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Treatment and Clinical Outcomes of Urinary Tract Infections Caused by KPC-Producing *Enterobacteriaceae* in a Retrospective Cohort

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Synopsis

Background—Optimal treatment regimens for infections caused by *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Enterobacteriaceae* are not well defined.

Objectives—This study describes the treatment and outcomes of patients with urinary tract infection (UTI) caused by KPC-producing *Enterobacteriaceae*.

Methods—Retrospective cohort study of adult inpatients with bacteriuria caused by KPC-positive organisms at Barnes-Jewish Hospital from June 1, 2006 to February 1, 2008. KPC-positive isolates were identified utilizing disk diffusion susceptibility testing and confirmed to contain bla_{KPC} via molecular methods.

Results—Twenty-one patients met inclusion criteria and all were classified as having symptomatic UTI. The majority of patients were female (15 of 21 – 71%) with a mean age of 62.4 years (SD ± 15.2). Successful clinical and microbiologic responses were observed in 16 patients (76%) for both outcomes. Patients with urinary catheters had them removed or replaced in 9 of 15 cases (60%). Antibiotics active against the isolated pathogen were provided in 14 of 21 cases

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The authors indicate that they have no conflicts of interest regarding the content of this article.

(67%), often after considerable delay (median: 72.5 hours, range: 4–312 hours). All seven patients receiving aminoglycoside therapy had successful clinical and microbiological responses, and *in vitro* testing of an extended antibiotic panel revealed high susceptibility rates for tigecycline (28 of 29 – 97%), minocycline (22 of 29 – 76%), and fosfomycin (25 of 29 – 86%) against the KPC-positive isolates.

Conclusions—Although delays to receipt of appropriate therapy were often experienced, clinical outcomes investigated revealed high rates of successful response in this limited group of patients. Therapy with aminoglycosides and tetracycline derivatives suggest therapeutic promise in the treatment of KPC-producing *Enterobacteriaceae* UTI.

Keywords

Urinary tract infection; Carbapenemase; KPC; Treatment Outcome

Introduction

A recent Infectious Diseases Society of America white paper crafted the acronym "ESKAPE" to identify pathogens for which our current antimicrobial armamentarium is being threatened by resistance [1]. One of these organisms is *Klebsiella pneumoniae*, in which *Klebsiella pneumoniae* carbapenemase (KPC) production is described with increasing frequency worldwide [2]. The gene coding for this carbapenemase is termed bla_{KPC}. bla_{KPC} is plasmid-mediated and transmissible, has also been reported with other Gram-negative organisms [3], and can be associated with additional antibiotic resistance genes and multi-drug resistant phenotypes [4,5]. Treatment of infections caused by KPC-producing bacteria is problematic, with options chosen on a case-bycase basis utilizing susceptibility results. There is very little published literature on urinary tract infection (UTI) due to KPC-producing organisms, which is among the most common sites of infection [6,7]. We report the clinical and microbiological outcomes of 21 hospitalized patients treated for KPC-producing *Enterobacteriaceae* urinary tract infections.

Methods

This single-center, retrospective cohort study evaluated patients who were hospitalized between June 1, 2006 and February 1, 2008 at Barnes-Jewish Hospital (BJH), a 1,250-bed tertiary-care medical center in St. Louis, MO. All inpatients admitted and found to have bacteriuria caused by carbapenem-non-susceptible bacteria were identified through a query of our medical informatics database. Only the initial isolate and associated infection for each patient identified during the study period was described clinically. Isolates were identified phenotypically using the VITEK-2 identification system (bioMérieux, Inc., Marcy, France). Antimicrobial susceptibility testing was performed using disk diffusion according to CLSI guidelines at the time of study initiation [8,9]. In addition, minimum inhibitory concentrations (MICs) of ertapenem, meropenem, imipenem, doripenem, fosfomycin, chloramphenicol, tetracycline, tigecycline, and minocycline were determined using E-test (AB Biodisk, Solna, Sweden). Detection of bla_{KPC} required extraction of total (chromosomal and plasmid) DNA from overnight cultures of carbapenem-resistant isolates using the QIAamp DNA mini extraction kit according to manufacturer recommendations

