Pneumologia

Description of an effective treatment regimen for ventilator-associated pneumonia due to pandrug-resistant *Providencia*: a case report

Elham Pourheidar¹, Rezvan Hassanpour¹, Mehrdad Haghighi², Seyedpouzhia Shojaei³, Mehran Kouchak³, MirMohammad Miri³, Sara Salarian³, Mohammad Sistanizad^{1,*}

¹Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

²Department of Infectious Diseases, Imam Hossein Teaching and Educational Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

³Department of Critical Care Medicine, Imam Hossein Medical and Educational Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

English:

Because of an increased prevalence of infections with resistant Gram-negative bacteria, finding optimal treatment regimens for these cases is one of the major healthcare concerns. *Providencia* is a Gram-negative bacteria belonging to the Enterobacteriaceae family. This article aims to describe an effective antibacterial regimen used for treating ventilator-associated pneumonia (VAP) with species of *Providencia* that are resistant to all antimicrobial classes. We present the case of a 74-year-old woman suffering from VAP caused by pandrug-resistant *Providencia*. The patient received high-dose intravenous meropenem (1 g every 12 h, infused over 4 h), intravenous amikacin (1,500 mg every 48 h) and nebulised amikacin (250 mg every 6 h). The dosages were calculated based on weight and renal function (GFR = 13.69 ml/min/1.73). After 23 days of treatment, following improvement in clinical signs (including fever), a drop in leucocytes counts, a higher than 80% reduction in procalcitonin levels (0.12), together with confirmed microbial eradication (negative sputum cultures), the antibacterial regimen was discontinued. In conclusion, when dealing with an infection with a pan-resistant microorganism, using combinations of antibiotics in high doses can be an option. These treatment regimens have the potential of overcoming in vitro resistance, leading to clinical improvement and microbial eradication.

Keywords

Providencia • drug-resistant • carbapenem-resistant Enterobacteriaceae • ventilator-associated pneumonia

Un regim terapeutic eficient în pneumonia de ventilator cu *Providencia* multirezistentă: prezentare de caz

Rezumat

Romanian:

Având în vedere prevalența crescută a infecțiilor cu bacterii Gram-negative multidrog rezistente, alegerea unei schemei de tratament optime pentru astfel de cazuri este o prioritate pentru domeniul sănătății. *Providencia* este o bacterie gram-negativă aparținând familiei Enterobacteriaceae. Scopul acestei lucrări este să descrie un protocol terapeutic folosit pentru tratarea pneumoniei de ventilator cu specii de *Providencia*, care au dezvoltat rezistența la toate clasele de antibiotice. Prezentăm cazul unei paciente în vârstă de 74 de ani, diagnosticată cu pneumonie de ventilator cu *Providencia* panrezistentă. Luând în considerare greutatea și funcția renală (RFG = 13.69 ml/min/1.73), s-au administrat meropenem intravenos

*Corresponding author: Mohammad Sistanizad

E-mail: sistanizadm@sbmu.ac.ir

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(1g la 12 ore, pe o durată de 4 ore), amikacina intravenos (1,500 mg la 48 ore) și s-au efectuat nebulizări cu amikacină (250 mg la 6 ore). După 23 de zile de tratament, ulterior ameliorării semnelor clinice (inclusiv a febrei), scăderii numărului de leucocite, scăderii valorilor procalcitoninei cu peste 80% (la momentul respectiv valori de 0.12) și a negativării culturilor bacteriene din spută, s-a decis întreruperea tratamentului antibiotic. În concluzie asocierile de antibiotice în doze mari sunt o opțiune în contextul infecțiilor cu germeni panrezistenți. Aceste scheme terapeutice au potențialul de a surmonta o rezistență demonstrată in-vitro și de a determina ameliorare clinică și eradicare bacteriană.

