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Ceftaroline activity tested against contemporary Latin American bacterial pathogens (2011)

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ABSTRACT

A total of 2484 target bacterial pathogens were collected (one per patient episode) from patients in 16 Latin American medical centers located in seven nations during 2011. Isolate identity was confirmed at a coordinating laboratory and susceptibility testing was performed for ceftaroline and comparator agents according to reference broth microdilution methods. A total of 30.0% of isolates were from respiratory tract, 29.4% from skin and skin structure, 21.4% from blood stream, 7.9% from urinary tract and 11.3% from other sites. Ceftaroline was active against *Staphylococcus aureus* (42.8% MRSA) with 83.6% of the isolates at ≤1 mg/L and all isolates at ≤2 mg/L (MIC_{5090}, 0.25/2 mg/L). National MRSA rates ranged from a low of 28.8% in Colombia to a high of 68.1% in Chile. All *Streptococcus pyogenes* and *Streptococcus agalactiae* were susceptible to ceftaroline ($MIC_{50/90}$ values were at ≤0.015/≤0.015 mg/L for both). All *Streptococcus pneumoniae* were susceptible to ceftaroline, linezolid, tigecycline and vancomycin. Susceptibility to ceftriaxone was at 88.4% (CLSI non-meningitis interpretive criteria) and 73.9% (CLSI meningitis interpretive criteria) for all *S. pneumoniae*. Ceftriaxone susceptibility was only at 33.3% (CLSI non-meningitis interpretive criteria) and 0.0% (CLSI meningitis interpretive criteria) for penicillin-intermediate (penicillin MIC, 4 mg/L) strains. All *Haemophilus influenzae* (29.4% β-lactamase-positive) isolates were susceptible to ceftaroline, amoxicillin–clavulanate, ceftriaxone, and levofloxacin. For the Latin American region, the ESBL-phenotype rate was 37.6% for *Escherichia coli* and 53.3% for *Klebsiella pneumoniae*. Ceftaroline was not active against ESBL-phenotype strains but was active against >90.0% of the non-ESBL-phenotype. The spectrum of activity of ceftaroline against pathogens from Latin America indicates that it merits further study for its potential use in the Latin American region.

Introduction

Ceftaroline fosamil (the prodrug of the active metabolite ceftaroline) is a new cephalosporin approved in the USA in 2010 for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia and in Europe in 2012 for community-acquired pneumonia and complicated skin and soft tissue infections.[1,2] It was shown that ceftaroline fosamil was non-inferior to comparator agents in clinical studies of the above indications.[3–6] Ceftaroline is a bactericidal agent that exhibits broad *in vitro* activity against *Staphylococcus aureus* including methicillin-resistant *S. aureus* (MRSA), *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus* spp., and

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Enterobacteriaceae.[7–13] Ceftaroline exhibits a level of binding affinity for PBPs in *S. aureus* including PBP2a in MRSA and in *S. pneumoniae* including PBP2B and 2X.[7,8]

Ceftaroline and comparator agent activities against pathogens have been monitored since 2008 in the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Program.[10–13] The program provides continuing longitudinal data on antimicrobial activity in order to provide contemporary information. In this report, we present the results of the Latin American regional surveillance program for 2484 target pathogens from 16 medical centers from seven countries collected during 2011 from SENTRY as part of the AWARE program.

Materials and methods

Organism collection

A total of 2484 target bacterial pathogens (*S. aureus*, *S. pneumoniae*, *S. pyogenes*, *S. agalactiae*, Group C streptococci, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Morganella morganii*) were collected (one per patient episode) from patients in Latin American medical centers during 2011. Isolates were obtained from specimens of patients with respiratory tract infections (30.0%), skin and skin structure infections, *e.g.* wound swabs or aspirated pus, *etc.* (29.4%), bloodstream infections (21.4%), urinary tract infections (7.9%), and other infection types (11.3%; includes bone/joint, central nervous system, ear/nose/throat, eye, genital tract, and intra-abdominal infections). Isolate identity was confirmed at the coordinating laboratory (JMI Laboratories, North Liberty, IA, USA). Sixteen medical centers participated from seven nations (nation [number of medical centers]): Argentina (2), Brazil (5), Chile (2) Colombia (1), Mexico (3), Panama (1), and Venezuela (2).

