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ORIGINAL RESEARCH

Epidemiology, susceptibility, and risk factors for acquisition of MDR/XDR Gram-negative bacteria among kidney transplant recipients with urinary tract infections

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Background: Multiple drug resistant/extensively drug resistant (MDR/XDR) Gram-negative urinary tract infections (UTIs) represent a growing threat to kidney transplant recipients. This retrospective study aimed to assess the incidence and microbiological profile of MDR/XDR Gram-negative UTIs, to identify drug susceptibility of MDR/XDR bacteria, and to determine the potential risk factors for MDR/XDR UTIs in kidney recipients.

Materials and methods: During the study period, 1569 patients underwent consecutive kidney transplantation in two transplantation centers. We studied the demographics, clinical characteristics, and urine culture data from kidney recipients with MDR/XDR Gram-negative UTIs, and verified the risk factors associated with MDR/XDR infections.

Results: Eighty-one kidney recipients yielded 88 episodes of MDR/XDR Gram-negative UTIs with five patients (6.2%) succumbing to all-cause in-hospital mortality. The most frequently isolated bacterium was *Escherichia coli* (62.5%). Almost all MDR/XDR Gram-negative bacteria were resistant to first- and second-generation cephalosporin, and monocyclic beta-lactam. They were relatively sensitive to meropenem, amikacin, and tigecycline. As for the 12 XDR bacteria, all of them were resistant to meropenem and 25% of them were resistant to tigecycline. All XDR *Acinetobacter baumannii* and *E. coli* were susceptible to tigecycline. Nosocomial infection (odds ratio [OR] = 11.429, 95% CI = 1.311–99.625, $P = 0.027$) was the only independent predictor of MDR/XDR Gram-negative UTIs. Non-fermenting bacterial infection (OR = 20.161, 95% CI = 3.409–119.240, $P = 0.001$), polycystic kidney disease (OR = 39.871, 95% CI = 1.979–803.384, $P = 0.016$), and serum creatinine level > 1.5 mg/dL (OR = 8.688, 95% CI = 1.354–55.747, $P = 0.023$) were significantly different between XDR and MDR Gram-negative UTIs.

Conclusion: Meropenem, amikacin, and/or tigecycline can be prescribed for MDR/XDR Gram-negative infections. Tigecycline can also be prescribed for XDR *A. baumannii* and *E. coli*. Nosocomial infection was a risk factor for MDR/XDR Gram-negative UTIs, while XDR UTIs were associated with non-fermenting bacterial infection, polycystic kidney disease, and impaired renal function.

Keywords: kidney transplantation, bacteria, urinary tract infections, risk factors, MDR, XDR

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Introduction

Urinary tract infection (UTI) ranks among the most common infectious complications among kidney transplant recipients, with up to 79% prevalence.[1–4] It can pose a significant risk indirectly by leading to bacteremia, acute rejection, or cytomegalovirus infection.[5]

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An international meeting in 2012 proposed an interim standard definition of multiple drug resistant (MDR): "resistant to at least one agent in three or more antimicrobial categories" and of extensively drug resistant (XDR): "resistant to at least one agent in all but two or fewer antimicrobial categories".[6] Magiorakos et al illustrated the interim standard definition of major MDR/XDR Gram-negative bacteria in detail, including Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. MDR/XDR *Pseudomonas putida* and *Burkholderia pseudomallei* were defined as MDR/XDR *P. aeruginosa* in this study.

Although kidney recipients are particularly susceptible to MDR/XDR Gram-negative UTIs, which can lead to increased cost and longer duration of hospitalization, published data in this field among this population are limited. Adapting this standard definition of MDR, only two previous studies have been conducted so far to determine the frequency, risk factors, and clinical impact of recurrent UTIs, or to investigate the change of resistance in Enterobacteriaceae in kidney recipients.[7,8] The risk factors for acquisition of MDR/XDR Gram-negative bacteria per se among kidney recipients with UTIs, up until now, have not been studied. Confirming these risk factors associated with MDR/XDR Gram-negative UTIs and preventing the first episode of UTI is of great importance. As this is the largest group of kidney transplant patients with UTIs due to MDR/XDR Gram-negative bacteria, being studied so far, goals of the present study were: 1) to analyze the incidence and microbiological profile of MDR/XDR Gram-negative bacteria, 2) to identify drug susceptibility of MDR/XDR bacteria, and 3) the most important, to determine the potential risk factors for MDR/XDR UTIs. Thus, our findings can offer new insight into prevention of MDR/XDR UTIs among this population.

