Table 2. Characteristics of clinical heteroresistant mother E. faecalis strains and heteroresistance-derived E. faecalis clones

Table 2. 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+CCCP	TGC+PABN
EF16C186	0.0625	Tig0.5-EF16C186-1	2	<=0.06	2
		Tig0.5-EF16C186-2	2	<=0.06	2
NEFA53	0.125	Tig0.5-NEFA53-1	1	<=0.06	2
		Tig0.5-NEFA53-2	1	<=0.06	2
NEFA5	0.25	Tig0.5-NEFA5-1	2	<=0.06	2
		Tig0.5-NEFA5-2	2	<=0.06	2
NEFA37	0.25	Tig0.5-NEFA37-1	2	<=0.06	2
		Tig0.5-NEFA37-2	2	<=0.06	2
NEFA26	0.5	Tig0.5-NEFA26-1	2	<=0.06	2
		Tig0.5-NEFA26-2	2	<=0.06	2
NEFA27	0.5	Tig0.5-NEFA27-1	2	<=0.06	1
		Tig0.5-NEFA27-2	2	<=0.06	1
NEFA32	0.5	Tig0.5-NEFA32-1	2	<=0.06	2
		Tig0.5-NEFA32-2	2	<=0.06	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

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

Name of gene	Locus name Deng	Gene	Mutation in the genome of *E. fecalis* strains		
			Deng-T10-3	Deng-T60-1	KOG
Membrane protein	DENG_ 00157		Ala54Glu His56Asn	Ala54Glu His56Asn	None
Recombinase/integrase	DENG_00476		Leu921Leu Pro925Pro Leu937Leu Glu926Asp Asp929Glu Met942Lys	Leu921Leu Pro925Pro Glu926Asp Asp929Glu Leu937Leu	None
Iron compound ABC transporter, substrate-binding protein	DENG_00164		Arg155Ser	Arg155Ser	K02016
Hypothetical protein	DENG_00426		Gly32Gly	Gly32Gly	None
PTS system, IIB component	DENG_00444	manX		Glu113Gly	K02794
Lipoprotein, YaeC family	DENG_02183	metQ		Ser355Asn	K02073
No	DENG_00473		Asp166Asp	Asp166Asp	None
Aspartyl/glutamyl-tRNA amidotransferase subunit B	DENG_00775	gatB	Gly210Gly	Gly210Gly	K02434
Hypothetical protein	DENG_01621		Gly32Gly	Gly32Gly	None
Hypothetical protein	DENG_01950		A446A T438T L437L P428P Y422Y E421E G419G A400A N399N	A446A T438T L437L P428P Y422Y E421E G419G A400A N399N	None
N0	DENG_00799		Gly261Gly	Gly261Gly	None
2-C-methyl-D-erythritol 2,4-cyclodiphosphate synthase	DENG_00043	ispF	267_268del	267_268del	K01770
Uncharacterized HTH-type transcriptional regulator in lacX 3'region	DENG_00489		L336fs	L336fs	None

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 16SrRNA 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 Enterobacteriales family in recent years. While carbapenem usage has been associated with increased antibacterial 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 Enterobacteriales to assess the impact of repeated exposure to ERT or MER on phenotypic susceptibility patterns.

Methods. Non-duplicate clinical Enterobacteriales 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 isolated was tested against both ERT and MER. Daily zones of inhibition were measured and interpreted. Baseline & final susceptibilities were determined by automated methods (Vitek 2).

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. cloacae* was the only species to show a significant change between drugs (P=0.010). Two of three 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, create an effective perioperative prophylaxis regimen, and manage 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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Session: P-66. Resistance Mechanisms

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 outbreak investigations rather than routine sampling. Additionally, the use of WGS to predict *E. faecium* AMR has not been tested systematically. Here we use WGS to characterize over 400 *E. faecium* clinical isolates to assess their strain diversity and AMR mechanisms.

