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Update on antimicrobial pharmacotherapy against multidrug-resistant Gram-negative bacilli

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New treatments for multidrug-resistant non-fermenting Gram-negative bacilli Infections

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ABSTRACT

Ceftolozane/tazobactam, ceftazidime/avibactam and cefiderocol belong to a novel generation of antibiotics that correspond with the β-lactam family. It is necessary to having new options in treating infections caused by Gram-negative, non-fermenting multidrug-resistant bacilli due to the significant increase in multidrug resistance in the last decades. Knowing the main characteristics of each drug is key for correct use.

Keywords: Ceftolozane/tazobactam, Ceftazidime/Avibactam, Cefiderocol, Gram-negative, non-fermenting multidrug-resistant bacilli

INTRODUCTION

Treatment of non-fermenting multidrug-resistant Gram-negative bacilli (NFGNB-MDR) infections is a current challenge for physicians due to both severity and the potential resistance to a high number of antibiotics. The most common and severe NFGNB-MDR includes *Pseudomonas aeruginosa*, which could be involved in a wide variety of nosocomial infections. Despite the severity caused by such infections, 50% of neutropenic patients have been recently reported to have had an infection due to MDR *Pseudomonas aeruginosa* (PAE-MDR) and received inappropriate antibiotic empirical therapy (IAET). This finding is related with higher mortality [1]. Both *Stenotrophomonas maltophilia* and *Acinetobacter baumannii* are not considered highly virulent pathogens [2] Nonetheless, *S. maltophilia* is an emerging nosocomial and MDR pathogen that causes respiratory tract infections and central venous catheter-associated bacteremia [3]. A total of 82% of bloodstream infections due to *S. maltophilia* in neutropenic patients were treated with IEAT, with the source of infection being mostly catheters. The impact of IEAT on outcomes was not significant in this situation due to both the low virulence of bacteria and quick changes to optimal antibiotics and catheter removal [1,3]. Finally, *A. baumannii* is responsible for infections in critically ill patients, mainly ventilator-associated pneumonia and bloodstream infections. Although it is not the most frequently isolated Gram-negative bacillus, the multidrug resistance rate is high, varying per geographic area. Carbapenem resistance rates, for example, exceed 30% in regions like Latin America [4].

Today, there is a new spectrum of promising antibiotics—all of which are β-lactams—to face the most important NF-GNB-MDR: ceftolozane/tazobactam, ceftazidime/avibactam and cefiderocol. We aimed to review the main characteristic of these antibiotics.

NEW BETA-LACTAMS

Use of ceftolozane/tazobactam (TOL/TAZ) for NF-GNB-MDR. Ceftolozane shares structural similarities with ceftazidime, associated with a β-lactamase inhibitor. The main difference between ceftolozane and ceftazidime is the presence of a higher side chain at position 3 of the dihydrothiazine ring [5]. This distinguishing characteristic is relevant as it confers: 1) stability against chromosomal AmpC β-lactamase, which is present in *P. aeruginosa;* 2) better affinity to penicillin-binding proteins (PBP) [5]; and 3) sub-optimal substrate for efflux pumps [6]). It is also not affected by OprD porin as it relates to entrance into the *P. aeruginosa* membrane. Due to all of these characteristics, minimum inhibitory concentration (MIC) values for *P. aeruginosa* are low (86.3% of isolates were inhibited at ≤8 mg/L when compared with the remaining antipseudomonal β-lactams [7]). It remains active even when facing a combined mechanism of resistance like hyperexpression of efflux pumps or loss of porins [8]. Consequently, TOL/TAZ has potent activity in infections caused by *P. aeruginosa*.

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Additionally, the rate of *P. aeruginosa* resistance in our area remains low [9].

It is important to note that the concentration that prevents the selection of resistant mutants (MPC) is fundamental to avoid an increase in resistance to antimicrobials. Remarkably, TOL/TAZ does not only have the lowest MPC values among β-lactams; indeed, these values are not far from those of MIC. This narrow window is what makes the drug important—given its potency in *P. aeruginosa* infections—and capable of preventing the appearance of resistant strains.

On the other hand, TOL/TAZ also has a β-lactamase inhibitor, which is absent in cephalosporins and adds activity to bacteria with β-lactamase. The intrinsic activity of TOL/TAZ to enterobacteria has been demonstrated to have lower MIC values when compared with piperacillin/tazobactam [10]. Of 3,841 cases of enterobacteria, 95.2% were susceptible (MIC ≤8 mg/L), making the drug one of the most currently active antibiotics (alongside meropenem and tigecycline) [11].