Material and methods

Study population

We performed a retrospective cohort study reviewing the medical records of patients who received a kidney transplantation at the Third Xiangya Hospital of Central South University, Changsha and Zhongnan Hospital of Wuhan University, Wuhan, China from January 1, 2007 to March 31, 2017. All patients received second- or third-generation cephalosporins or semi-synthetic penicillins/beta-lactamase inhibitors perioperatively, usually for 5 to 7 days. A double-J ureteral stent was inserted routinely in each kidney recipient and removed after 3 to 6 weeks from transplantation. A urethral catheter was inserted in each patient perioperatively and removed from the 5th to 7th day postoperatively. The study protocol was approved by the Medical Ethics Committee of the Third Xiangya Hospital of Central South University and Zhongnan Hospital of Wuhan University. The ethics committee waived the need for written informed consent provided by participants due to the retrospective nature of the study. All patient data were analyzed in anonymity, and therefore, no additional informed consent was required.

Study design and data collection

A retrospective cohort study was performed to analyze features of MDR/XDR Gram-negative bacteria from urinary tract specimens of kidney recipients, including distribution, sensitivity to antibiotics, and risk factors for acquisition. Clinical characteristics and the data of urine culture as well as other laboratory data were collected.

Routine microbiological tests of urine and rectal swabs were not performed before transplantation in these patients. Urine cultures were systematically performed every day within the first 3 days after kidney transplantation, and then once a week during the first post-transplant month. Later, at each outpatient visit, a urine culture was performed when the presence of either clinical or laboratory symptoms suggested UTI. The follow-up time for every kidney recipient was at least 3 months after the onset of UTI. All patients were initially maintained on a triple immunosuppression (tacrolimus/cyclosporine + mycophenolate mofetil + glucocorticosteroids) and an additional agent of monoclonal (basiliximab) or polyclonal antibody (ATG) was prescribed in some patients.

We compared demographics and clinical data, as well as other laboratory data between patients with UTIs due to susceptible Gram-negative bacteria, also between patients suffering from MDR and XDR UTIs. This included age, sex, underlying kidney diseases, re-transplant, type of donor, body temperature, nosocomial origin, empirical antimicrobial use, duration of days between transplantation and the onset of UTI, type of immunosuppressants, the duration of meropenem and the other wide-spectrum antibiotic therapy within 1 month before UTIs, septic shock, and laboratory data like serum creatinine level.

Definitions

The diagnosis of UTI was made when the presence of symptoms or signs of urinary infection accompanied a quantitative bacterial count $\geq 10^5$/high-power field in an appropriately collected urine specimen.[9] Urosepsis was defined as simultaneous positive blood and urine cultures obtained with the isolation of the same bacterial strain.[10] The UTIs were defined as polymicrobial if two or more different organisms were observed in

urine cultures.[11] Infection was defined to be early-onset when it occurred within the first 2 months after transplantation, and late-onset infection occurred beyond this time-point.[12] Patients were diagnosed with UTI-related septic shock when their urine cultures were positive, in conjunction with dysfunction of at least one organ that could only be explained by hypoperfusion despite adequate fluid resuscitation.[13] UTI-related mortality was considered when the death was related to clinical signs of active UTI without any other attributable cause.[11]

Microbiologic studies

Midstream urine samples or catheterized urine specimens of kidney recipients were obtained for bacterial culture. Species were identified using the Vitek-2 system (bioMérieux, Marcyl'Etoile, France). Antimicrobial susceptibility was determined by the Kirby-Bauer disk diffusion method, and the minimum inhibitory concentration was tested by agar dilution. Intermediate susceptibility was considered as having resistance.

Statistical analysis

Statistical analyses were executed with the statistical package SPSS for Windows, version 22.0 (IBM Corporation, Armonk, NY, USA). Results are listed as mean (± SD) and median (1st–3rd quartile) for continuous variables with normal and skewed distributions, respectively. Continuous variables were compared using Student's unpaired *t*-test or the Mann-Whitney *U* test. Categorical variables were compared by Pearson's χ^2 test or Fisher's exact test when appropriate. Variables with a *P*-value < 0.05 in the univariate analysis were introduced into the subsequent multivariate analysis based on forward stepwise logistic regression. Associations were given as odds ratios (ORs) with a 95% CI. Statistical tests were bicaudate and a value of $P < 0.05$ was considered to be statistically significant.

