

# Intra-Abdominal Hypertension Contributes to the Development of Ventilator-Associated Pneumonia from Intestinal Bacteria

Rui Zheng<sup>1,\*</sup>, Yaxian Jiang<sup>1,\*</sup>, Cheng Yan<sup>2,\*</sup>, Yikun Li<sup>1</sup>, Xiaozhou Song<sup>3</sup>, Pengcheng Zheng<sup>4</sup>

<sup>1</sup>Department of Clinical Laboratory, The First People's Hospital of Yunnan Province, The Affiliated Hospital of Kunming University of Science and Technology, Kunming, Yunnan, People's Republic of China; <sup>2</sup>Medical School, Kunming University of Science and Technology, The First People's Hospital of Yunnan, Kunming, People's Republic of China; <sup>3</sup>Department of Infection Control, The First People's Hospital of Yunnan Province, The Affiliated Hospital of Kunming University of Science and Technology, Kunming, Yunnan, People's Republic of China; <sup>4</sup>Department of Pharmacy, The First People's Hospital of Yunnan Province, The Affiliated Hospital of Kunming University of Science and Technology, Kunming, Yunnan, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Pengcheng Zheng, Department of Pharmacy, The First People's Hospital of Yunnan Province, No. 157 of Jingbi Road, Kunming, People's Republic of China, Tel +86 013888116045, Email [zpc1997@163.com](mailto:zpc1997@163.com); Xiaozhou Song, Department of Infection Control, The First People's Hospital of Yunnan Province, No. 157 of Jingbi Road, Kunming, People's Republic of China, Tel +86 013888144965, Email [13888144965@163.com](mailto:13888144965@163.com)

**Introduction:** Ventilator-associated pneumonia (VAP) is an ICU (intensive care unit)-acquired pulmonary parenchymal infection that is complicated by mechanical ventilation and is associated with high morbidity and mortality. *Klebsiella pneumoniae* (KPN) is known to asymptotically colonize the gastrointestinal tract and may increase the incidence of corresponding VAP. Our study aims were to investigate the exact origin of the carbapenem-resistant *Klebsiella pneumoniae* (CRKP) causing VAP in our patient.

**Methods:** Various environmental samples, including the patient's anal swab, were collected in order to find the source of the bacteria. Minimum inhibitory concentrations (MICs) for antimicrobial agents were determined according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI); resistant genes were detected by using PCR and sequencing; clone relationships were analyzed by using multilocus-sequence typing (MLST) and pulsed field gel electrophoresis (PFGE). The IAP values were obtained via urinary catheter.

**Results:** One CRKP strain was detected in the patient's anal swab; this strain was confirmed with the same gene type as the strain isolated from the sputum. We found that the patient's intra-abdominal pressure (IAP) was 29.41, 27.06, 24.12, and 22.66 mmHg; the IAP was either equal to or above 12 mmHg, on the operation day and the following three days. Intra-abdominal hypertension (IAH) occurred during the patient's hospitalization and was considered to be caused by the surgical procedure. Meanwhile, we found that there was a correlation between IAH and the detection of CRKP in the sputum. The findings suggested that his VAP was caused by intestinal colonial KPN, and not from the environment.

**Discussion:** Our research illustrated that the ST11 KPC-2-producing strain colonized the intestinal tract and caused the development of VAP when the IAP was elevated. Routine screening for the intestinal carriage of CRKP, among patients in ICUs, can limit and prevent current and future outbreaks.

