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Short Communication

In vitro activity of ceftazidime/avibactam against Gram-negative pathogens isolated from pneumonia in hospitalised patients, including ventilated patients☆

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ABSTRACT

The activities of the novel β-lactam/non-β-lactam β-lactamase inhibitor combination ceftazidime/avibactam and comparators were evaluated against isolates from pneumonia in hospitalised patients including ventilated patients (PHP, pneumonia not designated as VABP; VABP, pneumonia in ventilated patients). Isolates were from the European–Mediterranean region (EuM), China and the USA collected in the SENTRY Antimicrobial Surveillance Program between 2009 and 2011 inclusive. A total of 2393 organisms from PHP were from the EuM, 888 from China and 3213 from the USA; from VABP patients there were 918, 97 and 692 organisms collected, respectively. Among Enterobacteriaceae from PHP, ceftazidime/avibactam MIC_{90} values against *Escherichia coli* ranged from 0.25–0.5 mg/L and *Klebsiella* spp. MIC_{90} values were 0.5 mg/L in each region. Among VABP isolates, MIC_{90} values for ceftazidime/avibactam against *E. coli* were 0.25 mg/L; for *Klebsiella* spp. from VABP patients, MIC_{90} values were similar to those obtained against PHP isolates. The MIC of ceftazidime/avibactam was ≤8 mg/L against 92–96% of *Pseudomonas aeruginosa* isolated from PHP patients. Isolates of *P. aeruginosa* from VABP patients were of lower susceptibility to all antibacterial agents (e.g. depending on region, meropenem susceptibilities were 51.2–69.4% in contrast to 68.3–76.7% among PHP patients). However, ceftazidime/avibactam inhibited 79.2–95.4% of VABP isolates at an MIC of ≤8 mg/L. *Acinetobacter* spp. were resistant to many agents and only rates of susceptibility to colistin were >90% across all regions both for PHP and VABP isolates. Ceftazidime/avibactam was generally active against a high proportion of isolates resistant to ceftazidime from PHP and VAPB patients.

1. Introduction

Ceftazidime/avibactam is a new antibacterial agent active in vitro against isolates of Enterobacteriaceae and *Pseudomonas aeruginosa* that are resistant to ceftazidime through production of class A, C and some class D β-lactamases [1–3]. Resistant variants of these Gram-negative bacteria are prominent in nosocomial pneumonia, both hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) [4–7]. Based on its spectrum of in vitro activity, ceftazidime/avibactam is being studied as a potential treatment of nosocomial pneumonia [8].

Here we report the antibacterial activity of ceftazidime/ avibactam against bacteria from pneumonia in hospitalised patients, including VABP, in selected European–Mediterranean region (EuM) countries, the USA and China. The results support the evaluation of ceftazidime/avibactam in the treatment of nosocomial pneumonia in humans [8].

2. Methods

Isolates from the SENTRY Antimicrobial Surveillance Program were cultured from a prevalence sampling design from hospitalised patients with pneumonia, including VABP, between 2009 and 2011 inclusive [4,9–12]. Participating medical centres collected

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consecutive pathogens from lower respiratory tract sites determined to be significant by local criteria as the reported probable cause of pneumonia. The protocol required that the preferred specimen types for isolate collection would be from invasive sampling (transtracheal aspirates, bronchoalveolar lavage, protected brush samples, etc.). However, isolates from good-quality sputum samples meeting acceptable criteria for polymorphonuclear leukocytes and epithelial cells were allowed. These requirements were an effort to maximise the number of isolates from true infections and to reduce the number of possible colonising organisms. Only one isolate per patient episode was included in the study. Isolates referred by the participant medical centre as VABP were analysed separately from those not designated as VABP (PHP). Isolates were processed locally and were forwarded to a central laboratory (JMI Laboratories, Inc., North Liberty, IA) for reference identification and susceptibility testing [13] using validated dry-format broth microdilution trays produced by Thermo Fisher Scientific (formerly TREK Diagnostics, Cleveland, OH).

There were 66 medical centres that contributed HABP isolates: 28 centres from the USA, 25 centres from EuM countries (Belgium, 1; France, 5; Germany, 1; Greece, 1; Ireland, 2; Israel, 1; Italy, 2; Poland, 1; Portugal, 1; Slovenia, 1; Spain, 3; Sweden, 1; Switzerland, 1; Turkey, 2; UK, 2) and 13 centres from China. VABP isolates were contributed by 43 centres: 20 centres from the USA, 18 centres from EuM countries (Belgium, 1; France, 2; Germany, 1; Greece, 1; Ireland, 2; Israel, 1; Italy, 1; Poland, 1; Portugal, 1; Slovenia, 1; Spain, 2; Sweden, 1; Turkey, 2; UK, 1) and 5 centres from China.

Interpretive criteria utilised were those of the Clinical and Laboratory Standards Institute (CLSI) [14] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [15], except for ceftazidime/avibactam for which the minimum inhibitory concentration (MIC) susceptibility interpretive criteria assigned by the US Food and Drug Administration (FDA) were used: susceptible, ≤8 mg/L; and resistant, ≥16 mg/L [16]. The extended-spectrum β-lactamase (ESBL) phenotype for *Klebsiella* spp. and *Escherichia coli* was defined as an MIC of ≥2 mg/L for ceftazidime and/or ceftriaxone and/or aztreonam [14]. All routine quality control results for comparison antimicrobial agents were within the ranges as published [14].

