1240. *In Vitro* and *In Vivo* Activity of Single and Dual Antimicrobial Agents Against KPC-producing *Klebsiella pneumoniae*

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Background. Options for treatment of infections due to KPC-producing *K. pneumoniae* are limited, and combination therapy is often recommended. In this report, the *in vitro* and *in vivo* activity of potential therapeutic agents and combinations was assessed against four KPC-producing *K. pneumoniae* isolates.

Methods. Using clinically-relevant concentrations, time-kill experiments and the *Galleria mellonella* model of infection were used to examine the activity of polymyxin B, ceftazidime-avibactam, meropenem, rifampin, and amikacin alone and in combination. Four isolates of KPC-producing *K. pneumoniae* were studied, including two isolates that were resistant to polymyxin B and had ceftazidime-avibactam MICs of 8 μg/mL. The other two *K. pneumoniae* isolates were susceptible to polymyxin B and had lower MICs of ceftazidime-avibactam.

Results. Two isolates that were resistant to polymyxin B and with ceftazidime-avibactam MICs of 8 μg/mL were also resistant to amikacin and meropenem. When ceftazidime-avibactam was combined with either amikacin or meropenem, synergy was observed *in vitro*, and these combinations were associated with improved survival with the *in vivo* model. The other two *K. pneumoniae* isolates were susceptible to polymyxin B and had lower MICs of ceftazidime-avibactam. At concentrations four times the MIC, ceftazidime-avibactam had bactericidal activity *in vitro*; at one fourth the MIC, synergy was observed when combined with meropenem. Improved survival rates were observed with therapy with ceftazidime-avibactam, particularly when combined with a second agent for one isolate. In the *in vivo* model, polymyxin B with or without rifampin or meropenem, was ineffective against polymyxin B resistant strains.

Conclusion. Pending clinical studies, combining ceftazidime-avibactam with another agent (e.g., a carbapenem) should be encouraged when treating serious infections due to these pathogens, especially for isolates with ceftazidime-avibactam MICs near the susceptibility breakpoint.

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

1241. *In vitro* Activity of Ceftaroline Against Pathogens Collected Globally from the AWARE Surveillance Program, 2016

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Background. Ceftaroline, the active metabolite of ceftaroline fosamil, is a cephalosporin developed for treating infections caused by *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), *Streptococcus pneumoniae*, β-hemolytic streptococci, and some Gram-negative pathogens. This study reports the *in vitro* activity of ceftaroline against clinically relevant isolates collected in 2016 from the AWARE Surveillance Program.

Methods. 22,752 non-duplicate methicillin-sensitive *S. aureus* (MSSA), MRSA, *S. pneumoniae,* β-hemolytic streptococci (*S. pyogenes*, *S. agalactiae, S. dysgalactiae*) *Haemophilus influenzae,* and extended spectrum β-lactamase (ESBL)-negative *Enterobacteriaceae* were collected from (n/%) Asia/South Pacific (4,215/18.5%), Europe (12,962/57.0%), Latin America (3,384/14.9%), and Middle East/Africa (2,191/9.6%) during 2016. Isolates were from (n/%) complicated intraabdominal (2,149/9.5%), complicated urinary tract (3,029/13.3%), complicated skin and skin structure (8,271/36.4%), blood stream (2,422/10.6%) and lower respiratory tract infections (6,881/30.2%). MIC values were determined by broth microdilution and interpreted using CLSI breakpoints.

Results. Ceftaroline activity, based on % susceptibility (%S) and MIC_{90}, is shown in the table. Ceftaroline was active *in vitro* against both Gram-positive (100% of MSSA, 93.6% of MRSA and 99.7% of *S. pneumoniae*) and Gram-negative (99.7% of *H. influenzae* and 91.7% of ESBL-negative *Enterobacteriaceae*) isolates.

Organism (N)	% S	% I	% R	MIC50	MIC90
MRSA (5,022)	93.6	6.0	0.5	0.5	1
MSSA (3,675)	100	0	0	0.25	0.25
Streptococcus pneumoniae (2,024)	99.7	–	0.3	0.008	0.12
β-hemolytic streptococci (1,713)	100	–	–	0.008	0.015
Enterobacteriaceae, ESBL-Negative (9,647)	91.7	3.7	4.6	0.12	0.5
Haemophilus influenzae (671)	99.7	–	0.3	≤0.015	0.03

%S, %I, %R- percent susceptible, intermediate, resistant based on CLSI breakpoints; MIC_{50}, MIC_{90} in μg/mL.

Conclusion. Based on these data generated with isolates collected in 2016, ceftaroline exhibited potent *in vitro* activity against clinically relevant isolates, with >91% of all isolates susceptible at their CLSI breakpoints.