(Qiagen, Hilden, Germany). The presence of bla_{KPC} was verified using a SybrGreen® (BioRad, Hercules, CA) real-time PCR with primers specific for bla_{KPC} as described previously [10,11]. Epidemiologic analysis of all isolates available for testing during the study period was performed on total isolated DNA using repetitive sequence PCR with the RW3A primer set, as described previously [12,13]. Analysis of amplified fragments was conducted using the Agilent 2100 Bioanalyzer (Diversilab, Athens, GA) according to manufacturer procedures. A similarity index of 85% or greater was used as a threshold to determine epidemiological relatedness between isolates [12,13].

Patient data on demographics, residential status, medical history, initial presentation, clinical course, treatments, and outcomes were abstracted from medical records for the entire duration of their hospital admission. Criteria for defining types of UTI were in accordance with previously established IDSA guidelines [14]. Definitions of clinical treatment response were defined as “positive”, “negative”, or “uncertain”, as described elsewhere [15]. Microbiologic response was defined as “positive” (KPC-producing organism eradication from a repeat urine culture); “presumed” (patients judged clinical responders with no follow-up cultures obtained to verify KPC-producing organism eradication and having no readmission within 30 days with a positive culture for the same KPC strain); “negative” (persistence of the KPC-producing organism despite at least three days of appropriate antibiotics); or “not documented”. Crude mortality during hospitalization was also recorded. Hospital-acquired infection was defined as having occurred ≥48 hours following hospital admission. Community-acquired infection was defined as both not meeting the criteria for hospital-acquired infection and not having been a long-term care facility (LTCF) resident at the time of admission. Patients with greater than 10 white blood cells per high power field on urinalysis were considered to have pyuria. Active antibiotics were defined as agents for which *in vitro* susceptibility was determined to be either susceptible or intermediate, as it was assumed that moderate drug resistance may be overcome *in vivo* by high urinary drug concentrations. For patients receiving active antibiotic therapy, time to appropriate antibiotics was defined as hours between KPC-positive specimen collection and initial active antibiotic administration. Definitions for immunosuppression and other factors complicating urinary tract infections were utilized as described previously [16]. This study was approved by the Human Research Protection Office at Washington University in St. Louis. Since this study was retrospective, written informed consent was not required.

Results

Twenty-five patients were identified through the database when screening for KPC-producing urinary tract isolates during the defined study period. All were confirmed to be KPC-positive by PCR. Four of these patients were excluded because they received outpatient care only and detailed analysis of their treatment courses and clinical outcomes were not readily available. Thus, 21 patients made up the study cohort (Table 1). The majority of the patients were female (15 of 21 – 71%). The mean age was 62.4 years (SD ± 15.2). Patients had a median of three UTI-complicating factors (range 2–8).

All but one of the isolates identified were *K. pneumoniae*, the other being *Citrobacter freundii*. Nineteen *K. pneumoniae* isolates from seven unique patients were tested for

clonality and showed genotypic similarity (Figure 1). Ten patients (48%) were residents of a LTCF at the time of admission. Isolates were classified as hospital-acquired in 8 patients (38%) and only 6 isolates (29%) could be strictly considered community-acquired. All patients met criteria for symptomatic UTI; 12 patients (57%) had complicated cystitis and 9 patients (43%) had complicated pyelonephritis. All but one patient had a concordant urinalysis with pyuria (95%). Patients who had a urinary catheter in place at the time of bacteriuria had those catheters removed or replaced in 9 of 15 cases (60%). Three patients (14%) developed bacteremia with a KPC-producing isolate having the same susceptibility pattern as their urinary isolate; none of these patients died. Among patients receiving at least one Gram-negative active antibiotic during hospitalization and prior to isolation of their KPC-producing isolate (16 of 21 patients – 76%), the most common classes administered were fluoroquinolones and fourth-generation cephalosporins (eight patients each).