**Keywords:** ventilator-associated pneumonia, intra-abdominal pressure, intra-abdominal hypertension, *Klebsiella pneumoniae*, healthcare-associated infection

## Introduction

Mechanical ventilation has been widely applied for critically ill patients and can lead to nosocomial infections, especially in intensive care units (ICUs). Ventilator-associated pneumonia (VAP) is an ICU-acquired pulmonary parenchymal infection that is complicated by mechanical ventilation lasting over two days and which is associated with high morbidity and mortality.<sup>1</sup> Previous studies suggest that IAH is an independent risk factor for increased VAP incidence in critically ill patients.<sup>2-4</sup> Human and animal experiments physiological studies suggest that IAH can impair respiratory function.<sup>2,4</sup>

Increasing attention to intra-abdominal pressure (IAP) and changes in the clinical management of patients who are critically ill or injured have led to an increase in research relating to IAH.<sup>5</sup> IAH may induce physiological changes that could increase VAP frequency in ICU patients, but clinical data are very limited.<sup>4</sup>

Enterobacteriaceae are the most common pathogenic bacteria causing VAP.<sup>6</sup> *Klebsiella pneumoniae* (KPN), an Enterobacteriaceae species, is known to asymptomatically colonize the skin, mouth, and respiratory and gastrointestinal tracts. About 50% of KPN infections arise from patients' own microbiota.<sup>7</sup> KPN colonization may increase the incidence of corresponding infections in critically ill patients. Carbapenems are antibiotics that are frequently used to treat KPN infections. The emergence of carbapenem-resistant KPN (CRKP) poses a challenge for the treatment of KPN infections, especially among ICU patients. Antimicrobial resistance in these pathogens may impact the outcome of patients with VAP, as it limits antibiotic treatment to harsher drugs, such as ceftazidime-avibactam (CAZ/AVI).

The risk factors associated with ICU-acquired CRKP among patients who were negative for CRKP colonization at the time of admission included previous exposure to carbapenems,  $\beta$ -lactam/ $\beta$ -lactamases inhibitor, and invasive processes or surgical operations.<sup>8</sup>

Here, we show that IAH is a risk factor for VAP that is caused by the intestinal colonial microbiota ST11 KPC-2-producing KPN. We analyzed the gut microbiota of a patient with a pulmonary KPN infection to uncover the relationship between IAH and KPC-2-producing, KPN-induced VAP. Our findings can be used to help prevent or reduce the risk of CRKP infection in critical patients by allowing clinicians to design more effective therapeutic approaches.

## Materials and Methods

### Bacterial Isolates

To identify the source of KPC-2-producing KPN, we screened the environmental swabs of the ward in which patient G was hospitalized on the day the first sputum sample that contained CRKP was collected, including swabs of the bed linens, the door knob of the isolation ward, the surface of the call button, the ward's automatic faucet, the ward's mop pool the surface of ventilator, the surface of microinjection pump, the inspiratory and expiratory ports of the ventilator, the moisture trap of ventilator, the surface of the gas valve, the pump of bottles with hand-washing-free disinfectant inside and outside the isolation ward, all doctors' white coats, all nurses' white coats, the hand swab of patient's son, the care workers' nasal swabs, the care workers' throat swabs, and the care workers' anal swabs. Two ST641 CSKP isolates were obtained from care worker Z's throat swab and mop pool, with both a genotype and a phenotype completely different from those of previously isolated strains G1-G6.

### Ward Investigation

The ICU in the General Surgery Department of the First People's Hospital of Yunnan Province consists of one ward with nine beds and an isolation ward with one bed.

### VAP Diagnosis

Clinical criteria for the suspicion of VAP include a new and persistent (48h) or progressive radiographic infiltrate plus two of the following: temperature of 38°C or 36°C, blood leukocyte count of 10,000 cells/mL or 5000 cells/mL, purulent tracheal secretions, and gas exchange degradation.<sup>9</sup>

### Antimicrobial Susceptibility Testing

Antimicrobial susceptibility was determined using the disk diffusion method and the automated VITEK 2 Compact system with gram-negative bacteria cards (bioMérieux). The microdilution susceptibility testing method was employed to verify the minimal inhibitory concentrations (MICs) of the antibiotics, and the results were interpreted based on Clinical & Laboratory Standards Institute (CLSI) guidelines.<sup>10</sup> The antibiotics tested using microdilution included imipenem, meropenem, ceftriaxone, aztreonam, tigecycline, tetracycline, ciprofloxacin, gentamicin, and ceftazidime-avibactam. *Escherichia coli* (ATCC 25922) was used as the quality-control strain for antimicrobial susceptibility testing.

