***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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**Session:** 147. Expanded Spectrum – New Antimicrobial Susceptibility Testing
*Friday, October 6, 2017: 12:30 PM*

***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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**Session:** 148. C. difficile: From the Bench to Bedside
*Friday, October 6, 2017: 12:30 PM*

***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

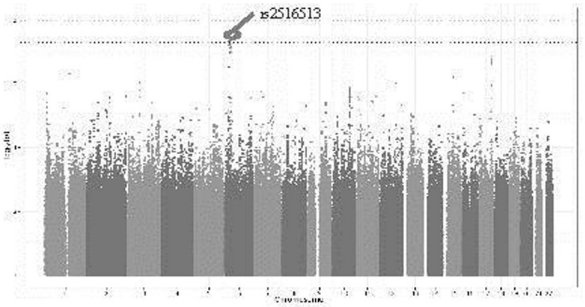


**Table1.** Proportion of Patients with rCDI stratified by SNP rs2516513 genotype and by risk category

| 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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**Session:** 148. C. difficile: From the Bench to Bedside
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