Active antibiotics were ultimately utilized in 14 of the 21 cases (67%). In patients receiving active antibiotic therapy, significant delays (median 72.5 hours, range 4–312 hours) in implementing these therapies were noted. Infectious Diseases consultation was obtained for seven patients (33%), of which six were given active antibiotics. Gentamicin was the most common active drug used for treatment in our cohort (7 of 14 patients), with no other single agent or class of agents used in more than 30% of cases. *In vitro* testing of an extended antibiotic panel revealed high rates of susceptibility for tigecycline (28 of 29 – 97%), minocycline (22 of 29 – 76%), and fosfomycin (25 of 29 – 86%) against these isolates (Table 2).

Positive clinical response was observed in 16 patients (76%), including all seven patients receiving aminoglycoside therapy. Positive microbiologic response was observed in six patients (29%), and presumed microbiologic response in an additional ten patients (48%). All-cause mortality during hospitalization was 19% (four patients). Of the four patients who died, only one had neither a positive clinical nor microbiologic response.

Discussion

This is one of the first reports of clinical and microbiological outcomes for a cohort of patients with UTI caused by KPC-producing *Enterobacteriaceae*. Multiple prior reports have focused on epidemiological investigations of outbreaks that included but were not limited to UTIs due to KPC-producing pathogens; however, defined criteria for identifying infection and clinical outcomes of treatment were not reported separately for UTIs [17,18]. A recent report described microbiologic clearance rates for KPC-producing UTI isolates using different therapeutic regimens, however, clinical treatment response and clonal relatedness were not investigated [7].

Other investigators have described that clonally-related KPC-producing isolates have rapidly spread to encompass a large proportion of isolates between institutions across a geographically vast area [19]. As depicted in the dendrogram (Figure 1), all 19 KPC-producing *K. pneumoniae* isolates available for testing were found to be clonally-related (similarity index > 90%), although there were three unique clusters within the dendrogram demonstrating a higher similarity index. This finding suggests the likely endemicity of this

pathogen in our area, possibly linked to local healthcare institutions, as patients were found to be epidemiologically heterogeneous. This postulate is further supported by our finding that a majority of patients had some form of readily-identifiable healthcare exposure, with only 29% (6/21) having community-acquired infections *sensu stricto*. The evolving endemic nature of KPC-producing organisms argues for improved identification and infection prevention measures within local healthcare institutions to prevent the further spread of these infections.

Our cohort was heavily antibiotic treatment-experienced, with a large proportion receiving at least one broad-spectrum Gram-negative active antibiotic prior to isolation of their KPC-producing isolate. Previous investigations have identified prior use of fluoroquinolones and broad-spectrum β-lactam antibiotics as risk factors for isolation of KPC-producing *Enterobacteriaceae* [10,20–23]. Consistent with these data, fluoroquinolones and cefepime were also the most common prior antibiotics utilized in our cohort, further suggesting that stewardship activities targeted towards these classes may yield benefit in reducing resistance development and complications of these infections.

Many patients experienced delays to appropriate antibiotic treatment, and some never received active antibiotics. In fact, all patients identified as having either negative or uncertain clinical response failed to receive active antibiotic therapy. In addition, a significant number of patients with urinary catheters at the time of KPC isolate identification did not have them removed during the treatment period, which is an important intervention for improving outcomes. One study reported that for carbapenem-resistant systemic infections, having the probable source of infection removed was an independent predictor for survival, whereas concurrent administration of active antibiotics was not [20]. Also, current UTI treatment guidelines favor catheter replacement prior to antibiotic treatment [24]. Regardless of occasional suboptimal management within our cohort, clinical outcomes were generally encouraging. Of those patients who died, all but one displayed either positive clinical or microbiologic response and none had concurrent KPC bacteremia, suggesting that mortality may have been due largely to factors other than UTI. Still, KPC UTIs are a potential precursor to KPC-associated systemic infections, which have consistently been reported to cause excess morbidity and mortality [20–22,25].

