# Outcomes of Kidney Transplantation Using Organs From A Donor Infected with Carbapenem-Resistant *Klebsiella Pneumoniae* in A Chinese Hospital: A Molecular Epidemiological Study

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**Short report**

**Keywords:** bacteremia, infection control, carbapenem resistant klebsiella pneumoniae, kidney transplantation, donation after cardiac death, whole genome sequencing

**Posted Date:** July 9th, 2020

**DOI:** https://doi.org/10.21203/rs.3.rs-40622/v1

## Abstract

**Introduction**: Although the high mortality rates and adverse events related to the post-operative infection have been extensively reported worldwide, to date, few studies have investigated the transmission of CRKP isolates between the Kidney Transplant Donors (KTDs) and Kidney Transplant Recipients (KTRs) with the aid of genetic and molecular study in mainland China. We sought to describe the antibiotic susceptibility, microbiological and clinical characteristics of CRKPs in donors and recipients admitted to our hospital, focusing on the clonal transmission between the donor and recipient in renal transplantation.

**Method**: A retrospective analysis of clinical data of CRKP-BSIs in KTRs and the corresponding cadaveric donors admitted to a Chinese hospital in Beijing, China, between January 1, 2012 and December 31, 2017 was performed. The microbiology, clinical characteristics, antimicrobial susceptibility of both donors and recipients were analyzed. The genetic relatedness and sequencing type of the strains was determined by whole genome sequencing.

**Results**: During the study period, there are total 297 KTRs from DCD performed in our hospital. Ten incidences of CRKP-BSIs in KTRs, and one CSKP-urinary tract infection in R3, were identified, and two of them (R1, R4) from the same foreign hospital. The incidence of CRKP-BSIs in the early stage (within 3 months) following kidney transplantation (KTx) from DCD was about 2.7% (8/297). Seven KTRs (R1-2, R4, R6-8, R10) associated with rupture of renal artery, occurring on the median 19th (16th-74th) day after KTx respectively, with the rate of rupture of renal artery of 63.6% (7/11), and in R4-5, the thrombus of renal transplant artery was presented on the 43th and 13th day after KTx respectively. Besides, Seven KTRs (R1-2, R4-5, R7-8, R10) underwent excision of transplanted graft on the median 19th(14th-43th) day after the KTx respectively in order to prevention of the further spread of CRKP to the remaining vital organs. Genomic analysis showed there existed two sequence types, ST290 strains and ST11, which fell into two separate clusters, with resistant genes including NDM, KPC and other carbapenemases genes identified. The $bla_{NDM-1}$ gene was only detected in the ST290 isolates, while the $bla_{KPC-1}$ gene detected in most isolates. Few SNPs were identified in isolates from donors and recipients.

**Conclusions**: The CRKP positive result of various cultures from DCD donors can contribute to the transmission of infection to the recipients. It is mandatory to perform pre-donation screening for CRKP colonization whether or not the result of culture, not excluding the possibility of false negativity, and, if positive, donation should be contraindicated. The effective infection control strategy was the application of combinational antibiotic scheme including ceftazidime-avibactam plus carbapenem, in conjunction with source control techniques such as allograft nephrectomy and/or thorough debridement.


## Introduction

Nowadays, the emergence and global spread of infections caused by carbapenem-resistant klebsiella pneumoniae (CRKP) is still of great concern worldwide associated with high mortality rates, even though the advent of innovative drugs and therapies (1,2). Due to the presence of mobile carbapenemase that confers resistance to carbapenem and multiple other antibiotic classes, the CRKP greatly challenges current antibiotic treatment, representing an enormous global public health threat (3).

Represented as one of the most cunning and heavily-armed super-bacteria, *K. pneumoniae* is notorious for resistance to most classes of antibiotics, even the newly approved non-lactam compound, for instance Avibactam. Through various mechanisms, such as production of carbapenem-hydrolyzing enzymes (carbapenemases) or changes in membrane permeability, accompanied by over-expression of the ampicillin-resistant gene or of the extended-spectrum beta-lactamase genes and widely transmission of the plasmids that carried various classes of drug resistance genes, carbapenem resistance can occur (4).

Klebsiella pneumoniae carbapenemases (KPCs), categorized as Ambler class A, are the most common carbapenemases found in Enterobacteriaceae, including Klebsiella pneumoniae. The zinc-dependent class B metallo-ß-lactamases (MßLs), represented mainly by the VIM, IMP, and NDM types, are the clinically important carbapenemase as well. The plasmid-expressed class D carbapenemases of the OXA-48 type complete the picture (5,6,7).

As the implementation of renal transplantation worldwide, many hard-to-treated issues and complications come with the surgical technique, ranging from the delay of function of grafts, the post-surgical infection to the rupture of the renal artery etc., becoming the obstacles to the development of transplantation. The kidney transplant recipients are vulnerable to the infection of KPC-producing *K. pneumoniae* (KPC-Kp-HAIs), owing to the cumulative effects of the risk factors, including solid organ transplantation (SOT), immunosuppressant therapy, mechanical ventilation, prolonged use of invasive devices, use of antimicrobial agents, and a high Acute Physiology and Chronic Health Evaluation score (8,9,10,11,12).

The renal transplantation in China began in 1960s and the number of transplantations has increased until 2004, with the increasing demanding for kidney sources from donors, both decreased and living (13). In 2015, the organ transplantation from donation after cardiac death has been performed widely in China and the transplanted organs from prisoners have been forbidden, therefore the civilian organ donation has been the sole source for organ transplant (14).

With a limited donor pool and an expanding transplant waiting lists, the consideration of organs from infected donation after cardiac death (DCD) is an available option (15,16,17,18). However, the procedure has brought many complications contributing to the donor derived infection (DDI), combined with the constantly reported high mortality (more than 17%) and reduced survival rate of transplanted graft. Sousa SR et al. have performing the graft survival analysis in the retrospective study showed significantly decreased transplanted graft survival rates 6 and 12 months after transplantation of 94.5% and 93.2% ($p < 0.05$) respectively, and the decreased patients' survival rates of 94.3% and 92.3%, when comparing with that of the patients without infectious episodes (19).

Among SOT recipients infected with KPC-producing *Enterobacteriaceae*, mortality can be as high as 71% (20,21,23,24,25) and high rate of loss of transplanted graft is presented. In the five renal transplantation cases showed by Wang et al, four kidney transplant recipients (KTR) experienced renal artery rupture and the other one was complicated with thrombosis of graft artery, with the rate of loss of transplanted graft and mortality of 80% (26). Orlando et al reported a case of early renal graft loss and recipient death due to arterial anastomosis rupture caused by Pseudomonas aeruginosa infection (27). Cai YS et al. have reported three recipients were diagnosed with donor transmitted CRKP infection. Although antibiotic treatment was enhanced once the preservation fluid

isolate was proved to be CRKP positive, lethal graft artery rupture occurred in all 3 recipients, causing 2 kidney allografts losses and 1 complicated intra-abdominal infection, accompanied by huge economic losses (approximate 300,000 USD) (28).

In terms of the clonal group of CRKP distributed in different parts of world, the isolates of clonal group (CG) ST258 is the most common CRKP, with ST258 and ST11 being the most prevalent multilocus sequence types (MLST) (29). In China, the national surveillance demonstrated that ST11 CRKP was the dominant clone (30), and reckoned as the most transmissible clone contributing to the increasing prevalence of CRKP.

Although the high mortality rates and adverse events related to the post-operative infection have been extensively reported worldwide, to date, few studies have investigated the transmission of CRKP isolates between the Kidney Transplant Donors (KTDs) and Kidney Transplant Recipients (KTRs) with the aid of genetic and molecular study in mainland China. The aim of the study was to describe the antibiotic susceptibility, microbiological and clinical characteristics of CRKPs in both KTDs and KTRs admitted to our hospital, focusing on the clonal transmission between the donor and recipient in renal transplantation.

# Method

### Study design and population

This was a retrospective cohort study aiming at investigating the transmission of CRKP infection to KTRs from DCD in the eighth medical center of Chinese PLA General hospital from January 2012 to December 2017, accompanied by describing the antibiotic susceptibility, microbiological and clinical characteristics of both KTDs and KTRs infected or not with CRKP. The eighth medical center of Chinese PLA General Hospital is a 1430-bed tertiary care hospital with a 20-bed comprehensive Intensive-care-unit (ICU) and approximately 40,000 hospital admissions per year in Beijing, China. Clinical and microbiological characteristic was retrieved from medical records.

Case was defined as KTRs who developed CRKP-BSI in the early stage (within 3 months) after KTx, identified by cultures of the patient's blood specimens and later confirmed by whole genome sequencing (WGS) during the study period. Patients were followed from KTx to death or automatically discharge or discharge upon recovery. The KTRs that proved to be colonized with *klebsiella pneumoniae* after KTx, even within 3 months, was excluded from the study, except that the KTRs donated from the same donor as the Case. All the recipients' donors, except the 2 unknown donors, were included in the study.

The study population consists of 9 kidney recipients of grafts from 5 DCD donors, combined with 2 kidney recipients (No.4 Recipient and No.1 Recipient) with unknown donors and transferred from foreign hospital, who were admitted into intensive care unit (ICU) of the Department of Transplant Surgery, the eighth medical center of Chinese PLA general hospital, China.

Clinical data collections of donors included donor age, gender, the main and other diagnosis, length of ICU stay and prognosis. In the analysis of the KTRs' profile of utilization of immunosuppression drugs following renal transplantation, we evaluated age; gender; cold ischemia time (CIT); immunosuppression drugs (calcineurin inhibitor, adjuvant drug and monoclonal and polyclonal antibodies) and etiology of chronic renal failure (CRF), including systemic arterial hypertension (SAH), diabetes, glomerulonephritis (GMN), IgA nephropathy and Charlson Comorbidity Index (CCI) score.

