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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.

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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