PhD[3]; [1]Mass General Hospital, Cambridge, Massachusetts; [2]University of Washington School of Medicine, Cambridge, Massachusetts; [3]Ragon Institute of MGH, MIT, and Harvard, Cambridge, Massachusetts; [4]Massachusetts General Hospital, Boston, Massachusetts

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.

Antimicrobial Drug	Genotype used for prediction	Overall suscep. rate (%)	Phenotypically resistant (n)		Phenotypically susceptible (n)		Prediction accuracy (%)	
			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

Luke F. Chen, MBBS MPH MBA FRACP FSHEA FIDSA[1]; Maria C. Losada, BA[1]; Kathryn A. Mahoney, PharmD[1]; Jiejun Du, PhD[1]; Michelle L. Brown, BS[1]; Robert Tipping, MS[1]; Katherine Young, MS[2]; C. Andrew DeRyke, PharmD[1]; Joan R. Butterton, MD[1]; Amanda Paschke, MD MSCE[1]; [1]Merck & Co., Inc., Kenilworth, New Jersey; [2]Merck & Co, Inc, Kenilworth, NJ

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.

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

Mary L. Staicu, PharmD[1]; Ian Murphy, PharmD[1]; Maryrose R. Laguio-Vila, MD[2]; [1]Rochester General Hospital, Rochester, NY; [2]Rochester Regional Health, Rochester, NY

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

was to describe 30-day all-cause readmission rates for patients that received ampicillin/sulbactam compared to ceftriaxone/metronidazole. The secondary objectives included hospital length of stay (LOS), 30-day all-cause mortality, *C.difficile* infection (CDI) within 3 months, and total antibiotic costs.

Results. A total of 86 patients (50 received ampicillin/sulbactam and 36 received ceftriaxone/ metronidazole) were included. Demographics were similar between groups. There was no significant difference in 30-day all-cause readmission rates (30% vs 19%, *p*=0.322). The ampicillin/sulbactam group, however, was found to have a significantly higher rate of 30-day all-cause mortality (12% vs 0%, *p*=0.038). Additionally, total duration of therapy was found to be significantly shorter in the ampicillin/sulbactam group (5 vs 7 days, *p*=0.002) with reduced overall cost of therapy($130 vs $235, *p*< 0.001). No differences were observed in hospital LOS or CDI within 3 months.

Conclusion. No difference was observed in 30-day all-cause readmissions in patients receiving ampicillin/sulbactam compared to ceftriaxone/metronidazole for the treatment of aspiration pneumonia. Further analyses are recommended to evaluate the impact on 30-day all-cause mortality.

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

1462. The protective effect of pneumococcal vaccination on cardiovascular disease in adults: A systematic review and meta-analysis

Fawziah Marra, BSc (Pharm), PharmD[1]; Angel Zhang, BSc[2]; Emma Gillman, BSc[2]; Katherine Bessai, BSc[2]; Kamalpreet Parhar, BSc (Pharm)[2]; Nirma Khatri Vadlamudi, BA, BS, MPH[3]; [1]University of British Columbia, Vancouver, British Columbia, Canada, Vancouver, BC, Canada; [2]University of British Columbia, Vancouver, British Columbia, Canada; [3]Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia, Canada

Session: P-67. Respiratory Infections - Bacterial

Background. Epidemiological studies suggest a link between pneumococcal infection and an adverse cardiovascular outcome such as myocardial infarction. Therefore, studies have evaluated the protective effect of the 23-valent polysaccharide pneumococcal vaccination (PPV23), but results have varied. We conducted a meta-analysis to summarize the available evidence on the impact of PPV23 on cardiovascular disease

Methods. A literature search from January 1946 to September 2019 was conducted in Embase, Medline and Cochrane. All studies evaluating PPV23 compared to a control (placebo, no vaccine or another vaccine) for any cardiovascular events including myocardial infarction (MI), heart failure, cerebrovascular events were included. Risk ratios (RRs) were pooled using random effects models.

