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Stenotrophomonas maltophilia susceptibility to ceftazidime-avibactam combination versus ceftazidime alone

Sensibilité de *Stenotrophomonas maltophilia* à l'association ceftazidime–avibactam versus ceftazidime seule

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Keywords: *Stenotrophomonas maltophilia*; second-generation beta-lactamase inhibitors; multidrug resistance

Mots clés : *Stenotrophomonas maltophilia* ; inhibiteurs de bêta-lactamase de deuxième génération ; multirésistance

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ABSTRACT

Objective. To compare the minimum inhibitory concentrations (MIC) of the ceftazidime-avibactam (CZA) combination versus ceftazidime alone (TZ) for *Stenotrophomonas maltophilia.*

***Patients and methods*.** MIC comparison was performed by E-tests. We assumed that CZA was more effective in vitro than TZ alone when CZA led to a category change from "Resistant" with TZ alone to "Susceptible" or "Intermediate" with CZA, or if the MIC of CZA was at least 4-fold lower than the MIC of TZ for TZ-susceptible isolates.

Results. For the 54 clinical isolates included in the study, CZA showed better results in terms of the proportion of susceptible isolates (66.7% vs. 38.9%, $p<0.01$), MIC_{50} (2 µg/mL vs. 12 µg/mL, $p<0.05$), and MIC distribution. According to our definition, CZA was also more effective in vitro than TZ alone for 50% of the isolates.

Conclusion. Using CZA for empirical treatments in severe or polymicrobial infections with *S. maltophilia* seems appropriate.

RÉSUMÉ

Objectif. Comparer les CMI de l'association ceftazidime-avibactam (CZA) et de la ceftazidime (TZ) seule sur *Stenotrophomonas maltophilia*.

Patients et méthodes. La comparaison a été réalisée par mesure des CMI (E-tests). Nous avons considéré que CZA était plus efficace in vitro que TZ seule lorsque CZA permettait de changer la catégorie de « Résistant » à « Sensible » ou à « Intermédiaire », ou d'obtenir une diminution de CMI d'un facteur ≥ 4 pour les isolats sensibles.

Résultats. Sur 54 isolats, CZA a montré de meilleurs résultats pour la proportion d'isolats sensibles (66,7 % vs. 38,9 %, $p < 0{,}01$), la CMI_{50} (2 µg/mL vs. 12 µg/mL, $p < 0{,}05$) et la distribution des CMI. De plus, d'après notre définition, CZA était plus efficace in vitro pour 50 % des isolats.

Conclusion. L'utilisation de CZA pour des traitements empiriques dans les infections sévères ou polymicrobiennes impliquant *S. maltophilia* parait envisageable.

Stenotrophomonas maltophilia is an important cause of hospital-acquired infections in immunocompromised patients and in patients with cystic fibrosis or hospitalized in intensive care units [1]. The case fatality rate associated with *S. maltophilia* infections in these patients is >30% [2]. *S. maltophilia* usually presents a multidrug-resistant phenotype. Intrinsic resistance to beta-lactams is due to two beta-lactamases (L1 and L2). The L1 metallo-beta-lactamase hydrolyzes carbapenems and is resistant to all beta-lactamase inhibitors. The L2 beta-lactamase is an inducible cephalosporinase that confers resistance to third-generation cephalosporins, but it can be inhibited by clavulanic acid [1, 3]. According to a study conducted in patients hospitalized for pneumonia in the United States and in European hospitals [4], most *S. maltophilia* strains isolated from respiratory samples were susceptible to minocycline and trimethoprim/sulfamethoxazole (99.5% and 96.3%, respectively). However, clinicians often prefer using beta-lactams instead of those antibiotics for severe infections, particularly in immunocompromised hosts or patients hospitalized in the intensive care unit. Conversely in the study by Sader *et al*. [4], only 36.8% of *S. maltophilia* isolates were susceptible to ceftazidime. The ceftazidime/avibactam (CZA) combination is a recent antibiotic combination, which demonstrated an interesting activity on some multidrug-resistant Gram-negative bacteria [5, 6]. However, little data is available on the activity of this combination against *S. maltophilia*.