Susceptibility testing

Bacterial isolates were tested for susceptibility to ceftaroline and comparator agents according to the reference broth microdilution methods of the Clinical and Laboratory Standards Institute (CLSI).[14] Susceptibility interpretations were based on CLSI (M100-S23) or EUCAST (2013) criteria; in the case of tigecycline the USA-FDA drug package insert criteria were used in lieu of CLSI criteria, as no CLSI interpretive criteria for tigecycline exist.[15–17] CLSI interpretive criteria for *S. aureus* for ceftaroline are susceptible, ≤1 mg/L; intermediate, 2 mg/L; resistant, ≥4 mg/L while EUCAST interpretive criteria are susceptible, ≤1 mg/L and resistant, >1 mg/L. Discussions on susceptibility presented in this report are based on CLSI interpretations unless otherwise specified. Cation-adjusted Mueller-Hinton broth (CA-MHB), supplemented with 2.5–5% lysed horse blood for streptococci, was used for susceptibility testing. For *Haemophilus* spp., Haemophilus Test Medium was used.[14] *E. coli* and *Klebsiella* spp. isolates were grouped as "ESBL-phenotype" based on the CLSI screening criteria for ESBL production, *i.e.* MIC of ≥2 mg/L for ceftazidime or ceftriaxone or aztreonam.[15] Concurrent quality control (QC) testing was performed. QC strains included: *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49247 and 49766, *E. coli* ATCC 25922 and 35218, and *Pseudomonas aeruginosa* ATCC 27853. All QC results were within published CLSI ranges.[15]

Results

The following numbers of organisms were collected from the 16 participating medical centers: *S. aureus* (956), *S. pneumoniae* (249), *S. pyogenes* (66), *Streptococcus agalactiae* (78), Group C streptococcus (5), *H. influenzae* (126), *H. parainfluenzae* (6), *E. coli* (518), *K. pneumoniae* (379), *K. oxytoca* (40), and *M. morganii* (61). Thirty percent were from respiratory tract, 29.4% from skin and skin structure, 21.4% from blood stream, 7.9% from urinary tract, and 11.3% from other sites.

Ceftaroline was active against *S. aureus* with MICs for 83.6% of the isolates at ≤1 mg/L and all isolates at ≤2 mg/L ($MIC_{50/90}$, 0.25/2 mg/L; Table 1). Ceftaroline was four- to eight-fold more active against MSSA (MIC_{50} and MIC_{90}, 0.25 and 0.25 mg/L) than MRSA (MIC_{50} and MIC_{90}, 1 and 2 mg/L). A total of 42.8% of *S. aureus* were MRSA (Tables 1 and 2). For MRSA, the $MIC_{50/90}$ values for ceftaroline were 1/2 mg/L with 61.6% of MIC values at ≤1 mg/L (Tables 1 and 2). Ceftaroline was 16-fold more active than ceftriaxone against MSSA (data not shown). By definition all MRSA are resistant to ceftriaxone and all other β-lactams except for the anti-MRSA cephalosporin ceftaroline.[15,16] National MRSA rates ranged from a low of 28.8% in Colombia to a high of 68.1% in Chile (Table 3). All *S. aureus* were susceptible to daptomycin, linezolid, tigecycline, and vancomycin (Table 2).

The overall susceptibility of *S. aureus* to ceftaroline was 83.6% (Table 2). For MSSA, susceptibility to ceftaroline was 100.0% and for MRSA it was 61.6% (Table 2). All ceftaroline non-susceptible *S. aureus* isolates (16.4% of all *S. aureus*) were MRSA and exhibited a MIC value of 2 mg/L (intermediate by CLSI criteria, resistant by EUCAST criteria) (Table 1). MRSA with a ceftaroline MIC at 2 mg/L were found in all sampled countries and rates varied from country to country. The percent of MRSA isolates which exhibited a MIC of 2 mg/L are listed for each country in rank order: Columbia (6.7%), Mexico (15.5%), Argentina (35.5%), Brazil (39.8%), Venezuela (41.9%), Panama (47.8%) and Chile (83.9%) (data not shown). Isolates with a ceftaroline MIC at 2 mg/L were found in respiratory, skin and soft tissue, bloodstream, and other infection types.

All *S. pyogenes* and *S. agalactiae* were susceptible to ceftaroline and $MIC_{50/90}$ values were at ≤0.015/≤0.015 mg/L (Tables 1 and 2). *S. pyogenes* was highly susceptible to many other agents including ceftriaxone, penicillin, daptomycin, tigecycline, vancomycin and linezolid, each at 100.0% susceptibility (Table 2). However, susceptibility to tetracycline was only at 81.8% and erythromycin at 90.9% (Table 2). All isolates were susceptible to levofloxacin based on CLSI criteria; however, 7.6% of isolates were non-susceptible to levofloxacin based on EUCAST criteria (Table 2). All *S. agalactiae* were susceptible to all tested β-lactams, as well as daptomycin, linezolid, tigecycline and vancomycin (Table 2).

All *S. pneumoniae* were susceptible to ceftaroline, linezolid, tigecycline and vancomycin (Table 2). Susceptibility to