28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Madrid, Spain
21 – 24 April 2018

P1671 Antimicrobial activity of Ceftazidime and Piperacillin-Tazobactam tested in combination with a potentiator molecule (SPR741) against Enterobacteriaceae causing urinary-tract infections

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Background: Urinary tract infections (UTI) caused by bacteria displaying an ESBL phenotype, especially due to CTX-M enzymes, are commonplace. SPR741 is a novel polymyxin B derivative with minimal intrinsic antibacterial activity and reduced nonclinical nephrotoxicity. This study assessed *in vitro* activity of ceftazidime (CAZ) or piperacillin-tazobactam (TZP) in combination with SPR741 against UTI pathogens.

Materials/methods: 424 isolates causing documented UTI in US (233; 55%) and European (191; 45%) hospitals during 2016 were selected. Species included *Escherichia coli* (160), *Klebsiella pneumoniae* (160), and *Enterobacter cloacae* (104). Isolates were tested for susceptibility by CLSI methods. SPR741 was held at a fixed concentration of 8 mg/L. MICs were interpreted based on EUCAST breakpoints, which were also applied to the combinations for comparison purposes.

Results: Adding SPR741 lowered the CAZ ($MIC_{50/90}$, 0.06/0.06 mg/L) and TZP ($MIC_{50/90}$, 0.12/0.25 mg/L) MIC_{50} and MIC_{90} results 4- to 64-fold and 64- to 128-fold, respectively, when compared with the associated co-drug tested alone against *E. coli.* Meropenem ($MIC_{50/90}$, ≤0.015/0.03 mg/L) and CAZ-SPR741 ($MIC_{50/90}$, 0.06/0.06 mg/L) showed the lowest MIC_{90} values against *E. coli*, which values were 2- and 8-fold lower than ceftriaxone ($MIC_{50/90}$, ≤0.06/0.12 mg/L) and TZP-SPR741 ($MIC_{50/90}$, 0.12/0.25 mg/L). The CAZ and TZP MIC_{90} values decreased 32- to 64-fold when adding SPR741 ($MIC_{50/90}$, 0.12/0.25 mg/L and $MIC_{50/90}$, 0.25/1 mg/L, respectively) against *K. pneumoniae.* CAZ-SPR741 ($MIC_{50/90}$, 0.12/0.25 mg/L), ceftriaxone ($MIC_{50/90}$, ≤0.06/0.25 mg/L), and cefepime ($MIC_{50/90}$, ≤0.12/0.5 mg/L) showed similar MIC_{90} results against *K. pneumoniae*, while TZP-SPR741 ($MIC_{50/90}$, 0.25/1 mg/L) and meropenem ($MIC_{50/90}$, 0.03/0.03 mg/L) showed the highest susceptibility rates 97.5–98.8% against this species. The TZP ($MIC_{50/90}$, 4/256 mg/L) MICs were 32- to 128-fold higher than TZP-SPR741 ($MIC_{50/90}$, 0.12/2 mg/L) against *E. cloacae*, which was similar in activity (95.2%) to meropenem (99.0% susceptible). Levofloxacin had marginal activities (81.2–85.6% susceptible) against these 3 species, while nitrofurantoin ($MIC_{50/90}$, 16/32 mg/L; 98.8% susceptible) was active against *E. coli.*

Conclusions: Data herein suggest further development of these combinations are warranted. The ability of SPR741 to extend the potency of these standard of care agents against Gram-negative UTI pathogens suggests the combination(s) has the potential to prevent delayed appropriate therapy for better outcomes.