In the analysis of clinical characteristics, underlying diseases, results of cultures and outcomes of the 11 kidney transplant recipients with/without DCD donor-derived infection, we analyzed age; gender; ureteral stent; indwelling catheters; use of continuous renal replacement therapy (CRRT); dialysis; blood transfusion; intervention for focus control (< 48 h); polymicrobial infection; acute rejection; cytomegalovirus disease; carbapenem resistant klebsiella pneumonia Bloodstream infection (CRKP-BSI); complication of infection; infectious pathogens; time (days) from kidney transplantation to the excision of the transplanted kidney; time (days) from kidney transplantation to ICU department; time (days) from kidney transplant to rupture/thrombus of the artery of the transplant kidney; time (days) from kidney transplant to the first bloodstream infection (BSI); time (days) from kidney transplantation to death/automatically discharge/discharge upon recovery; Length of stay (LOS, days) after first BSI onset; ICU-LOS (days); Total LOS (days); Pitt bacteria score (PBS) on the onset of first BSI; Acute Physiology and Chronic Health Evaluation II (APACHE II) score on the onset of first BSI; Sequential Organ Failure Assessment (SOFA) score on the onset of first BSI; serum creatinine (μmol/L) before/after renal transplant;; serum creatinine (μmol/L) at first BSI; serum creatinine (μmol/L) at the 7th and 14th day after first BSI; combinational antibiotic therapy; the total medical costs (¥) and prognosis.

The research project has been approved by the Ethics Committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

### Definition

The clinical and microbiological outcomes were analyzed. Transmission of the organisms was confirmed (proven/probable) when bacterial or fungal isolates from donor and at least one of the kidney recipients or two recipients from the same donor showed a similar clonal type or similar antimicrobial resistance profile and when the absence of pre-transplant infectious disease in the recipients was documented [31]. BSI was defined according to the Centers for Disease Control and Prevention guidelines (available at: http://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf). BSI onset was defined as the collection date of isolate. The probable infectious source was determined on the basis of the microbiological results and the analysis by at least 2 physicians. Crude mortality was defined as death occurring after the collection of the first blood culture positive for K. pneumoniae. Mortality attributable to BSI was defined by clinical evidence of active infection and positive cultures, or when death occurred as the result of organ failure that developed or deteriorated during the onset of infection [32]. Appropriate treatment was defined as ≥48 h of treatment with at least one antimicrobial agent that has been proven in vitro activity against CR-KP strains [33]. Sepsis was defined as life-threatening organ dysfunction resulting from dysregulated host responses to infection [34].

### MIC determination

With an automated susceptibility testing system (VITEK; bioMérieux, Marcy l'Étoile, France), carbapenem resistant strains of *K. pneumoniae* were identified. In total, 8 antimicrobial agents were used to test the susceptibility of CRKP. Among them, 7 were tested by micro-broth dilution method, including but not limited Imipenem, Meropenem, Gentamicin, Amikacin, Ciprofloxacin, Levofloxacin and Tobramycin. The susceptibilities toward Tigecycline and Minocycline were determined by Kirby-Bauer method. Minimum inhibitory concentration (MICs) were interpreted according to the Clinical and Laboratory Standards Institute breakpoints [34]. Minocycline/Tigecycline susceptibility was interpreted according to breakpoints approved by the US Food and Drug Administration [36].

### Whole Genome sequencing and analysis

All of the 24 isolates were submitted to whole genome sequencing. Genomic DNA was extracted from cultures using the High Pure PCR Template Preparation Kit (Roche Diagnostic, USA). Whole genome sequencing was performed on Illumina NovaSeq 6000 (Novogene Company, Beijing, China) with PE150 mode. Paired-end reads were de novo assembled using SPAdes (v3.6.2) [37]. Resistance genes were annotated by aligning assembled contigs against the Comprehensive Antibiotic Resistance Database [39] using blast (v2.10.0) [39]. Using *Klebsiella pneumonia* HS11286 (GenBank accession number: CP003200) as a reference, raw reads of 24 isolates were mapped against the reference using Bowtie2 (v2.2.9) [39] and SNPs were called using SAMTools (v1.3.1) [41]. FastTree (v2.1.11) [42] was used to construct phylogenetic tree based on the concatenated SNPs. The tree and heat map of resistance genes were visualized using ggtree (v1.8.2) [43].

## Results

The retrospective cohort study included 297 adults (older than 18 years of age) kidney transplant recipients who received kidney from donors according to Chinese type donation after cardiac death (DCD) [44] at our center during the study period. There are 11 kidney recipients of grafts from 7 DCD donors, including 2 kidney recipients with grafts obtained from 2 unknown donors and transferred from the same foreign hospital, with the incidence of CRKP-BSI of 2.7% (8/297) after the renal transplantation performed in our hospital. The pre-donation screening for CRKP colonization in donors and recipients was routinely performed.

All of the kidney transplant donors with urinary and/or bloodstream and/or sputum and/or OSSS infection developed confirmed transmission of infection, affecting eleven kidney recipients and resulting in five out of eleven (45.5%) crude mortality that all attributes to the infection-related death. Among the overall bacterial or fungal infection of KTDs, the *K. pneumoniae* infection takes up about 3 out of 5 (60%), except for the 2 unknown donors, leading to the transmission to all of the recipient, with the crude mortality of 44.4% (4/9).

### The clinical characteristics of KTD with donor-derived infection

As the clinical characteristics summarized in Table 1, the median age was 46 years, with a gender distribution of 4 males/1 females (sex ratio 4). All of the KTD had undergone the invasive procedure with indwelling catheters, having short term of treating in intensive care unit (median 5 days), with death as the outcome, proving to be decreased kidney donors. No difference was observed between the origin of death that evenly distributed in the following causes, including Central nervous system infection (CNSI), Traumatic brain injury (TBI), Intracerebral hemorrhage (ICH), Hypertension (HTN) and Benign pituitary tumor (BPT). The most common main diagnosis was ICH (40%), evenly followed by CNSI (20%), TBI (20%) and LI (20%). In contrast to main diagnosis, Lung infection (LI) and Tracheostomy status (TS) are ranked as the most common diagnosis in the other diagnosis, and Ventriculoperitoneal shunt (VPS), Cerebral hernia (CH) and Hypertension (HTN) are followed in the second rank, each occupying the same percentage of 40%. The most frequent isolates with positive results was sputum isolates (5/5), followed by blood (3/5), urine (3/5), sputum+urine (3/5) and blood+sputum (3/5) isolates, with the urine+drainage (1/5), sputum+drainage+urine (1/5), blood+drainage+urine (1/5), blood+drainage+urine+sputum (1/5) isolates ranked as the least. For the KTDs with positive urine results, 2/3 of KTDs received appropriate antimicrobial therapy, while 1/5 of KTDs with positive sputum results and none of the KTDs with positive blood results received the appropriate therapy. Notably, except that the organ procurement coordinator (OPC) gave up the decision to donate the other side of kidney of Donor 5 after be notified the CRKP infection of the kidney that had been transplanted to the KTR, all the other donors had donated both kidneys.

Results of urinary, sputum, bloodstream and OSSS cultures of the donors are shown in Table 2. As for the blood culture, the percentage of Gram-negative bacteria (50%; 2/4) was higher than Gram-positive bacteria (25%; 1/4) and Fungi (25%; 1/4), with Klebsiella pneumoniae and Acinetobacter baumannii occupying the same proportion. The majority (30.8%; 4/13) pathogens isolated from donor's sputum cultures were *Pseudomonas aeruginosa*, followed by *Candida albicans* (23.1%; 3/13), *Klebsiella pneumoniae* (15.4%; 2/13), *Serratia marcescens* (15.4%; 2/13) and *Stenotrophomonas maltophilia* (15.4%; 2/13). By contrast, *C. albicans* (40%; 2/5) was more frequently isolated from donor's urine cultures, with *K. pneumoniae* (20%; 1/5), *Escherichia coli* (20%; 1/5) and *Enterococcus faecium* (20%; 1/5) sharing the remainder equally. Last, the proportion of Gram-positive bacteria, *Enterococcus faecium* (66.7%; 2/3), weighing was heavier than Gram-negative bacteria, *E. coli* (33.3%; 1/3) for OSSS cultures.

### The Characteristics of recipients with donor-derived infection

Table 3 showed the characteristics of the donors and the corresponding kidney recipients to make a clearer relationship between donors and recipients. Five kidney recipients developed confirmed donor-derived KP infection. Based on the similarity between the antimicrobial resistance profile of KTDs (Table 6) and KTRs (Table 7), Recipients 5-9 were classified as a proven donor-derived KP infection. Except for the transmitted pathogens caused by klebsiella pneumoniae, other pathogens may contribute to the transmitted infection after KTx, for instance Candida albicans and Pseudomonas aeruginosa each in 2 cases, have been observed.

Following renal transplantation, various cultures (blood, urine, sputum, catheter, throat swab and organ-space surgical site infections) were routinely taken. When neglecting the frequency of specific cultures per KTR, the blood culture revealed advantages of the highest positive rate for *K. pneumoniae* (10/11) among these KTRs, with the shortest culture-positive time, followed by OSSS (8/11), urine (6/11), throat swab (3/11) and sputum (1/11). No KTR had a

presumed or confirmed invasive bacterial or fungal infection pre-transplantation. All *K. pneumoniae* strains isolated from KTRs, except for R3, were multidrug resistant (MDR) that confirmed by susceptibility test (Table 7).