Gentamicin was the most common antibiotic administered in our cohort, and aminoglycosides generally displayed high rates of activity against tested isolates (Table 2). Aminoglycoside monotherapy was described in a meta-analysis to be equally efficacious to comparator antibiotics in the treatment of UTIs [26]. In patients with KPC-producing *Enterobacteriaceae*, aminoglycosides are often one of the few remaining therapeutic options, despite their potential nephrotoxicity and requirement for parenteral administration [27]. Of our patients that received gentamicin as a component of their treatment regimen, all had positive clinical response, and either or presumed microbiologic response. A recent investigation has also described favorable responses with aminoglycosides in the treatment of KPC-producing UTI [7]. These findings suggest that aminoglycosides are a viable option for treatment of UTIs caused by susceptible KPC-producing strains.

One patient in our study received tigecycline as a part of their treatment regimen, with clinical but without microbiologic response. High rates of *in vitro* susceptibility to this agent against KPC-producing isolates have been described in this and other studies [28]. It is generally thought that since tigecycline has limited excretion into the lower urinary system, caution should be exercised with its use for UTIs. However, recent investigations challenge this assumption [29]. The structurally-related minocycline was also found to have high rates of activity in our study, which suggests that either this agent or doxycycline may be potential oral options. We did not routinely determine doxycycline *in vitro* susceptibilities in our cohort, however, in three cases activity was presumed based on minocycline susceptibility and these patients received doxycycline as a component of therapy, with uniformly positive clinical outcomes. Although not clinically administered in our study, fosfomycin was also found to have *in vitro* activity against the isolates tested. A number of recent reports have reported high rates of activity of fosfomycin against KPC-producing organisms [30–32]. Pending additional data on clinical use, fosfomycin may be a viable option for UTIs that are confined to the lower urinary tract and caused by fosfomycin-susceptible strains of KPC-producing bacteria.

Limitations of this study include its retrospective design, small cohort size, availability of molecular epidemiological data for only a subset of our patients, and the possibility that bla_{KPC}-positive strains without phenotypic carbapenem resistance may have been missed in our screening. Outpatient and long-term treatment outcomes, as well as potential adverse effects, could not be adequately evaluated with this study design. Although we describe *in vitro* MIC results for our urinary isolates which have been strictly validated for predicting drug efficacy at concentrations achieved in the bloodstream, drug concentrations above the MIC can be achieved in the treatment of UTI as a result of renal drug elimination.

Conclusion

The majority of patients were reported as having positive clinical responses to treatment of KPC-producing UTI, despite delay or lack of administration of active antibiotic therapy and/or failure to remove indwelling urinary catheters. Aminoglycoside therapy was most commonly used for treatment in our study, and the data suggest that it was effective in this limited group of patients; tetracycline derivatives also appeared to be promising options. Although not used clinically in our study, fosfomycin was highly active *in vitro* against the studied KPC-producing strains.