## Detection of Phenotypes

The production of carbapenemases was evaluated in all isolates using Modified Carbapenem Inactivation Methods according to CLSI-M100.<sup>10</sup> *Klebsiella pneumoniae* (ATCC BAA-1705, ATCC BAA-1706 and ATCC BAA-2146) were used as the quality-control strain.

## Detection of Drug-Resistant Genes

Bacterial chromosomal DNA was obtained with a TIANamp Bacterial DNA Kit according to the manufacturer's instructions (TIANGEN BIOTECH, Beijing, China). PCR and DNA sequence analysis were performed to confirm the presence of drug-resistant genes, including carbapenemase, extended spectrum  $\beta$ -lactamases, and plasmid-mediated AmpC genes. The primers used in this study were described previously.<sup>11–17</sup> The  $\beta$ -lactamase genes included Ambler class A (*bla*<sub>CTX-M</sub>, *bla*<sub>TEM</sub>, *bla*<sub>SHV</sub>, *bla*<sub>KPC</sub>, and *bla*<sub>GES</sub>), class B (*bla*<sub>NDM</sub> and *bla*<sub>IMP</sub>), class C (*bla*<sub>CMY</sub> and *bla*<sub>DHA</sub>), and class D (*bla*<sub>OXA-48</sub>). All amplicon sequences were compared with those in the GenBank database ([www.ncbi.nlm.nih.gov/blast/](http://www.ncbi.nlm.nih.gov/blast/)).

## Molecular Typing

All nine isolates were genotyped using multilocus sequence typing (MLST) and pulsed-field gel electrophoresis (PFGE). Seven housekeeping genes (*aroC*, *dnaN*, *hemD*, *hisD*, *purE*, *sucA*, *thrA*) were amplified according to the protocol described on the MLST website (<https://pubmlst.org>). Genotyping was carried out by referring to the PFGE molecular typing method used for *Salmonella* serotypes for the PulseNet China platform. *Salmonella* was entrapped with SeaKem Gold Agarose and digested with the restriction enzyme XbaI. The obtained DNA fragments underwent PFGE and were then classified by the CHEF Mapper XA system (Bio-Rad, Hercules, California, United States). Finally, cluster analysis was performed with BioNumerics (bioMérieux).

## Measurement of Intra-Abdominal Pressure

An IAH diagnosis is based only on the IAP value, which can be obtained via urinary catheter because urinary blood pressure is a close approximate of IAP.

## Results

### Bacterial Isolates

Nine KPN isolates were identified by simultaneously using the VITEK 2 Compact and VITEK MS systems (bioMérieux, Lyon, France). Six of nine KPN isolates were isolated from the sputum of patient G on postoperative days 5, 6, 7, 8, 9, and 10, and were numbered G1 to G6. The other three KPN isolates were isolated from an anal swab of patient G (isolate number PW3), care worker Z's throat swab (isolate number PW1), and from the mop pool (isolate number PW2).

### Antimicrobial Susceptibility Testing

The drug-resistance profiles of G1, G2, G3, G4, G5, G6, and PW3 showed high resistance to third-generation cephalosporins, carbapenems, and monobactam. The MIC values of aminoglycoside and tetracycline were also high. The other two isolates (PW1 and PW2) were susceptible to  $\beta$ -lactam drugs, including carbapenems. These results are summarized in Table 1.

### Intra-Abdominal Pressure

IAP is a steady-state pressure within the abdominal cavity, and the normal range is 0–5 mmHg. Our patient's IAP was measured on the day of operation and on postoperative days 1, 4, 6, 9, 12, and 14, yielding measurements of 29.41, 27.06, 24.12, 22.66, 12.21, 7.33, and 5.23 mmHg, respectively (Table 2). The first four testing values were beyond 12 mmHg, which is the threshold for IAH.