The demographic characteristics and utilization of immunosuppression drugs of patients following renal transplantation have been demonstrated in Table 4. Underlying kidney diseases of these eleven recipients consisted of 11 systemic arterial hypertension cases, 7 chronic glomerulonephritis cases, 3 diabetic nephropathy cases, and 2 IgA nephropathy. All of these patients received similar postoperative intensive care with a routine triple immunosuppression regimen including cyclosporin (n=2) or tacrolimus (n=11), mycophenolate mofetil (n=11) and corticosteroids (n=10). Besides, anti-thymocyte globulin (n=2) or basiliximab (n=6) was applied during the induction phase of immunosuppression after kidney transplantation. Time from kidney transplant to onset of donor-derived infection (the first BSI) was a median of 19 days (2-37 days) for survivors, while the time was a median of 15 days (5-43 days) for non-survivors. Organ-space surgical site infection (9/11) and pleural effusion (9/11) was the predominate type of complication of infection, equally followed by pneumoniae (8/11) and urinary tract infection (8/11). Strikingly, there are 3 cases occurring pneumothorax close to the end of the progression of disease in the non-survivor group, in contrast to the survivor group. Furthermore, the huge economic cost in the non-survivor group was remarkably comparable to that in the survivor group. The characteristics, underlying kidney diseases, complications of infection, standardized scores for critical care on the onset of infection and various culture results concerning the eleven patients with donor-derived infection are shown in Table 5.

### Outcomes of kidney recipients with donor-derived infection

In terms of the in-hospital mortality of the 11 KTRs with donor-derived infection, there was an astonishing high crude mortality rate of 45.4% (5/11). Seven KTRs (R1-2, R4, R6-8, R10) associated with rupture of renal artery, occurring on the 40th, 16th, 43th, 74th, 18th, 18th and 19th after KTx respectively, with the rate of rupture of renal artery of 63.6% (7/11) and in R4-5, the thrombus of renal transplant artery was presented on the 43th and 13th day after KTx respectively. Besides, Seven KTRs (R1-2, R4-5, R7-8, R10) underwent excision of transplanted graft on the 39th, 14th, 43th, 17th, 19th, 19th, 19th day after the KTx respectively for the sake of prevention of the further spread of CRKP to the remaining vital organs. Among various sites of infection, the organ space surgical sites (9/11) were the most common, followed by respiratory and urinary tract (8/11) and the surgical wound (3/11). With regards to the complications of infection for these KTRs, pleural effusion (9/11) numbered the most, abdominal effusion (7/11) numbered the second and pneumothorax (3/11) numbered the least, which having the occurrence rate of about 27.3%, however associated with high mortality (3/3).

In the non-surviving group, three KTRs (3/5) died due to rupture of renal artery and one KTR (1/5) died from thrombus of the transplanted renal artery, with all the decreased KTRs dying related to septic shock. Three KTRs (R1-2, R5) underwent the excision of transplanted graft, with the rate of excision of 60%. All the recipients have confirmed donor-derived CRKP infection, except for the R3, and one case (R2) associated with the mixed infection of CRKP and aspergillus that confirmed by the pathologic report that shown in previous study [26]. The *K. pneumoniae* was the causative microorganism leading to high frequency (60%) of rupture of renal artery. The KTRs (R1, R2, R6) who suffered from CRKP infection due to rupture of renal artery also inflicted with pneumothorax close to the end of the progression of illness, presented on 45th, 51th and 32th day after KTx, consistent with the result of culture of organ-space surgical site (OSSS). None of KTRs (0/5) did not receive appropriate combinational antimicrobial therapy, basically Meropenem+Tigecycline, after infection and 1 KTR (R9) died even the newly arrival antimicrobial, Ceftazidine Avibatan, was added to the regimen, as demonstrated by Table 8. Of 5 KTRs with crude hospital mortality, 2 KTR (R1, R2) developed allograft dysfunction and the serum creatinine level was summited at the 7th day after first BSI and at the first BSI (Serum creatinine were 543.7umol/L and 487.6umol/L, respectively).

Comparing with the non-surviving group, all the KTRs received appropriate combinational antimicrobial therapy after infection in the surviving group, and 3 KTRs (R8, R10, R11) survived after the newly approved combinational antimicrobial therapy (Ceftazidine Avibatan+Meropenem). To reducing the further dissemination of pathogens to vital organs, 4 KTRs underwent excision of transplanted graft and obtained satisfactory effects, with the rate of excision of 66.7%. Besides, the APACHE II score and SOFA score on the onset of first BSI were lowered to median 14 and 6 respectively.

### Relation revealed by Whole Genome sequencing

In silico MLST analysis revealed that three isolates (R3_urine_2016/3/27, R2_blood_2016/2/20, and R2_catheter_2016/2/22) belongs to ST290, while the other isolates all belongs to ST11. Phylogenetic tree showed the ST290 and ST11 isolates formed two separate clusters, and the latter fell into five subclades. Isolates from the donor and recipient fell into the same subclades, and few SNPs were observed in these isolates.

A number of resistance genes, including NMD-1, KPC-1, SHV-1, SHV-2, CTX-M, TEM-1 and et al. (Figure 1,2), and the epidemiologically-related isolates showed similar pattern of resistance genes. The NDM-1 and SHV-1 gene only existed in the three ST290 isolates, while the KPC-1 gene were observed in most of the ST11 isolates.

Interesting, in the bifurcation led by D2 with relationship to multiform isolates collected from the corresponding recipients, named D2 Bifurcation, whole genome sequencing showed the donor (D2) lacked the catII, KPC-1 and SHV-12 genes, which were found in all the isolates from the recipients. Genomic analysis revealed that these three resistance genes located on a plasmid similar to plasmid pA1750-KPC (GenBank accession number: MT108207), which was obtained by the isolates of the recipients.

## Discussion

Since the limited donor pool, it represented as a strategy to the use of grafts from infection risk donors, even though the numerous reports of fatal donor-derived infection affecting approximate to 3% of solid organ transplantation [45]. Previous study showed that prolonged duration of dialysis is a crucial risk factor for patient mortality, thus it is beneficial to utilize the infection risk kidneys, taking advantage of shortening waiting time and improving long-term patient outcomes [46,47].

However, the patients undergoing renal transplant are at risk for infection with multidrug-resistant organisms related to the surgical procedure, necessity for invasive devices, clinical complications and immunosuppression, especially in renal transplant was identified as a risk factor for the acquisition of KPC [48,49,50], and if infected with KPC-producing Enterobacteriaceae, the mortality can be as high as 71% [20,23,25,49].

The donor-derived CRKP infection from cadaveric kidney donors are the predominate causative reason that contributes to the rupture of transplanted renal artery of recipients, with alarming high mortality. Owing to the antimicrobial resistance to common classes of antibiotics, the clinical outcome can be irreversible. Due to the anatomic location of infection, CRKP infection has different clinical manifestation, characterized by strong local invasion and low probability of distant organ proliferation.

In our study, there are 11 KTRs with CRKP donor-derived infection, with high crude mortality rate of 45.4%, in accordance with the mortality 42.9% reported by Wan et al. [51] and 50% reported by Wang et al.[52]. Notably, in the non-surviving group, 3 KTRs (R1-2, R6) developed pneumothorax close to the end of their treatment, on the contrary, there are no KTRs developed in the surviving group, indicating the urgent to the improvement of antibiotic therapy and some accessory therapies, for instance oxygen therapy, mechanical ventilation and etc., to avoid the occurrence of pneumothorax during the procedure of treatment, thereby decreasing the mortality.

Our study retrospectively analyzes the clinical characteristics of a series of eleven KTRs with the corresponding five KTDs, except for the two unknown KTDs, acknowledging that 1 donor (D2) with positive result of CRKP in urine culture, 1 donor (D3) with positive result of CRKP in sputum culture, 1 donor (D5) with positive result of CRKP in blood+tip+sputum culture and 2 cases (D1, D4) with negative result of all cultures. It is noteworthy that the 4 KTRs (R2-3, R10-11) corresponding to the 2 donors (D1, D4) with negative result of all cultures are inevitably inflicted with the CRKP infection, with the consequence of positive result of blood, urine and OSSS cultures.

Although MLST analysis shows that the isolates from R2 and R3 are belonged to ST290 that differentiate to the sequence type of isolates from R10 and R11, the various isolates from these recipients donated from the same donor belongs to the similar clonal type, in other words, the same strain of klebsiella pneumoniae, suggesting that there is high possibility that the negative result of cultures can be false negative. It's crucial to repetitively perform the various bacterial culture, for instance, blood, urine, sputum, OSSS and so on. Whatever positive result obtained from donors can indicate the donor-derived infection of CRKP for recipients. Unavoidably, even though all the culture is negative, the false negativity can not be excluded, there is still chance resulting in the donor-derived infection for KTRs. Therefore, when evaluating the solid organ transplant donors, it is necessary to repetitively perform the various bacterial culture from donors, including but not limit the blood, urine and sputum culture. Emphatically, it's valuable to diagnosis the CRKP kidney transplant donors by performing the culture of renal lavage fluid, with excellent applicative prospective.

There are 10 KTRs (10/11) showing the positive result of blood culture for KP, ranking the highest positive rate in various cultures, including blood, urine, OSSS, throat stab and sputum cultures, with the shortest first culture-positive time. It can be inferred that it is the paramount indice to make the judgment of whether there is CRKP infection of the KTD after KTx, with better time-efficacy than other cultures.

Based on the phylogenetic tree, we can observe that there are arbitrarily two clades in the strains, ST290 strain and ST11 strain, which furthermore divided into five clades, genetic different from each other, each led by the specific strain of KTDs, except for the 2 unknown donors, confirming the existence of donor-derived CRKP infection. Furthermore, there are also minor alteration of genetic expression, for example R9 lacking the AAC(3)-IId gene when compared with the genes from D5, R4 lacking the oqxA and oqxB genes when compared with genes from R1, R8 and R7 obtaining the AAC(3)-IId and mphA genes when compared with genes from D3, R5 and R6 obtaining the catII, KPC-1and SHV-12 genes, suggesting the antimicrobial gene components carried by the plasmids are horizontally transmitted at multifaceted levels, under the great antimicrobial pressure. Although there exists the loss of some gene carried by plasmids between the transmission for the sake of biological fitness, the trend of gaining more antibiotic resistance genetic component is remarkable in order to survive in various extremely dangerous environment, more exposure to multiple antimicrobials that may fostered the selection of resistant strains.