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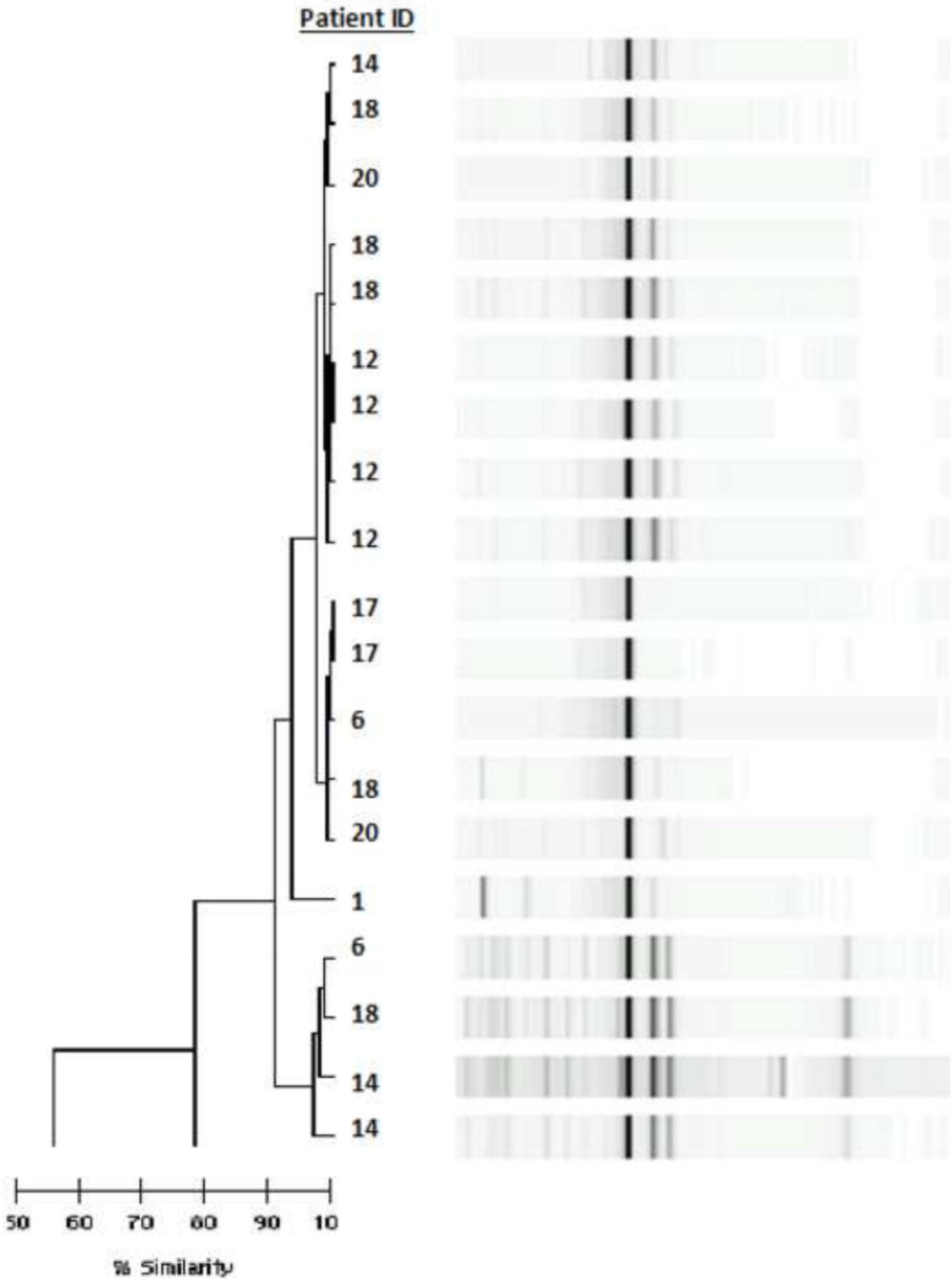

Figure 1.

Dendrogram generated from 19 bla_{KPC}-positive *K. pneumoniae* isolates using RW3A primers from seven patients. All isolates were found to be clonally-related (similarity index > 90%).