Results. Eighteen studies were included, with a total of 716,108 participants. Vaccination with PPV23 was associated with decreased risk of any cardiovascular event (RR: 0.91;95% CI: 0.84-0.99), and MI (RR of 0.88; 95% CI:0.79-0.98) in all age groups, with a significant effect in those 65 years and older, but not in the younger age group. Similarly, PPV23 vaccine was associated with significant risk reduction in all-cause mortality in all ages (RR: 0.78; 95%CI: 0.68-0.88), specifically in those aged 65 years and older (RR: 0.71; 95%CI: 0.60-0.84). A significant risk reduction in cerebrovascular disease was not observed following pneumococcal vaccination.

Conclusion. Polysaccharide pneumococcal vaccination decreases the risk of a cardiovascular event, specifically acute MI in the vaccinated population, particularly those 65 years of age and older. It would be highly beneficial to vaccinate the population who is at greater risk for cardiovascular diseases.

Disclosures. Fawziah Marra, BSc (Pharm), PharmD, Pfizer Inc (Research Grant or Support) Nirma Khatri Vadlamudi, BA, BS, MPH, Pfizer Inc (Research Grant or Support)

1463. Activity of Delafloxacin against Multi-Drug-Resistant Fastidious Respiratory Pathogens from European Medical Centers (2014-2019)

Dee Shorttidge, PhD[1]; Jennifer M. Streit, BS[1]; Michael D. Huband, BS[1]; Robert K. Flamm, PhD[2]; [1]JMI Laboratories, North Liberty, Iowa; [2]United States Committee on Antimicrobial Susceptibility Testing (USCAST), North Liberty, IA

Session: P-67. Respiratory Infections - Bacterial

Background. Delafloxacin (DLX) is an anionic fluoroquinolone (FQ) that has been approved in the United States and in Europe for the treatment of acute bacterial skin and skin structure infections and was recently approved in the US for treatment of community-acquired bacterial pneumonia (CABP). In the present study, *in vitro* susceptibility (S) results for DLX and comparator agents were determined for CABP pathogens including *Streptococcus pneumoniae* (SPN), *Haemophilus influenzae* (HI), *H. parainfluenzae* (HP) and *Moraxella catarrhalis (*MC) clinical isolates from European hospitals participating in the SENTRY Program during 2014-2019.

Methods. A total of 2,835 SPN, 1,484 HI, 959 MC, and 20 HP isolates were collected from community-acquired respiratory tract infections (CARTI) during 2014-2019 from European hospitals. Sites included only 1 isolate/patient/infection episode. Isolate identifications were confirmed at JMI Laboratories. Susceptibility testing was performed according to CLSI broth microdilution methodology, and EUCAST (2020) breakpoints were applied where applicable. Other antimicrobials tested included levofloxacin (LEV) and moxifloxacin (MOX; not tested in 2015). Multidrug-resistant (MDR) SPN isolates were categorized as being nonsusceptible (NS) to amoxicillin-clavulanate, erythromycin (ERY), and tetracycline; other SPN phenotypes were ERY-NS, or penicillin (PEN)-NS. β-lactamase (BL) presence was determined for HI, HP, and MC.

Results. The activities of the 3 FQs are shown in the table. The most active agent against SPN was DLX, with the lowest $MIC_{50/90}$ values of 0.015/0.03 mg/L. DLX activities were the same when tested against the MDR or PEN-NS for SPN phenotypes. ERY-NS isolates had DLX $MIC_{50/90}$ results of 0.015/0.03 mg/L. DLX was the most active FQ against HI, HP, and MC. BL presence did not affect FQ MIC values for HI or MC; only 1 HP isolate was BL-positive.

Conclusion. DLX demonstrated potent *in vitro* antibacterial activity against SPN, HI, HP, and MC. DLX was active against MDR SPN that were NS to the agents commonly used as treatments for CABP. These data support the utility of DLX in CABP including when caused by antibiotic resistant strains.