Funding: This study was sponsored by AstraZeneca. The AstraZeneca product ceftaroline fosamil was acquired by Pfizer in December 2016.

Disclosures. **J. Iaconis**, AstraZeneca: Employee and Shareholder, Salary and Shareholder in AstraZeneca

1242. Activity of Ceftazidime–Avibactam Against Respiratory Isolates of *Enterobacteriaceae* and *Pseudomonas aeruginosa* Collected in Latin America as Part of the INFORM Global Surveillance Program, 2014–2016

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Background. The β-lactam/non-β-lactam β-lactamase inhibitor combination ceftazidime-avibactam (CAZ-AVI) is active *in vitro* against isolates producing class A, C, and some class D β-lactamases, including extended-spectrum β-lactamases, stably derepressed AmpC, and serine carbapenemases. This study evaluated the *in vitro* activity of CAZ-AVI and comparators against respiratory isolates of *Enterobacteriaceae* (*Eba*) and *Pseudomonas aeruginosa* (*Pae*) collected in Latin America from 2014–2016 as part of the INFORM surveillance program.

Methods. Non-duplicate isolates from hospitalized patients with lower respiratory tract infections were collected from 24 medical centers in Argentina, Brazil, Chile, Colombia, Mexico, and Venezuela. Susceptibility (S) testing was performed by broth microdilution and interpreted using CLSI breakpoints except for CAZ-AVI (U.S. FDA) and colistin (EUCAST; *Eba*only). AVI was tested at a fixed concentration of 4 μg/mL with doubling dilutions of CAZ. Multidrug resistance (MDR) phenotype was defined as resistant by CLSI breakpoints to sentinel agents from ≥3 drug classes. Isolates were screened for β-lactamase genes by PCR and sequencing.

Results. CAZ-AVI showed potent *in vitro* activity against *Eba* isolates (MIC_{90}, 0.5 μg/mL; 99.3% S) and against CAZ-non-susceptible (CAZ-NS), colistin-resistant (CST-R) and MDR subsets (>93% S). CAZ-AVI activity against meropenem-non-susceptible (MEM-NS) *Eba* (89.7% S) was reduced due to production of metallo-β-lactamases (MBL); MEM-NS MBL-negative isolates were 100% S. CAZ-AVI showed greater *in vitro* activity against *Pae* isolates (MIC_{90}, 32 μg/mL; 85.4% S) than CAZ (69.2% S) or MEM (59.9% S). CAZ-AVI activity against CAZ-NS, CST-R, MEM-NS, MEM-NS MBL-negative, and MDR *Pae*isolates (50.4–92.6% S) also exceeded that of CAZ and MEM against these resistant subsets.

Conclusion. CAZ-AVI is a potential treatment option for respiratory infections in Latin America that are caused by *Eba* and *Pae* resistant to commonly used and last-in-line agents.

Funding: This study was sponsored by AstraZeneca. The AstraZeneca product ceftazidime-avibactam was acquired by Pfizer in December 2016.

Disclosures. **G. G. Stone**, Pfizer: Employee, Salary AstraZeneca: Shareholder, Capital Gains

1243. Activity of Ceftazidime–Avibactam Against Respiratory Isolates of *Enterobacteriaceae* and *Pseudomonas aeruginosa* Collected in Asia/Pacific as part of the INFORM Global Surveillance Program, 2014–2016

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Background. Avibactam (AVI) is a non-β-lactam β-lactamase inhibitor that restores the *in vitro* activity of ceftazidime (CAZ) against class A, class C, and some class D β-lactamases, including extended-spectrum β-lactamases, serine carbapenemases, and the chromosomal AmpC of *Pseudomonas aeruginosa* (*Pae*). This study evaluated the *in vitro* activity of CAZ-AVI and comparators against *Enterobacteriaceae* (*Eba*) and *Pae* collected from patients with lower respiratory tract infections (LRTI) in Asia/Pacific in 2014–2016 as part of the INFORM surveillance program.

Methods. Non-duplicate isolates from patients with LRTI were collected from 28 medical centers in Australia, Hong Kong, Japan, Malaysia, Philippines, South Korea, Taiwan, and Thailand. Susceptibility (S) testing was performed by broth microdilution and interpreted using FDA breakpoints for CAZ-AVI and CLSI breakpoints for comparators. AVI was tested at a fixed concentration of 4 μg/mL with doubling dilutions of CAZ. Multidrug resistance (MDR) phenotype was defined as resistant by CLSI breakpoints to sentinel agents from ≥3 drug classes.