Table 1 Molecular Characteristics of Isolated KPN

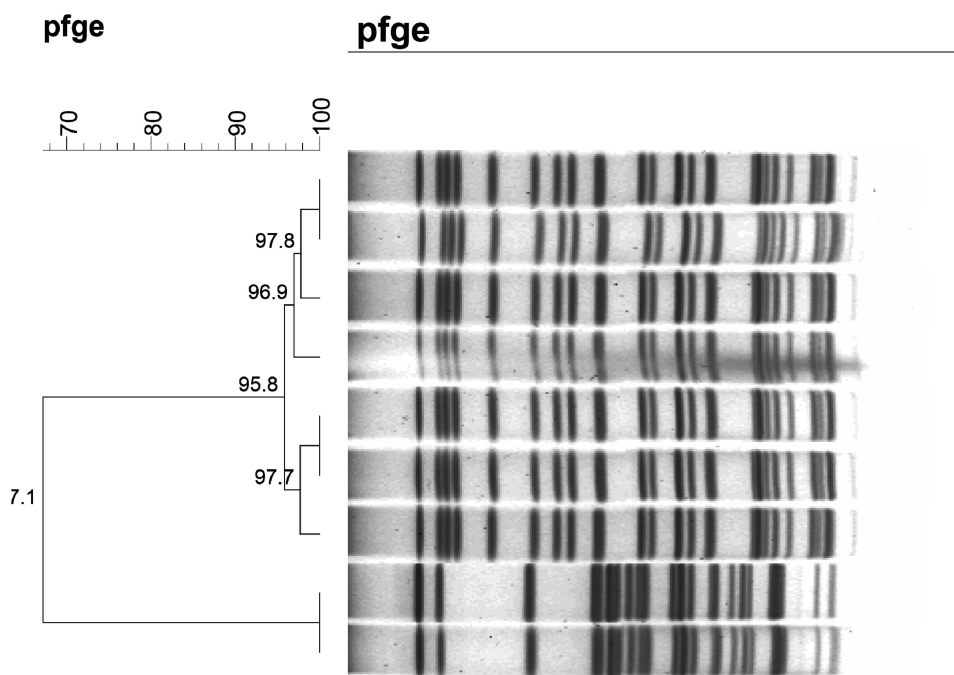
Isolate	Organism	Source	ST Type	Drug Resistant Genes											MICs, µg/mL								KB, mm	MICs, µg/mL
				bla <sub>KPC</sub>	bla <sub>IMP</sub>	bla <sub>OXA</sub>	bla <sub>NDM</sub>	Bla <sub>OXA-48</sub>	Bla <sub>GES</sub>	bla <sub>TEM</sub>	bla <sub>SHV</sub>	bla <sub>CTX</sub>	bla <sub>CMY</sub>	bla <sub>DHA</sub>	GN	TGC	ATM	CRO	CIP	MEM	IPM	TE	CZA	CZA
G1	KPN	Sputum	ST11	bla <sub>KPC-2</sub>	-	-	-	-	-	bla <sub>TEM-2</sub>	-	-	-	-	256	>256	>256	>256	>32	>32	>32	>256	22	0.5
G2	KPN	Sputum	ST11	bla <sub>KPC-2</sub>	-	-	-	-	-	bla <sub>TEM-2</sub>	-	-	-	-	1024	>256	>256	>256	>32	>32	>32	>256	23	0.5
G3	KPN	Sputum	ST11	bla <sub>KPC-2</sub>	-	-	-	-	-	bla <sub>TEM-2</sub>	-	-	-	-	1024	>256	>256	>256	>32	>32	>32	>256	22	0.5
G4	KPN	Sputum	ST11	bla <sub>KPC-2</sub>	-	-	-	-	-	bla <sub>TEM-2</sub>	-	-	-	-	1024	>256	>256	>256	>32	>32	>32	>256	24	0.5
G5	KPN	Sputum	ST11	bla <sub>KPC-2</sub>	-	-	-	-	-	bla <sub>TEM-2</sub>	-	-	-	-	>1024	>256	>256	>256	>32	>32	>32	>256	23	0.5
G6	KPN	Sputum	ST11	bla <sub>KPC-2</sub>	-	-	-	-	-	bla <sub>TEM-2</sub>	-	-	-	-	>1024	>256	>256	>256	>32	>32	>32	>256	22	0.5
PW1	KPN	A	ST641	-	-	-	-	-	-	-	-	-	-	-	8	0.5	1	1	0.032	0.25	0.25	>256	27	0.5
PW2	KPN	mop pool	ST641	-	-	-	-	-	-	-	-	-	-	-	1	0.5	1	0.5	0.032	0.125	0.25	>256	27	0.5
PW3	KPN	anal swab	ST11	bla <sub>KPC-2</sub>	-	-	-	-	-	bla <sub>TEM-2</sub>	-	-	-	-	>1024	>256	>256	>256	>32	>32	>32	>256	23	0.5

