Introduction

Antimicrobial resistance in Gram-negative bacilli including Enterobacteriaceae and Pseudomonas aeruginosa has complicated the treatment of serious infections. P. aeruginosa is an important pathogen harboring resistance due to the production of β-lactamase enzymes, along with other resistance mechanisms. The spread of β-lactamase is particularly problematic due to the acquisition of resistance mechanisms that alter their spectrum of hydrolysis, as well as their ability to disseminate.

Ceftazidime-avibactam is the combination of the established 2nd generation cephalosporin, with the novel non-β-lactamase β-lactamase inhibitor avibactam. Avibactam inhibits a broad range of β-lactamases, including CTX-M class (ESBL), AmpC (CM) and some class 1 (CMA-4) enzymes. Thus in combination with ceftazidime, avibactam restrains activity of P. aeruginosa against a number of clinically relevant β-lactamase-producing Gram-negative pathogens causing serious infections.

We evaluated the in vitro antibacterial activity and susceptibility patterns of ceftazidime-avibactam and comparator compounds: Amikacin, piperacillin-tazobactam and meropenem. Using breakpoints and susceptibility criteria as published by CLSI and EUCAST, we determined susceptibility of 1,743 isolates collected from nine Census regions in the United States (USA).

Methods

A total of 1,743 P. aeruginosa isolates collected from 69 medical centers within the nine USA Census Regions for 2014 were included in the International Network for Optimal Resistance Surveillance (INFORM) surveillance study.

Susceptibility testing: Broth microdilution susceptibility testing was performed according to the CLSI (Clinical Laboratory Standards Institute) (CLSI) guidelines (CLSI document M100-A15, 2015) using validated dry-plate methodology per reference Thermo Fisher Scientific (Cleveland, OH, USA).

Susceptibility interpretive criteria for comparator compounds amikacin (CLSI, 2015) and EUCAST (2015) breakpoint criteria, where available. The recently approved, US Food and Drug Administration (FDA) breakpoint interpretative criteria were applied for cefepime (M100, 2015) and meropenem (CLSI, 2015). The recently approved, US Food and Drug Administration (FDA) breakpoint interpretative criteria were applied for colistin (M100, 2015). The recently approved, US Food and Drug Administration (FDA) breakpoint interpretative criteria were applied for gentamicin (M100, 2015). Criteria as published by CLSI [2015] and EUCAST [2015].

Conclusions

Ceftazidime-avibactam consistently demonstrated the highest susceptibility rates among the β-lactam comparators, including cefepime and meropenem. Against P. aeruginosa infections, ceftazidime-avibactam was consistently demonstrated the highest % activity against MDR P. aeruginosa isolates, followed by cefepime, meropenem and piperacillin-tazobactam. Against P. aeruginosa, ceftazidime-avibactam activity (MIC<0.5 μg/ml and 95% susceptible ≤8 μg/ml) was enhanced compared to ceftazidime alone (MIC≥32 μg/ml and ≤44% susceptible ≤8 μg/ml) and was more active than other β-lactam comparators including ticarcillin, meropenem and piperacillin-tazobactam (65.8, 63.0 and 62.0 susceptible, respectively; Table 1 and Figure 1).

In each of the nine USA Census Regions, P. aeruginosa susceptibility rates to ceftazidime-avibactam were greater than ceftazidime alone, cefepime, piperacillin-tazobactam, meropenem, and piperacillin-tazobactam (See Table 1).

Against the 1,743 P. aeruginosa, the addition of avibactam to ceftazidime increased the percentage susceptibility across all the USA Census Regions by 72 to 82% over those treated with ceftazidime alone (Table 1).

Susceptibility was lowest for CAZ (79.1%) and piperacillin- tazobactam (72.5%) against P. aeruginosa in the East South Central (Region 5) and Mountain (Region 8) Census Regions, respectively. In the Mountain Census Region 97.5% susceptible to ceftazidime-avibactam.

Ceftazidime was highest in the East South Central region (91.6%) and for MEM (77.7%) in the West North Central Census Region.

Criteria as published by CLSI [2015] and EUCAST [2015].

Revised Abstract

Background: Ceftazidime-avibactam (CAZ-AVI) is a novel β-lactam-β-lactamase inhibitor combination for the treatment of Gram-negative bacterial infections including those caused by multidrug resistant (MDR) isolates. It is the first in vitro antibacterial activity of CAZ-AVI and comparators was evaluated against a collection of contemporary P. aeruginosa (PSA) isolates collected from nine Census regions in the United States (USA).

Methods: 1,743 PSA isolates were collected from 69 medical centers in the USA. MICs of CAZ-AVI and comparators were determined by broth microdilution according to CLSI guidelines. CAZ-AVI activity against MDR PSA isolates was determined.

Results: When compared to ceftazidime (CAZ) alone (MIC≥32 μg/ml), CAZ-AVI (MIC≤8 μg/ml, 89.8% inhibited at ≤4 μg/ml) was four-fold more active against 1,743 PSA isolates. Applying breakpoint interpretive criteria (Table 1), 9, 84, 60, and 83.0% of PSA isolates were susceptible to CAZ-AVI, MEM, and piperacillin-tazobactam (PTT), respectively. Against 273 CAZ-van (65.7%), 57, 40.1, and 14.4% were S=CAZ-AVI, MEM, and PT, respectively. Similarly, against 296 MEM-NS isolates, 81, 41.3, and 40.5% were S=CAZ-AVI, CAZ-AVI and CAZ, respectively. Of PSA isolates collected from nine Census regions in the United States (USA).

Conclusions: CAZ-AVI demonstrated potent in vitro antibacterial activity against PSA, including non-susceptible isolates to NS to CAZ-AVI, MEM, and PT. In each of the nine Census regions, CAZ-AVI had the highest % of S isolates in each of the Census regions. The addition of CAZ to MIC range is S by 73.6% over CAZ-AVI tested alone. Susceptibility was lowest for CAZ (79.1%) and PT (72.5%) in the Mountain Census Region and for MEM in the West North Central Census Region.

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Methods

In vitro Antibacterial Activity of Ceftazidime-avibactam Tested against Contemporary Pseudomonas aeruginosa Medical Isolates from Centers by Census Region.

Ceftazidime-avibactam activity against 296 MDR PSA isolates demonstrated the highest % of S isolates in each of the Census regions. The addition of CAZ to MIC range is S by 73.6% over CAZ-AVI tested alone. Susceptibility was lowest for CAZ (79.1%) and PT (72.5%) in the Mountain Census Region and for MEM in the West North Central Census Region.