Results

A total of 1569 patients underwent consecutive kidney transplantation during the study period. In this group, 134 (8.5%) patients experienced 153 culture-proven bacterial UTI episodes and 93 (5.9%) patients yielded 101 episodes of Gram-negative infections, in which there were 16 episodes of non-fermenting bacteria, including ten episodes of *A. baumannii*, four of *P. aeruginosa*, and one each of *P. putida* and *B. pseudomallei*.

Eighty-one patients (32 males and 49 females, mean age 41.4 ± 11.8 years, range 10–65 years) were diagnosed with 88 episodes of MDR/XDR Gram-negative UTIs, representing a 5.2% (81/1569) prevalence. There were six patients who suffered from urosepsis among these 81 patients with MDR/XDR Gram-negative UTIs, and one patient suffered from urosepsis among the remaining patients with non-MDR/XDR UTIs. Demographic and clinical features of these 81 patients are illustrated in Table 1. All patients received grafts from donation after cardiac death or living related donors, apart from 16 who received them from deceased donors.

Table 1 Demographic and clinical characteristics of 81 kidney transplant patients diagnosed with urinary tract infections due to MDR/XDR Gram-negative bacteria

Characteristics	Value
Age, mean years ± SD	41.4 ± 11.8
Sex, number of females, n (%)	49 (60.5)
Underlying kidney diseases	
Chronic glomerulonephritis	62 (76.5)
Polycystic kidney disease	3 (3.7)
Diabetic nephropathy	2 (2.5)
Other/unknown	14 (17.3)
Re-transplant	4 (4.9)
Temperature of 38°C or greater, n (%)	25 (30.9)
Median body temperature of °C at infection onset (IQR)	37.1 (36.6–38.4)
Nosocomial origin, n (%)	37 (45.7)
Inappropriate empirical antimicrobial use, n (%)	32 (39.5)
Average duration of days between transplant and infection onset (IQR)	110 (36.5–1158)
Type of organisms no. of cases (%)	
Monomicrobial	74 (91.4)
Polymicrobial	7 (8.6)
Drug resistance, n (%)	
MDR	70 (86.4)
XDR	11 (13.6)
PDR	0 (0)
Type of donor, no. of cases (%)	
Donation after cardiac death	40 (49.4)
Living, related	25 (30.9)
Deceased	16 (19.8)
Use of antilymphocyte or antithymocyte globulin, no. of cases (%)	28 (34.6)
Patient immunosuppressant treatment, no. of cases (%)	
Tacrolimus	66 (81.5)
Cyclosporine A	14 (17.3)
None	1 (1.2)
Laboratory variables from blood, no. of cases (%)	
WBC count > 15,000/mm^3	14 (17.3)
Platelet count < 10,0000/mm^3	7 (8.6)
Lymphocyte count < 500/mm^3	12 (14.8)
Albumin level < 35 mg/dL	16 (19.8)
Creatinine level > 1.5 mg/dL	32 (39.5)
Septic shock at urinary tract infections onset	3 (3.7)
All-cause in-hospital mortality	5 (6.2)
Urinary tract infection-related mortality	1 (1.2)

Abbreviations: IQR, interquartile range; MDR, multiple drug resistant; PDR, pandrug resistant; WBC, white blood cell; XDR, extensively drug resistant.

Single UTI owing to MDR/XDR Gram-negative bacteria was demonstrated among 74 (91.4%) patients, and seven (8.6%) patients experienced two MDR/XDR Gram-negative infections. As for XDR Gram-negative infections, eleven patients experienced 12 episodes. No pandrug resistant (PDR) Gram-negative bacteria were isolated in the present study. Approximately 40% of cases with MDR/XDR Gram-negative UTIs had an increased serum creatinine level (> 1.5 mg/dL). Three cases (3.7%) of septic shock occurred at the onset of UTI. All-cause in-hospital mortality rate was 6.2% (5/81). One (1.2%) patient with UTI due to an XDR *Klebsiella pneumoniae* progressed to *K. pneumoniae* bacteremia and died.

