Ceftazidime/Avibactam for Refractory Bacteremia, Vertebral Diskitis/Osteomyelitis with Pre-Vertebral Abscess and Bilateral Psoas Pyomyositis Secondary to *Klebsiella Pneumoniae* Carbapenemase-Producing Bacteria (KPC)

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A 36-year-old man was admitted to the intensive care unit due to diabetic ketoacidosis and pneumonia requiring mechanical ventilation. Three weeks after admission, he developed a refractory bacteremia with *Klebsiella pneumoniae* carbapenemase-producing bacteria (KPC). He remained febrile and with bacteremia for six weeks despite therapy with polymyxin B, carbapenems, and amikacin. Imaging studies looking for deep-seated infection revealed vertebral L1-L2 diskitis and osteomyelitis with pre-vertebral abscess and bilateral psoas pyomyositis that were not amenable for drainage. In view of the refractory infection and the activity against KPC described in the literature, we decided to switch the patient to ceftazidime/avibactam. After six weeks of therapy, there was complete resolution of the infectious processes. We present an instance of clinical success with ceftazidime/avibactam for the treatment of refractory KPC bacteremia, vertebral diskitis and osteomyelitis with pre-vertebral abscess and bilateral psoas pyomyositis. This experience serves as reference to support treatment with ceftazidime/avibactam in similar complicated cases. [*P R Health Sci J 2018;37:128-131*]

Key words: Ceftazidime/Avibactam, KPC, Bacteremia, Diskitis/Osteomyelitis, Pre-vertebral abscess, Psoas pyomyositis

The incidence of carbapenem-resistant enterobacteriaceae (CRE) has risen in medical facilities, but there is a limited effective armamentarium to target them, creating a therapeutic challenge (1-2).

The Centers for Disease Control and Prevention (CDC) reports that the two most common CRE (*Klebsiella spp.* and *Escherichia coli*) cause 600 deaths yearly with up to 50% mortality rates associated to bloodstream infection. They have classified these alarming rates as an urgent threat since 2013 (1).

There are few antimicrobials in the drug development pipeline and clinicians have had to endorse older therapeutic agents such as polymyxin B to treat infections by multidrug-resistant (MDR) Gram-negative bacteria (3). Tigecycline is an alternative for MDR *Acinetobacter baumannii* and *Klebsiella pneumoniae* carbapenemase-producing bacteria (KPC), but it is not recommended for bacteremia because it does not achieve adequate serum concentration levels and is associated to an increased risk of death (4-5). Furthermore, resistance to these agents has been reported (6). This leads to a newer antimicrobial agent in the market to treat CRE infections: ceftazidime/avibactam (7-9). It is an established third-generation cephalosporin with a novel B-lactam inhibitor that restores the activity of ceftazidime against many β-lactamase-producing Gram-negative bacteria, including extended-spectrum β-lactamases and KPC. Even though it is a potent antimicrobial tool, current Food and Drug Administration (FDA) indications are confined to complicated intra-abdominal infections, complicated urinary tract infections, and bacterial pneumonia (hospital-acquired and ventilator-associated only) (10). Data regarding the use of ceftazidime/avibactam for the treatment of KPC causing bacteremia or spinal infections is very limited but rising (11-15). We present an instance of

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clinical success with ceftazidime/avibactam for the treatment of KPC bacteremia and vertebral diskitis/osteomyelitis with pre-vertebral abscess and bilateral psoas pyomyositis.

Case Report

A 36-year-old man with obesity and Type 2 diabetes mellitus returned to our institution with nausea, vomiting, and moderate abdominal pain for one day. He had a recent short admission because of a depressed fracture of the right lamina papyracea, mildly displaced fracture through the greater tuberosity of the right humerus, and a wedge compression fracture at L1 vertebral body after a motor vehicle accident, but he was discharged at that time because no surgical intervention was required. Upon return, he was now acutely ill with tachycardia, tachypnea and rhonchi on pulmonary auscultation. Laboratories were remarkable for leukocytosis (14.3Thou/uL), neutrophilia (86%), bandemia (7%), high anion gap metabolic acidosis (31mEq/L), hyperglycemia (484mg/dL) with large blood ketones, and elevated creatinine phosphokinase (2227U/L) and creatinine (3.45mg/dL) levels. He was admitted to the intensive care unit (ICU) with diabetic ketoacidosis and pneumonia by *Enterobacter cloacae* and methicillin-sensitive *Staphylococcus aureus* requiring mechanical ventilation. He received cefepime with eventual resolution of pneumonia.

