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EDITORIAL COMMENTARY

Aztreonam Combination Therapy: An Answer to Metallo-β-Lactamase–Producing Gram-Negative Bacteria?

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(See the Brief Report by Yasmin et al on pages 1095–8.)

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Carbapenemase-producing Enterobacteriaceae (CPE) are global priority pathogens owing to their multidrug resistance phenotypes and propensity to exchange resistance genes via mobile genetic elements. In the United States where *Klebsiella pneumoniae* carbapenemases (KPCs) predominate [1], patient outcomes have improved significantly after the introduction of the novel β-lactamase inhibitors (BLIs) avibactam, vaborbactam, and relebactam [2–5]. Each of these agents provides potent inhibition of KPC, restoring the activity of its partner β-lactam (BL) (ceftazidime, meropenem, and imipenem-cilastatin, respectively) against KPC-producing pathogens. Among CPE globally, however, metallo-β-lactamases (MBLs) are more common than KPC in many regions [1]. MBLs with global distribution include New Delhi metallo- (NDM; common in the Indian subcontinent), Verona integron–mediated (Southern Europe), and imipenemase (East Asia) groups [1]. Of pressing concern, MBLs have replaced KPC as the most common carbapenemase in some hospitals following increased use of ceftazidime-avibactam [6]. MBLs use zinc ions to catalyze the hydrolysis of BLs and are not inhibited by the commercialized diazabicyclooctane (avibactam and relebactam) or cyclic boronic acid (vaborbactam) BLIs. Treatment of infections caused by MBL-producing Enterobacteriaceae therefore represents a critical and ongoing unmet medical need.

Aztreonam, the only monobactam currently in clinical use, is not hydrolyzed by MBLs owing to poor, nonproductive binding with the enzymes [7]. Unfortunately, most MBL-producing strains coproduce extended-spectrum β-lactamase (ESBL), AmpC β-lactamase, or other β-lactamases that hydrolyze aztreonam. The combined substrate profile includes all known BLs, as demonstrated by the case report by Yasmin and colleagues in this issue of *Clinical Infectious Diseases* [8]. To exploit the unique characteristics of aztreonam, recent investigations have explored the utility of aztreonam in combination with BL/BLIs. With this approach, a BL/BLI, such as ceftazidime-avibactam, inhibits ESBL and AmpC β-lactamases, whereas aztreonam evades MBL-mediated hydrolysis and exerts its bactericidal effects. Indeed, the combination of aztreonam and ceftazidime-avibactam is highly synergistic against NDM-producing Enterobacteriaceae [9] and *Stenotrophomonas maltophilia*, which intrinsically produces the L1 MBL [10]. Based on this in vitro activity and the dearth of alternative treatment options, the combination of aztreonam and ceftazidime-avibactam is increasingly used clinically. In Spain, 10 patients (including 5 with bacteremia) infected with *K. pneumoniae* producing 3 β-lactamases, NDM-1, OXA-48, and CTX-M-15, were treated with aztreonam and ceftazidime-avibactam; 6 of 10 patients were cured within 30 days [11].

Herein, Yasmin and colleagues [8] report a case of bacteremia in a neutropenic child due to carbapenem-resistant *Enterobacter hormaechei* after the child received an allogenic bone marrow transplant at a hospital in the United States. The strain was resistant to both ceftazidime-avibactam and meropenem-vaborbactam, which prompted screening with a commercially available polymerase chain reaction assay that identified both bla_{KPC} and bla_{NDM} (later confirmed as KPC-4 and NDM-1 by whole-genome sequencing). In response, combination therapy with aztreonam and ceftazidime-avibactam was initiated. In vitro synergy testing of the *E. hormaechei* strain confirmed synergy between the 2 agents, and steady-state therapeutic drug monitoring was performed. Free drug concentrations >2 μg/mL were maintained throughout the dosing interval for aztreonam and ceftazidime, while free

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avibactam concentrations were >2.5 μg/mL for approximately 50% of the dosing interval. The patient received a 2-week treatment course that led to clinical and microbiologic cure.