Among these 88 MDR/XDR Gram-negative bacteria recovered, the most frequently isolated pathogen was *Escherichia coli* (62.5%, n = 55), followed by *K. pneumoniae* (17%, n = 15), and *A. baumannii* (10.2%; n =9) (Table 2). As presented in Table 3, MDR/XDR Gram-negative bacteria were highly resistant to first- and second-generation cephalosporin, and monocyclic beta-lactam, with the resistance rates of 96.6%, 96.6%, and 93.2%, respectively. On the other hand, they showed relative sensitivity to meropenem, amikacin, and tigecycline at resistance rates of 28.4%, 28.4%, and 11.4%, respectively. As for the 12 XDR Gram-negative bacteria, all of them were resistant to meropenem and piperacillin/tazobactam with 25% and 58.3% of them being resistant to tigecycline and cefoperazone/sulbactam, respectively. All XDR *A. baumannii* and *E. coli* were susceptible to tigecycline (Table 4).

As shown in Table 5, when compared with UTIs due to susceptible Gram-negative bacteria, the factors associated with MDR/XDR Gram-negative ones in univariate analysis were nosocomial infection and the use of wide-spectrum antibiotics for 5 days or more within 1 month before the onset of UTI. Nosocomial infection (OR = 11.429, 95% CI = 1.311–99.625, $P = 0.027$) was the only risk factor associated with MDR/XDR UTIs in multivariate analysis. No significant risk factors were determined among immunosuppressive drugs, including the use of tacrolimus and antilymphocyte or antithymocyte globulin.

The potential risk factors associated with XDR Gram-negative UTIs are outlined in Table 6. When compared with MDR UTIs, factors associated with XDR ones in univariate analysis were polycystic kidney disease, nosocomial infection, early-onset infection, non-fermenting bacterial infection, the use of wide-spectrum antibiotics for 5 days or more within 1 month before the onset of UTI, the use of meropenem for 4 days or more within 1 month before the onset of UTI, and serum creatinine level > 1.5 mg/dL. In multivariate analysis, the independent risk factors for XDR Gram-negative UTIs were polycystic kidney disease (OR = 39.871, 95% CI = 1.979–803.384, $P = 0.016$), followed by non-fermenting bacterial infection (OR = 20.161, 95% CI = 3.409–119.240,

Table 2 Classification and percentage of 88 MDR/XDR bacteria isolated from urinary tract specimens in kidney transplant recipients

Microorganism	Organisms (n = 88)	Percentage
Escherichia coli	55	62.5
Klebsiella pneumoniae	15	17
Acinetobacter baumannii	9	10.2
Pseudomonas aeruginosa	2	2.3
Enterobacter aerogenes	2	2.3
Proteus mirabilis	2	2.3
Enterobacter cloacae	1	1.1
Pseudomonas putida	1	1.1
Burkholderia pseudomallei	1	1.1

Abbreviations: MDR, multiple drug resistant; XDR, extensively drug resistant.

Table 3 Resistance rates of 88 MDR/XDR Gram-negative bacteria to 12 antibiotics (n, [%])

Antimicrobial	*Escherichia coli* (n=55)	*Klebsiella pneumoniae* (n=15)	Non-fermenting bacteria (n=13)	The other *Enterobacteria* (n=5)	Total drug resistance rate (%)
TIG	2 (3.6)	3 (20)	3 (23.1)	2 (40)	11.4
MEM	9 (16.4)	3 (20)	12 (92.3)	1 (20)	28.4
AN	8 (14.5)	5 (33.3)	11 (84.6)	1 (20)	28.4
LVF	35 (63.6)	9 (60)	11 (84.6)	0 (0)	62.5
SXT	35 (63.6)	10 (66.7)	13 (100)	4 (80)	70.5
PIT	19 (34.5)	6 (40)	12 (92.3)	2 (40)	44.3
ATM	54 (98.2)	11 (73.3)	13 (100)	4 (80)	93.2
CZO	54 (98.2)	13 (86.7)	13 (100)	5 (100)	96.6
CXM	54 (98.2)	13 (86.7)	13 (100)	5 (100)	96.6
CAZ	46 (83.6)	11 (73.3)	12 (92.3)	3 (60)	81.8
FEP	48 (87.3)	10 (66.7)	12 (92.3)	4 (80)	84.1
CFS	30 (54.5)	5 (33.3)	3 (23.1)	3 (60)	46.6

Abbreviations: AN, amikacin; ATM, aztreonam; CAZ, ceftazidime; CFS, cefoperazone/sulbactam; CXM, cefuroxime; CZO, cefazolin; FEP, cefepime; LVF, levofloxacin; MDR, multiple drug resistant; MEM, meropenem; PIT, piperacillin/tazobactam; SXT, trimethoprim/sulfamethoxazole; TIG, tigecycline; XDR, extensively drug resistant.