Table 1

Characteristics and outcomes for 21 patients treated for KPC-producing UTIs

Patient	Age (years)	Sex	ICU Patient	Transplant or Immuno-suppressed Patient	LTCF Patient	Hospital-Acquired Infection	Complicating Factors $a_{(N)}$	Total LOS (days)	Causative Organism	Antibiotic Susceptibility	KPC Bacteremia	Polymicrobial Culture	Pyuria	Urinary Infection Type	Active Antibiotics Administered	Time to Appropriate Antibiotics (hours)	Urinary Catheter Changed or Removed	Prior Antibiotics During Admission	Response		Survived Hospitalization
																			Clinical	Microbiologic	
1	61	F	Yes	Yes	No	Yes	5	23	KPN	S=GEN R=AMP, CEF, CFZ, CIP, CTX, MEM, NTF, T-S, P-T	No	No	Yes	CC	None	N/A	No	VAN, CEF	Uncertain	Positive	No
2	69	F	No	No	Yes	Yes	4	10	KPN	S=AMK, CST, DOX, GEN, IMI, TIG I=MIN, TOB R=AMP, A-S, AZT, CFZ, CEF, CIP, CLF, MEM, NTF, P-T, T-C, T-S	No	Yes, *E. cloacae*	Yes	CC	None	N/A	Yes	VAN, CIP, MET	Negative	Not Documented	No
3	76	M	Yes	No	No	Yes	4	115	KPN	I=GEN R=AMP, CFZ, CEF, CTX, CIP, MEM, NTF, P-T, T-S	Yes	Yes, *P. aeruginosa*	Yes	CC	None	N/A	No	MEM, P-T	Positive	Presumed	Yes
4	90	F	No	No	No	Yes	4	41	KPN	S=AMK, CST, GEN, IMI, NTF, TOB I=CEF, MIN R=AMP, AZT, CFZ, CLF, CTX, CIP, MEM, P-T, T-C, T-S	No	No	Yes	CC	None	N/A	Yes	VAN, CEF, LNZ, CIP	Uncertain	Not Documented	Yes
5	61	F	No	Yes	No	No	2	6	CFR	S=CIP, GEN, NTF R=IMI, MEM, T-S	No	No	Yes	CC	CIP 250mg PO BID × 10d	4	Yes	None	Positive	Presumed	Yes
6	48	F	No	No	Yes	Yes	3	10	KPN	S=AMK, CST, GEN, TOB I=MIN R=AMP, AZT, CFZ, CTX, CEF, CLF, CIP, IMI, MEM, NTF, P-T, T-C, T-S	No	No	Yes	CC	None	N/A	No	LNZ, CIP	Uncertain	Not Documented	Yes
7	73	F	Yes	No	Yes	No	3	8	KPN	S=AMK, CST, MIN I=GEN R=AMP, AZT, CFZ, CTX, CEF, CLF, CIP, IMI, MEM, NTF, P-T, T-C, TOB, T-S	No	Yes, *E. faecalis*	Yes	CP	DOX 100mg PO BID × 5d	157	No	VAN, CEF, MET, LNZ	Positive	Presumed	Yes
8	63	F	No	No	Yes	No	3	5	KPN	S=GEN, IMI I=CEF, CIP R=AMP, AZT, CFZ, CTX, MEM, NTF, P-T, T-S	No	No	Yes	CP	CIP 250mg PO BID × 7d	76	Yes	T-S	Positive	Presumed	Yes

Patient	Age (years)	Sex	ICU Patient	Transplant or Immuno-suppressed Patient	LTCF Patient	Hospital-Acquired Infection	Complicating Factors $a_{(N)}$	Total LOS (days)	Causative Organism	Antibiotic Susceptibility	KPC Bacteremia	Polymicrobial Culture	Pyuria	Urinary Infection Type	Active Antibiotics Administered	Time to Appropriate Antibiotics (hours)	Urinary Catheter Changed or Removed	Prior Antibiotics During Admission	Response		Survived Hospitalization
																			Clinical	Microbiologic	
9	55	M	No	No	Yes	No	4	24	KPN	S=AMK, CST, DOX, GEN, MIN, TIG, TOB I=CEF, CIP, IMI, NTF R=A-S, AZT, CFZ, CTX, CLF, MEM, P-T, T-C, T-S	Yes	No	No	CC	- GEN 90mg IV × 1d - CST 150mg IV BID × 3d - DOX 100mg PO BID × 14d	312	Yes	MEM	Positive	Positive	Yes
10	56	M	No	No	Yes	No	8	12	KPN	S=AMK, CST, IMI, TIG I=GEN R=AMP, AZT, CFZ, CEF, CTX, CLF, CIP, MEM, MIN, NTF, P-T, T-C, TOB, T-S	No	No	Yes	CP	None	N/A	Yes	CEF, CIP, MEM, IMI	Negative	Not Documented	Yes
11	72	F	No	No	No	No	4	5	KPN	S=AMK, CST, GEN, MIN, NTF, TIG I=CEF, CIP. TOB R=AMP, AZT, CFZ, CTX, CLF, IMI, MEM, P-T, T-C, T-S	No	No	Yes	CP	GEN 200mg IV daily × 14d	8	N/A	None	Positive	Presumed	Yes
12	20	M	No	No	Yes	Yes	3	11	KPN	S=GEN R=AMP, AZT, CEF, CIP, CFX, CFZ, CTX, IMI, NTF, P-T, T-S	No	No	Yes	CP	GEN 160mg IV daily × 7d	69	No	LNZ, CEF, MET	Positive	Presumed	Yes
13	55	F	No	No	No	Yes	3	42	KPN	S=AMK, CST, TIG I=CEF, CIP, GEN, MIN, NTF, TOB R=AMP, AZT, CFZ, CTX, CLF, IMI, MEM, P-T, T-C, T-S	No	No	Yes	CP	CIP 400mg IV BID × 3d	20	Yes	VAN, CEF, MET, P-T	Positive	Presumed	Yes
14	52	F	No	Yes	No	No	3	4	KPN	S=AMK, CST, GEN, MIN I=TOB R=AMP, AZT, CFZ, CEF, CTX, CLF, CIP, IMI, MEM, NTF, P-T, T-C, T-S	No	No	Yes	CP	None	N/A	N/A	CEF	Positive	Positive	Yes
15	52	M	No	No	No	No	2	10	KPN	S=AMK, CST, GEN, TOB I=CEF, MIN	No	No	Yes	CC	GEN 325mg IV daily × 5d	84	N/A	AMO, VAN, CIP, A-S	Positive	Presumed	Yes