This case raises several key issues for consideration. First, though KPC remains the most common acquired carbapenemase in the United States, Enterobacteriaceae producing MBL are increasingly reported [12]. Most cases are linked with international travel to endemic regions; however, domestic cases may also occur, as demonstrated by the current one. It is also noteworthy that many regions in the United States have reported an emerging diversity of carbapenemase enzymes among CPE, including MBLs [13, 14]. Taken together, the assumption that all CPE are mediated by KPC enzymes susceptible to the new BL/BLI combinations carries the risk of implementing ineffective therapy. Although knowledge of local epidemiology is critical, the use of these agents should always be accompanied by susceptibility testing and rapid diagnostic tests to determine carbapenemase types. Several molecular and immunochromatographic tests are now available to this end [15].

Second, the current case highlights the paucity of clinical data available to support aztreonam combination therapy against MBL-producing organisms. The mechanistic rationale, in vitro synergy data, and preclinical animal studies each provide compelling evidence [9, 16–18]. On balance, the limited clinical experience reported to date is subject to significant heterogeneity and publication bias [11, 19–21]. Moreover, the optimal dosing approach for combination therapy with aztreonam and ceftazidime-avibactam has not been established. Because avibactam protects aztreonam from hydrolysis by non-MBL β-lactamases, such as ESBL and AmpC, the logical approach is to administer ceftazidime-avibactam followed by aztreonam; however, the short half-life of avibactam and requirements for prolonged infusion in combination with ceftazidime (≥2 hours) have justifiably raised concerns that the available avibactam concentrations may not be sufficient. Because BLIs are not active individually, their pharmacodynamic (PD) target is based on the threshold concentration (cycle threshold [Ct]) needed to restore BL activity rather than the drug minimum inhibitory concentration [22]. Against pathogens producing NDM with ESBL or AmpC β-lactamases, the avibactam Ct is 2.5 mg/L [23]. From in vitro hollow-fiber and neutropenic murine thigh and lung models, the pharmacokinetic (PK)/PD index that best correlates with restoration of aztreonam antibacterial activity by avibactam is the percentage of time free drug concentrations exceed Ct. To achieve a 1–$\log_{10}$ kill against MBL-producing bacteria, this is required to be approximately 50% [23], a threshold that was met in the present case.

Although these data provide important insights into the efficacy of a potential dosing regimen for the combination, it is important to note that the PK characteristics of BLIs have not been well characterized in patient populations at highest risk for suboptimal exposures [22], including patients who are critically ill and/or receiving renal replacement therapy [24, 25]. Because BL/BLI agents, like ceftazidime-avibactam, are available only as fixed-dose combinations, there are limits on potential dose adjustments in the setting of altered drug elimination or elevated minimum inhibitory concentrations against target pathogens. Accordingly, it is assumed that exposures of both BLs and BLIs are consistent and sufficient to achieve their desired effects across patient populations and diverse pathogens are made.

These assumptions are challenged when aztreonam is coadministered with ceftazidime-avibactam for the treatment of serious infections caused by MBL-producing pathogens. Ideally, the clinical development of an aztreonam-avibactam combination will reach the clinic with maximal exposures of each agent. In the interim, further research is needed to explore the PK/PD exposures of patients treated with aztreonam and ceftazidime-avibactam, including the possibility of using prolonged or continuous infusions of one or both agents. The commercialization of stand-alone BLIs also merits future consideration, because exposures could be tailored to individual patients and pathogens without the potential collateral damage of administering unnecessary BLs [22]. Finally, the combination of aztreonam with other commercially available BLs or BLIs as an alternative to ceftazidime-avibactam has been explored in vitro [17, 26], but not yet in dynamic model systems or in patients. Although well-controlled, randomized studies in these areas would be valuable, they are also impractical. Therefore a registry of patient cases coupled with detailed PK assessments may be more realistic as the clinical adoption of aztreonam combination approaches expands.

In conclusion, the case presented in this issue of *Clinical Infectious Diseases* offers hope that we may finally be close to a reasonable treatment strategy for infections caused by MBL-producing Enterobacteriaceae, or more broadly MBL-producing gram-negative bacteria, for which very few options currently exist. Creative solutions, such as combining ceftazidime-avibactam and aztreonam have demonstrated clinical utility and may well stem the tide until novel agents with potent in vitro activity against MBLs in the late stages of clinical development are available to patients.

Notes

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