Three weeks after admission, the course of hospitalization deteriorated, as manifested by fever (38.9°C), leukopenia (2.5Thou/L), and tachycardia (108bpm). Blood cultures preliminarily showed Gram-negative bacilli. He was started on imipenem/cilastatin, but *Klebsiella pneumoniae* resistant to all antimicrobials except for amikacin (MIC≤16mg/L on VITEK) was finally identified. KPC was presumed in view of the susceptibility pattern. Specific confirmatory tests for KPC (Modified Hodge Test and polymerase-chain reaction) and susceptibility disk for ceftazidime/avibactam were not available in our laboratory. Although the Clinical and Laboratory Standards Institute currently does not have colistin or polymyxin B breakpoints for *Klebsiella*, polymyxin B was added empirically to the antimicrobial therapy.

One week later, he developed high-grade fever (39.9°C) and a drug eruption that clinically and histologically was confirmed to be secondary to the carbapenem. Consequently, the regimen was changed to amikacin. Nevertheless, the patient continued with high-grade fever and persistent bacteremia. Polymyxin B was restarted while renal function and amikacin trough levels were closely monitored. Since bacteremia had persisted for six weeks and because he was on close monitoring at ICU setting, we decided to restart carbapenems by adding meropenem. A transthoracic echocardiogram showed no valvular vegetations, but an abdomino-pelvic computed tomography scan showed an L1 Chance fracture with severe retropulsion, 50% decrease in vertebral body height and changes suggestive of diskitis/osteomyelitis over T12 and L2 and associated inflammation tissue reaction suggestive of a paraspinal abscess.

In view of refractory bacteremia, resistance pattern of the isolated organism, and in vitro activity against KPC documented in the literature for ceftazidime/avibactam, we decided to discontinue meropenem and to start ceftazidime/avibactam while continuing polymyxin B and amikacin. Lumbar magnetic resonance imaging (MRI) confirmed the vertebral L1-L2 diskitis/osteomyelitis with pre-vertebral abscess (3.4cm x 2.5cm x 3cm) causing spinal canal stenosis and bilateral pyomyositis (Figures 1 and 2). Orthopedic Spine Service considered that the abscesses were small and not amenable to surgery. Fever subsided six days after starting ceftazidime/avibactam and subsequent blood cultures (13 days after starting the new therapy) were negative. Therefore, polymyxin B and amikacin were discontinued. Eventually, the patient completed 6 weeks of ceftazidime/avibactam attaining complete resolution of the infectious processes. No side effects were reported and the patient was discharged home.

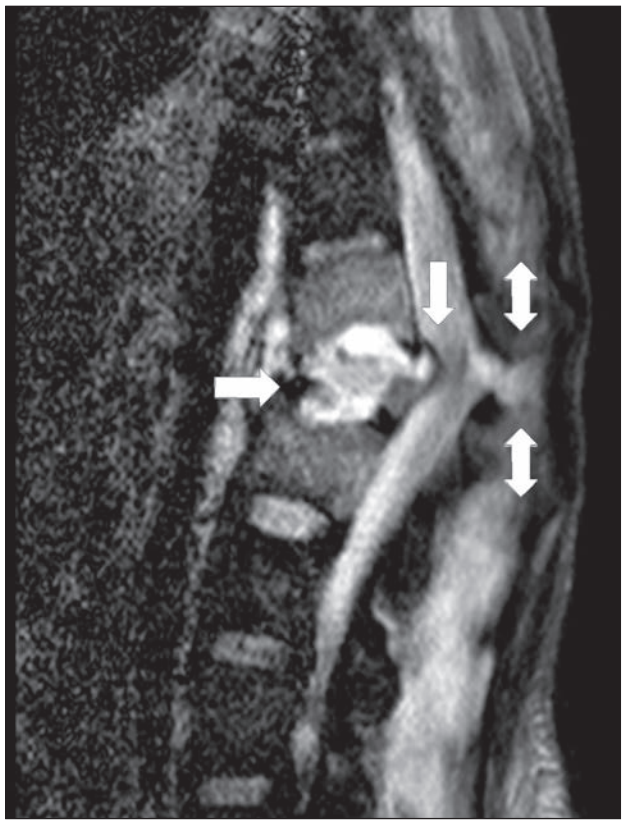

Figure 1. Sagittal STIR shows pre-vertebral abscess and diskitis/osteomyelitis causing destruction of the vertebral body of L1 (right arrow) with slight retropulsion into the spinal canal (down arrow). There is also disruption of the ligamentum flavum (double up-down arrows).

