First report of carbapenem-resistant *Providencia stuartii* in Saudi Arabia

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Abstract

We present the case of 31-year-old man who developed hospital-acquired pneumonia in the intensive care unit. Pathogens were identified to be carbapenem-resistant isolates of *Providencia stuartii* and *Klebsiella pneumoniae.* The patient was treated with an extended infusion of double-dose meropenem (targeting the carbapenem-resistant *P. stuartii*) and colistin (targeting the carbapenem-resistant *K. pneumoniae*) for 2 weeks. The patient's disease responded well to the prescribed regimen; his chest X-ray became normal, and all other signs of infection subsided. To our knowledge, this is the first description of the emergence of carbapenem-resistant *P. stuartii* due to AmpC hyperproduction in Saudi Arabia.

Keywords: Carbapenem resistant, extended infusion, meropenem, *Providencia stuartii*
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Introduction

Providencia species are Gram-negative bacilli that belong to the *Enterobacteriaceae* family. The genus *Providencia* contains five species: *P. stuartii, P. rettgeri, P. alcalifaciens, P. heimbachae* and *P. rustigianii* [1]. Among the *Providencia* species, *P. stuartii* and *P. rettgeri* are the most common causes of nosocomial infections including urinary tract infections, pneumonia, and wound and bloodstream infections [1,2]. Nosocomial infections with *P. stuartii* greatly affect patients' outcomes [3].

We present a case of a patient with hospital-acquired pneumonia caused by carbapenem-resistant isolates of *P. stuartii* and *Klebsiella pneumoniae.* To our knowledge, this is the first report of carbapenem-resistant *P. stuartii* due to AmpC hyperproduction in Saudi Arabia.

Case presentation

A 31-year-old man was admitted to our intensive care unit (ICU) from another hospital with postexploratory laparotomy and right thoracotomy for a gunshot wound to the abdomen and chest on February 2017. The patient had left arm injury with a left elbow fracture, for which he underwent open reduction internal fixation (ORIF). His condition was complicated by septic shock and acute kidney injury. At his arrival at hospital, the patient was found to have a chest infection and an infected laparotomy wound, for which empiric piperacillin/tazobactam therapy was provided. During his prolonged ICU stay (56 days), he received several antibiotics; the patient had continuous fever, leukocytosis and persistent source of infection (abdominal wound and left-hand ORIF site wound for which he underwent frequent dressing and debridement). Written informed consent was obtained from the patient's family for publication of this case report. The study was approved by our local institutional review board (H2RI-16-Apr17-01).

P. stuartii isolates were identified using the VITEK 2 system (bioMérieux, Marcy l'Étoile, France). Susceptibility testing was determined by disc diffusion and interpreted by the Clinical and Laboratory Standards Institute criteria [4]. Phenotypic assay for

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detection of extended-spectrum β-lactamase, AmpC and carbapenamase production was performed as described previously [5].

The first carbapenem-resistant *P. stuartii* isolate was detected in the sputum on day 22 of ICU admission. The isolate was resistant to ciprofloxacin, trimethoprim/sulfamethoxazole, gentamicin, imipenem and meropenem; it was only sensitive to amikacin. We did not treat the patient according to the results of this culture because the chest X-ray was unremarkable at that time. The patient became highly febrile on day 30, so piperacillin/tazobactam 4.5 g was provided intravenously (iv) every 6 hours. On the third day of piperacillin/tazobactam therapy (day 32 of ICU admission), the fever was persistent and leukocytes were increasing, so the patient underwent septic screening (tracheal aspirate, urine, laparotomy site wound and blood), and piperacillin/tazobactam was changed to meropenem 1 g provided iv every 8 hours. Three days later (day 35), we received the results of the septic screening, which showed growth of *P. stuartii* and carbapenem-resistant *K. pneumoniae* in the urine, wound and blood. On day 37 we received the tracheal aspirate culture report, which revealed growth of carbapenem-resistant isolates of *P. stuartii* and *K. pneumoniae*. The carbapenem-resistant *P. stuartii* isolate was resistant to amikacin, ciprofloxacin, trimethoprim/sulfamethoxazole, gentamicin and imipenem, while it was intermediate to meropenem.

Because the patient's condition was not improving while receiving therapy with a conventional dose of meropenem (1 g provided iv every 8 hours), we changed the dosing regimen of meropenem to be 2 g delivered iv every 8 hours with extended infusion over 3 hours instead of 30 minutes. Also, we added colistin to treat the carbapenem-resistant *K. pneumoniae*. Colistin was prescribed as a loading dose of 9 million units iv followed by 3 million units iv every 8 hours. A follow-up septic screen was repeated on day 44. On day 47 the septic screen showed the positive growth of multidrug-resistant (MDR) *Acinetobacter baumannii* in the left-hand ORIF site wound and tracheal aspirate. A chest X-ray was ordered; it revealed nothing abnormal. Meropenem and colistin were discontinued after completing a course of 2 weeks. The patient was transferred to the ward after 56 days of ICU admission. He was stable with no signs and symptoms of infection.

Discussion

Antimicrobial resistance in *P. stuartii* is uncommon in our ICU. However, the extensive consumption of colistin, tigecycline and carbapenems in our ICU because of high rates of MDR *A. baumannii,* carbapenem-resistant *K. pneumoniae* and extended-spectrum β-lactamase-producing *Enterobacteriaceae* might have played a role in the emergence of carbapenem-resistant *P. stuartii.* Our patient received multiple antibiotics before the isolation of the first carbapenem-resistant *P. stuartii;* he completed prolonged courses of colistin, tigecycline and imipenem. The use of colistin and tigecycline is associated with superinfections with *P. stuartii* and many MDR Gram-negative bacteria [6,7].

Many carbapenem-resistant *P. stuartii* cases have been reported [2]. Carbapenamase production (mainly New Delhi metallo-β-lactamase 1) is the main mechanism of carbapenem resistance in *P. stuartii.* Molecular typing helps in identifying the resistance genes in *Providencia* species. Unfortunately, our microbiology laboratory does not perform molecular typing. However, a phenotypic assay was performed and revealed AmpC production in carbapenem-resistant *P. stuartii* isolates recovered from our patient. Prolonged hospitalization before detection of carbapenem-resistant *P. stuartii* was present in one outbreak of carbapenem-resistant *P. stuartii,* ranging from 24 to 106 days [8]. In another outbreak of carbapenem-resistant *P. stuartii* [9], the median length of ICU stay was 39 days, while acquisition of carbapenem-resistant *P. stuartii* occurred in a median of 16 days after ICU admission. In our case, the first carbapenem-resistant *P. stuartii* was recovered on day 22 and the second on day 32. Both isolates were recovered from respiratory sites.

Nosocomial infections caused by carbapenem-resistant *P. stuartii* strains represent a challenging serious clinical threat because these strains are intrinsically resistant to last-resort agents, mainly colistin and tigecycline. Because reports of carbapenem-resistant *P. stuartii* are scarce, its treatment was rarely described. Our patient received a 2-week course of double-dose meropenem every 8 hours provided as an extended infusion over 3 hours. In addition, colistin was prescribed to treat the carbapenem-resistant *K. pneumoniae* coinfection. The use of extended infusion of meropenem for patients with hospital-acquired pneumonia has many advantages compared to a 30-minute infusion regimen; the severity of the disease can be reduced and the clinical efficacy can be improved, and organ failure recovery and long-term prognosis can be improved [10].

Conflict of interest

This report did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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