We aimed to assess the potential benefit of CZA for the treatment of infections caused by these bacteria by comparing the minimum inhibitory concentrations (MICs) of CZA with the MICs of ceftazidime alone (TZ) on isolates obtained from clinical samples.

MICs of CZA and TZ were determined in parallel by the E-test method (Liofilchem, Italy) on Mueller-Hinton plates (Thermo Fisher, United Kingdom). The isolates were

prospectively collected in 2017 and during the first six months of 2018 in clinical samples obtained from patients hospitalized in the University Hospital of Angers, France. Bacterial identifications were performed by MALDI-TOF mass spectrometry (bioMérieux, France). Isolates were kept in a storage agar medium (Bio-Rad, France) at room temperature. Duplicates (*S. maltophilia* isolated in more than one sample from the same patient during the study period) were excluded. We considered that CZA was more effective in vitro than TZ alone if CZA led to a category change (from "Resistant" with TZ to "Susceptible" or "Intermediate" with CZA), or if the MIC of CZA was at least 4-fold lower than the MIC of TZ for isolates susceptible to TZ. Categories were defined according to the EUCAST breakpoints [7]. As no specific recommendations are available for CZA and *S. maltophilia*, the breakpoints defined for *Pseudomonas aeruginosa* were used. The benefit of CZA was assessed by comparing the proportion of resistant isolates, the proportion of isolates for which CZA was more effective in vitro than TZ according to our definition, and the distribution of MICs for the two antibiotics. In addition, MICs of CZA were compared using the same method with MICs of ticarcillin/clavulanic acid (TCC), the other beta-lactam that can be used for infections caused by *S. maltophilia*. Proportions were compared using the Chi^2 test.

Overall, 54 *S. maltophilia* isolates were included. Among them, 21 had been isolated from patients hospitalized in intensive care units, seven in hematology or oncology wards, 13 in other medical wards, six in surgical wards, and eight from cystic fibrosis patients. Most isolates (57.4%) were isolated from respiratory secretions. Overall, 61.1% of isolates were resistant to TZ and 33.3% were resistant to CZA ($p<0.01$). According to our definition, CZA was more effective in vitro than TZ alone for 25 (50%) isolates. Indeed, CZA led to a category change from "Resistant" to "Susceptible" or from "Resistant" to "Intermediate" for 13 and 2

isolates, respectively. In addition, a ≥4-fold MIC decrease (from 4 to 16) was observed when adding avibactam for 12 (60%) of the 20 isolates susceptible to TZ. The distribution of MICs for TZ and CZA is presented on Figure 1. The MIC of CZA was <1 µg/mL for 30% of isolates, whereas such low MICs were recorded in only 2% of isolates for TZ (p<0.001). MIC_{50} was 12 µg/mL for TZ and 2 µg/mL for CZA. MIC_{90} was >256 µg/mL for the two antibiotics. Lastly, the proportion of isolates susceptible to CZA was significantly higher than the proportion of isolates susceptible to TCC (66.7% vs. 40.7%, p<0.01).

The present study demonstrated an increased proportion of susceptible *S. maltophilia* isolates when adding avibactam to TZ versus TZ alone. It also demonstrated that CZA was the best beta-lactam against those bacteria. A recent multicenter international study [8] conducted with a panel of 106 *S. maltophilia* strains isolated from cystic fibrosis patients demonstrated that 35% of the isolates were susceptible to TZ. This result is concordant with our results showing that 38.9% of our isolates were susceptible to TZ. To the best of our knowledge little data comparing the MICs of those antibiotics for this microorganism is available. For instance, a large study [6] of CZA MICs of Gram-negative bacteria isolated from patients hospitalized for pneumonia in the United States did not include *S. maltophilia*. With a panel of 30 *S. maltophilia* strains exclusively isolated from respiratory samples of cystic fibrosis patients, Farfour *et al.* [9] reported 35% of isolates susceptible to CZA, with a MIC_{50} of 140 µg/mL. The proportion of isolates susceptible to CZA in our study was almost two times higher and the MIC_{50} was 2 µg/mL. However, it is noteworthy that the MICs of TZ and CZA were >256 µg/mL for five of the eight *S. maltophilia* strains isolated from patients with cystic fibrosis.

