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LETTER TO THE EDITOR

Experimental prescription, rising resistance: the alarming misuse of ceftazidime-avibactam in healthcare systems

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Dear editor,

The emergence of carbapenem-resistant Gram-negative bacteria (CR-GNB) co-carrying multiple carbapenemases, especially *Klebsiella pneumoniae*, represents a public health problem worldwide, causing nosocomial outbreaks and having limited therapeutic options (1, 2). Currently, new β-lactam/β-lactamase inhibitor (BL/BLI) combinations, such as ceftazidime–avibactam (CAZ-AVI), imipenem–relebactam and meropenem–vaborbactam and a new siderophore cephalosporin (cefiderocol) have been recommended as the first choice of therapy for infections caused by CR-GNB. These combinations are active against class A (KPC) and class C β-lactamases (AmpC) but have no activity against metallo-β-lactamases (MBL); CAZ-AVI is also active on OXA-48 producing Enterobacterales and *Pseudomonas aeruginosa* isolates, whereas, cefiderocol demonstrates promising *in vitro* activity against all clinically important carbapenemases including MBL (1, 3).

Previous studies revealed that the main carbapenemase genes in most provinces of Iran are Ambler class D (OXA-48-like) and Ambler class B (especially NDM), while class A (KPC) being the least common (4, 5). However, in recent years, studies have shown that *K. pneumoniae*, the most common carbapenem-resistant organism in our country, carries both types of NDM with the same OXA-48 gene. Therefore, given the prevalence of carbapenemase genes in Iran, aztreonam plus CAZ-AVI would find greater utility and CAZ-AVI should not be prescribed experimentally and as monotherapy. Recently, the first report of failure of ceftazidime/avibactam experimental therapy in a 91-year-old man with *K. pneumoniae* ST11 co-producing NDM-1 and OXA-48 carbapenemases infection was reported in Iran (5).

It should be noted that in an ongoing study, the results show that out of 78 carbapenem-resistant *K. pneumoniae* isolated from patients in two medical centers in Isfahan, 87.2% are resistant to CAZ-AVI due to NDM production in approximately 50% of cases. These results confirm that CAZ-AVI as monotherapy is not a suitable treatment choice for patients.

The indiscriminate and experimental use of CAZ-AVI without proper diagnostic support has led to a cascade of detrimental consequences, including but not limited to:

1. Escalation of antimicrobial resistance
2. Increased mortality rates
3. Prolonged hospital stays
4. Unnecessary economic burden on patients and

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families

5. Increased financial strain on the healthcare system
6. Loss of foreign currency (unnecessary outflow of a country's financial resources, particularly foreign exchange reserves, to purchase goods or services from other countries when those resources could be better utilized domestically).
7. Damage to global perceptions of medical tourism

In conclusion, it is suggested that countries that intend to give permission to prescribe BL/BLI combinations for the first time, in cooperation with medical microbiologists and other specialists, conduct comprehensive epidemiological studies in order to determine the prevalence and distribution of carbapenemase classes to choose the appropriate treatment options. Also, intensive antibiotic surveillance initiatives should also be undertaken, and microbiology laboratories should be equipped with appropriate diagnostic equipment to enable accurate antibiotic resistance profiling for BL/BLI combinations and cefiderocol. Most importantly, these measures should be prioritized before considering the import or purchase of new antibiotics to avoid empirical prescribing, ensure wise treatment choices, improve clinical outcomes, increase survival rates, and reduce unnecessary medical and financial burdens.

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