**Note:** A: care worker Z's throat swab.  
**Abbreviations:** KPN, *klebsiella pneumoniae*; GN, gentamicin; TGC, tigecycline; ATM, aztreonam; CRO, ceftriaxone; CIP, ciprofloxacin; IMP, imipenem; TE, tetracycline; CZA, ceftazidime-avibactam.

**Table 2** Clinical Treatment Course of Patient G

Time	Culture Result		Environmental Swabs	Antibiotic	IAP (mmHg)	Measures Were Taken	Creatinine Clearance Rate	WBC	N%	PCT
	Sputum	Blood								
Preoperative	/	/	/	Cefuroxime (1.5g)	/	/	40.39	14.16	79.3	0.1
Day of operation	/	/	/	Meropenem 0.5g q12	29.41	/	32.27	12.48	80.2	2.38
Postoperative day 1	/	/	/	Meropenem 0.5g q12	27.06	/	13.67	6.19	87.6	/
Postoperative day 2	/	/	/	Meropenem 0.5g q12	/	/	14.78	3.83	85.4	3.81
Postoperative day 3	Negative	/	/	Meropenem 0.5g q12	/	/	12.36	4.45	84.6	21.23
Postoperative day 4	Negative	Negative	/	Meropenem 0.5g q12	24.12	/	11.62	/	/	/
Postoperative day 5	CRKP (G1)	Negative	/	Meropenem 0.5g q12	/	1. Patient G was put in an isolation ward. 2. Environmental swabs were taken. Switch usage of antibacterial drug to CZA	14.63	3.92	76.6	5.28
Postoperative day 6	CRKP (G2)	Negative	CSKP (PW1 and PW2)	CZA 0.75/0.19g iv q12	22.66		16.71	5.08	82.2	3.26
Postoperative day 7	CRKP (G3)	Negative	/	CZA 0.75/0.19g iv q12	/	/	16.37	5.41	88.7	/
Postoperative day 8	CRKP (G4)	Negative	CRKP (PW3)	CZA 0.75/0.19g iv q12	/	/	17.11	8.74	93.1	4.37
Postoperative day 9	CRKP (G5)	Negative	/	CZA 0.75/0.19g iv q12	12.21	/	17.22	7.76	90.6	5.17
Postoperative day 10	CRKP (G6)	Negative	/	CZA 0.75/0.19g iv q12	/	/	19.74	7.24	90.7	/
Postoperative day 11	Negative	Negative	/	CZA 0.75/0.19g iv q12	/	/	18.16	5.95	92.6	/
Postoperative day 12	Negative	Negative	/	CZA 0.75/0.19g iv q12	7.33	/	20.09	5.86	89.6	4.9
Postoperative day 13	Negative	Negative	/	CZA 0.75/0.19g iv q12	/	/	14.22	5.14	88.7	2.2
Postoperative day 14	Negative	Negative	/	CZA 0.75/0.19g iv q12	5.23	/	16.56	7.6	87.6	1.78
Postoperative day 15	Negative	Negative	/	CZA 0.75/0.19g iv q12	/	/	20.09	5.56	91.3	/
Postoperative day 16	Negative	Negative	/	CZA 0.75/0.19g iv q12	/	/	24.77	5.59	79.8	/
Postoperative day 17	Negative	Negative	/	CZA 1.00/0.25g iv q8	/	/	33.02	4.6	71.3	/
Postoperative day 18	Negative	Negative	/	CZA 1.00/0.25g iv q8	/	/	46.28	4.4	86.6	1.25
Postoperative day 19	Negative	Negative	/	CZA 1.00/0.25g iv q8	/	/	65.66	3.48	80.7	/
Postoperative day 20	Negative	Negative	/	Drug withdrawal	/	Patient Discharge	68.86	4.85	79.9	0.84