The 54 *S. maltophilia* isolates were collected from a single hospital. As they were not genotypically compared, we cannot exclude that some of them could be clonally related. We believe there are three arguments against this hypothesis: *S. maltophilia* is not considered to have high epidemic potential in terms of cross-transmission; the study was conducted over a long period of time (18 months); and the isolates were obtained from wards located in different buildings of the hospital.

Few studies evaluating the clinical effectiveness of CZA in *S. maltophilia* infections have been published. A recent article reported the successful treatment of a bloodstream infection due to a multidrug-resistant *S. maltophilia* isolate in a renal transplant patient with a combination of CZA and aztreonam [10]. In our study, even though one third of the isolates remained resistant to CZA, 30% showed low MICs (<1 μg/mL). This finding highlights the potential benefit of CZA when beta-lactams are indicated, especially for the treatment of severe infections, infections in immunocompromised hosts, or polymicrobial infections including *S. maltophilia* and other multidrug-resistant Gram-negative bacteria.

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CM determined the MICs by E-tests and collected the isolates stored. ME contributed to the study design, wrote the article, and performed the statistical analyses. CL, RC, and HP contributed to the study design and reviewed the article. MK coordinated the study and reviewed the article.

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Figure 1. Distribution of minimum inhibitory concentrations (MICs) of ceftazidime/avibactam and ceftazidime alone for 54 isolates of *Stenotrophomonas maltophilia*.
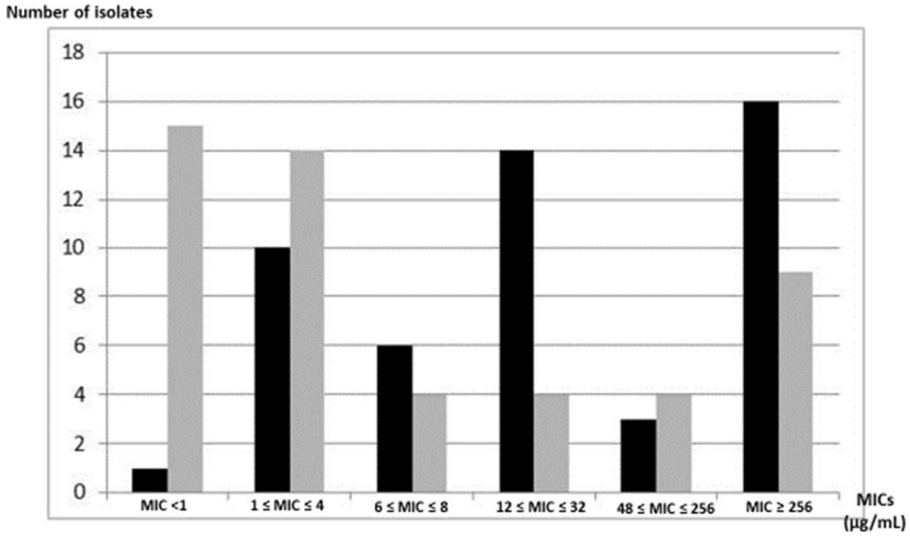
Figure 1. Répartition des concentrations minimales inhibitrices (CMI) de l'association ceftazidime-avibactam et de la ceftazidime seule pour 54 isolats de *Stenotrophomonas maltophilia*.