Results. CAZ-AVI showed potent *in vitro* activity against the overall population of *Eba* (MIC_{90}, 0.5 μg/mL; 98.0% S) and against ceftazidime-nonsusceptible (CAZ-NS), colistin-resistant (CST-R), and MDR isolates, with >91% of these resistant subsets testing as susceptible (MIC ≤8 μg/mL). Reduced activity against meropenem-nonsusceptible (MEM-NS) *Eba* was attributable to the presence of class B metallo-β-lactamases (MBL); 95.7% of MEM-NS, MBL-negative isolates were susceptible to CAZ-AVI. CAZ-AVI also showed good activity against most *Pae* isolates (MIC_{90}, 8 μg/mL; 92.5% S), as well as CST-R isolates (MIC_{90}, 8 μg/mL; 100% S). Activity of CAZ-AVI was reduced against CAZ-NS, MEM-NS, MEM-NS MBL-negative, and MDR *Pae* subsets (46.9–82.3% S) but exceeded the activity of CAZ and MEM.

Conclusion. CAZ-AVI is a potential therapeutic option for treating respiratory infections in the Asia/Pacific region caused by *Eba* and *Pae* isolates resistant to commonly used and last-in-line agents.

Disclosures. **G. G. Stone**, Pfizer: Employee, Salary AstraZeneca: Shareholder, Capital Gains

1244. Activity of Ceftolozane-Tazobactam Against Global *Pseudomonas Aeruginosa* and Non-Susceptible Phenotypes: SMART 2016

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Background. *Pseudomonas aeruginosa* (PA), one of the species of the ESKAPE pathogens that are known to "escape" the effects of many antimicrobials, is often difficult to treat. Ceftolozane-tazobactam (C/T) is an anti-pseudomonal cephalosporin/β-lactamase inhibitor recently approved by FDA and EMEA. We examined its activity against global clinical isolates of PA, including isolates non-susceptible (NS, intermediate or resistant) to other agents.

Methods. In 2016, 158 hospitals in 51 countries collected 5533 PA from intra-abdominal (IAI), urinary (UTI), and respiratory tract infections (RTI). MICs were determined using CLSI broth microdilution and interpreted with both CLSI and EUCAST breakpoints, as the susceptible breakpoints for C/T, cefepime (FEP), meropenem (MEM), and piperacillin-tazobactam (P/T) are the same using both criteria.

Results. Overall regional susceptibility of PA to C/T, prevalence of FEP-NS, MEM- NS, and P/T- NS phenotypes, and susceptibility of these phenotypes to C/T are shown below:

	Africa	Asia*	Europe	Latin America	Middle East	North America	South Pacific
All PA (n)	405	795	1628	759	379	1137	430
C/T susceptibility (%)	87.9	89.1	90.3	85.0	89.7	94.6	97.7
PA, FEP-NS [n(% of region total)]	111 (27.4)	194 (24.4)	438 (26.9)	203 (26.7)	88 (23.2)	299 (26.3)	57 (13.3)
C/T susceptibility (%)	56.8	55.7	66.0	45.3	59.1	80.6	84.2
PA, MEM- NS [n(% of region total)]	138 (34.1)	203 (25.5)	525 (32.2)	258 (34.0)	135 (35.6)	247 (21.7)	55 (12.8)
C/T susceptibility (%)	68.8	62.1	72.2	58.1	72.6	82.2	85.5
PA, P/T- NS [n(% of region total)]	124 (30.6)	246 (30.9)	557 (34.2)	254 (33.5)	125 (33.0)	334 (29.4)	68 (15.8)
C/T susceptibility (%)	66.1	69.1	73.3	57.9	69.6	82.6	86.8

* Does not include China or India
Differences in C/T susceptibility across isolates from IAI (91.4%), RTI (90.5%), and UTI (89.3%) were small.

Conclusion. Overall susceptibility to C/T ranged from 85% in Latin America to 98% in South Pacific. FEP-NS, MEM-NS, and P/T-NS isolates were least prevalent in South Pacific. C/T was active against these phenotypes in >80% of isolates in North America and South Pacific and against 62–73% of MEM-NS and P/T-NS isolates in all other regions except Latin America. Monitoring of C/T susceptibility to PA is warranted in light of increasing resistance to first line agents.

Disclosures. **M. Hackel**, IHMA: Employee, Salary; **R. Badal**, IHMA, Inc: Employee, Salary; **K. Young**, Merck: Employee and Shareholder, Dividends and Salary **M. Motyl**, Merck & Co., Inc.,: Employee, Salary

1245. Genome Wide Analysis Reveals Host Genetic Variants that Associate with Reduction in *Clostridium difficile* Infection Recurrence (rCDI) in Patients Treated with Bezlotoxumab

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Background. Bezlotoxumab (BEZ) and actoxumab (ACT) are monoclonal antibodies against *C. difficile* toxins B and A, respectively. Patients receiving a single infusion of BEZ alone or with ACT in the MODIFY I/II trials showed a consistent reduction in the rate of rCDI over a 12-week period compared with a placebo (PBO) infusion. Exploratory genome wide analyses were conducted to determine whether genetic variants across the genome were associated with treatment response (rCDI).