Most of the strains belong to ST11, in line with the national surveillance conducted in mainland China [30]. Interesting, there are three strains (R3_urine_2016/3/27, R2_blood_2016/2/20 and R2_catheter_2016/2/22) are proved to belong to ST290 that has been sporadically reported by Wang et al. [53] and Kong et al.[54] in the tertiary hospitals in Zhejiang province and Shanghai in recent years. Taking in account the earlier morbidity in the timeline among the KTRs and the unknown donors from foreign hospital, the ST290 isolates from R2 and R3 can be inferred to be imported to our hospital, without leading to the massive dissemination of ST290 MDR klebsiella pneumoniae nosocomial infection so far. However, the ST11 isolates from R1 and R4 are imported from the same foreign hospital, with the high possibility of causing the wide-spreading dissemination of ST 11 CRKP nosocomial infection afterwards, meanwhile evolving to adapt to the environment in the dissemination course, mainly by the transmission of antimicrobial resistance components carried by various plasmids.

Among the 11 KTRs, there are seven KTRs (R1-2, R4, R6-8, R10) associated with rupture of renal artery, with the median time 19 days (16-74 days). Notably, it happened that the KTRs (R7, R8) donated from D3 occurring the rupture of transplanted renal artery on the same day (Day 19) after KTx and received the excision of transplanted graft, indicating that there is rather stable time point, 2-3 weeks post-operation, for the happening of rupture of renal artery resulted from cadaveric donor-derived CRKP infection. In a study conducted by Wang et al. [53] indicated that within 2 to 3 weeks after transplantation, CRKP rapidly spread from kidney to the contiguous tissue by direct inoculation with mass bacterial replication. Subsequently, spontaneous arteries rupture, sudden hemorrhage, and hemorrhagic shock are presented owing to the mechanical destruction of vessel wall by infiltration of inflammatory cells and endothelial cell.

The transplanted renal artery is the main target organ for the CRKP infection, possibly associated with tissue damage around the renal artery anastomosis caused by surgery and the destruction of intact of vascular endothelium. The change of hemodynamics causes the turbulence of local blood flow, contributing to the colonization of bacterial strains. Such surgical procedures include transplanted renal artery cannulation, the fixation of renal artery of kidney donors and the tissue damage related to the suture of blood vessels during the artery anastomosis. However, it is inevitable to perform the surgical procedure targeted at

the transplanted renal artery during the renal transplantation. Therefore, it is critical to prevent or treat the CRKP infection after surgery by applying the antimicrobial susceptibility sensitive antibiotics.

Most of current antibiotics utilized in practice have no therapeutic effect on CRKP infection after renal transplantation, with the mortality can be as high as 40% to 70% [55,56], and the 30-days mortality rate was 50% to 60% [57,58]. In recent years, the resistance rate of CRKP to polymyxin and tigecycline was increasing [59,60]. As a novel non-ß-lactam compound, Avibatan has a higher therapeutic effect than three traditional non-ß-lactam compound, for instance clavulanic acid, sulbactam and tazobactam [61], with in vitro activity against CRE expressing Klebsiella pneumoniae carbapenemases (KPCs) but not Ambler class B or some class D ß-lactamases [62]. When utilized in combination with carbapenem, it can eradicate multiform of MDR bacteria including CRKP [63]. Among the 11 KTRs, 9 KTRs (R1-2, R4-6, R8-11) did not begin the carbapenem combinational therapy until the positive result of blood culture, with the mortality of 55.6% (5/9). Genomic analysis showed the all the recipients with ST11 strains expressed the $bla_{KPC-1}$ gene, indicating the appropriateness of applying of Ceftazidine Avibatan whether or not in combination with other susceptibility sensitive antibiotics. Noteworthy, of the 4 KTRs who utilized the novel combinational therapy (Ceftazidine Avibatan+Meropenem), there are 3 KTRs survived (75%) and subsequently the blood culture turned to negative, corroborating the clinical efficacy of ceftazidime-avibactam against CRKP. In conjunction with surgical source control, three survived patients in our series survived were treated with ceftazidime-avibactam indicating that ceftazidime-avibactam represented a great potential agent for the treatment of CRKP. It was worth mentioning that surviving 2 KTRs (R8, R10) received the antibiotic salvage treatment right after the rupture of renal artery, with the result of the recovery of dialysis. By contrast, 1 KTR (R9) died from sepsis, partly attributed to delay of application of Avibatan. 1 KTR (R11) received the preemptive antibiotic therapy after notified the warning of CRKP infection of the other recipient from the same donor on the 19th day post-operation, with the recovery of function of kidney. To sum up, the effective strategy to treat CRKP cadaveric donor-derived infection can be the application of combinational antibiotic therapy (Ceftazidine Avibatan+Meropenem) in conjunction with surgical source control.

### Limitation

Our study has several limitations. Firstly, based on the nature of retrospective study, clinical data were obtained retrospectively from medical records and may had introduced bias, and therefore, there may exist some differences in physician practices or accuracy of information. Additionally, the data for patients who may have had significant BSI symptoms such as septic shock and hyperpyrexia, but were not tested owing to the patient refusal or because their blood culture was negative, were not included. Finally, this was a single-center study having described small number of infections, showing all the 11 recorded CRKP-BSIs derived from 7 cadaveric donors, including 2 unknown donors, with detailed clinical analysis and whole genome sequencing and analysis. A large scale of study on the clinical characteristics of cadaveric donor derived CRKP-BSI infections after renal transplantation is underway to provide more evidence on the clinical significance of hard-handled multi-resistant superbug worldwide.

## Conclusion

To summarize, cadaveric donor-derived CRKP infection in renal transplantation recipients was essentially a necrotic hemorrhagic inflammation, characterized by recurrent hemorrhage and high mortality. The CRKP positive result of various cultures from DCD donors can contribute to the transmission of infection to the recipients. It is mandatory to perform pre-donation screening for CRKP colonization whether or not the result of culture, not excluding the possibility of false negativity, and, if positive, donation should be contraindicated. Furthermore, the effective infection control strategy was the application of combinational antibiotic scheme including ceftazidime-avibactam plus carbapenem, in conjunction with source control techniques such as allograft nephrectomy and/or thorough debridement. Nevertheless, the drug toxicology, pharmacodynamics and pharmacokinetics of the new pharmacotherapeutic scheme, ceftazidime-avibactam, are required to be further investigated.

## Abbreviations

A: Abdominal cavity; AMK: Amikacin; ATG: Anti-thymocyte globulin; AVY/CAZ: Ceftazidine avibatan ; blaESBL: Extended spectrum beta-lactamase; B: Blood; BPT: Benign pituitary tumor; BSI: Bloodstream infection; CAZ/TAZ: Ceftazidime/tazobactam; CCI: Charlson Comorbidity index; CDR: Cefidinir; CH: Cerebral hernia; CI: Cerebral infarction; CIT: Cold ischemia time; CNSI: Central nervous system infection; CPZ/SBT: Cefoperazone sulbactam; CRF: Chronic renal failure; CRKP: Carbapenem resistant klebsiella pneumoniae; CRKP-BSI: Carbapenem resistant klebsiella pneumoniae bloodstream infection; CRRT: Continual renal replacement therapy; CTX/SBT: Cefotaxime sulbactam; CVA: Cerebral vascular accident; DCD: Donation after cardiac death; DNA: Deoxyribonucleic acid; E: External iliac artery; FOS: Fosfomycin; G: Gallbladder; GMN: Glomerulonephritis; HAI: Hospital acquired infection; HI: Hepatic insufficiency; HTN: Hypertension; I: Incision; ICH: Intracerebral hemorrhage; ICU: Intensive care unit; IMP: Imipenem; KP: Klebsiella pneumoniae; KTD: Kidney transplant donor; KTR: Kidney transplant recipient; KTx: Kidney transplantation; L: Lung; LI: Lung infection; LOS: Length of stay; LVFX: Levofloxacin; LZD: Linezolid; MDR: Multidrug resistance; MEM: Meropenem; MIC: Minimum inhibitory concentration; MIN: Minocycline; MLST: Multilocus sequencing typing; MMF: Mycophenolate mofetil; MODS: Multiorgan dysfunction syndrome; NA: Non-applicable; O: Organ-space surgical site; OPC: Organ procure coordinator; OSSS: Organ-space surgical site; P: Pericardial effusion; PBS: Pitt bacteria score; PCR: Polymerase chain reaction; PE: Pleural effusion; PIP/TAZ: Piperacillin tazobactam; PLA: People's liberation army; PMB: Polymyxin B; POPT: Postoperative pituitary tumor; R: Resistant; S: Sensitive; SAH: Systemic arterial hypertension; SMZ: Sulfamethoxazole; SNPs: Single nucleotide polymorphisms; SOFA: Sequential organ failure assessment; SS: Septic sepsis; ST: Sequence type; T: Thoracic cavity; TBI: Traumatic brain injury; TEIC: Teicoplanin; Ti: Tip of catheter; TS: Tracheostomy status; U: Urinary tract; UTI: Urinary tract infection; VOR: Voriconazole; VPS: Ventriculoperitoneal shunt; WGS: Whole genome sequencing.

## Declarations

### Acknowledgement

We thank Dr. Fang Wang, department of infection prevention and control, the eighth medical center of Chinese PLA General hospital, for her provision for Medical Data base for the research. We thank all the physicians and nurses who have contributed to the research.

**Funding**

The study was supported by grants from Beijing Municipal Science & technology Commission (no. Z181100001718026) and the National Science and Technology Major Project (no. 2018ZX10305410-004).

**Availability of data and material**

The raw data can be made available to the interested researchers by the authors of this article if requested.