Table 1

Organism/Phenotype (n)	Delafloxacin $MIC_{50/90}$ (mg/L)	Levofloxacin $MIC_{50/90}$ (mg/L)	Moxifloxacin $MIC_{50/90}$ (mg/L, n[a])
S. pneumoniae (2,835)	0.015/0.03	1/2	≤0.12/0.25 (2,715)
MDR (253)	0.015/0.03	1/2	≤0.12/0.25 (240)
PEN-NS (799)	0.015/0.03	1/2	≤0.12/0.25 (762)
ERY-NS (651)	0.015/0.03	1/2	≤0.12/0.25 (620)
H influenzae (1,484)	≤0.001/0.002	≤0.015/0.03	0.03/0.03 (1,400)
BL-positive (268)	≤0.001/0.002	≤0.015/0.03	0.03/0.03 (254)
H. parainfluenzae (20)	0.008/0.03	0.03/0.06	0.06/0.25 (14)
M. catarrhalis (959)	0.004/0.008	0.03/0.06	0.06/0.06 (868)
BL-positive (833)	0.004/0.008	0.06/0.06	0.06/0.06 (833)

[a]Number of isolates tested for moxifloxacin, not tested in 2015.

Disclosures. Jennifer M. Streit, BS, A. Menarini Industrie Farmaceutiche Riunite S.R.L. (Research Grant or Support)A. Menarini Industrie Farmaceutiche Riunite S.R.L. (Research Grant or Support)Allergan (Research Grant or Support)Melinta Therapeutics, Inc. (Research Grant or Support)Melinta Therapeutics, Inc. (Research Grant or Support)Melinta Therapeutics, Inc. (Research Grant or Support)Merck (Research Grant or Support)Paratek Pharma, LLC (Research Grant or Support) Robert K. Flamm, PhD, A. Menarini Industrie Farmaceutiche Riunite S.R.L. (Research Grant or Support)Amplyx Pharmaceuticals (Research Grant or Support)Basilea Pharmaceutica International, Ltd (Research Grant or Support)Department of Health and Human Services (Research Grant or Support)Melinta Therapeutics, Inc. (Research Grant or Support)

1464. Adjuvant Systemic Steroid Therapy and Length of Hospital Stay in Pneumonia Patients: A Retrospective Cohort Study in a Community Hospital

Rattanaporn Mahatanan, MD[1]; [1]Harvard T.H Chan school of public health, Skowhegan, ME

Session: P-67. Respiratory Infections - Bacterial

Background. Pneumonia is a leading cause of morbidity and mortality worldwide resulting in a substantial healthcare expenditure. Antimicrobial agents are the main treatment. Recent studies showed the benefits of steroid therapy as an adjuvant therapy for patients with pneumonia; however, the overall evidence is still controversial.

Methods. Electronic medical records of hospitalized patients (age >18) at a community hospital in a rural Maine with the discharge diagnosis of pneumonia in 2015 and 2016 were reviewed. Demographics, comorbidities, physical examination, initial laboratory, and Pneumonia Severity Index (PSI) were collected for each patient. The exposure was a systemic steroid administered by either oral or intravenous. The outcomes included length of hospital stay (LOS), inpatient mortality, and transfer to tertiary care center. Competing-risks regression was utilized to examine the association between steroid and LOS. Multivariable logistic regression analysis adjusted for propensity score was used for other outcomes.

Results. A total of 414 patients were included. 277(63%) patients received systemic steroids. Overall, steroid use was significantly associated with shorter LOS (HR 1.26, 95%CI 1.03-1.54, p=0.02) and decrease inpatient mortality (OR 0.11, 95%CI 0.03-0.45, p< 0.01). In subgroup analysis, steroid associated with shorter LOS only in patients with PSI class IV (HR 1.38, 95%CI 1.02-1.89, p=0.04) and PSI class V (HR 2.04, 95%CI 1.11-3.74, p=0.02). There was an association of steroid and shorter LOS in subgroup of COPD patients (HR 1.42, 95%CI 1.02-1.97, p=0.03).