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Evaluation of KPC Positive Colistin Resistant *Klebsiella pneumoniae* in A Patient With Ventilator Associated Pneumonia: A Case Report And Literature Review.

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Abstract

Klebsiella pneumoniae producing KPC-type carbapenemase causes severe nosocomial infection at a high mortality rate. Nosocomial pneumonia in particular is associated with high mortality, likely due to the unfavorable pulmonary pharmacokinetics of the antibiotics used against this agent. Therefore, early and accurate microbiological identification and susceptibility evaluation are crucial in order to optimize antibiotic therapy. We report a case of ventilator-associated pneumonia caused by colistin-resistant K. pneumoniae producing KPC-type carbapenemase treat edusing a carbapenem-sparing therapy and tailored according to the serum procalciton in concentration in order to limit the duration of antibiotic therapy.

Keywords: Ventilator-associated pneumonia, Colistin-resistant KPC producing, Klebsiella pneumoniae, Intensive care unit, Drug pharmacokinetics

Introduction

Infection caused by Klebsiella pneumoniae producing KPC-type carbapenemase(KPC-Kp)is an emerging problem epidemiologically, diagnostically, and therapeutically. KPC-Kp causes severe nosocomial infection with a high mortality rate and few pharmacological therapeutic options (1). An accurate evaluation of the antibiotic susceptibility using multiple techniques is crucial for optimizing therapy and improving patient outcomes (2).

To date, the optimal Antimicrobial therapy for these infections has not been defined, but a combination of antibiotic therapies seems to be more effective than monotherapy (3–5). Colistin is one of the few antibiotics active against KPC-Kp, but unfortunately, emerging data on drug-resistance have further restricted therapeutic options involving colistin. In addition, colistin-resistant isolates have been associated with an increased mortality rate (6,7). Antibiotics against KPC-Kp pneumonia (colistin, tigecycline, and gentamicin) have poor lung penetration; therefore, their intravenous administration is not recommended. These antibiotics are sometimes used in combination with carbapenems, which have good pulmonary pharmacokinetics based on their minimum inhibitory concentrations(MICs) of o16 mg/L (5), but clinical experience suggests that this combination may favor prolonged bacterial colonizationin treated patients and may facilitate the spread of KPC-Kp within hospitals.

In 1996,the first cases of KPC-Kp were detected in the USA, and the infection has since spread in a pandemic-like fashion. In Europe in 2009, KPC-Kp infections were diagnosed in less than 5% of patients; the next year, this value increased to 10% and to approximately 25% in some areas (8). In North western Tuscany, Italy, the KPC-Kp epidemicis an emerging problem;from April 2010 to December 2011, 174 cases of KPC-Kp were reported, including 86 first-time infections (40%sepsis, 25%respiratory infections, 15%urinary tract infections, 13% abdominal infections, and 7% other infections) (9).

We present a case of ventilator-associated pneumonia (VAP) caused by colistin-resistant

KPC-Kp in a young polytrauma patient successfully treated with carbapenem sparing antibiotic therapy. Furthermore, we review current literatüre on KPC-Kp nosocomial pneumonia.

Case report

A 28-year-old Caucasian man was hospitalized in a 10-bed intensive care unit (ICU) that serves as a referral center for polytrauma patients due to polytrauma caused by a traffic accident. He presented with a closed head injury (peri-hemi-spheric subdural right hematoma, diffuse axonal injury, and Glasgow Coma Scale [GCS]score¼5), chest trauma with multiple lung contusions, and bilateral rib fractures. The Sequential Organ Failure Assessment (SOFA) score and the Simplified Acute Physiologic Score II (SAPSII) were 10 and 43, respectively. On day 2, due to an increased intracranial pressure (ICP), evacuation of the subdural hematoma and repositioning of the skull bone were necessary. Early tracheotomy was also performed. On day 6, the ICP worsened further, requiring the clinicians to induce a barbiturate coma, and on day 8, a bilateral decompressive craniotomy was performed because the ICP could no longer be controlled by medical therapy.

On day 13, direct phenotypic screening with phenylboronic acid on a surveillance rectal swab was positive for KPC-Kp (DID Diagnostic, Milan, Italy; and Sigma Chemical Co., St. Louis, MO, USA) (10); therefore, the patient was isolated under contact precautions according to hospital protocol. On day 16, the patient was diagnosed with VAP (11) and exhibited signs of severe sepsis (12), decreased gas Exchange (PaO2/ FiO2¼132), and increased procalcitonin (0.42–12.26 mg/L). The patient's bronchoalveolar lavage (BAL) culture was positive for KPC-Kp, and chest radiographs showed are as of parenchymal consolidation.

The antibiotic susceptibility tests, performed using an automated broth microdilution system (Vitek-2s system, expert rulesversion5.04), indicated only intermediate susceptibility to gentamicin (MIC¼4 mg/mL) and tigecycline (MIC 2 mg/mL), and revealed that the strain was colistin-resistant. Based on this microbiological phenotype, a confirmation antibiogram by E-test (AB-Biodisk,Solna,Sweden) was performed. The susceptibility results were interpreted in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints (version 2.0). TheKPC-Kp was sensitive to fosfomycin (MIC¼16 mg/mL) and gentamicin (MIC¼2 mg/mL) and intermediate to tigecycline (MIC¼2 mg/mL). The bacterium was also resistant to colistin (MIC¼4 mg/mL) on the E-test, but at only one dilution above the clinical break point, which was significantly lower than theMIC measured by Vitek-2s (MIC416 mg/mL). Furthermore, the MIC for meropenem was 8 mg/mL on the E-test, which was still in the range of non-susceptibility, but was lower than the MIC reported by the Vitek-2s system (416 mg/mL). The susceptibility test results of the BAL- positive KPC-Kp performed using theVitek-2s system and E-test were compared.