Table 4 Resistance rates of 12 XDR Gram-negative bacteria to five antibiotics that MDR/XDR bacteria remain relatively susceptible to (n, [%])

Antimicrobial	*Acinetobacter baumannii* (n=4)	*Escherichia coli* (n=3)	*Klebsiella pneumoniae* (n=2)	*Pseudomonas spp.* (n=3)[a,b]	Total drug resistance rate (%)
TIG	0 (0)	0 (0)	1 (50)	2 (66.7)	25
MEM	4 (100)	3 (100)	2 (100)	3 (100)	100
AN	4 (100)	1 (33.3)	1 (50)	3 (100)	75
PIT	4 (100)	3 (100)	2 (100)	3 (100)	100
CFS	2 (50)	2 (66.7)	2 (100)	1 (33.3)	58.3

Notes: [a] Including one isolate of *Pseudomonas putida*, one *Burkholderia pseudomallei*, and one *Pseudomonas aeruginosa* wherein *Burkholderia pseudomallei* is susceptible to TIG and *Pseudomonas putida* is resistant to CFS. [b] *P. aeruginosa* is intrinsically resistant to tigecycline.
Abbreviations: AN, amikacin; CFS, cefoperazone/sulbactam; MDR, multiple drug resistant; MEM, meropenem; PIT, piperacillin/tazobactam; TIG, tigecycline; XDR, extensively drug resistant.

Table 5 Univariate and multivariate analysis of risk factors associated with the occurrence of MDR/XDR Gram-negative UTIs

Characteristics	MDR/XDR UTIs	Non-MDR/XDR UTIs	*P*-value^	OR (95% CI)
Total, n (%)	81 (87.1)	12 (12.9)		
Univariate analysis, n (%)				
Age ≥ 40 years	49 (60.5)	7 (58.3)	0.887	0.613 (0.065–5.808)
Male sex	32 (39.5)	4 (33.3)	0.682	4.893 (0.219–109.073)
Re-transplant	4 (4.9)	1 (8.3)	0.627	0.129 (0.003–5.266)
Polycystic kidney disease	3 (3.7)	0 (0)	0.498	0.423 (0.040–4.434)
Temperature ≥ 38°C	25 (30.9)	5 (41.7)	0.455	0.279 (0.024–3.183)
Nosocomial infection	37 (45.7)	1 (8.3)	0.014*	9.250 (1.140–75.031)
Graft from DCD donors	16 (19.8)	3 (25)	0.114	1.979 (0.227–17.235)
Early-onset infection	25 (30.9)	3 (25)	0.416	0.796 (0.033–19.297)
Non-fermenting bacteria	12 (14.8)	3 (25)	0.371	0.037 (0.001–1.569)
Use of antilymphocyte or antithymocyte globulin	28 (34.6)	3 (25)	0.512	1.508 (0.200–11.358)
Use of tacrolimus	66 (81.5)	8 (66.7)	0.235	2.134 (0.207–22.018)
Use of wide-spectrum antibiotics for 5 days or more within 1 month before UTIs	49 (60.5)	3 (25)	0.021*	4.594 (1.155–18.269)
Use of meropenem for 4 days or more within 1 month before UTIs	11 (13.4)	0 (0)	0.21	1.729 (0.203–14.744)
Septic shock	3 (3.7)	1 (8.3)	0.498	0.423 (0.040–4.434)
WBC count > 15,000/mm^3	14 (17.3)	2 (16.7)	0.958	2.029 (0.106–38.865)
Platelet count < 10,0000/mm^3	7 (8.6)	3 (25)	0.088	0.110 (0.002–5.634)
Lymphocyte count < 500/mm^3	12 (14.8)	3 (25)	0.371	0.071 (0.002–2.219)
Albumin level < 35 mg/dL	16 (19.8)	2 (16.7)	0.801	12.439 (0.351–440.472)
Creatinine level > 1.5 mg/dL	32 (39.5)	2 (16.7)	0.125	0.897 (0.055–14.676)
Multivariate analysis				
Nosocomial infection			0.027*	11.429 (1.311–99.625)

Notes: ^*P*-value from Pearson's χ^2 test or Fisher's exact test in univariate analysis and from multiple logistic regression in multivariate analysis. *The *P*-values are statistically significant.
Abbreviations: DCD, donation after cardiac death; MDR, multiple drug resistant; UTIs, urinary tract infections; WBC, white blood cell; XDR, extensively drug resistant.

