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Ceftolozane/tazobactam activity tested against aerobic Gram-negative organisms isolated from intra-abdominal and urinary tract infections in European and United States hospitals (2012)

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Summary Ceftolozane/tazobactam is under clinical development for treatment of complicated intra-abdominal infections (IAI), complicated urinary tract infections (UTI) and ventilator-associated pneumonia. We evaluated the in vitro activity of ceftolozane/tazobactam and comparator agents tested against Gram-negative aerobic bacteria causing IAI and healthcare-associated UTI (HCA-UTI). The organisms were consecutively collected from January to December 2012 from 59 medical centers located in the United States (USA) and 15 European countries by the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS). The collection included 809 organisms from IAI and 2474 organisms from HCA-UTI, and susceptibility testing was performed by reference broth microdilution methods as described by the Clinical and Laboratory Standards Institute (CLSI) M07-A9 document. Overall, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were the most frequently isolated pathogens from both infection types. Ceftolozane/tazobactam was very active against *E. coli* ($MIC_{50/90}$, 0.25/0.5 mg/L; 98.5–99.9% inhibited at an MIC of ≤8 mg/L) and retained activity against many of the multidrug-resistant (MDR; $MIC_{50/90}$, 0.5/2–>32 mg/L) and ESBL-phenotype strains ($MIC_{50/90}$, 0.5/2–32 mg/L). Ceftolozane/tazobactam was active against most *K. pneumoniae* strains ($MIC_{50/90}$, 0.25/16 mg/L, 88.9–89.6% inhibited at an MIC of ≤8 mg/L), but some ESBL-phenotype ($MIC_{50/90}$, 4–8/>32 mg/L) and MDR ($MIC_{50/90}$, 16/>32 mg/L) isolates exhibited elevated MIC values. Ceftolozane/tazobactam was the most active agent tested against *P. aeruginosa* ($MIC_{50/90}$, 0.5/4 mg/L; 93.4–95.7% inhibited at ≤8 mg/L) and retained potency against many MDR ($MIC_{50/90}$, 2–4/>32 mg/L), ceftazidime-nonsusceptible ($MIC_{50/90}$, 2–4/

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>32 mg/L) and meropenem-nonsusceptible ($MIC_{50/90}$, 2/>32 mg/L) strains. Ceftolozane/tazobactam was also active against *Klebsiella oxytoca* ($MIC_{50/90}$, ≤0.12–0.25/0.5–1 mg/L), *Enterobacter* spp. ($MIC_{50/90}$, 0.25–0.5/4–8 mg/L), *Citrobacter* spp. ($MIC_{50/90}$, 0.25/2–32 mg/L), *Proteus mirabilis* ($MIC_{50/90}$, 0.5/0.5 mg/L), indole-positive *Proteae* ($MIC_{50/90}$, 0.25/0.5–1 mg/L), and *Serratia* spp. ($MIC_{50/90}$, 0.5/1–2 mg/L). In summary, ceftolozane/tazobactam demonstrated potent in vitro activity when tested against contemporary aerobic Gram-negative pathogens causing IAI and HCA-UTI in USA and European medical centers.

Introduction

Ceftolozane is a novel cephalosporin that is currently under clinical development in combination with the β-lactamase inhibitor tazobactam for treatment of complicated intra-abdominal infections (IAI; http://clinicaltrials.gov, identifiers NCT01147640, NCT01445665 and NCT01445678), complicated urinary tract infections (UTI; NCT01345955, NCT01345929 and NCT00921024) and ventilator-associated pneumonia (VAP; NCT01853982). This compound has shown remarkable stability against various resistance mechanisms employed by *Pseudomonas aeruginosa* to other β-lactam compounds, and has demonstrated activity against ceftazidime-resistant, as well as meropenem-resistant strains.[1–3]

Ceftolozane has also demonstrated good activity against members of the Enterobacteriaceae, but similar to other established oxyimino-cephalosporins, its activity can be compromised by production of extended-spectrum β-lactamases (ESBLs), carbapenemases and, to some degree, hyperproduction of AmpC β-lactamases. Thus, the addition of tazobactam, a well-established β-lactamase inhibitor, broadens the spectrum of ceftolozane activity to include many ESBL-producing organisms as well as some anaerobes, such as *Bacteroides* spp.[4–6]

In this study, we evaluated the activity of ceftolozane/tazobactam and comparator agents tested against Gram-negative aerobic bacteria causing IAI and healthcare-associated UTI (HCA-UTI) in United States (USA) and European hospitals during 2012.