**Authors' contributions**

YZ and HL designed and supervised the study. YW collected and analyzed the medical records, and wrote the manuscript, while YZ monitored the study. LG and ZW gave their constructive opinion for the manuscript. JL, JW, CX, JY, YG, BW, XL and YL provided the clinical data retrieved from patients at first hand. CD cultivated and collected the isolates. XD performed the drug susceptibility test. YM provided the microbiological data and performed the data processing. FW provide the electronic patient records that searched in the patient electronic data base for the research. YJ and HL performed the whole genome sequencing and analysis, constructed the phylogenetic tree, conducted the MLST analysis and wrote the method for the procedure, under the supervision of PL. All of the authors read and approve the final manuscript and have been met the requirements for authorship.

**Competing interests**

The authors declare that they have no competing interests

**Consent for publication**

Not applicable

**Ethic approval and consent to participate**

Ethical approval was obtained from the Ethics committee board of the eighth medical center of Chinese PLA General hospital, and the need for individual patient consent was waived (reference number: 309202007011000).

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## Tables

Table 1 The clinical characteristics of the 5 DCD Kidney donors

| Varibles | ALL | Donor 1 | Donor 2 | Donor 3 | Donor 4 | Donor 5 |
|---|---|---|---|---|---|---|
| Median age (years) | 46 | 11 | 30 | 62 | 48 | 46 |
| Gender (male n%) | 80 | Male | Male | Female | Male | Male |
| Indwelling catheters (n%) | 100 | Yes | Yes | Yes | Yes | Yes |
| Blood transfusion (n%) | 20 | No | No | No | No | Yes |
| Origin of Death (n%) | | | | | | |
| CNSI | 20 | Yes | No | No | No | No |
| TBI | 20 | No | Yes | No | No | No |
| ICH | 20 | No | No | Yes | No | No |
| HTN | 20 | No | No | No | Yes | No |
| BPT | 20 | No | No | No | No | Yes |
| The Main Diagnosis (n%) | | | | | | |
| CNSI | 20 | Yes | No | No | No | No |
| TBI | 20 | No | Yes | No | No | No |
| ICH | 40 | No | No | Yes | Yes | No |
| LI | 20 | No | No | No | No | Yes |
| The Other Diagnosis(n%) | | | | | | |
| LI | 80 | Yes | Yes | Yes | Yes | No |
| VPS | 40 | Yes | Yes | No | No | No |
| TS | 80 | No | Yes | Yes | Yes | Yes |
| HTN | 40 | No | No | Yes | Yes | No |
| CH | 40 | No | Yes | No | Yes | No |
| Others | | TBI | NA | CI | HI | TI,SS,MODS,POPT,PE |
| ICU stay, median days (IQR) | 5(1-8) | 1 | 7 | 8 | 5 | 2 |
| Donors with positive result | | | | | | |
| Positive blood results | 3 | Yes | No | Yes | No | Yes |
| Positive sputum results | 5 | Yes | Yes | Yes | Yes | Yes |
| Positive drainage results | 2 | Yes | No | No | No | Yes |
| Positive urine results | 3 | No | Yes | Yes | No | Yes |
| Positive sputum+urine results | 3 | No | Yes | Yes | No | Yes |
| Positive urine+drainage results | 1 | No | No | No | No | Yes |
| Positive blood+drainage results | 2 | Yes | No | No | No | Yes |
| Positive blood+sputum results | 3 | Yes | No | Yes | No | Yes |
| Positive blood+urine results | 2 | No | No | Yes | No | Yes |
| Positive sputum+drainage results | 2 | Yes | No | No | No | Yes |
| Positive blood+sputum+drainge results | 2 | Yes | No | No | No | Yes |
| Positive blood+sputum+urine results | 2 | No | No | Yes | No | Yes |
| Positive sputum+drainage+urine results | 1 | No | No | No | No | Yes |
| Positive blood+drainage+urine results | 1 | No | No | No | No | Yes |
| Positive blood+drainage+urine+sputum results | 1 | No | No | No | No | Yes |
| Blood cultures, number of donors with/without available results | 3/5 | Yes | NA | Yes | NA | Yes |

| | | | | | | |
|---|---|---|---|---|---|---|
| Appropriate antimicrobial use, donor/all donors with positive blood results | 0/3 | No | NA | No | NA | No |
| Urine  cultures, number of donors with/without available results | 3/5 | NA | Yes | Yes | NA | Yes |
| Appropriate antimicrobial use, donor/all donors with positive urine results | 2/3 | NA | No | Yes | NA | Yes |
| Sputum cultures, number of donors with/without available results | 5/5 | Yes | Yes | Yes | Yes | Yes |
| Appropriate antimicrobial use, donor/all donors with positive sputum results | 1/5 | No | No | No | Yes | No |
| Both kidney donation,both kidney donor/all donors | 4/5 | Yes | Yes | Yes | Yes | No |
| Prognosis (death/total, %) | 100 | Death | Death | Death | Death | Death |

BPT=Benign pituitary tumor;CNSI=Central nervous system infection;CH=Cerebral hermia;CI=Cerebral infarction;CVA=Cerebral vascular accident;ICH=Intracerebral hemorrhage;HI=Hepatic insufficiency;HTN=Hypertension;LI=Lung infection;MODS=Multiorgan dysfunction syndrome;PE=pleural effusion;POPT=postoperative pituitary tumor;SS=Septic shock;TBI=Traumatic brain injury;TS=Tracheostomy status; VPS=Ventriculoperitoneal shunt

Table 2 Classification and percentage of organisms from donors

| Organisms | Strains(n=25) | Percentages |
|---|---|---|
| **Blood culture** | 4 | 16 |
| Gram-positive bacteria | | |
| Staphylococcus hominis | 1 | 4 |
| Gram-negative bacteria | | |
| Acinetobacter baumannii | 1 | 4 |
| Klebsiella pneumoniae | 1 | 4 |
| Fungi | | |
| Candida albicans | 1 | 4 |
| | | |
| **Sputum culture** | 13 | 52 |
| Gram-negative bacteria | | |
| Pseudomonas aeruginosa | 4 | 16 |
| Klebsiella pneumoniae | 2 | 8 |
| Serratia marcescens | 2 | 8 |
| Stenotrophomonas maltophilia | 2 | 8 |
| Fungi | | |
| Candida albicans | 3 | 12 |
| | | |
| **Urine culture** | 5 | 20 |
| Gram-positive bacteria | | |
| Enterococcus faecium | 1 | 4 |
| Gram-negative bacteria | | |
| Klebsiella pneumoniae | 1 | 4 |
| Escherichia coli | 1 | 4 |
| Fungi | | |
| Candida albicans | 2 | 8 |
| | | |
| **OSSS culture** | 3 | 12 |
| Gram-positive bacteria | | |
| Enterococcus faecium | 2 | 8 |
| Gram-negative bacteria | | |
| Escherichia coli | 1 | 4 |

Table 3 The characteristics of the donors and the corresponding kidney reci

| Donor | Diagnosis | Culture Result | Inappropriate antimicrobics | Recipient | No.recipient | Culture Result |
|---|---|---|---|---|---|---|
| D1 | CNSI | C.albicans(sputum+blood)<br>Serratia marcescens(sputum) | Yes | R1 | 2 | K.pneumoniae(OSSS+blood)†<br>A.baumanii(sputum+tip)<br>Enterococcus faecalis(sputum) |
| | | | | R2 | 3 | K.pneumoniae(urine)#<br>Enterococcus faecium(urine)<br>C.albicans(urine) |
| D2 | HI | Pseudomonas aeruginosa(sputum)<br>K.pneumoniae(urine)†<br>Serratia marcescens(sputum)<br>C.albicans(sputum) | Yes | R1 | 5 | K.pneumoniae(OSSS+urine+blood |
| | | | | R2 | 6 | K.pneumoniae(OSSS+blood+urine<br>Gram positive cocci(sputum)<br>Candida tropicalis(sputum+urine)<br>Pseudomonas aeruginosa(sputum-<br>Proteus mirabilis(sputum)<br>A.baumanii(OSSS) |
| D3 | CH | E.coli(urine)<br>Stenotrophomonas maltophilia(sputum)<br>Staphylococcus hominis(blood)<br>Candida albicans(urine)<br>K.pneumoniae(sputum)†<br>Pseudomonas aeruginosa(sputum) | Yes | R1 | 7 | K.pneumoniae(urine+blood+OSSS |
| | | | | R2 | 8 | K.pneumoniae(blood)†<br>Enterococcus avium(blood) |
| D4 | CVA | Pseudomonas aeruginosa(sputum)<br>Candida albicans(sputum) | No | R1 | 10 | K.pneumoniae(blood+OSSS)†<br>Enterococcus faecalis(sputum)<br>Pseudomonas aeruginosa(OSSS) |
| | | | | R2 | 11 | K.pneumoniae(urine+blood)†<br>Enterococcus faecium(urine) |
| D5[] | LI | A.baumanii(blood)<br>E.coli(OSSS)<br>K.pneumoniae(blood+tip+sputum)†<br>Enterococcus faecium(urine+OSSS)<br>Candida albicans(urine) | Yes | R | 9 | K.pneumoniae(blood+OSSS)† |
| NA | NA | NA | NA | R | 1 | K.pneumoniae(blood+OSSS+sputu<br>Staphylococcus aureus(blood) |
| NA | NA | NA | NA | R | 4 | K.pneumoniae(blood+OSSS+urine |

CH-cerebral hernia; CNSI-central nervous system injury; CVA-cerebrovascular accident; HI-head injury; LI-lung infection; OSSS-Organ-space s
donated; #Carbapenem sensitive klebsiella pneumoniae; †Carbapenem resistant kelbsiella pneumoniae