$P = 0.001$), and creatinine level > 1.5 mg/dL (OR = 8.688, 95% CI = 1.354–55.747, $P = 0.023$).

Discussion

UTIs, mainly bacterial, are a common infectious complication and remain one of the risk factors for graft loss and patient death in kidney recipients.[1,3] Extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae is associated with UTIs and recurrent UTIs, which may cause subsequent impaired renal function or even graft loss among kidney recipients.[4,7,9,14] However, MDR/XDR Gram-negative bacteria, a growing threat to transplant populations, have not been well-studied in kidney recipients with UTIs since the interim standard definition of MDR/XDR was proposed.[6]

UTIs were more common in female kidney recipients. Several other papers confirmed female sex to be the strongest risk factor for various types of UTIs.[15,16] In our present study, however, female sex did not increase the risk for MDR/XDR UTIs when compared with UTIs due to susceptible Gram-negative bacteria.

Table 6 Univariate and multivariate analysis of risk factors associated with the occurrence of XDR Gram-negative UTIs

Characteristics	XDR UTIs	MDR UTIs	*P*-value^	OR (95% CI)
Total, n (%)	11 (13.6)	70 (86.4)		
Univariate analysis, n (%)				
Age ≥ 40 years	4 (36.4)	45 (64.3)	0.078	0.209 (0.027–1.630)
Male sex	6 (54.5)	26 (37.1)	0.272	0.637 (0.070–5.782)
Re-transplant	0 (0)	4 (36.4)	0.416	2.566 (0.022–283.083)
Polycystic kidney disease	2 (18.2)	1 (1.4)	0.006*	15.333 (1.260–186.600)
Temperature ≥ 38°C	3 (27.3)	22 (31.4)	0.781	1.108 (0.151–8.140)
Nosocomial infection	9 (81.8)	28 (40)	0.01*	6.750 (1.356–33.603)
Graft from DCD donors	7 (63.6)	33 (47.1)	0.309	0.848 (0.129–5.567)
Early-onset infection	8 (72.7)	22 (31.4)	0.008*	5.818 (1.407–24.061)
Non-fermenting bacteria infection	6 (54.5)	6 (8.6)	<0.001*	11.627 (1.442–93.755)
Use of antilymphocyte or antithymocyte globulin	3 (27.3)	25 (35.7)	0.584	0.033 (0.001–1.071)
Use of tacrolimus	9 (81.8)	57 (81.4)	0.975	7.948 (0.365–172.903)
Use of wide-spectrum antibiotics for 5 days or more within 1 month before UTIs	11 (100)	38 (54.3)	0.026*	8.421 (1.022–69.371)
Use of meropenem for 4 days or more within 1 month before UTIs	4 (36.4)	7 (10)	0.018*	5.143 (1.200–22.049)
Septic shock	1 (9.1)	2 (2.9)	0.309	3.400 (0.282–41.031)
WBC count > 15,000/mm^3	1 (9.1)	13 (18.6)	0.439	0.438 (0.051–3.734)
Platelet count < 10,0000/mm^3	2 (18.2)	5 (7.1)	0.226	4.630 (0.298–71.833)
Lymphocyte count < 500/mm^3	2 (18.2)	10 (14.3)	0.735	1.786 (0.154–20.724)
Albumin level < 35 mg/dL	1 (9.1)	15 (21.4)	0.339	0.367 (0.043–3.096)
Creatinine level > 1.5 mg/dL	9 (81.8)	23 (32.9)	0.002*	7.474 (1.053–53.022)
Multivariate analysis				
Creatinine > 1.5 mg/dL			0.023*	8.688 (1.354–55.747)
Non-fermenting bacteria			0.001*	20.161 (3.409–119.240)
Polycystic kidney disease			0.016*	39.871 (1.979–803.384)

Notes: ^*P*-value from Pearson's χ^2 test or Fisher's exact test in univariate analysis and from multiple logistic regression in multivariate analysis. *The *P*-values are statistically significant.

Abbreviations: DCD, donation after cardiac death; MDR, multiple drug resistant; UTIs, urinary tract infections; WBC, white blood cell; XDR, extensively drug resistant.