Methods. DNA was extracted from blood obtained from patients who consented to genetic analysis (PGx population). Genetic data were generated on a commercial Axiom array platform (Affymetrix). Genotype imputation was performed using the 1000 Genomes Phase 3 reference data and Impute2 software after genetic quality control. Data from BEZ and ACT+BEZ arms were combined to provide increased power. The logistic regression with likelihood ratio test was used to search for single nucleotide polymorphisms (SNPs) that were strongly associated with a treatment effect on rCDI.

Results. An SNP rs2516513 located in the extended major histocompatibility complex (xMHC), region with a minor allele frequency of 25% in the general population, was associated with rCDI (P = 3.04E-08) (Figure 1). rCDI rates for the PGx population and in subgroups at high/low risk for rCDI stratified by SNP rs2516513 are shown in Table 1. Carriers of the T allele of SNP rs2516513 were associated with a statistically significant reduction in rCDI in BEZ-treated patients but not in PBO-treated patients (DrCDI = -21.5%). The magnitude of the effect of the T allele on rCDI is most prominent in patients who have ≥1 risk factor for rCDI (DrCDI = -24.6%), but is also present in patients without risk factors (DrCDI = -10.6%). In CC homozygous patients, rCDI rates are similar in both treatment groups and in patients at high and low risk of rCDI.

Conclusion. An SNP variant rs2516513 is associated with a lower rate of rCDI recurrence in patients treated with BEZ. The location of the associated genetic variant on chromosome 6 within xMHC, suggests that a host driven, immunological mechanism may play a role in rCDI and may predict patients most likely to respond to BEZ. As this is an exploratory finding, the results should be replicated in an independent validation study.

Figure 1. Manhattan plot of the p-values of the genome0wide associations SNPs and treatment effect on rCDI

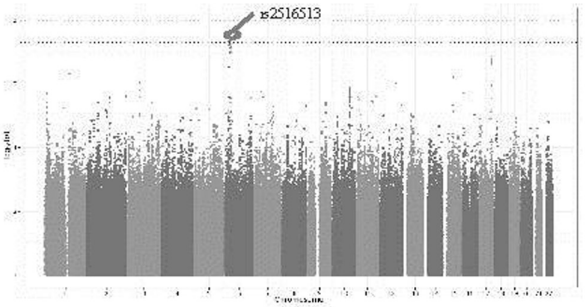

Table1. Proportion of Patients with rCDI stratified by SNP rs2516513 genotype and by risk category

Genotype	CC			TC or TT		
	BEZ and ACT+BEZ	PBO	Difference (%)	BEZ and ACT+BEZ	PBO	Difference (%)
	% (n/N)		%	% (n/N)		%
PGx dataset	31.8 (87/274)	35.3 (48/136)	-3.5	11.2 (21/187)	32.7 (34/104)	-21.5
High Risk*	31.5 (69/219)	35.8 (39/109)	-4.3	13.7 (20/146)	38.3 (31/81)	-24.6
Low Risk±	32.7 (18/55)	33.3 (9/27)	-0.6	2.4 (1/41)	13.0 (3/23)	-10.6

PGx= pharmacogenetic; n=number of patients in the analysis population meeting the criteria for endpoint; N=number of patients included in the analysis population; *Had ≥ 1 of the following risk factors for rCDI: prior episode of CDI in the past 6 months, severe CDI at baseline (per Zar score), age ≥ 65 years, CDI due to a hypervirulent strain (027, 078, or 244 ribotypes), immunocompromised, received concomitant systemic antibiotics.
±Had none of the above risk factors for rCDI

Disclosures. **P. Shaw**, Merck & Co., Inc.: Employee, May own stock/hold stock options in Company; **J. Shen**, Merck & Co., Inc.: Employee, may hold stock/hold stock options in the Company; **M. B. Dorr**, Merck & Co., Inc.: Employee and Shareholder, may own stock/hold stock options in the Company; **J. Li**, BGI-Shenzhen: Employee, Salary; **R. Mogg**, Merck & Co., Inc.: Employee, May hold stock/stock options in the Company; **D. V. Mehrotra**, Merck & Co., Inc.: Employee, may own stock/hold stock options in the Company; **R. L. Blanchard**, Merck & Co., Inc.: Employee, may own stock/hold stock options in the Company

1246. Engraftment and Augmentation of Microbiome Following Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection

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