Cuvinte-cheie

Providencia • Enterobacteriaceae rezistente la carbapeneme • pneumonie de ventilator

Introduction

Because of an increased prevalence of infections with resistant Gram-negative bacteria, finding optimal treatment regimens for these cases is one of the major healthcare concerns. Carbapenems were an important treatment option in these cases, but with the growing incidence of multi-drug-resistant (MDR) strains, finding an appropriate treatment course has become an issue (1).

Due to the global importance of drug resistance, in 2018, WHO recommends the development of novel antibiotics against carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacteriaceae (2).

Providencia is a Gram-negative bacteria belonging to the Enterobacteriaceae family. There are some reports regarding infections with this organism, including urinary tract infections, pneumonia, meningitis, endocarditis, wound and bloodstream infections (3,4).

Although, some studies have been conducted to evaluate effective treatment regimens against resistant species of *Providencia*, optimal therapeutic regimens are still not well known. *Providencia* strains resistant to all antimicrobial classes, including third- and fourth-generation cephalosporins, piperacillin/tazobactam, aminoglycosides, fluoroquinolones (ciprofloxacin) and carbapenems are considered as pandrug-resistant (PDR) (5).

Because of *Providencia*'s resistance to antibiotics, such as colistin and tigecycline (4), finding an appropriate antimicrobial regimen for infections with PDR species is a challenge (6).

To the best of our knowledge, there are no available reports of ventilator-associated pneumonia (VAP) with PDR *Providencia*. This case report aims to describe an effective antibacterial regimen for the treatment of this infection.

Case presentation

We had an outbreak due to PDR *Providencia* in November and December 2018, at the 30-bed medical-surgical intensive care unit of Imam Hossein Medical Center, affiliated to Shahid Beheshti University of Medical Sciences, in Tehran, Iran.

There were a total of seven reported cases. We isolated the strain in sputum samples (five cases), a central vein catheter sample and a cerebrospinal fluid sample.

In two cases with bacteraemia and meningitis due to PDR *Providencia*, the samples expired before the culture report. From the remaining five cases with positive sputum cultures, we excluded two of them because we considered them contaminations due to the absence of clinical and radiological signs. VAP was confirmed in the remaining three cases who had positive cultures for PDR *Providencia* along with clinical and radiological signs.

The course of treatment was different for the remaining patients. One of the patients received a combination of two antibiotics—meropenem and amikacin. We administered high doses of meropenem intravenously (2 g every 8 h) together with intravenous amikacin (20 mg/kg) and inhalation of amikacin (250 mg every 6 h) via mesh nebulizer. In this case, the treatment course proved to be successful, with clinical improvement and bacterial eradication; thus, we decided to report it.

In this general context, we present the case of a 74-year-old woman brought to the hospital after losing consciousness. She received initial treatments in the emergency ward but following respiratory distress, reduced oxygen saturation and loss of consciousness; was intubated and was transferred to the ICU. On the first day of admission, there was no significant lung parenchymal involvement.

At the 17th day of ICU admission, we diagnosed VAP based on clinical signs, including fever and increased pulmonary secretions, leucocytosis and alveolar infiltrations on the chest X-ray (CXR). Sputum cultures revealed the presence of an *Acinetobacter* strain, which was sensitive to ampicillin-sulbactam and colistin. Considering the results of the antibiogram, on the 17th day of hospitalisation, the patient began receiving a course of ampicillin-sulbactam.

After 3 days of treatment, the patient still presented fever and leucocytosis with an increase in procalcitonin (PCT) levels from 0.11 to 21.48 and serum creatinine levels from 1.4 mg/dl to 4 mg/dl. The patient also started showing signs of septic

shock—the blood pressure dropped from 120/80 mmHg to 80/50 mmHg, and we administered norepinephrine.