**Abbreviations:** CRKP, Carbapenem-resistant *Klebsiella pneumoniae*; CSKP, Carbapenem-susceptible *Klebsiella pneumoniae* (CSKP); CZA, CAZ-AVI.



**Figure 1** Dendrogram of PFGE patterns of chromosomal DNA restriction fragments from 9 *K. pneumoniae* isolates in present study.

## Detection of Phenotypes

G1-G6 and PW3 showed positive results for mCIM test and negative results for eCIM (EDTA-modified carbapenem inactivation method) which suggested these strains produce serine carbapenemase.

## Drug-Resistant Genes

A total of 11 drug-resistant genes were amplified. The six strains isolated from sputum and one strain isolated from the anal swab produced KPC-2 carbapenemase and all had a 989-bp positive band. No carbapenemase gene was found in the two KPN isolates from the mop pool and the care worker's throat swab. Other  $\beta$ -lactamase-resistance genes *bla*<sub>TEM-1</sub> were detected. These results are summarized in Table 1.

## Gene Type

All nine isolates were subjected to PFGE and MLST typing. Two PFGE genotypes were identified. Seven KPN isolates from patient G were classified into the same PFGE cluster and sequence type 11 (ST11). Another two KPN isolated from the mop pool and the nursing worker's throat swab were in the same PFGE cluster and belonged to sequence type 641 (Figure 1).

## Discussion

VAP is one of the most frequent ICU-acquired infections associated with prolonged mechanical ventilation and ICU stays. The organisms associated with VAP vary due to factors including cumulative exposure to antimicrobials and the local ecology. Multivariable analysis showed that ICU stays longer than seven days,  $\beta$ -lactamase inhibitor antibiotics, and carbapenems are independent risk factors for VAP that is caused by carbapenem-resistant Enterobacteriaceae.<sup>1</sup> More specifically, KPC-2-producing KPN leads to prolonged hospitalization, which in turn increases the risk of developing VAP. Our patient had two of these risk factors because they were in the ICU for over seven days and they were treated with meropenem, which is carbapenem. KPN was isolated from the patient's sputum on six consecutive days. All the blood cultures sent to the laboratory were negative for KPN; we speculate that this may be due to continuous administration of antimicrobial agents. All six KPN isolates isolated from

sputum carried *bla*<sub>KPC-2</sub> and were resistant to carbapenems. Patient G's pulmonary CT scan appeared normal upon the emergency visit to the hospital, which verifies that this patient developed pneumonia during their hospitalization.

