolates obtained from the patient within a 17-month period, before and after a double-lung transplant were analyzed by whole genome sequencing (WGS) and RNAseq in order to understand the genetic basis of the observed resistance phenotypes, establish the genomic population diversity, and define the nature of sequence changes over time.

**Results.** Our phylogenetic reconstruction demonstrates that these isolates represent a genotypically and phenotypically heterogeneous population. The pattern of mutation accumulation and variation of gene expression suggests that a group of closely related strains was present in the patient prior to transplantation and continued to evolve throughout the course of treatment regardless of antibiotic usage. Our findings challenge antimicrobial stewardship programs that assist with the selection and duration of antibiotic regimens in critically ill and immunocompromised patients based on single-isolate laboratory-derived resistant profiles. We propose that an approach sampling the population of pathogens present in a clinical sample instead of single colonies be applied instead when dealing with XDR P. aeruginosa, especially in patients with CF.

**Conclusion.** In complex cases such as this, real-time combination testing and genomic/transcriptomic data could lead to the application of true "precision medicine" by helping clinicians choose the combination antimicrobial therapy most likely to be successful against a population of MDR pathogens present.

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1459. Whole Genome Sequencing Analysis of Enterococcus faecium Clinical Isolates Reveals High Strain Diversity and High Accuracy Prediction of Antimicrobial Resistance
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Background. Whole genome sequencing (WGS) is a powerful tool to uncover transmission patterns and antimicrobial resistance (AMR) mechanisms of Enterococcus faecium, a major cause of hospital-acquired infections. Most E. faecium genomic studies include isolates from outbreaks or defined genetic lineages. In contrast, we have applied routine WGS to characterize over 400 E. faecium isolates, known AMR genes and SNPs can be simply applied to predict phenotypic susceptibility with high accuracy for seven routinely tested antibiotics. Further testing will be performed on defined genotypic features. The intermediate category is considered with the susceptible category.

Table 1. Summary of validation set predictions of antimicrobial susceptibility based on defined genotypic features.

| Antibiotic/Drug | Genotype used for prediction | Overall accuracy (%) | Genotype resistant (%) | Genotype susceptible (%) | Predictive accuracy (%) |
|----------------|-----------------------------|----------------------|-----------------------|-------------------------|------------------------|
| Ampicillin     | Mutation of pef450H         | 95.8%                | 10.0%                 | 95.8%                   | 97.1%                  |
| Ceftriaxone    | Mutation of pef450H         | 95.8%                | 10.0%                 | 95.8%                   | 97.1%                  |
| Doxycycline    | Mutation of pef450H         | 95.8%                | 10.0%                 | 95.8%                   | 97.1%                  |
| Gentamicin     | Mutation of pef450H         | 95.8%                | 10.0%                 | 95.8%                   | 97.1%                  |
| Levofloxacin   | Mutation of pef450H         | 95.8%                | 10.0%                 | 95.8%                   | 97.1%                  |
| Metronidazole  | Mutation of pef450H         | 95.8%                | 10.0%                 | 95.8%                   | 97.1%                  |
| Vancomycin     | Mutation of pef450H         | 95.8%                | 10.0%                 | 95.8%                   | 97.1%                  |

Conclusion. In a diverse and challenging set of clinical E. faecium isolates, known AMR genes and SNPs can be simply applied to predict phenotype susceptibility with high accuracy for seven routine antibiotics. Further testing will be performed to resolve phenotype-genotype discrepancies.

Summary of validation set predictions of antimicrobial susceptibility based on defined genotypic features. The intermediate category is considered with the susceptible category.

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1460. Imipenem/Cilastatin (IMI)/Relebactam (REL) in Hospital-Acquired/Ventilator-Associated Bacterial Pneumonia (HABP/VABP): Subgroup Analyses of the RESTORE-IMI 2 Trial

Methods. Randomized, controlled, double-blind, phase 3 trial in adult pts with HABP/VABP. Lower respiratory tract (LRT) specimens were obtained ≤48 hours prior to screening. Pts were randomized 1:1 to IMI/REL 500 mg/250 mg or PIP/TAZ 4 g/500 mg, given IV every 6 h for 7-14 d. The primary endpoint was Day 28 all-cause mortality (ACM) and the key secondary endpoint was clinical response at early follow-up (EUF)-7-14 d after completing therapy. Outcomes were also assessed in the subgroups of pts with moderate/severe renal impairment (creatinine clearance < 60 mL/min) and pts who received vasopressors.

Results. Of MITT pts (n=531) at baseline, 66.1% (175 IMI/REL, 176 PIP/TAZ) were female, 47.5% (122 IMI/REL, 127 PIP/TAZ) 75% with APACHE II score ≥25, and 24.7% (71 IMI/REL, 60 PIP/TAZ) had moderate/severe renal impairment. Further, 20.9% (54 IMI/REL, 57 PIP/TAZ) received vasopressors within 72 h of first dose of study drug and/or during the study. In each subgroup, baseline demographics, clinical characteristics, and causative LRT pathogens (mostly Enterobacteriaceae, and A. calcoaceticus-baumannii complex) were generally comparable between treatment arms. In pts with APACHE II score ≥25, Day 28 ACM and clinical response rates with IMI/REL were favorable compared to PIP/TAZ (Table). Day 28 ACM was also favorable with IMI/REL in patients receiving vasopressors. Remaining outcomes were similar between treatment arms.

Conclusion. IMI/REL is an efficacious treatment option for critically ill pts with HABP/VABP.

Table. Primary and key secondary efficacy outcomes by subgroup (MITT population)

| Pts in the ICU at baseline |
|---------------------------|
| Day 28 all-cause mortality (MITT) | Favorable clinical response at EFU (MITT) |
| IMI/REL n (%) | PIP/TAZ n (%) | Difference (95% CI) |
| 30/175 (17.1%) | 42/176 (23.9%) | -6.7% (15.2, 1.8) |
| 103/175 (58.9%) | 96/176 (54.5%) | 4.3% (6.1, 1.4) |

| Pts with moderate/severe renal impairment at baseline |
|---------------------------|
| Day 28 all-cause mortality (MITT) | Favorable clinical response at EFU (MITT) |
| IMI/REL n (%) | PIP/TAZ n (%) | Difference (95% CI) |
| 30/71 (42.3%) | 19/60 (31.7%) | 0.7% (15.4, 16.5) |
| 20/75 (26.7%) | 27/80 (33.7%) | -2.0% (13.2, 10.0) |

| Pts receiving vasopressors |
|---------------------------|
| Day 28 all-cause mortality (MITT) | Favorable clinical response at EFU (MITT) |
| IMI/REL n (%) | PIP/TAZ n (%) | Difference (95% CI) |
| 25/54 (46.3%) | 32/57 (56.1%) | -19.1% (36.5, -0.4) |
| 24/54 (44.4%) | 16/57 (28.1%) | 16.4% (1.8, 33.5) |

CI, confidence interval. N, total number of pts in analysis population in treatment arm, n, number of pts who died/discharged missing survival status or number of pts with favorable response (depending on endpoint).

*Renal impairment, based on creatinine clearance as calculated by the Cockcroft-Gault formula, defined as modulus (<=45 mL/min) or serum (<=2.5 to 3.5 mg/dL).

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