According to isolation of *Klebsiella* strain, in sputum, which was sensitive only to colistin, we administered colistin as intravenously plus oral inhalation. Repeated sputum cultures, was PDR *Providencia* that considering the clinical and radiological improvement, together with an 80% reduction in PCT levels (from 21.48 to 0.86), we concluded it as contamination. We continued the antibiotic treatment previously instated and requested new tests. After 5 days, the patient started presenting fever and an increased leucocytes count, with sputum cultures reconfirming a PDR *Providencia* infection. Her chest X-ray revealed alveolar infiltration, mostly in the right lower lobe, mild pleural effusion and lung infiltration. The modifications were more severe than the ones detected in the *Acinetobacter* pneumonia.

Based on these findings, we changed the treatment regimen. We administered high-dose intravenous meropenem (1 g every 12 h), infused over 4 h, intravenous amikacin (1500 mg every 48 h) and nebulised amikacin (250 mg every 6 h) by mesh nebuliser. The doses were calculated based on the patient's weight and renal function [Cockcroft–Gault estimated creatinine clearance by using lean body weight (13.69 ml/min/1.73)].

We defined a clinical response as the resolution of pneumonia-related signs and symptoms for at least 48 h, including fever and reduced bronchial secretions. We considered a clinical failure based on the presence of one of the following signs: fever ($T \geq 38^{\circ}\text{C}$) or hypothermia ($T < 35.5^{\circ}\text{C}$), copious and purulent pulmonary secretion, >50% increase in pulmonary infiltrate on CXR, lack of recovery, septic shock and multi-organ failure (9, 10). Clinical signs were monitored and recorded daily, CXR and PCT levels requested every 3 days, and sputum cultures requested every 5 days.

After 23 days, following improvement in clinical signs (including fever), a drop in leucocytes counts, a higher than 80% reduction in PCT levels (0.12), together with confirmed microbial eradication (negative sputum cultures), the antibacterial regimen was discontinued.

Discussion

Hospital-acquired pneumonia (HAP), including VAP, the most common infection in the ICU, is associated with prolonged hospital and ICU stays, high costs and poor outcomes (11). Studies, including a prospective 1-year microbiological study, showed that antibiotic-resistant bacteria are one of the proven causes of high mortality rates in pneumonia (12).

Although patients received several treatment regimens, as part of specially designed studies, with the desire of obtaining

favourable outcomes, there are no definite recommendations for treating infections caused by resistant *Providencia* (13).

Providencia's resistance to colistin makes the treatment of carbapenem-resistant strains difficult, especially in countries where new, effective, avibactam-based antibiotic combinations, including, ceftazidime+avibactam and aztreonam+avibactam, are not available (13).

In 2018, Abdallah published the results of a meta-analysis. According to that paper, the prolonged infusions of carbapenems in high doses (meropenem 2 g every 8 h, infused over 3–4 h) are effective against carbapenemase-producing Enterobacteriaceae, including carbapenem-resistant *Providencia* (CRP) (3,14). Tshisevhe also showed in his study that carbapenems were effective in treating four patients with urinary tract infection due to CRP (15). Since aminoglycosides together with beta-lactams proved to be efficient in treating PDR *Providencia* (7,8), we selected these antibiotics when treating our patients.

Douka et al. designed an antimicrobial synergy test using 15 isolated samples of PDR *Providencia* and proved that a combination of piperacillin/tazobactam (4.5 g every 8 h) and amikacin (1 g every 24 h) was an effective choice (7). In another study, Zavascki et al. reported three effective antimicrobial regimens used for treating CRP infections in three patients. The regimens included high-dose piperacillin/tazobactam (4.5 g every 6 h) plus high-dose meropenem (2 g every 8 h), amikacin (1 g every 24 h) plus imipenem (500 mg every 6 h) and levofloxacin (doses unavailable) (8).

Combined therapy was effective in our case; the patient showed clinical improvement and sputum culture conversion. In conclusion, when dealing with an infection with a pan-resistant microorganism, using combinations of antibiotics in high doses can be an option. These treatment regimens have the potential of overcoming *in vitro* resistance, leading to clinical improvement and microbial eradication.

Ethical approval

Inform consent was obtained from the patients in order to participate to the study and write the article.

Conflict of interest

The authors declare that they have no conflicts of interest.

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