Bloodstream Infections Caused by *Klebsiella pneumoniae* Carbapenemase 2-producing *K. pneumoniae* at a Hematology Department in Wenzhou, China

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**Abstract**

The increasing prevalence of *Klebsiella pneumoniae* carbapenemase 2-producing *K. pneumoniae* (KPC-2-KP) infections can become a new life-threatening complication for hematological patients. Five cases of KPC-2-KP bloodstream infections have been identified in our hematology department over the past 10 years. The current treatment options do not show satisfactory efficacy, especially for bloodstream infections. The treatment of these five cases was unsuccessful, mainly due to the high minimum inhibitory concentrations of carbapenem, fosfomycin resistance, or the inaccessibility of polymyxin. Further investigations into the optimal treatment modalities are therefore imperative. The present study provides insights into the epidemiology and clinical challenges of treating KPC-2-KP bloodstream infections.

**Key words:** Bloodstream infections, carbapenemases, *Klebsiella pneumoniae*, antibiotic resistance


**Introduction**

*Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-KP) is a multidrug-resistant, pathogenic Enterobacteriaceae that can result in considerable morbidity and mortality. The emergence of *K. pneumoniae* strains with carbapenem resistance is a matter of clinical significance in hematology departments. As a new multidrug-resistant nosocomial pathogen, extensive research on KPC has been conducted around the world (1-4). In China, KPC-KP was first reported in 2007 (5, 6). Most studies involving KPC-KP have focused on the molecular epidemiological aspects or its in vitro antimicrobial susceptibility. However, the epidemiological link between the patient from whom the carbapenem-resistant *K. pneumoniae* was isolated and the clinical settings remains unclear. In addition, very few studies show the clinical outcomes of patients treated for KPC bloodstream infections. In our tertiary care hospital, the first Affiliated Hospital of Wenzhou Medical University, Zhejiang, China, no cases of KPC-KP bloodstream infection were identified in our hematology department until April 2014, when an isolate was confirmed to harbor the KPC-2 gene. Our cases of KPC-2-KP bloodstream infection demonstrated high treatment failure and mortality rates. The optimal treatment for KPC-KP bloodstream infection remains to be established in future prospective clinical studies. These data also extend the geographical area where KPC-2-KP strains are known to exist.

**Case Reports**

**Case 1**

A 40-year-old man with a parotid gland mass of 6 months in duration was diagnosed with T/natural killer (NK) lymphoma two months prior to consulting our department. Five days after the initiation of CHOP chemotherapy (cyclophosphamide, epirubicin, vincristine and prednisone) he was hospitalized with a recurrent high fever of more than 39°C and...
a cough with yellow-green sputum. A physical examination showed a right parotid mass of 2×3 cm in size and a 4×5 cm mass located anteriorly to the sternum. Chest CT showed multiple cotton regiment-like nodular lesions. He was treated with imipenem/cilastatin plus vancomycin and voriconazole and immunoglobulin. Three days later, after his fever failed to subside, a chemotherapy regimen which consisted of mitoxantrone plus gemox (gemcitabine and oxaliplatin) and dexamethasone was administered. During chemotherapy, his fever subsided; however, it returned after the discontinuation of dexamethasone. At that time, both the right parotid mass and the mass anterior to the sternum showed significant reductions in size. Chest CT showed the significant improvement of the nodular lesions on both sides of the lung. The improvement of the patient’s clinical symptoms only lasted for approximately 10 days, after which he developed dyspnea and a fever of 41°C. Chest CT showed diffuse nodular lesions, right cervical lymph node enlargement, and the enlargement of multiple lymph nodes at the mediastinum. These findings indicated that his lymphoma had progressed with infection. Moxifloxacin, sulbactam/cefoperazone, vancomycin, and voriconazole were intravenously administered. Meanwhile, he underwent chemotherapy with the SMILE (methotrexate, ifosfamide, etoposide, dexamethasone, and pegaspargase) regimen. After the discontinuation of chemotherapy, the patient again developed a high fever. The re-examination of the patient’s chest CT scan showed a marked improvement of the diffuse nodular lesions. A blood culture showed KPC-KP (Table). A blood analysis revealed a neutrophil count of 1,845/µL, a C-reactive protein (CRP) level of 59.4 mg/L (normal range: 0-8.0 mg/L), and a procalcitonin (PCT) level of 4.19 ng/mL (normal range: 0-0.5 ng/mL). He was treated with the intravenous administration of tigecycline (200 mg for the first dose, then 100 mg every 12 hours) plus fosfomycin and imipenem/cilastatin for 7 days. However, his fever did not subside. His family then decided to decline further treatment. The patient died two days after being discharged from hospital.

