TITLE: CEFTAZIDIME/AVIBACTAM RESISTANCE IN A POLYMYXIN B-RESISTANT KPC-PRODUCING *Klebsiella pneumoniae* ISOLATED FROM A CRITICALLY ILL PATIENT AFTER INITIATING CEFTAZIDIME/AVIBACTAM THERAPY

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ABSTRACT:

In Brazil, ceftazidime/avibactam (CAZ/AVI), a novel β-lactam/β-lactamase inhibitor combination, has been approved by ANVISA (2018) for the treatment of infections due to multidrug-resistant (MDR) Gram-negative pathogens. Unfortunately, despite current clinical use, the emergence of resistance to this new antimicrobial has been described. Here, we report the isolation of polymyxin B-resistant KPC-producing *K. pneumoniae* (PMBR-KPC-Kpn) after initiating ceftazidime/avibactam therapy from a catheter-related bloodstream infection in a pediatric patient. Clinical and laboratory data regarding the patient were retrospectively retrieved from medical records. In addition, the antimicrobial therapy regimens implanted during hospitalization were also registered. A 15-year male patient with suspected viral meningoencephalitis presented multiple convulsions. Even with acyclovir, phenytoin, phenobarbital, and diazepam, he continued convulsions, had decreased consciousness, and was admitted to ICU (July 2021). During 30 days in the ICU, he underwent invasive procedures and used various antimicrobials. No significant clinical improvement; he received CAZ-AVI (2,5 g every 8 hours) due to earlier cultures with MDR-*P. aeruginosa* and PMBR-KPC-Kpn susceptible only to CAZ-AVI. Three days after the onset of CAZ-AVI, the patient presented fever, hemodynamic and hepatic worsening. New cultures were collected, CVC was exchanged, and vancomycin and micafungin were combined. A catheter blood culture bottle revealed the growth of a PMBR-KPC-Kpn also resistant to CAZ-AVI and only susceptible to imipenem (MIC of 0.5 mg/L performed by E-test). This isolate showed a negative Blue-Carba test but a positive double-disk synergy test further mCIM test. PCR detected only bla_{KPC}. CAZ-AVI was stopped, and imipenem (1 g every 8 hours) was added per seven days. The patient had other episodes of fever with laboratory parameters of infection and new therapeutic regimens. He was discharged from the hospital after 323 days with sarcopenia, malnutrition, sclerosing cholangitis, and unresolved liver abscesses. In summary, we report a case of CAZ-AVI resistance in a PMBR-KPC-Kpn isolated from a catheter blood culture three days after initiating CAZ-AVI therapy. Molecular mechanisms have not been elucidated; however, nonsynonymous mutations, mainly in bla_{KPC-2} and $bla_{KPC-3,}$ have been reported with restored susceptibility to imipenem as in this isolate.

Keywords: *Enterobacterales*; extended-drug resistance; novel β-lactams/β-lactamase inhibitors

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