3. Results

3.1. Occurrence of organisms in pneumonia in hospitalised ventilated and non-ventilated patients

A total of 2393 organisms from PHP were collected from the EuM, 888 from China and 3213 from the USA; from VABP patients there were 918, 97 and 692 organisms collected, respectively. Table 1 presents the 10 most commonly isolated species for each region. *Pseudomonas aeruginosa* was the most commonly occurring organism in the EuM in PHP and in the VABP subset (21.6% and 22.6% of isolates, respectively) (Table 1). In China, *Acinetobacter* spp. were the most commonly occurring organisms (24.1% and 34.0%, respectively) and in the USA *Staphylococcus aureus* was the most common (37.4% and 36.9%) (Table 1). *Staphylococcus aureus* occurred as one of the three most frequently occurring organisms in the EuM, China and the USA in patients hospitalised with pneumonia (20.9%, 20.3% and 37.4%, respectively) (Table 1). Although *Acinetobacter* spp. were the most common organisms isolated from Chinese patients with PHP, it was the seventh most common organism in EuM patients (5.4%) and the eighth (3.0%) in the USA (Table 1). In the case of VABP, *Acinetobacter* spp. were again the most common pathogens isolated from Chinese patients (34.0%), second most common in EuM patients (16.3%) and fifth most common in patients from the USA (5.8%) (Table 1). *Klebsiella* spp. were either the third or fourth most common organisms in each of the three regions in either PHP or VABP patients (Table 1). In the EuM, 72.7% of PHP and 60.7% of VABP isolates that were *Klebsiella* spp. were *Klebsiella pneumoniae* (Table 1). In China this was 94.3% and 85.7%, respectively, and in the USA it was 77.8% and 77.9%, respectively (Table 1). *Escherichia coli* ranged from the third to the sixth most common organism among PHP or VABP among all regions (Table 1). *Enterobacter* spp. ranged from the fourth to sixth most common organism across regions in patients with either PHP or VABP (Table 1). These six groups of organisms (*P. aeruginosa*, *S. aureus*, *Acinetobacter* spp., *Klebsiella* spp., *E. coli* and *Enterobacter* spp.) represented 76.6% (EuM) to 91.4% (China) of isolates from patients with PHP and 82.5% (China) to 84.9% (EuM) of isolates from VABP patients (Table 1).

3.2. Activity of ceftazidime/avibactam tested against pathogens isolated from pneumonia in hospitalised ventilated and non-ventilated patients

Combination with avibactam generally reduced the MIC_{90} values of ceftazidime against Enterobacteriaceae by 32 to ≥64 fold (Tables 2 and 3). Among Enterobacteriaceae isolated from PHP, ceftazidime/avibactam MIC_{90} values against *E. coli* ranged from 0.25 mg/L in the EuM and the USA to 0.5 mg/L in China (Table 2). In contrast, the *E. coli* MIC_{90} of ceftazidime alone against PHP isolates was 8 mg/L in the EuM, 16 mg/L in the USA and >32 mg/L in China (Table 2). Among VABP isolates, the MIC_{90} values for ceftazidime/avibactam against *E. coli* were 0.25 mg/L in the EuM and the USA but there were only six isolates from China so an MIC_{90} could not be reported (Table 3). The ceftazidime/avibactam MIC_{90} values against VABP isolates of *E. coli* were similar to the MIC_{90} values obtained against PHP isolates (Tables 2 and 3). For VABP isolates of *E. coli*, the MIC_{90} value for ceftazidime alone was 0.5 mg/L in the USA owing to the low prevalence of ESBL phenotypes, but it was 32 mg/L in the EuM. The MIC_{90} values for ceftazidime/avibactam tested against ESBL-phenotype *E. coli* from PHP and VABP ranged from 0.25–0.5 mg/L across regions (Tables 2 and 3). MIC_{90} values for ceftazidime/avibactam against *Klebsiella* spp. from VABP were 0.5 mg/L in the EuM and the USA (Table 3). The MIC_{90} value of ceftazidime alone for *Klebsiella* spp. and for *K. pneumoniae* from PHP was ≥32 mg/L in USA, the EuM and China (Table 2). For *Klebsiella* spp. isolated from VABP patients, the MIC_{90} values for ceftazidime/avibactam were 0.5 mg/L in the EuM and the USA (Table 3), similar to the MIC_{90} value obtained against PHP isolates (Tables 2 and 3). For *K. pneumoniae* isolated from VABP patients, the MIC_{90} values for ceftazidime/avibactam were 1 mg/L in the EuM and 0.25 mg/L in the USA (Table 3), similar to the MIC_{90} value obtained against PHP isolates (0.5 mg/L) (Table 2). For *Klebsiella* spp. from VABP, MIC_{90} values for ceftazidime were 16 mg/L in the USA and >32 mg/L in the EuM, and for ESBL-phenotype isolates of *Klebsiella* spp. the ceftazidime/avibactam MIC_{50} and MIC_{90} values were from 0.25–1 mg/L (Table 3). For *K. pneumoniae* from VABP, MIC_{90} values for ceftazidime were 16 mg/L in the USA and >32 mg/L in the EuM, and for ESBL-phenotype isolates of *K. pneumoniae* ceftazidime/avibactam MIC_{50} and MIC_{90} values ranged from 0.25–2 mg/L (Table 3). MIC_{90} values for ceftazidime/avibactam against *Enterobacter* spp. and *Serratia* spp. isolated from PHP and VABP were 0.5 mg/L (Tables 2 and 3). In the case of *Enterobacter* spp., the ceftazidime MIC_{90} value was >32 mg/L whether isolates were from PHP (i.e. non-ventilated patients) or from VABP (Tables 2 and 3), which suggested that the expression of AmpC β-lactamase was likely stably derepressed in a high proportions of the isolates.

The MIC_{90} value for ceftazidime/avibactam against *P. aeruginosa* isolated from PHP was 8 mg/L in each region (Table 2). The MIC_{90} values for ceftazidime alone against *P. aeruginosa* isolated from