A total of 153 culture-proven bacterial UTI episodes were verified during the study period and the episodes of Gram-negative infections accounted for 66% (n = 101) of all bacterial UTI episodes. Our findings were consistent with a previous study claiming that Gram-negative bacteria led to 70% of UTIs among kidney recipients.[16] Furthermore, the most frequent MDR/XDR Gram-negative organisms obtained from urinary tract specimens were *E. coli* (62.5%), consistent with earlier studies reporting *E. coli* to be the major pathogen in kidney recipients with UTIs.[14,15,17]

Several prior studies demonstrated that MDR isolates were responsible for up to 69.1% of all organisms leading to symptomatic UTIs in kidney recipients.[8,15,17] Although MDR/XDR Gram-negative UTI-related mortality was as low as 1.2% (1/81), we found the majority (87.1%, n = 81) of Gram-negative bacteria causing UTIs were MDR/XDR. The finding of low UTI-related mortality is extremely similar to previous studies reporting that no mortality associated with UTIs was observed in kidney recipients with UTIs.[10,18] However, Chuang et al reported 4.7% (10/213) of kidney recipients with UTIs died.[19] We also found all-cause in-hospital mortality in kidney recipients with MDR/XDR Gram-negative UTIs was at a relatively high level of 6.2%, in line with a recent study reporting that UTI alone predicted an increased first-year mortality rate of 41% in kidney recipients.[20] XDR bacteria accounted for 13.6% of all MDR/XDR Gram-negative bacteria recovered from kidney recipients with UTIs, which represents a therapeutic problem. Fortunately, no PDR Gram-negative bacterium was found during the present study.

The drug susceptibility test showed the highest resistance rate (> 90%) of MDR/XDR Gram-negative bacteria to first- and second-generation cephalosporins and monocyclic beta-lactam, and relatively high resistance rate (> 80%) to third- and fourth-generation cephalosporins. More than 90% of MDR/XDR non-fermenting bacteria were resistant to meropenem. Fortunately, only 11.4% of all MDR/XDR bacteria were resistant to tigecycline. After eliminating the influence of *P. aeruginosa* on the drug resistance rate, only 9.1% of the other MDR/XDR bacteria were resistant

to tigecycline, as *P. aeruginosa* is intrinsically resistant to tigecycline. As for the 12 XDR Gram-negative bacteria, all of them were resistant to meropenem and piperacillin/tazobactam. A large amount of them (58.3%) were cefoperazone/sulbactam resistant, but only 25% of them were tigecycline resistant. Furthermore, all XDR *A. baumannii* and *E. coli* were tigecycline sensitive. After eliminating the influence of *P. aeruginosa*, only 16.7% of the other XDR bacteria were resistant to tigecycline.

Combination therapies of two to three different antibiotic classes (beta-lactam + aminoglycoside ± fluoroquinolone) for 10–14 days for the treatment of XDR *P. aeruginosa* infections have been recommended by a previous study.[21] For XDR *A. baumannii*, previous studies suggested that colistin-carbapenem or colistin-sulbactam combinations may result in improved clinical responses and survival in transplant recipients.[22–24] Bader et al suggested that aminoglycosides, colistin, and tigecycline were considered alternatives in MDR Gram-negative UTIs in patients with limited therapeutic options.[25] According to our results of antibiotic susceptibility profile, as tigecycline, meropenem, and amikacin were among the most active drugs against MDR/XDR Gram-negative bacteria, we could suggest monotherapy or combination therapy of these three antibiotics in kidney recipients with UTIs owing to MDR/XDR bacteria. And for XDR Gram-negative bacteria, a combination of tigecycline and cefoperazone/sulbactam may be an effective treatment option.

To improve the outcome of kidney transplantation, several studies have investigated the risk factors for the first episode of UTI/recurrent UTIs. The risk factors for the first episode of UTIs were age, use of grafts from deceased donors, glomerulonephritis, re-transplant, reflux kidney disease, cytomegalovirus disease, recurrent UTI prior to transplant, use of azathioprine, presence of urological abnormalities, acute rejection, and underlying diabetes mellitus.[19,26–29] Whereas the variables associated with a higher risk of recurrent UTIs included a first or second episode of UTI caused by MDR bacteria, age > 60 years, and reoperation.[7] The risk factors associated with UTIs caused by ESBL-producing bacteria in kidney transplant patients were also investigated, which included older age, longer time from kidney transplantation to the first positive urine culture, previous episodes of UTI, and reoperations.[4,30]