Nine months later, he was submitted to an extensive yet successful surgery (posterior osteotomy over T12-L1, posterior spinal instrumentation with bone graft at T10-L3, anterior corpectomy, release decompression, and interbody fusion with femur shaft) because remained with a traumatic thoracic

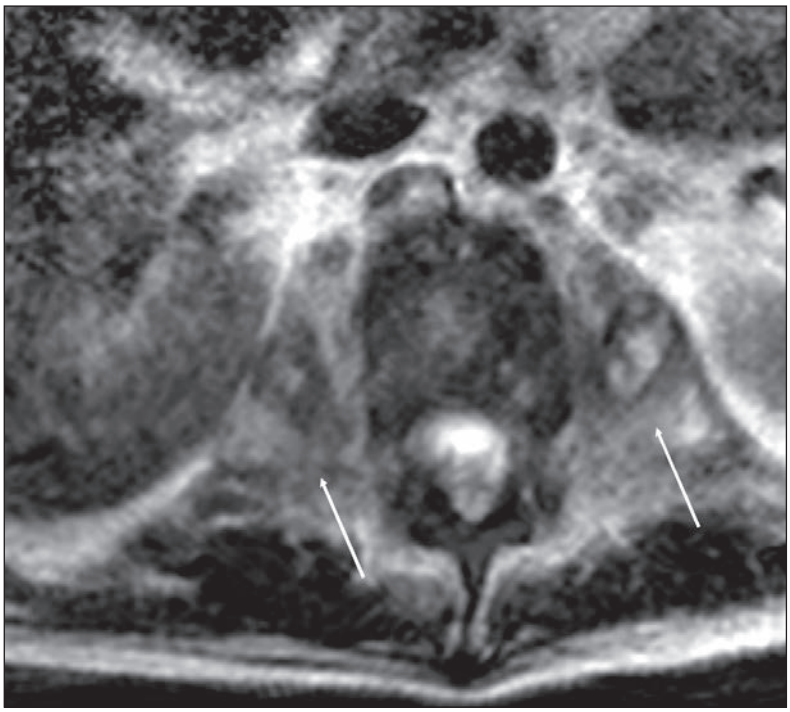

Figure 2. T2 axial image shows small abscesses (see arrows) in the psoas muscles (pyomyositis).

hyperkyphosis. On follow-up at our Infectious Diseases ambulatory clinic, he has remained stable and has not required further antimicrobial therapy or hospital admissions.

Discussion

Ceftazidime/avibactam has no FDA indication for bacteremia or bone infections. However, it is a bactericidal antibiotic with proven activity against KPC. Therefore, it was theoretically possible to warrant its use in such a complex setting, refractory to the highly toxic aminoglycoside-based and polymxin-based regimens that most clinicians would have relied on. To our knowledge, this is the first reported case of clinical success with ceftazidime/avibactam for the treatment of KPC bacteremia in Puerto Rico and one of the very few reports available in the literature regarding successful use of this antibiotic for the treatment of spinal infections. This difficult case was a therapeutic challenge with a successful outcome. In the absence of new FDA-approved agents and indications for such resistant bacteria, this experience serves as reference to support treatment with ceftazidime/avibactam in similar complicated scenarios.

Resumen

Un hombre de 36 años se admitió a cuidado intensivo por cetoacidosis diabética y neumonía que requirió ventilación mecánica. Tres semanas más tarde, desarrolló una bacteremia refractaria por *Klebsiella pneumoniae* productora de carbapenemasa (KPC, por sus siglas en inglés). El paciente se mantuvo febril y bacterémico por seis semanas a pesar de recibir polimixina B, carbapenemas y amikacina. Se le realizaron estudios de imagen buscando una infección profunda que revelaron una disquitis y osteomielitis de L1-L2 con absceso pre-vertebral y piomiositis bilateral del psoas que no podían drenarse quirúrgicamente. En vista de la infección refractaria y la actividad en contra de KPC que se describe en la literatura, se comenzó al paciente en ceftazidime/avibactam. A las seis semanas de terapia, hubo resolución completa de sus procesos infecciosos. En este caso se utilizó ceftazidime/avibactam exitosamente para una bacteremia refractaria por KPC y disquitis y osteomielitis vertebral con absceso pre-vertebral y piomiositis bilateral del psoas. Esta experiencia pudiera servir como referencia para sustentar el uso de ceftazidime/avibactam en casos con severidad similar.

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