Based on these microbiological data, antibiotic therapy was initiated without loading doses comprising off-label, high doses of tigecycline (100mg intravenously every12h), fosfomycin (3g intravenously every 8h), and colistin methane sulfonate (4.5million IU intravenously every 12h).

After 9 days of antibiotic therapy, the patient showed a gradual improvement in gas Exchange (PaO2/FiO2¼300), normalized procalcitonin (0.8 mg/mL), and stabilized neurological findings (stable ICP and progressive reduction of sedative dose). Based on these improvements, antibiotic therapy was discontinued. Fifteen days later, the patient was transferred to a rehabilitation unit in a minimally conscious state, maintaining bronchial and rectal KPC-Kp colonization, but without clinical signs of infection.

Discussion

The management of this case raises some interesting considerations that may help intreating future cases of KPC-Kp infections in the ICU. At present, Gram-negative MDR infections have limited therapeutic options; therefore, it is necessary to optimize the available resources (6). Most fundamentally, clinicians should obtain the

most precise microbiological data and accurately determine the MIC of potential therapeutic agents. In the present case, we found significant differences between the two microbiological methods used: Vitek-2s vs. E-test. Normally, automated tests generate MIC values that are higher than the values resulting from manual tests, which are time consuming and effort intensive. In severe infections, such as those caused by KPC-Kp, it is advisable to follow automatic tests with confirmatory tests of antibiotic susceptibility in order to avoid choosing an inappropriate antibiotic. This is particularly relevant in cases of colistin resistance, which is a proven independent risk factor for mortality in KPC-Kp infection (7,13).

The protocols adopted by our department recommend performing microbiological culture evaluation at admission and twice weekly for early identification of the pathogen responsible for infection. As reported in several studies, this strategy allows clinicians to identify, with high probability, the causative agent of VAP and initiate reasonable empiric antibiotic therapy to improve the outcome (14).

To date, the treatment of KPC-Kp infections has not been univocal, but a combination of antibiotic therapies seems to have a more favorable outcome than monotherapy.On this matter, the inclusion of carbapenems in therapy remains unresolved, especially because the MIC of meropenem is low, although is not in the non-susceptiblerange (o16 mg/L) (5). In the present case, a carbapenem-sparing combination therapy comprising tigecycline, fosfomycin, and colistin at high doses was administered to over come their pharmacokinetic limitations as single agents (3,15). Carbapenem-sparing antibiotic therapy has been proven effective in treating infections inpolytrauma ICU patients without comorbidities (2), though has failed in patients with comorbidities (16). Furthermore, carbapenem-sparing therapy is useful in decreasing selective pressure on the gut microflora, which is the natural reservoir of KPC-Kp.

The duration of antibiotic therapy can be adjusted according to the clinical and biohumoral response. Multiple studies and a recent Cochrane review (17) have shown that antibiotic therapy guided by procalcitonin values, compared without comes in standard therapy, are not burdened with a higher mortality rate or treatment failure and allow significant reductions in consumption, toxicity, and selective pressure related to antibiotic therapy. In our experience, this strategy has been used to treat complex infections (18), includingVAP, caused by KPC-Kp (19).

To date,there are no studies evaluating cases of nosocomial pneumonia caused by KPC-Kp, but data are available investigating KPC-Kp bacteremia (1,3,5,6), epidemiology (20–22), and case series (23). Despite this limitation,the available data can be subjected to analysis. Qureschietal. (3) reported that KPC-Kp pneumonia was associated with significant mortality in 10 of 41 reported cases. Caponeetal. (7) reported a 42.9% mortality rate inpatients with VAP caused by KPC-Kp, confirming that colistin resistant KPC-Kp is an independent risk factor formortality. These studies were not conducted only in ICUs as in other caseseries (2), which reported VAP in 62% (n¼16) of infected patients and observed a good prognosis due to the absence of comorbidities and treatment with combination antibiotic therapy.

Tumbarello etal. (5) reported 28 cases of pneumoniain a series of KPC-Kp bacteremia cases, butthey did not specify the characteristics (VAPvs. hospital-acquired pneumoniae) and outcomes in the patients. Lee et al. (4), in a review of published case series and case reports, found higher mortality in cases of nosocomial pneumonia associated with bacteremia and other infections, and recommended combination therapy for respiratory infections because monotherapy exhibited a higher rate of treatment failure. This suggestion is also supported by Petrosillo et al. (15), who are careful to recommend drugs with pharmacodynamic and pharmacokinetic characteristics according to the targeted infection.

Considering that the drugs used to treat colistin-resistant KPC-Kp do not have a favorable pharmacokinetic profile for the lung, we believe that information on the management and treatment of these infections is necessary for physician scaring for patients in the ICU, especially those with pneumonia. In the present report, starting with a presentation of a case of VAP caused by KPC-Kp, we discuss a potential management strategy of this infection using surveillance cultures, confirmatory microbiological testing, carbapenem-sparing multi-antibiotictherapy,and the use of new biomarkers, such as procalcitonin, to limit the duration of antibiotic therapy.

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