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Original article

Ceftolozane-tazobactam activity against drug-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* causing healthcare-associated infections in Latin America: report from an Antimicrobial Surveillance Program (2013–2015)

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ABSTRACT

This study evaluated the *in vitro* activity of ceftolozane-tazobactam and comparator agents tested against Latin American isolates of *Enterobacteriaceae* and *Pseudomonas aeruginosa* from patients with healthcare-associated infection (HAI). Ceftolozane-tazobactam is an antipseudomonal cephalosporin combined with a well-established β-lactamase inhibitor.

A total of 2415 Gram-negative organisms (537 *P. aeruginosa* and 1878 *Enterobacteriaceae*) were consecutively collected in 12 medical centers located in four Latin American countries. The organisms were tested for susceptibility by broth microdilution methods as described by the CLSI M07-A10 document and the results interpreted according to EUCAST and CLSI breakpoint criteria.

Results: Ceftolozane-tazobactam ($MIC_{50/90}$, 0.25/32 μg/mL; 84.2% susceptible) and meropenem ($MIC_{50/90}$, ≤0.06/0.12 μg/mL; 92.6% susceptible) were the most active compounds tested against *Enterobacteriaceae*. Among the *Enterobacteriaceae* isolates tested, 6.6% were carbapenem-resistant *Enterobacteriaceae* (CRE) and 26.4% exhibited an extended-spectrum β-lactamase (ESBL) non-CRE phenotype. Whereas ceftolozane-tazobactam showed good activity against ESBL non-CRE phenotype strains of *Enterobacteriaceae* ($MIC_{50/90}$, 0.5/>32 μg/mL), it lacked useful activity against strains with a CRE ($MIC_{50/90}$, >32/>32 μg/mL; 1.6% S)-resistant phenotype. Ceftolozane-tazobactam was the most potent ($MIC_{50//90}$, 0.5/16 μg/mL) β-lactam agent tested against *P. aeruginosa* isolates, inhibiting 86.8% at a MIC of ≤4 μg/mL. *P. aeruginosa* exhibited high rates of resistance to cefepime (16.0%), ceftazidime (23.6%), meropenem (28.3%), and piperacillin-tazobactam (16.4%).

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Conclusions: Ceftolozane-tazobactam was the most active β-lactam agent tested against *P. aeruginosa* and demonstrated higher *in vitro* activity than available cephalosporins and piperacillin-tazobactam when tested against *Enterobacteriaceae*.

Introduction

The epidemiology of microbial pathogens causing health care-associated infections (HAIs) has changed dramatically over the last decades with a concomitant increase in antibiotic resistance.[1–5] Whereas resistant Gram-positive cocci (GPC) were a major concern during the 1990s,[1,6] more recently multidrug-resistant (MDR; resistant to ≥3 classes of agents) Gram-negative bacilli (GNB) have become increasingly prevalent in the hospital setting.[1–4] This is especially true in Latin American countries where MDR-GNB, such as *Pseudomonas aeruginosa*, carbapenem-resistant (CRE), and extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* are a serious threat.[2–4] Due to the relative lack of new agents to treat these infections,[7] empirical therapy is often ineffective and requires combinations of antibacterial agents to achieve optimal coverage.[2,8]

These findings underscore the continued importance of antibiotic resistance surveillance and the need to assess the potential impact of newly introduced and novel antibacterial agents targeting specific resistance phenotypes.[9,10] Systematic and comprehensive antibiotic resistance surveillance is essential to document the extent of the resistance problem and to inform local, regional, national, and global efforts to combat the resistance challenge.[9] The SENTRY Antimicrobial Surveillance Program has monitored the predominant pathogens and antimicrobial resistance patterns of HAI pathogens *via* a network of sentinel sites in Latin America since 1997 and has documented the steady emergence of MDR-GNB in those countries.[2,3,6,11]

Ceftolozane-tazobactam is a novel antibacterial agent with activity against *P. aeruginosa*, including antibiotic-resistant strains, and other common GNB, including most ESBL-producing *Enterobacteriaceae* strains.[10,12–15] Ceftolozane-tazobactam has limited activity against *Acinetobacter* spp.; *Stenotrophomonas maltophilia*; GPC; organisms producing carbapenemases or metallo-β-lactamases; or a minority of AmpC β-lactamases found in *Enterobacteriaceae*.[10,16] Ceftolozane-tazobactam was recently approved to treat complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI).[10] A Phase 3 clinical trial of ceftolozane-tazobactam to treat nosocomial pneumonia is ongoing.

In 2012 North American and European antimicrobial resistance surveys, we described the *in vitro* activity of ceftolozane-tazobactam tested against isolates of *Enterobacteriaceae* and *P. aeruginosa* from different infection sites.[13,14] In this study, we extended those observations and focused on the activity of ceftolozane-tazobactam and comparators against 2415 isolates collected from 2013 through 2015 comprising *P. aeruginosa* (537 isolates) and *Enterobacteriaceae* (1878 isolates) from patients with HAIs hospitalized at 12 Latin American medical centers (four countries). The analysis includes the activity of ceftolozane-tazobactam against specific resistant phenotypes (e.g., ESBL non-CRE phenotype and MDR strains of *Enterobacteriaceae* and *P. aeruginosa*) as well as the frequencies of resistance phenotypes among the Latin American countries.

Materials and methods

Sampling sites and organisms

A total of 2415 non-duplicate isolates of GNB, including 1878 *Enterobacteriaceae* and 537 *P. aeruginosa*, were consecutively collected in 12 medical centers in four Latin American countries between January 1, 2013, and December 31, 2015. Each participating medical center identified species that were confirmed by the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) using the VITEK 2 System (bioMérieux, Hazelwood, Missouri, USA) or matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker, Billerica, Massachusetts, USA), when necessary.

Antimicrobial susceptibility testing

Minimal inhibitory concentrations (MICs) were determined using the reference Clinical and Laboratory Standards Institute (CLSI) broth microdilution method.[17] Quality control (QC) and interpretation of results were performed in accordance with CLSI M100-S26 and European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2016 guidelines.[18,19] *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* were grouped as "ESBL phenotype" based on the CLSI screening criteria for potential ESBL production, i.e., MIC of ≥2 μg/mL of ceftazidime, ceftriaxone, or aztreonam.[18] CRE were defined as isolates displaying MIC values of ≥4 μg/mL[18] for imipenem (*P. mirabilis* and indole-positive Proteeae were not included due to the intrinsically elevated MIC values), meropenem, and/or doripenem. Since carbapenemase-producing isolates may also appear to have an ESBL phenotype, non-carbapenem-resistant ESBL-phenotype isolates were analyzed (ESBL non-CRE). *P. aeruginosa* isolates were classified as ceftazidime nonsusceptible (NS; MIC, >8 μg/mL) and meropenem-NS (MIC, >2 μg/mL).

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