The role of TOZ/TAZ in NFGNB-MDR non-*P. aeruginosa*, such as *S maltophilia* isolates, is controversial, with low activity being previously reported (12).

Use of ceftazidime/avibactam (CAZ/AVI) for NFGNB-MDR. This antimicrobial complex combines a well-known cephalosporin with a new β-lactamase inhibitor. The latter is distinct, given that it does not contain the β-lactam ring in its structure. Avibactam is a diazabicyclooctane inhibitor member and can covalently and reversibly bind to β-lactamases, thus reducing their ability to hydrolyze (unlike other inhibitors such as clavulanic or tazobactam) and return to its original form [13–15]. This agent also has activity against producers of β-lactamases from classes A and C per the Ambler classification (and also varying activity against class D, albeit not class B enzymes, i.e., metallo-β-lactamases [MLB]) [16]. It is because of its ability to have good *in vitro* activity—even for KPC-producing strains—that this combination is recommended in recently published guidelines on empirical treatment of patients with severe gram-negative bacilli infections [17]. CAZ/AVI is a very good agent (>99% susceptibility) against more than 8,000 *Enterobacteriaceae* isolates (MIC_{50}/MIC_{90}, 0.12/0.25 mg/L) collected from hospitals in the United States (US) [18]. For NFGNB-MDR, CAZ/AVI recovers activity against *P. aeruginosa* lost by ceftazidime due to derepression of the inducible chromosomal AmpC-type β-lactamase. Of the 7,062 *P. aeruginosa* isolates obtained in four different geographic regions, 92% were susceptible to CAZ/AVI with a MIC_{90} of 8 mg/L, thus recovering up to 65% susceptibility to ceftazidime alone [19]. In another study of US hospitals, CAZ/AVI inhibited 82% of strains that were resistant to ceftazidime. CAZ/AVI is active in approximately 30% of *S. maltophilia*. The remaining strains may produce two types of β-lactamases, one of which is the MLB type—resistant to all β-lactamase inhibitors. Aztreonam (AZT) has activity in these strains. The other β-lactamase is a cephalosporinase, which confers resistance on third-generation cephalosporins and aztreonam; however, it is susceptible to β-lactamase inhibitors such as avibactam (AVI). Thus, the combination of AZT and CAZ/AVI has been successfully tested for the treatment of *S. maltophilia* infections. CAZ/AVI was up to 81.58% more active when compared to CAZ alone, and AVI potentiated the activity of AZT up to 94% [20]. The activity of CAZ/AVI against *A. baumannii* remains limited. More than 50% are resistant to CAZ/AVI.

Use of cefiderocol for NFGNB-MDR. This is a new parenteral cephalosporin that has a complex chemical structure with summatory characteristics of cefepime and ceftazidime, as well as the presence of a catechol-like side chain with siderophore capacity. This allows it to cross iron transport channels present in the GNB outer membrane ("*Trojan Horse*") and enter the periplasmic space at high concentrations, thus evading classical resistance mechanisms such as hyperexpression of efflux pumps or mutations in porin channels [21–23]. It has been shown to have a higher affinity *in vitro* than ceftazidime for PBP3 binding, as well as for PBP1 in *P aeruginosa* or PBP2 in *Klebsiella pneumoniae* [24]. Another characteristic is the high stability present in hydrolysis of most β-lactamases, including those of the metallo-β-lactamase type.

Consistent with these characteristics, cefiderocol confers broad-spectrum coverage against Gram-negative bacilli, even those difficult-to-treat NFGNB-MDR like *Acinetobacter* or *Stenotrophomonas*.

In a recent publication on the SIDERO-WT surveillance program conducted between 2014-2019 that collected clinical samples from hospitals in both Europe and North America, cefiderocol inhibited 99.9% of *P aeruginosa* isolates and 96.0% of *A. baumannii* isolates with MIC ≤4 mg/L. Likewise, 98.6% of *S. maltophilia* were susceptible with MIC ≤1 mg/L [25]. Nowadays, most centers in Spain have limited experience with the use of cefiderocol; however, some trials have been reported as presenting good results [26–28].The role of this antibiotic in such aforementioned NFGNB-MDR infections seems promising.

CONFLICT OF INTEREST

Authors declare no conflict of interest

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