Case 2

A 54-year-old man was admitted for headache with faint double lower limbs. At the time of consultation, his symptoms had persisted for 40 days. Head CT revealed an occupying lesion and edema with central shift. After decompressive craniectomy, the occupying lesion tissue was biopsied. A pathological examination revealed diffuse large B cell lymphoma (non-germinal center B cell-like). The patient was diagnosed with central nervous system lymphoma and received chemotherapy, which included high-dose methotrexate plus dexamethasone. Five days after the initiation of chemotherapy, the patient developed a high fever of 39.7°C with chills. The patient’s neutrophil count was 6,450/µL, his CRP level was 67.5 mg/L, and his PCT was 1.41 ng/mL. He was treated with the intravenous administration of meropenem (1.0 g every 8 hours). Four days later, blood cultures collected at two different time points showed KPC-KP (Table). Based on this finding, meropenem was switched to tigecycline (50 mg every 12 hours) for 10 days. His fever then gradually subsided. At a follow-up examination five months later, the patient received another four cycles of chemotherapy without any recurrence of infection.

Case 3

A 59-year-old man was hospitalized with a recurrent high fever of one week in duration. Two years prior to consultation, the patient had been diagnosed with acute lymphoblastic leukemia. He was diagnosed with diabetes mellitus one year prior to consultation. During those two years, the patient had received several cycles of chemotherapy, including VDCLP (vincristine, idarubicin, cyclophosphamide, L-asparaginase, and prednisone), hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone), and three cycles of high-dose methotrexate plus cytarabine. The patient was also taking methotrexate orally as a maintenance therapy. Methotrexate was discontinued due to thrombocy-
topenia. Three months prior to consultation, the patient re-
lapsed and VDCLP chemotherapy was administered. After 
chemotherapy, the patient developed a lung infection, and a 
sputum culture showed *K. pneumoniae*. His lung infection 
was treated with tigecycline plus cefoperazone/sulbactam. 
One week prior to the confirmation of the infection, the pa-
tient developed chills and a high fever while he was receiv-
ing a platelet transfusion at a local hospital. The patient sub-
sequently experienced a recurrent high fever of 40°C (with-
out cough) and abdominal pain. Two days prior to admi-
sion, the patient developed painful, reddened, and swollen 
lower extremities. Upon admission, his leukocyte count was 
270/μL, his CRP level was 199 mg/L, and his PCT level 
was 30.62 ng/mL. Blood cultures that were independently 
conducted by a local hospital and our hospital both showed 
KPC-KP (Table). Based on this finding, the patient was 
treated with tigecycline plus cefoperazone/sulbactam. 
However, his fever did not sub-
side. After six days of tigecycline plus cefoperazone/sulbac-
tam treatment, the patient lapsed into a coma. His family de-
cided to decline further therapy and re-
quested his discharge from hospital. The patient expired 
at home on the day of discharge.

**Case 4**

A 58-year-old man was admitted for fatigue which had 
developed 2 months prior to consultation, as well as chest 
distress and shortness of breath which had arisen 20 days 
before consultation. He was diagnosed with acute granulo-
cytic monocytic leukemia. The patient received a che-
motherapeutic regimen of idarubicin and cytarabine. After 
the initiation of chemotherapy, the patient developed agranu-
locytosis and a high fever of more than 39°C. The patient’s 
infection was treated with meropenem and telcoplanin. 
When his fever did not subside, voriconazole was adminis-
tered as an injectable. One week after the initiation of vori-
conazole treatment, his fever had still not subsided. A blood 
culture showed KPC-KP (Table). The leukocyte count of the 
patient was 290/μL, his CRP level was 261 mg/L, and his 
PCT level was 1.2 ng/mL. For economic reasons, he was 
treated with the intravenous administration of moxifloxacin 
(0.4 g per day) plus amikacin (0.4 g per day) for 5 days. 
The patient then developed a reddened, swollen left leg and 
shock. His family decided to decline treatment and re-
quested his discharge from hospital. The patient expired at 
home on the day of discharge.

**Case 5**

A 44-year-old woman was diagnosed with aplastic anemia 
two months prior to consultation and was treated with cy-
closporine and testosterone. One month prior to consulta-
tion, the patient developed left facial tissue swelling and a 
high fever of 40°C. Her fever subsided after treatment with 
imipenem/cilastatin and vancomycin. Five days prior to con-
sultation, the patient again developed a high fever of more 
than 40°C with abdominal pain, diarrhea, and fatigue, but no 
chills. The patient’s leukocyte count was 260/μL, her CRP 
level was 106 mg/L, and her PCT level was 0.205 ng/mL. A 
blood culture showed KPC-KP (Table). Based on these find-
ings, the patient was treated with the intravenous administra-
tion of tigecycline (50 mg every 12 hours) plus amikacin 
(0.4 g per day) and fosfomycin (8 g every 12 hours) for 10 
days. The patient’s fever showed slight improvement; it de-
creased to less than 39°C. However, the patient developed 
heavy hemoptysis with right chest pain and slipped into a 
coma. Her family decided to decline further therapy and re-
quested her discharge from hospital. The patient expired 
upon returning home.