Patient	Age (years)	Sex	ICU Patient	Transplant or Immuno-suppressed Patient	LTCF Patient	Hospital-Acquired Infection	Complicating Factors $a_{(N)}$	Total LOS (days)	Causative Organism	Antibiotic Susceptibility	KPC Bacteremia	Polymicrobial Culture	Pyuria	Urinary Infection Type	Active Antibiotics Administered	Time to Appropriate Antibiotics (hours)	Urinary Catheter Changed or Removed	Prior Antibiotics During Admission	Response		Survived Hospitalization
																			Clinical	Microbiologic	
										R=AMP, AZT, CFZ, CTX, R=AMP, AZT, CFZ, CTX, CLF, CIP, IMI, MEM, NTF, P-T, T-C, T-S										
16	65	F	No	Yes	No	Yes	2	166	KPN	S=GEN R=AMP, CFZ, CFX, CEF, CIP, CTX, IMI, NTF, P-T, T-S	No	No	Yes	CC	GEN 250mg IV daily × 3d	106	N/A	VAN, CIP, CEF, LNZ, MET, IMI, CLI, T-S, CFX	Positive	Positive	No
17	85	F	No	No	Yes	No	2	14	KPN	S=AMK, CST, GEN, TOB, MIN, NTF, TIG I=CEF, CIP R=AMP, AZT, CFZ, CTX, CLF, IMI, MEM, P-T, T-C, T-S	No	Yes, *A. urinae*	Yes	CC	NTF 100mg PO BID × 10d	94	Yes	MOX, MET	Positive	Positive	Yes
18	71	F	No	No	Yes	No	2	10	KPN	S=GEN I=NTF R=AMP, CFZ, CEF, CTX, CIP, MEM, P-T, T-S	No	No	Yes	CP	- NTF 100mg PO BID × 4d - GEN 100mg IV daily × 16d	22	N/A	None	Positive	Presumed	Yes
19	78	M	No	No	No	No	3	4	KPN	S=AMK, GEN, MIN, TOB I=CEF, CIP, IMI, NTF R=AMP, AZT, CFZ, CTX, CLF, MEM, P-T, T-C, T-S	No	Yes, *P. mirabilis*	Yes	CC	CIP 250mg PO BID × 2d	16	N/A	None	Positive	Presumed	Yes
20	42	F	No	No	No	No	4	17	KPN	S=AMK, CST, DOX, GEN, MIN, TIG, TOB R=AMP, A-S, AZT, CFZ, CEF, CTX, CLF, CIP, IMI, MEM, NTF, P-T, T-C, T-S	Yes	Yes, *A. baumannii*	Yes	CP	- DOX 100mg PO BID × 5d - TIG 50mg IV BID × 11d - CST 100mg IV BID × 7d	170	Yes	CIP, NTF	Positive	Negative	Yes
21	66	F	No	No	Yes	No	3	18	KPN	S=GEN I=CIP, NTF	No	No	Yes	CC	GEN 350mg IV daily × 8d	21	No	LNZ, P-T	Positive	Positive	No