Table 4. Demographic characteristics and utilization of immunosuppression drugs of patients following renal transplantation

| Varibles | Survivors (n=6) | Non-survivors (n=5) | R1 | R2 | R3 | R4 | R5 | R6 | R7 | R8 | R9 | R10 | R11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ages (year), at transplantation, median (range) | 51 (27-56) | 47 (37-54) | 47 | 47 | 56 | 51 | 44 | 54 | 44 | 55 | 37 | 51 | 27 |
| Male gender, n(%) | 5(83.3) | 2(40) | Male | Female | Male | Male | Female | Male | Male | Male | Female | Male | Female |
| CIT(hours), median(range) | 2(0.5-7) | 2(2-6) | 6 | 2 | 0.5 | 7 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Immunosuppression | | | | | | | | | | | | | |
| Calcineurin inhibitor | | | | | | | | | | | | | |
| Cyclosporin, n(%) | 1(16.7) | 1(20) | No | No | No | Yes | Yes | No | No | No | No | No | No |
| Tacrolimus, n(%) | 6(100) | 5(100) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Adjuvant drug | | | | | | | | | | | | | |
| MMF, n(%) | 6(100) | 5(100) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Prednisone, n(%) | 6(100) | 4(80) | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Monoclonal and polyclonal antibodies | | | | | | | | | | | | | |
| ATG, n(%) | 1(16.7) | 1(20) | Yes | No | No | Yes | No | No | No | No | No | No | No |
| Basiliximab, n(%) | 1(16.7) | 5(100) | Yes | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No |
| Etiology of CRF | | | | | | | | | | | | | |
| SAH, n(%) | 100 | 100 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Diabetes, n(%) | 33.3 | 20 | No | No | No | No | No | Yes | Yes | No | No | Yes | No |
| GMN, n(%) | 83.3 | 40 | No | No | Yes | Yes | Yes | No | Yes | Yes | Yes | No | Yes |
| IgA nephropathy, n(%) | 16.7 | 20 | No | No | No | Yes | Yes | No | No | No | No | No | No |
| CCI, median(range) | 3.5(2-6) | 4(3-6) | 3 | 5 | 3 | 3 | 3 | 6 | 4 | 6 | 4 | 6 | 2 |

ATG=Anti-thymocyte globulin; CIT=cold ischemia time; CRF=Chronic renal failure; MMF=mycophenolate mofetil; SAH=systemic arterial hypertension; GMN=glomerulonephritis; CCI=charlson comorbidity Index

Table 5 Characteristics, underlying kidney diseases, results of cultures and outcomes of the 1

| Variables | Survivors (n=6) | Non-survivors (n=5) | R 1* | R 2 | R 3# | R 4* | R 5 |
|---|---|---|---|---|---|---|---|
| Date of admission | NA | NA | 09-Dec-15 | 14-Jan-16 | 15-Jan-16 | 11-Jun-16 | 28-Jun-1 |
| Age (years) at renal transplant, median(range) | 51 (27-56) | 47 (37-54) | 47 | 47 | 56 | 51 | 44 |
| Male gender, n(%) | 5(83.3) | 2(40) | Male | Female | Male | Male | Femal |
| Ureteral stent, n(%) | 6(100) | 5(100) | Yes | Yes | Yes | Yes | Yes |
| Indwelling catheters, n(%) | 6(100) | 5(100) | Yes | Yes | Yes | Yes | Yes |
| Continual renal replacement therapy (CRRT), n(%) | 3(50) | 4(80) | Yes | Yes | No | Yes | Yes |
| Dialysis,n(%) | 5(83.3) | 4(80) | Yes | Yes | Yes | Yes | Yes |
| Blood transfusion, n(%) | 5(83.3) | 5(100) | Yes | Yes | Yes | Yes | Yes |
| Intervention for focus control <48h, n(%) | 4(66.7) | 5(100) | Yes | Yes | Yes | Yes | Yes |
| Polymicrobial Infection, n(%) | 4(66.7) | 3(60) | Yes | Yes | Yes | No | No |
| Acute rejection, n(%) | 2(33.3) | 2(40) | No | Yes | No | Yes | Yes |
| Cytomegalovirus disease, n(%) | 2(33.3) | 2(40) | Yes | No | Yes | Yes | No |
| CRKP-BSI, n(%) | 5(83.3) | 5(100) | Yes | Yes | No | Yes | Yes |
| **Complication of infection** | | | | | | | |
| Organ-space surgical site(OSSS)， n(%) | 4(66.7) | 5(100) | Yes | Yes | No | Yes | Yes |
| Surgical wound， n(%) | 1(16.7) | 2(40) | Yes | No | No | Yes | No |
| Pneumoniae，n(%) | 3(50) | 5(100) | Yes | Yes | No | Yes | Yes |
| Urinary tract，n(%) | 4(66.7) | 4(80) | Yes | Yes | Yes | Yes | Yes |
| Pleural effusion， n(%) | 4(66.7) | 5(100) | Yes | Yes | No | Yes | Yes |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pneumothorax，n(%) | 0(0) | 3(60) | Yes | Yes | No | No | No |
| Abdominal effusion，n(%) | 3(50) | 4(80) | Yes | No | No | Yes | Yes |
| Organisms | | | | | | | |
| Klebsiella pneumoniae, n(100%) | 6(100) | 5(100) | Yes | Yes | Yes | Yes | Yes |
| Candida albicans, n(100%) | 1(16.7) | 0(0) | No | No | Yes | No | No |
| Staphylococcus aureus, n(100%) | 0(0) | 1(20) | Yes | No | No | No | No |
| Acinetobacter baumannii, n(100%) | 0(0) | 2(40) | No | Yes | No | No | No |
| Pseudomonas aeruginosa, n(100%) | 1(16.7) | 1(20) | No | No | No | No | No |
| Enterococcus faecalis, n(100%) | 1(16.7) | 1(20) | No | Yes | No | No | No |
| Enterococcus faecium, n(100%) | 2(33.3) | 0(0) | No | No | Yes | No | No |
| Enterococcus avium, n(100%) | 1(16.7) | 0(0) | No | No | No | No | No |
| Time (days) from kidney transplant to the excision of the transplanted kidney, median(range) | 19(19-43) | 17(14-39) | 39 | 14 | NA | 43 | 17 |
| Time (days) from kidney transplant to ICU department, median(range) | 19(0-43) | 1(0-39) | 39 | 1 | 0 | 43 | 0 |
| Time (days) from kidney transplant to rupture of the artery of the transplanted kidney, median(range) | 18.5(18-43) | 40(16-74) | 40 | 16 | NA | 43 | NA |
| Time (days) from kidney transplant to thrombus of the artery of the transplanted kidney, median(range) | 43 | 13 | NA | NA | NA | 43 | 13 |
| Time (days) from kidney transplant to the first BSI, median(range) | 19(2-37) | 15(5-43) | 43 | 32 | NA | 37 | 5 |
| Time (days) from kidney transplant to death/automatically discharge/discharge upon recovery, median (range) | 72.5(35-140) | 53(25-90) | 90 | 53 | 128 | 63 | 25 |
| LOS after first BSI onset, Days, median (range) | 28(16-138) | 35(13-61) | 48 | 21 | NA | 28 | 13 |
| ICU-LOS, Days, | 18.5(0-26) | 20(3-42) | 20 | 36 | 7 | 20 | 13 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| median (range) | | | | | | | |
| Total LOS, Days, median (range) | 73.5(35-144) | 58(37-90) | 90 | 58 | 132 | 64 | 37 |
| PBS score on the onset of first BSI, median (range) | 1(0-4) | 2(0-4) | 0 | 2 | NA | 3 | 4 |
| APACHE II score on the onset of first BSI, median(range) | 14(7-17) | 20(5-24) | 23 | 24 | NA | 17 | 5 |
| SOFA score on the onset of first BSI, median (range) | 6(0-9) | 8(1-13) | 11 | 13 | NA | 9 | 1 |
| Serum creatinine(μmol/L) before renal transplant, median(range) | 1067.2(331.2-1506.75) | 887.6(353.1-1025.4) | 977 | 1025.4 | 1014 | 1280 | 353.1 |
| Serum creatinine(μmol/L) after renal transplant, median(range) | 885.2(259.3-1106) | 284.2(100-712) | 712 | 244.9 | 1003.1 | 800 | 100 |
| Serum creatinine (μmol/L) at first BSI, median (range) | 278.3(127.9-789.26) | 437.03(64.8-487.6) | 473.6 | 487.6 | NA | 609.4 | 64.8 |
| Serum creatinine (μmol/L) at the 7th day after first BSI, median (range) | 368.1(108.5-638.7) | 251.9(75.9-543.7) | 543.7 | 329.8 | NA | 453.4 | 120.8 |
| Serum creatinine (μmol/L) at the 14th after first BSI, median (range) | 382.7(102.8-658.67) | 148(42.6-329.3) | 329.3 | 148 | NA | 473.8 | 42.6 |
| Combination antibiotic therapy, n(%) | 100 | 100 | Yes | Yes | Yes | Yes | Yes |
| The total medical costs, ¥, median(range) | 425164.485(128137.0-681226.15) | 752672.57(389384.58-823905.48) | 752672.57 | 823905.48 | 573221.17 | 396499.9 | 389384. |
| Prognosis（Survival or Death/Total, %） | 54.5 | 45.5 | Death | Death | Survival | Survival | Death |

*Kidney donors from foreign hospital; #Infected with CSKP; BSI: Bloodstream infection; CRKP: Carbapenem resistant klebsiella pneumo length of stay; NA: non-applicable; PBS: Pitt bacteria score; SOFA: Sequential organ failure assessment

Table 6. Antibiotic susceptibility of 3 stains of carbapenem-resistant K. pneumoniae from first specimen of various isolates in kidney transplant donors

| Antibiotic | Proportion of resistance(%) | Donor 2 | Donor 3 | Donor 5 |
|---|---|---|---|---|
| | | (MIC or Zone diameter) | (MIC or Zone diameter) | (MIC or Zone diameter) |
| Type of Specimen | NA | Urine | Sputum | Tip of Catheter |
| Imipenem | 66.7 | ≦1_S | ≥16_R | ≥16_R |
| Meropenem | 100 | NA | ≥16_R | ≥16_R |
| Gentamicin | 100 | ≥16_R | ≥16_R | ≥16_R |
| Amikacin | 100 | ≥64_R | ≥64_R | ≥64_R |
| Minocycline/Tigecycline* | 0 | NA | NA | 21_S |
| Ciprofloxacin | 100 | ≥4_R | ≥4_R | ≥4_R |
| Levofloxacin | 100 | ≥8_R | ≥8_R | ≥8_R |
| Tobramycin | 100 | ≥16_R | ≥16_R | ≥16_R |

K. pneumoniae: Klebsiella pneumoniae; MIC: minimum inhibitory concentration; NA: Non-applicable; R: Resistant; I: Intermediate; S: Sensitive;
* The susceptibility test was shown in zone diameter, based on disc-diffusion method.