**Discussion**

KPC-KP bloodstream infections are rare at our hematol-
gy department, with only five cases being reported in the 
past 10 years. The KPC isolates were confirmed to harbor 
the KPC-2 gene by a PCR using specific primers (F: 5’-GC 
TACACCTAGCTCCACCTTC-3’; and R: 5’-TCAGTGCTCT 
ACAGAAAACC-3’) (7). The sequences of the PCR prod-
ucts were compared to those in GenBank (http://blast.ncbi.nlm.nih.gov/Blast.cgi) which showed the highest homology (>98%) with the KPC-2 sequence. Furthermore, a modified 
Hodge test was clearly positive and demonstrated the pres-
ence of KPC activity (8).

The sporadic emergence of KPC-2-KP bloodstream infec-
tions at our hematology department may be due to the wide-
spread use of carbapenem antibiotics, which has resulted 
from a remarkable increase in extended-spectrum β-
lactamase (ESBL)-producing enterobacteria. The source of 
KPC-KP bloodstream infections could not be identified in 
the four patients, thus suggesting that these could have been 
primary bacteremia. In Case 3, the infection could have 
been secondary KPC-2-KP, due to the detection of *K. pneu-
moniae* in the patient’s sputum and the cellulitis of the pa-

tient’s lower extremities. No catheter-related KPC-2-KP in-
fec tions were reported in this study. Four cases occurred in 
patients with malignant hematological diseases, one of 
which was aplastic anemia. The patients were in an im-
munocompromised state and had received intensive im-
munosuppressive treatment 30 days prior to the infection; 
three of the patients had agranulocytosis. Cases 1 and 3 
were diagnosed several years prior to consultation and had 
received multiple chemotherapies, while Cases 2, 4, and 5 
were diagnosed less than two months prior to consultation. 
It is therefore critical to prevent the further spread of 
multidrug-resistant organisms from heavily treated patients. 
Patients with KPC-KP may have received carbapenem ther-

yapy prior to infection as carbapenem therapy was adminis-
tered prior to KPC infection in the five cases of the present 
study.

Most of the isolates collected from our patients were sus-
ceptible to tigecycline, and partially susceptible to amikacin. 
Polymyxin was not available at our hospital, thus the MIC 
value of polymyxin was not tested. The MIC values of er-
tapenem and imipenem were ≥4 μg/mL in most cases (In Case 3, the imipenem MIC was 2 μg/mL). Although carbapenems can be hydrolyzed by KPCs, recent clinical studies on KPC-blood stream infections have revealed that colistin-based combination therapy with meropenem and tigecycline was associated with significantly decreased mortality rates in comparison to monotherapy (9, 10). Daikos et al. reported that when the carbapenem MIC value was ≤4 μg/mL, carbapenem combined with one other active drug (an amino-glycoside, colistin, or tigecycline) was associated with significantly lower mortality than in combination regimens that included a noncarbapenem drug (11). Therefore, based on the high MIC values that were observed for carbapenem in these five cases, carbapenem was determined to be inappropriate for treatment. Although there were more data on tigecycline-based combinations than tigecycline monotherapy, no significant differences have been found between the two types of therapy (12, 13). Case 2 was successfully treated with tigecycline monotherapy. Tigecycline therapy achieved a more extensive tissue distribution, thus resulting in a larger volume of distribution in the steady state and, subsequently, lower AUCs in plasma/serum (14). For this reason, Case 1 was given off-label high-dose tigecycline. Fosfomycin has been recommended as an adjunct to other active agents for treatment of KPC-KP infections (15). Cases 1 and 5 had received fosfomycin in combination with tigecycline. Unfortunately, these treatments failed, which is in agreement with a recent report which describes the prevalence of fosfomycin resistance and plasmid-mediated resistance among KPC-KP isolates from clinical samples in China (16). The high mortality rate that was observed in our KPC-2-KP cases was consistent with the rates of previous reports (17-19). As seen in the Table, Case 3 was the only case that did not display total resistance to sulbactam/cefoperazone. In addition, Case 3 had a history of lung infection with K. pneumoniae which was successfully treated by tigecycline plus cefoperazone/sulbactam. As a result, tigecycline plus cefoperazone/sulbactam were administered to Case 3. In Case 4, moxifloxacin plus amikacin were given according to drug sensitivity test results because the patient’s family could not afford the cost of tigecycline (Table).

In conclusion, the recent emergence of KPC-2-KP means that the patients with hematological diseases in our area are at risk of additional life-threatening complications. That polymyxin, a carbapenem with a high MIC value is not available, and fosfomycin resistance may be the main causes of treatment failure. Furthermore, the efficacy of current treatment options, which include tigecycline, aminoglycosides, and polymyxin, has been unsatisfactory, especially for the treatment of bloodstream infections. Further investigations into optimal treatment modalities are imperative. Our observations provide insights into the epidemiology and clinical significance of a KPC-2-KP, an emerging multidrug-resistant nosocomial pathogen.

The authors state that they have no Conflict of Interest (COI).

References