Immunosuppression and selective antibiotic pressure are risk factors for the emergence of antibiotic resistant uropathogens.[15,31] After analyzing five studies of urinary tract bacteria (14,348 participants), Costelloe et al revealed that the pooled OR for resistance was 2.5 (95% CI 2.1 to 2.9) within 2 months of antibiotic treatment and 1.33 (1.2 to 1.5) within 12 months.[32] However, we failed to identify the association between the use of immunosuppressants and the predominance of MDR/XDR Gram-negative uropathogen. We found that the use of wide-spectrum antibiotics for 5 days or more within 1 month before UTIs was associated with more frequent MDR/XDR UTIs in the univariate analysis, but this variable did not reach statistical significance in the multivariate analyses. Although the use of wide-spectrum antibiotics for 5 days or more and meropenem for 4 days or more within 1 month before UTIs were associated with the predominance of XDR UTIs, it failed to remain in our final multivariate logistic regression model. However, we found that nosocomial infection, which also represents selective antibiotic pressure, was a risk factor for MDR/XDR UTIs, in line with previous studies which claimed that one of the independent risk factors for MDR/XDR *P. aeruginosa* BSIs in transplant recipients was hospital acquisition.[33,34]

UTIs were more common in kidney recipients with impaired function.[17] Approximately 40% of cases with MDR/XDR Gram-negative UTIs had an increased serum creatinine level (> 1.5 mg/dL) in our present study. Munoz reported serum creatinine levels > 2 mg/dL to be a post-transplant risk factor of having a delayed UTI (> 6 months post-procedure).[35] Wu et al found that baseline serum creatinine level > 1.3 mg/dL before first UTI represented an independent predictor of UTI with concomitant bacteremia.[36] We also found that elevated serum creatine level was associated with XDR Gram-negative UTIs in comparison with MDR ones. Gołezbiewska et al thought that the patients with initially worse renal graft function may be more prone to develop UTIs.[37] The possible explanations for this phenomenon include a need for longer hospitalization, the requirement of prolonged venous catheterization, more antibiotic exposure, and greater impaired immunity.[31,36]

XDR non-fermenters are progressively growing as a cause of infection in solid organ transplant patients, and represent a global threat.[38] We found that 43.8% (7/16) of all non-fermenting bacteria were XDR and that a risk factor associated with XDR UTIs was non-fermenting bacterial infection. Our findings herein agree with two previous studies claiming that 63% each of *P. aeruginosa* and non-fermenting bacteria causing bacteremias were XDR *P. aeruginosa* and XDR non-fermenting bacteria in solid organ transplant recipients.[34,39]

Another risk factor we found in the present study for XDR Gram-negative UTIs was polycystic kidney disease, one of the risk factors for UTIs confirmed by a prior study.[35]Although routine pre-transplantation nephrectomy

is not recommended, bilateral native nephrectomy might be indicated if the native polycystic kidneys act as a "reservoir" for infection.[35]

To the best of our knowledge, the present study is the first to report the incidence, strains, susceptibility, and risk factors for acquisition of MDR/XDR Gram-negative bacteria isolated from kidney recipients with UTIs, since the interim standard definition of MDR/XDR was proposed.

Study limitations include the retrospective nature of the study. The wide CIs in this analysis reflect the relatively small numbers of XDR and susceptible Gram-negative bacteria, with a consequent loss of statistical power. Also, urine cultures were not routinely performed beyond the first post-transplant month and as a result, the actual prevalence of UTIs might have been underestimated.

In conclusion, this study confirmed that MDR/XDR bacteria were responsible for the majority of pathogens recovered from kidney recipients with Gram-negative UTIs. XDR bacteria accounted for 13.6% of all MDR/XDR Gram-negative bacteria and represented a severe therapeutic issue. The drug resistance of Gram-negative bacteria to commonly used antibiotics was intensely severe since 90% of MDR non-fermenting bacteria and all XDR Gram-negative bacteria were resistant to meropenem. Nosocomial infection was associated with MDR/XDR Gram-negative UTIs among kidney recipients. The independent predictors of XDR Gram-negative UTIs included non-fermenting bacterial infection, polycystic kidney disease, and elevated creatinine level. However, the reader should bear in mind that this study was based on retrospective data with a limited number of kidney recipients with XDR or susceptible Gram-negative UTIs, thus, the findings need to be further verified.

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Disclosure

The authors report no conflicts of interest in this work.

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