Table 7. Antibiotic susceptibility of 10 stains of carbapenem-resistant K. pneumoniae isolated from first bloodstream infections in kidney trans

| Antibiotic | Proportion of resistance(%) | R1 | R2 | R4 | R5 | R6 | R7 | R8 | R9 |
|---|---|---|---|---|---|---|---|---|---|
| | | (MIC or Zone diameter) | (MIC or Zone diameter) | (MIC or Zone diameter) | (MIC or Zone diameter) | (MIC or Zone diameter) | (MIC or Zone diameter) | (MIC or Zone diameter) | (MIC o Zone diamete |
| Imipenem | 90 | ≧16_R | 4_R | ≧16_R | ≧16_R | 2_I | ≧16_R | ≧16_R | 8_R |
| Meropenem | 100 | 6_R | 4_R | NA | ≧16_R | NA | ≧16_R | ≧16_R | ≧16_R |
| Gentamicin | 100 | ≧16_R | ≧16_R | ≧16_R | ≧16_R | ≧16_R | ≧16_R | ≧16_R | ≧16_R |
| Amikacin | 90 | ≧64_R | ≦2_S | ≧64_R | ≧64_R | ≧64_R | ≧64_R | ≧64_R | ≧64_R |
| Minocycline/Tigecycline* | 0 | 13_I | NA | 18_S | NA | 24_S | 18_S | 22_S | 22_S |
| Ciprofloxacin | 90 | ≧4_R | 1_S | ≧4_R | ≧4_R | ≧4_R | ≧4_R | ≧4_R | ≧4_R |
| Levofloxacin | 90 | ≧8_R | 1_S | ≧8_R | ≧8_R | ≧8_R | ≧8_R | ≧8_R | ≧8_R |
| Tobramycin | 90 | ≧16_R | 4_S | ≧16_R | ≧16_R | ≧16_R | ≧16_R | ≧16_R | ≧16_R |

K. pneumoniae: Klebsiella pneumoniae; MIC: minimum inhibitory concentration; NA: Non-applicable; R: Resistant; I: Intermediate; S: Sensitive;
* The susceptibility test was shown in zone diameter, based on disc-diffusion method.

Table 8. Summary of carbapenem resistant klebsiella pneumoniae (CRKP) isolation site, episodes of sepsis, antibiotic treatments adopted for bacterial infection, outcon cause of death

| Recipient No. | Site of CRKP isolation | Sepsis | The antibiotic regimen | | Antibiotic regimen at first BSI/UTI | Adjusted antibiotic regimen | | |
|---|---|---|---|---|---|---|---|---|
| | | | Intraoperation | Postoperation | | Time (Days) after transplantation | Antibiotic regimen | Reason |
| 1 | A,B,G,I,L,O,T,U | + | NA | From Day 1 to Day 7 after surgery,PIP/TAZ(3.375g q8h) was applied. On Day 9, the patient was complaint with cough and fever, with the temperature rising up to 38.5℃, thus CAZ/TAZ(2g q12h)+MXF(0.4g qd) was administrated, following by CTX (2g/1g q12h) and CEF(100mg bid) . | TGC(100mg q12h)+MEM(2g q8h) | 63 | TGC(100mg bid)+MXF(0.4g qd) | The exploratory antibiotic application |
| | | | | | | 84 | MEM(1g bid)+TGC(100mg bid) | Follow the recommended antibiotic regimen |
| 2 | B,E,L,O,Ti | + | NA | From Day 1 to Day 2 and from Day 6 to Day 12 after surgery, CTX/SBT(4.5g bid) was applied,combining with SMZ(2co bid) from Day 8 to Day 17.Based on the result of sputum culture of gram positive cocci, TEIC(0.2g qd ) was administrated from Day 10 to 17. | MEM(1g tid)+TGC(50mg bid)+AMK(0.6g bid)+CAZ/TAZ(2.4g bid) | 46 | CPZ/SBT(3g q6h)+MIN(100mg bid)+AMK(0.6g bid) | Based on drug sensitivity test |
| 3* | P,T,U | - | NA | From Day 3 to Day 16 after surgery, MEM (1g q12h) was applied. Thereafter,CPZ/SBT(3g q12h) was administrated from Day 16 to Day 27, following by PIP/TAZ(2.5g q12h) from Day 27 to Day 34 and CTX/SBT(2.25g bid) from Day 49 to Day 52. | CTX/SBT(2.25g bid)+CEF(0.1g bid)+LVFX(0.3g qd)+MEM(1g qd) | 79 | MEM(1g bid) | The urine culture showed carbapenem sensitive klebsiella pneumoniae |
| | | | | | | 112 | CPZ/SBT(3g q12h) | The preventative antibiotic application |
| 4 | B,I,L,O,U | + | NA | From Day 1 to Day 11 and from Day 17 to Day 21 after surgery, PIP/TAZ(3.375g q12h)was applied, following by CPZ/SBT(1.5g q12h) from Day 21 to Day 26 and FOS(4g q12h)+LZD(0.6g q12h) from Day 21 to Day 24. | MEM(0.5g q12h)+TGC(50mg q12h) | 46 | MEM(0.5g q12h)+TGC(50mg q12h)+LVFX(0.6g qd)+FOS(5g q8h) | Reinforce the recommended antibiotic regimen |
| 5 | B,O,U | + | NA | From Day 1 to Day 4 after surgery, CPZ/SBT(3g q12h)was applied. | MEM(1g q12h)+TGC(50mg q12h) | 18 | MEM(2g tid)+TGC(50mg bid) | Multiple results of blood culture showed carbapenem resistant klebsiella pneumoniae, thus escalating the dose of antibiotic regimen |
| 6 | B,I,L,O,U | + | NA | From Day 1 to Day 4, CPZ/SBT (3g q12h) was applied, following by MEM (1g q12h) from Day 4 to Day 7 and LZD (0.6g qd) from Day 7 to Day 19. | MEM(2g tid)+TGC(50mg q12h)+MXF(0.4g qd) | 23 | MEM(2g tid)+TGC(100mg q12h)+MIN(100mg q12h) | Based on drug sensitivity test and follow the recommended antibiotic regimen |
| | | | | | | 37 | MEM(1g qid)+TGC(100mg bid) | Follow and reinforce the recommended antibiotic regimen |
| | | | | | | 43 | PIP/TAZ(2.5g tid)+MEM(1g qid)+TGC(50mg bid) | Follow the recommended antibiotic regimen |
| | | | | | | 58 | TGC(50mg bid)+MEM(2g tid) | Reinforce the recommended |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | antibiotic regimen |
| | | | | | | 72 | TGC(50mg bid)+MEM(2g tid)+PIP/TAZ(1.25g tid) | Follow and reinforce the recommended antibiotic regimen |
| 7 | B,O,T,U | + | NA | From Day 1 to Day 3 after surgery,CPZ/SBT(3g q12h) was applied. | PIP/TAZ(1.25g bid)+TGE(50mg bid)+SMZ(2co bid) | NA | NA | NA |
| 8 | B,O,P,T | + | NA | From Day 1 to Day 15 after surgery, CPZ/SBT(3g q12h) was applied. | CPZ/SBT(3g q12h) | 19 | TGC(50mg q12h)+MEM(1g bid)+IMP(1g q8h)+FOS(2g q6h)+SMZ(2co bid) | The result of blood culture was CRKP twice and the first sample of blood culture may be contaminated |
| | | | | | | 50 | MEM(1g q12h)+AVY/CAZ(1.25g q12h)+IMP(1g q12h) | The Klebsiella Pneumoniae causing bacteremia was considered and the pulmonary infection cannot be excluded. The newly approved medication was administrated. |
| 9 | B,O,T | + | TGC(50mg) | From Day 1 to Day 4 after surgery,CPZ/SBT(3g q12h)was applied,combining with TGC(50mg q12h) from Day 1 to Day 10 and IMP(0.25g/0.5g q12h/q8h) from Day 1 to Day 4. | TGC(100mg q12h)+IMP(0.5g q8h)+MEM(1g q8h)+CPZ/SBT(3g q8h)+SMZ(2co q8h)+FOS(2g q6h) | 8 | TGC(100mg/50mg q12h)+FOS(2g q6h)+CPZ/SBT(3g q8h)+SMZ(2co q8h)+MEM(1g q8h) | Based on drug sensitivity test and follow the recommended antibiotic regimen |
| | | | | | | 26 | AVY/CAZ(1.25g q12h)+MEM(0.5g q12h)+FOS(2g q6h)+TGC(50mg q12h) | The newly approved medication was administrated. |
| 10 | B,O,P,T | + | NA | From Day 1 to Day 10 and from Day 15 to Day 16 after surgery, CPZ/SBT(3g q12h)was applied. | MEM (1g/2g tid)+AVY/CAZ(1.25g bid/tid)+TGC(100mg q12h) | 29 | AVY/CAZ(1.25g tid)+SMZ(2co qid)+TGC(100mg bid)+FOS(2g tid) | Based on drug sensitivity test and follow the recommended antibiotic regimen. The newly approved medication was administrated. |
| | | | | | | 31 | AVY/CAZ(1.25g bid)+SMZ(2co qid)+TGC(50mg bid)+MEM(2g tid)+PMB(500,000iu, bid) | Reinforce the recommended antibiotic regimen.The newly approved medication was administrated. |
| 11 | B,U | + | NA | From Day 1 to Day 10 after surgery,CPZ/SBT(3g bid)was applied, following by CDR (0.1g tid) from Day 12 to Day 16 and Day 19 to Day 20. | MEM (1g q12h)+AVY/CAZ(2.5g q12h) | 20 | AVY/CAZ (1.25g q12h)+MEM (2g q8h) | Reinforce the newly approved medication by strengthening the dose of Meropenem and lessening the dose of Ceftazidine Avibatan |
| | | | | | | 24 | AVY/CAZ(1.25g q8h)+MEM(2g q8h) | Reinforce the newly approved medication by increasing the frequency of Ceftazidine Avibatan |