Patient	Age (years)	Sex	ICU Patient	Transplant or Immuno-suppressed Patient	LTCF Patient	Hospital-Acquired Infection	Complicating Factors $a_{(N)}$	Total LOS (days)	Causative Organism	Antibiotic Susceptibility	KPC Bacteremia	Polymicrobial Culture	Pyuria	Urinary Infection Type	Active Antibiotics Administered	Time to Appropriate Antibiotics (hours)	Urinary Catheter Changed or Removed	Prior Antibiotics During Admission	Response		Survived Hospitalization
																			Clinical	Microbiologic	
										R=AMP, CFZ, CEF, CTX, R=AMP, CFZ, CEF, CTX, MEM, P-T, T-C											

Abbreviation: AMO, amoxicillin; AMK, amikacin; AMP, ampicillin; A-S, ampicillin-sulbactam; AZT, aztreonam; CC, complicated cystitis; CEF, cefepime; CFR, *Citrobacter freundii*; CFX, cefoxitin; CFZ, cefazolin; CIP, ciprofloxacin; CLI, clindamycin; CLF, chloramphenicol; CP, complicated pyelonephritis; CST, colistin; CTX, ceftriaxone; DOX, doxycycline; GEN, gentamicin; ICU, intensive care unit; IMI, imipenem; KPN, *Klebsiella pneumoniae*; LNZ, linezolid; LOS, length-of-stay; MEM, meropenem; MET, metronidazole; MIN, minocycline; MOX, moxifloxacin; N/A, not applicable; NTF, nitrofurantoin; P-T, piperacillin-tazobactam; T-C, ticarcillin-clavulanate; TIG, tigecycline; TOB, tobramycin; T-S, trimethoprim-sulfamethoxazole; VAN, vancomycin

^{a}Complicating Factors are as defined by Neal [16]: Indwelling urinary catheter ≥ 48hrs, urinary tract obstruction, male sex, age < 12 years, diabetes mellitus, CrCL < 30mL/min, immunosuppression, urolithiasis, urinary tract surgery, voiding dysfunction, urethral valves, vesicoureteral reflux, pregnancy, and nosocomial acquisition (> 48 hours after admission or direct admission from a long-term care facility)

Table 2

In vitro antibiotic susceptibilities for KPC-producing *Enterobacteriaceae*

Antibiotic	Disk Diffusion Susceptibility % S / % I / % R	E-test MICs	
		MIC_{50}	MIC_{90}
Amikacin	100% / 0% / 0%		
Ampicillin	0% / 0% / 100%		
Ampicillin/sulbactam	0% / 0% / 100%		
Aztreonam	0% / 0% / 100%		
Cefazolin	0% / 0% / 100%		
Cefepime	0% / 40% / 60%		
Cefoxitin	0% / 0% / 100%		
Chloramphenicol		256	256
Ciprofloxacin	5% / 33% / 62%		
Colistin	100% / 0% / 0%		
Ceftriaxone	0% / 0% / 100%		
Doripenem		32	32
Doxycycline	100% / 0% / 0%		
Ertapenem		32	32
Fosfomycin[a]		16	205
Gentamicin	81% / 19% / 0%		
Imipenem		32	32
Meropenem		32	32
Minocycline		4	22
Nitrofurantoin	19% / 24% / 57%		
Piperacillin/tazobactam	0% / 0% / 100%		
Tetracycline		6	18
Ticarcillin/clavulanate	0% / 0% / 100%		
Tigecycline[b]		1	2
Tobramycin	54% / 31% / 15%		
Trimethoprim/sulfamethoxazole	0% / 0% / 100%		

Abbreviation: S, sensitive; I, intermediate; R, resistant

[a] Clinical and Laboratory Standards Institute susceptibility breakpoints for fosfomycin: susceptible – ≤64 mg/L; intermediate – 128 mg/L; resistant – ≥256 mg/L

[b] US Food and Drug Administration susceptibility breakpoints for tigecycline: susceptible – ≤2 mg/L; intermediate – 4 mg/L; resistant – ≥8 mg/L