1241. In Vitro and In Vivo Activity of Cefazidime Against Pathogens Collected Globally from the AWARE Surveillance Program, 2016

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**Session:** 147. Expanded Spectrum – New Antimicrobial Susceptibility Testing

**Friday, October 6, 2017: 12:30 PM**

**Background.** Cefazidime, the active metabolite of cefazolin, 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 cefazidime 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), H. influenzae, 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 (2,129/10.4%), complicated urinary tract (3,029/13.3%), complicated skin and skin structure (8,271/36.4%), blood stream (4,223/20.6%) and lower respiratory tract infections (6,881/30.2%). MIC values were determined by broth microdilution and interpreted using CLSI breakpoints.

**Results.** Cefazidime activity, based on % susceptibility (%S) and MIC₉₀, is shown in the table. Cefazidime 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 (%)**

| %S | %I | %R | MIC5₀ | MIC₉₀ |
|----|----|----|------|------|
| MRSA (0.022) | 93.6 | 6.0 | 0.5 | 0.5 |
| MSSA (3,875) | 100 | 0 | 0 | 0.25 |
| Streptococcus pneumoniae (2,024) | 99.7 | - | 0.3 | 0.008 |
| β-hemolytic streptococci (1,713) | 100 | - | - | 0.008 |
| Enterobacteriaceae, ESBL-negative (9,647) | 91.7 | 3.7 | 4.6 | 0.12 |
| Haemophilus influenzae (671) | 99.7 | - | 0.3 | ≤0.015 |

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

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**Disclosures.** J. Iaconis, AstraZeneca: Employee and Shareholder, Salary and Shareholder in AstraZeneca.
Conclusion. CAZ-AVI is a potential therapeutic option for treating respiratory infections in the Asia/Pacific region caused by Ebs and Fae 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
Sibylle Leh, MD, MPH, for 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. Exemplary 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 imputed 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 protect 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 genome-wide associations SNPs and treatment effect on rCDI rCDI

Table 1. Proportion of Patients with rCDI stratified by SNP rs2516513 genotype and by risk category

| Genotype | CC | BEZ and ACT+BEZ | PBO | Difference (%) | BEZ and ACT+BEZ | PBO | Difference (%) |
|----------|----|----------------|-----|----------------|----------------|-----|----------------|
| % (n/100) | % (n/100) | % (n/100) | % (n/100) | % (n/100) | % (n/100) | % (n/100) | % (n/100) |
| PA | 111 (27.4) | 204 (26.9) | 88 (23.2) | 295 (26.3) | 57 (13.3) | 57 (13.3) |
| PA | 138 (34.1) | 203 (52.5) | 525 (32.2) | 258 (34.0) | 135 (35.6) | 247 (21.7) |
| PA | 124 (30.6) | 246 (30.9) | 557 (34.2) | 254 (33.5) | 130 (33.9) | 334 (29.4) |
| PA | 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. C/T was active against these phenotypes in >80% of isolates in North America and South Pacific.

Disclosures. M. Hackel, IHMA: Employee, Salary. R. Badal, IHMA, Inc.; Employee, Salary. J. Shen, Merck & Co., Inc.: Employee, May own stock/hold stock options in 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. Mogh, 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 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. Exemplary 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 imputed 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 protect patients most likely to respond to BEZ. As this is an exploratory finding, the results should be replicated in an independent validation study.

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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 war