A: Abdominal cavity; AMK:Amikacin; AVY/CAZ: Ceftazidine avibatan; B: Blood; CAZ/TAZ: Ceftazidime/tazobactam; CDR: Cefidinir; CEF:Ceftizoxime; CPZ/SBT:Cefoperazone sulbact

External iliac artery; FOS:Fosfomycin; G: Gallbladder; I: Incision; IMP:Imipenem; L: Lung; LVFX: Levofloxacin; LZD:Linezolid; MEM: Meropenem; MIN: Minocycline; MXF:Moxiflo
Pericardial effusion; PIP/TAZ: Piperacillin tazobactam; PMB:Polymyxin B; SMZ:Sulfamethoxazole; T: Thoracic cavity; TEIC:Teicoplanin; TGC: Tigecycline; Ti: Tip of catheter; U: Ur
culture showed the carbapenem sensitive klebsiella pneumoniae; +: positive; -: negtive

## Figures

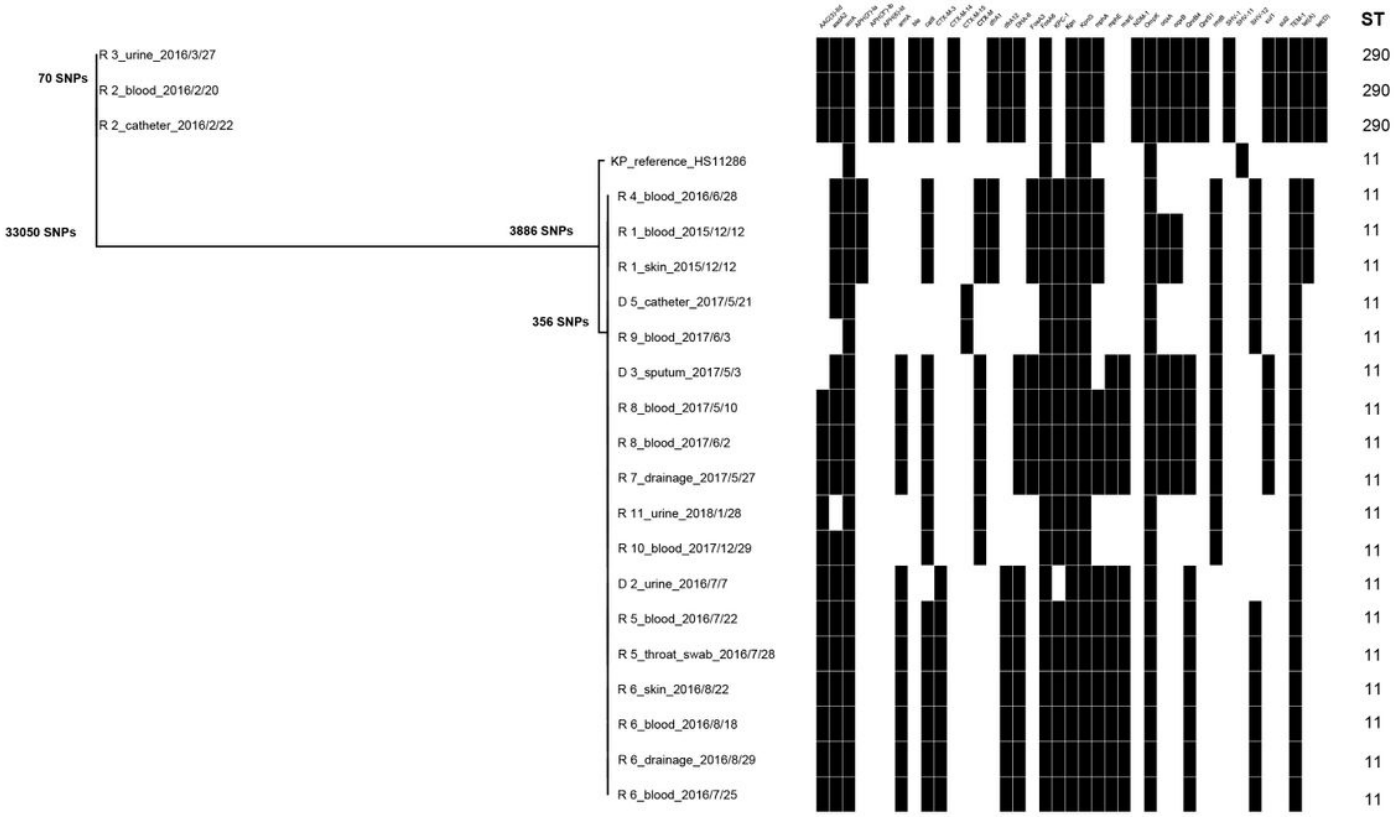


**Figure 1**

The phylogenetic tree constructed using the 21 isolates from KTDs and KTRs, labeling the KP_HS11286 as reference, in combination with the MLST analysis. SNP: single nucleotide polymorphisms; ST: sequence type

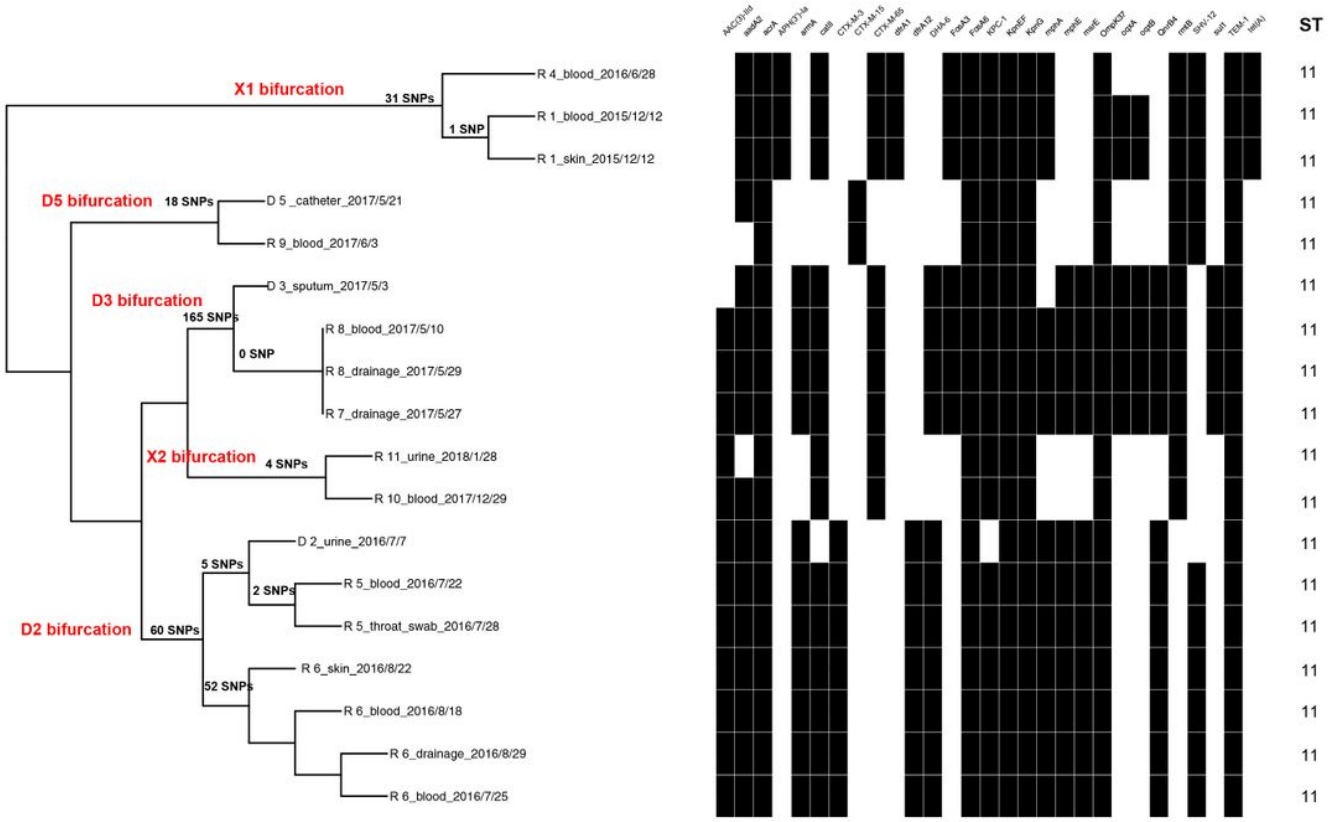


Figure 2

The local enlargement of ST11 bifurcation of the phylogenetic tree, showing the five bifurcations, each led by the different KTD. SNP: single nucleotide polymorphisms; ST: sequence type