Material and methods

Bacterial isolates

The organism collection included only aerobic Gram-negative bacilli collected from hospitalized patients with a diagnosis of IAI or HCA-UTI. The organisms were consecutively collected from January to December 2012 from 28 medical centers located in the USA and 31 medical centers in 15 European countries by the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS). A total of 809 organisms from IAI and 2474 organisms from UTI were included in this investigation. Species identification was performed at each participating medical center and confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) using the VITEK 2 System (bioMerieux, Hazelwood, Missouri, USA) or MALDI-TOF (Bruker, Billerica, Massachusetts, USA), when necessary. Only one strain per patient infection episode was included in this surveillance study.

Susceptibility testing

Isolates were tested for susceptibility to multiple antimicrobial agents at a reference laboratory (JMI Laboratories) by standardized broth microdilution methods as described by the Clinical and Laboratory Standards Institute (CLSI) M07-A9 document.[7] Minimum inhibitory concentration (MIC) results were interpreted according to CLSI criteria in M100-S23,[8] as well as EUCAST breakpoint tables (version 3.0).[9]

Escherichia coli and *Klebsiella pneumoniae* isolates were grouped as "ESBL-phenotype" based on the CLSI screening criteria for potential ESBL production, ie, MIC of ≥2 mg/L for ceftazidime or ceftriaxone or aztreonam.[8] Although the "ESBL-phenotype" strains were not submitted to an ESBL confirmation test, and other β-lactamases, such as AmpC and *K. pneumoniae* carbapenemases (KPC), may also produce an "ESBL-phenotype," these strains were grouped together because they usually demonstrate resistance to various broad-spectrum β-lactam compounds. Meropenem-nonsusceptible *K. pneumoniae* indicates a meropenem MIC of ≥4 mg/L.[8] Multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacteria were classified per recently recommended guidelines[10] using the following antimicrobial class representative agents and EUCAST interpretive criteria[9]: i) for *P. aeruginosa* – ceftazidime (≥16 mg/L), meropenem (≥4 mg/L), piperacillin/tazobactam (≥32/4 mg/L), levofloxacin (≥2 mg/L), gentamicin (≥8 mg/L), and colistin (≥4 mg/L); and ii) for Enterobacteriaceae – ceftriaxone (≥2 mg/L), meropenem (≥4 mg/L), piperacillin/tazobactam (≥16/4 mg/L), levofloxacin (≥2 mg/L), gentamicin (≥4 mg/L), tigecycline (≥2 mg/L), and colistin (≥4 mg/L). Classifications were based on the following recommended parameters: MDR = nonsusceptible to ≥1 agent in ≥3 antimicrobial classes; XDR = nonsusceptible to ≥1 agent in all but ≤2 antimicrobial classes; pandrug-resistant (PDR) = nonsusceptible to all antimicrobial classes tested.[10] Quality control (QC) was performed according to CLSI[8] methods. *E. coli* ATCC 25922 and 35218 and *P. aeruginosa* ATCC 27853 strains were used all QC results were within the published ranges.[8]

Results

Intra-abdominal infections

The aerobic Gram-negative bacilli most frequently isolated from IAI were *E. coli* (42.2%), *K. pneumoniae* (15.6%) and *P. aeruginosa* (14.2%). Ceftolozane/tazobactam was very active ($MIC_{50/90}$, 0.25/0.5 mg/L) against 341 *E. coli* isolates and retained activity against many of the 16 (4.7%) MDR