Gut colonization is a critical first step for many pathogens that cause both intestinal and extra-intestinal infection. The risk factors associated with acquiring CRKP colonization during an ICU stay among patients who are negative for CRKP colonization at admission included undergoing invasive processes or surgical operations and previous exposure to carbapenem, tigecycline, or  $\beta$ -lactam/ $\beta$ -lactamases inhibitor.<sup>8</sup> Intestinal colonization by CRKP is consistently associated with subsequent infection, and patients are predominantly infected with their colonizing strain.<sup>18–20</sup> In this study, patient G's anal swab was screened for rectal carriage of KPN after isolation of KPC-2-producing KPN. After ST11 KPC-2-producing KPN (PW3) was obtained from patient G's anal swab, PFGE was performed and confirmed that PW3 was the same strain as strains G1–G6, which were isolated from patient G's sputum. CRKP was found in patient G's anal swab, indicating that the gut is a reservoir of infectious KPN.

Animal experiments<sup>21</sup> have shown that increased IAP could cause severe intestinal ischemia, and significant decreases in mesenteric artery and portal vein blood flow, bacterial translocation, and gut-induced lung injury occurred from intestinal sites as IAP increased from 10 to 15 mmHg. IAH in humans is defined as a sustained increase in IAP equal to or above 12 mmHg. The highest incidence of IAH is observed in ICU patients who have undergone an emergency laparotomy.<sup>22,23</sup> Our patient G was diagnosed with a bilateral iliac aneurysm and a ruptured iliac aneurysm, and underwent a surgical operation that involved endovascular abdominal aortic aneurysm repair, balloon dilation of the abdominal aorta, right internal iliac artery embolization, and balloon dilation of the right iliac artery. The patient's IAP was 29.41, 27.06, 24.12 and 22.66 mmHg on the operation day and the next three days. The IAP data show that our patient presented with IAH during his stay in the ICU. Meanwhile, the same PFGE clone was isolated from both the patient's sputum and their intestinal tract, confirming that the ST11 KPC-2-producing strain colonized the intestinal tract of patient G, causing the development of VAP when IAP was elevated.

Carbapenem-resistant *Enterobacterales* (CRE)-induced HAP is associated with a significantly higher infection-related mortality rate than that observed in CRE infections at other sites (61.4% versus 34.6%). Microbiological confirmation of VAP infection is crucial, and antibiotic treatments should be based on in vitro drug sensitivity tests. Ceftazidime-avibactam (CAZ-AVI) is a promising option for the treatment of carbapenem-resistant, gram-negative bacteria, has been approved by the US Food and Drug Administration (FDA) and European Medicines Agency for the treatment of HAP/VAP owing to its attractive bactericidal broad-spectrum activity, linear pharmacokinetics with a moderate degree of lung penetration, and low risk of serious adverse events. According to CRKP detection, we use CAZ-AVI at a dosage of 1.00/0.25g IV q8hr, based on creatinine clearance rate (Table 2). In our patient, CAZ-AVI maintain a good antibacterial effect of KPC-2-producing KPN, given its low mortality and recurrence rates even following monotherapy. Patient G improved and was discharged after a 14-day course of CAZ-AVI treatment.

Because KPN colonization may serve as a reservoir for ICU-acquired infections,<sup>8</sup> routine screening for intestinal carriage of CRKP among patients in ICUs could limit and prevent current and future outbreaks. In the near future, the use of bacteriophages to control pathogens may offer a non-antibiotic-based approach to treat multidrug-resistant infections such as CRKP.<sup>24</sup>

## Conclusion

Our research illustrated that the ST11 KPC-2-producing strain colonized the intestinal tract and caused the development of VAP when the IAP was elevated. Ceftazidime-avibactam has a positive effect in the treatment of KPC-2-producing KPN-induced VAP even when used as monotherapy. Routine screening for the intestinal carriage of CRKP, among patients in ICUs, can limit and prevent current and future outbreaks.

## Ethics Statement

The clinical isolates in this study were specifically isolated for this research. Ethical approval was obtained from the Institutional Ethics Committee (The First People's Hospital of Yunnan Province, Kunming, Yunnan, China). Written



informed consent was received from patient G's son, aged 40, and care worker Z before sample collection that the study participants gave consent to publish.

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## Disclosure

The authors report no conflicts of interest in this work.

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