Methods. Clinical *E. faecium* isolates from the MGH Microbiology Laboratory were collected at random from 1/2016-12/2017 (derivation set; 193 isolates) and with enrichment for more resistant isolates from 1/2018-9/2019 (validation set; 226 isolates). Species identification was performed using the bioMérieux VITEK MS instrument. Susceptibility testing was performed using the AST-GP75 card (bioMérieux VITEK 2), with confirmation by disk diffusion or ETEST when needed. Bacterial DNA from isolates was extracted, purified, sequenced (Illumina NextSeq), and quality filtered. Samples with >20x genome coverage were analyzed with SRST2 and AliView.

Results. MLST analysis of the derivation set demonstrated strikingly high diversity compared to previously published studies, with the three most frequent types (ST412, ST18, ST736) comprising fewer than half of samples. We identified and confirmed four novel MLST types comprising 12% of samples. We next analyzed the derivation isolate set to determine which genes and SNPs, if applicable, predicted resistance to seven antibiotics routinely tested at our institution: ampicillin, ciprofloxacin, doxycycline, high-level gentamicin, levofloxacin, tetracycline, and vancomycin. These rules were uniformly applied to the validation isolate set and demonstrated that genotypic AMR prediction has an overall positive predictive value of 97.0% and negative predictive value of 97.1% compared to standard susceptibility methods.

Table 1. Summary of validation set predictions of antimicrobial susceptibility based on defined genotypic features. * The intermediate category is considered with the susceptible category.

			Phenotypically resistant (n)		Phenotypically susceptible (n)		Prediction accuracy (%)	
Antimicrobial Drug	Genotype used for prediction	Overall suscep. rate (%)	Genotyp. resistant (TP)	Genotyp. suscep. (FN)	Genotyp. resistant (FP)	Genotyp. suscep. (TN)	PPV	NPV
Ampicillin	Mutation of *prp5* 485M	14	186	2	2	26	98.9	92.8
Ciprofloxacin*	Mutation of *gyrA* 84S or *parC* 82S	17	177	1	1	31	99.4	96.9
Doxycycline	Presence of *tetM*	27	116	1	17	43	87.2	97.7
Gentamicin high-level	Presence of *aac(6')-Ie-aph(2")-Ia*	95	11	1	0	202	100.0	99.5
Levofloxacin*	Mutation of *gyrA* 84S or *parC* 82S	16	185	1	1	31	99.5	96.9
Tetracycline	Presence of *tetL, tetM,* or *tetS*	23	152	0	8	42	95.0	100.0
Vancomycin	Presence of *vanA* or *vanB*	22	172	2	2	45	98.9	95.7

Conclusion. In a diverse and challenging set of clinical *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 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.

			Phenotypically resistant (n)		Phenotypically susceptible (n)		Prediction accuracy (%)	
Antimicrobial Drug	Genotype used for prediction	Overall suscep. rate (%)	Genotyp. resistant (TP)	Genotyp. suscep. (FN)	Genotyp. resistant (FP)	Genotyp. suscep. (TN)	PPV	NPV
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1460. Imipenem/Cilastatin (IMI)/Relebactam (REL) in Hospital-Acquired/ Ventilator-Associated Bacterial Pneumonia (HABP/VABP): Subgroup Analyses of Critically Ill Patients in the RESTORE-IMI 2 Trial

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Session: P-67. Respiratory Infections - Bacterial

Background. HABP/VABP are serious infections associated with high mortality. Critically ill patients (pts) are at particularly high risk of adverse clinical outcomes. In the RESTORE-IMI 2 trial, IMI/REL was non-inferior to PIP/TAZ in primary and key secondary endpoints. We evaluated outcomes specifically in critically ill pts, according to several definitions, from that 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 (EFU; 7-14 d after completing therapy) in the modified intent-to-treat (MITT) population (randomized pts with ≥1 dose of study drug, excluding pts with only gram-positive cocci present on baseline Gram stain). This analysis assessed efficacy outcomes specifically in pts in the ICU and in pts with APACHE II score ≥15, both prespecified subgroups. In post-hoc analyses, outcomes were also specifically 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 in the ICU, 47.5% (125 IMI/REL, 127 PIP/TAZ) had APACHE-II score ≥15, 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 Enterobacterales, *P. aeruginosa,* and *A. calcoaceticus-baumannii* complex) were generally comparable between treatment arms. In pts with APACHE-II score ≥15, 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)

	IMI/REL n/N (%)	PIP/TAZ n/N (%)	Difference (95% CI)
Pts in the ICU at baseline			
Day 28 all-cause mortality (MITT)	30/175 (17.1%)	42/176 (23.9%)	-6.7% (-15.2, 1.8)
Favorable clinical response at EFU (MITT)	103/175 (58.9%)	96/176 (54.5%)	4.3% (-6.1, 14.6)
Pts with APACHE-II score ≥15 at baseline			
Day 28 all-cause mortality (MITT)	25/125 (20.0%)	45/127 (35.4%)	-15.4% (-26.2, -4.4)
Favorable clinical response at EFU (MITT)	71/125 (56.8%)	51/127 (40.2%)	16.6% (4.3, 28.5)
Pts with moderate/severe renal impairment[a] at baseline			
Day 28 all-cause mortality (MITT)	23/71 (32.4%)	19/60 (31.7%)	0.7% (-15.4, 16.5)
Favorable clinical response at EFU (MITT)	30/71 (42.3%)	27/60 (45.0%)	-2.7% (-19.6, 14.1)
Pts receiving vasopressors[b]			
Day 28 all-cause mortality (MITT)	20/54 (37.0%)	32/57 (56.1%)	-19.1% (-36.5, -0.4)
Favorable clinical response at EFU (MITT)	24/54 (44.4%)	16/57 (28.1%)	16.4% (-1.6, 33.5)

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

[a]Renal impairment, based on creatine clearance as calculated by the Cockcroft-Gault formula, defined as moderate (<60 to ≥30mL/min) or severe (<30 to ≥15 mL/min). [b]Received ≥1 vasopressor dose within 72 h of first dose of study drug and last dose of study drug.

Disclosures. Luke F. Chen, MBBS MPH MBA FRACP FSHEA FIDSA, Merck & Co., Inc. (Employee, Shareholder)Merck & Co., Inc. (Employee, Shareholder) Maria C. Losada, BA, Merck & Co., Inc. (Employee, Shareholder) Kathryn A. Mahoney, PharmD, Merck (Employee, Shareholder) Jiejun Du, PhD, Merck & Co., Inc. (Employee, Shareholder) Michelle L. Brown, BS, Merck & Co., Inc. (Employee, Shareholder) Robert Tipping, MS, Merck & Co., Inc. (Employee, Shareholder) Katherine Young, MS, Merck & Co., Inc. (Employee, Shareholder)Merck & Co., Inc. (Employee, Shareholder) C. Andrew DeRyke, PharmD, Merck & Co., Inc. (Employee, Shareholder) Joan R. Butterton, MD, Merck & Co., Inc. (Employee, Shareholder) Amanda Paschke, MD MSCE, Merck & Co., Inc. (Employee, Shareholder)

1461. Impact of the Ampicillin/Sulbactam Shortage on Antibiotic Prescribing and Clinical Outcomes for Adult Inpatients with Aspiration Pneumonia

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Session: P-67. Respiratory Infections - Bacterial

Background. Ampicillin/sulbactam is a recommended first-line agent for the treatment of aspiration pneumonia. Due to the ampicillin/sulbactam shortage, beginning in March 2019, alternative therapies, such as ceftriaxone plus metronidazole, have been utilized more frequently. The objective of this study is to examine clinical outcomes in adult inpatients treated with either ampicillin/sulbactam or ceftriaxone/metronidazole for aspiration pneumonia.

Methods. An electronic health record report identified patients ≥18 years of age that received ampicillin/sulbactam (pre-March 2019) or ceftriaxone/metronidazole (post-March 2019) with the indication of aspiration pneumonia. The primary objective