Antibiotic Resistance and Virulence Genes of *Escherichia coli* Isolated from Patients with Urinary Tract Infections After Kidney Transplantation from Deceased Donors

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Objective: This study aimed to determine the prevalence of antibiotic resistance and virulence genes of *Escherichia coli* strains among patients with urinary tract infections (UTIs) after kidney transplantation from deceased donors.

Methods: Between January 2014 and June 2018, 64 patients who received kidney transplants from deceased donors at our institution developed a UTI due to *E. coli*. Polymerase chain reaction was used to detect virulence genes in *E. coli* strains. The Kirby–Bauer method was used to evaluate the antibiotic susceptibility pattern of the isolates.

Results: Among the study cohort, 46 (71.9%) UTIs were community-acquired (CA), and 18 (28.1%) were hospital-acquired (HA). The percentages of isolated *E. coli* strains that showed antibiotic resistance were as follows: 92.2% to ampicillin, 76.6% to cefalotin, 81.3% to carbenicillin, 29.7% to ciprofloxacin, 62.5% to cotrimoxazole, 35.9% to gentamicin, 34.4% to levofloxacin, 28.1% to norfloxacin, 68.8% to pefloxacin, 57.8% to trimethoprim/sulfamethoxazole, and 20.3% to amikacin. HA *E. coli* showed higher resistance to ciprofloxacin, cotrimoxazole, trimethoprim/sulfamethoxazole and amikacin, compared with CA *E. coli* ($P<0.05$). The most prevalent virulence genes among the *E. coli* strains were *fim* (64.1%), followed by *irp2* (56.3%), *iroN* (46.9%), *pap GII* (45.3%), *sfa* (31.3%), *pap* (25%), *iuc* (23.4%), *pap GI* (15.6%), *pap GIII* (14.1%), *hly* (9.4%), and *cnf* (4.7%). The *irp2* and *iroN* genes were found more frequently in the HA *E. coli* than in the CA *E. coli* ($P<0.05$).

Conclusion: The *E. coli* strains, especially HA *E. coli*, isolated from UTI patients after kidney transplantation from deceased donors showed resistance to multiple antibiotics and harbored numerous virulence genes. These findings provide insight for genetic characterizations and epidemiological studies of *E. coli* strains causing UTIs in patients after kidney transplantation from deceased donors.

Keywords: *Escherichia coli*, antimicrobial resistance, virulence genes, urinary tract infections, kidney transplantation

Introduction

The increasingly frequent use of kidneys from deceased donors could address the gap between the demand for kidney transplants and the restricted supply of organs. Urinary tract infections (UTIs) are the main infectious complication among kidney transplant patients, particularly among recipients of kidneys from deceased donors.^{1–3} UTIs were reported to be associated with poor prognosis and elevated risks of graft dysfunction and mortality.^{4–6} Uropathogenic *Escherichia coli* (UPEC),

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the primary causative agent of UTIs, account for nearly 90% of community-acquired UTIs (CA-UTIs) and 30%–77% of all hospital-acquired infections (HA-UTIs).⁷ *E. coli* strains possess a variety of virulence factors that promote their survival and infection of hosts.⁸ Specific virulence genes can be used to identify the UPEC from non-uropathogenic *E. coli* and are known to correlate with the severity of UTIs.⁹ Some of the most important virulence genes have been linked to severe UTIs, such as genes coding for adhesions (*fim*, *pap*, *pap GI*, *pap GII*, *pap GIII*, and *sfa*), iron acquisition systems (*irp2* and *iuc*), and synthesis of cytotoxins (*hly* and *cnf*).¹⁰ However, few studies have explored the epidemiology and prevalence of virulence genes in UPEC strains causing UTIs in deceased donor kidney recipients. The objective of the present study was to determine the prevalence of virulence genes among UPEC strains isolated from deceased donor kidney recipients experiencing UTIs, in order to gain insight into the pathogenesis of these UTIs and prevent post-transplant infectious complications in deceased donor kidney recipients.

Materials and Methods

Study Participants

We performed a retrospective cohort study of all adult patients undergoing kidney transplantations at our institution between January 2014 and June 2018. Patients who died within the first week after transplantation or who received a living donor transplant were excluded. All eligible patients in the present study suffered UTIs for the first time, and all 64 urine samples were collected from different patients. Non-repetitive samples of patients and isolates were confirmed after screening of the electronic records of the patients. The primary outcome of the study was a UTI after kidney transplantation. A UTI was diagnosed based on classic symptoms of fever ($>38^{\circ}\text{C}$), urinary urgency, increased frequency of urination, dysuria, suprapubic tenderness, and burning on micturition, together with a positive urine culture ($>100,000$ colony-forming units of a pathogenic organism per milliliter of urine). Eligible patients were divided into a hospital-acquired infections (HA-UTIs) group and a community-acquired UTIs (CA-UTIs) group. HA-UTIs were defined as infections for which the onset of symptoms occurred after hospital admission or within 10 days of hospital discharge. CA-UTIs were defined as infections for which the onset of symptoms occurred before hospital admission

or beyond 10 days after hospital discharge.¹¹ Demographic characteristics, including gender, age, BMI, pretransplantation conditions, induction therapy, CMV mismatch, delayed graft function, extended spectrum β -lactamase (ESBL) positivity, length of hospital stay and catheter retention time were analyzed.

The donated organs were obtained with full informed consent from the next of kin of the donor. This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (Qingdao, China; no. QYFYWZLL 26483). All procedures involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethics standards. Written informed consent was obtained from all individual participants included in this study.

Immunosuppression Regimens

The routine induction regimens at our institution were as follows: (1) intravenous anti-CD25 mono-antibody Basiliximab (20 mg), followed by a second administration of Basiliximab on day 4 post-transplantation; and (2) rabbit anti-human thymocyte immunoglobulin (rATG, 1.25–2.5 mg/kg, qd) for 5 days. After the kidney transplantation, all patients received the same immunosuppressive regimens using tacrolimus in combination with mycophenolate mofetil and prednisone. Tacrolimus was started at 0.1–0.2 mg/kg/day in two divided doses, and the targeted 12-h trough level was 9–12 ng/mL by the first 3 months post-transplantation and then 8–10 ng/mL by 6 months post-transplantation. Mycophenolate mofetil was orally administered at a dose of 1000 mg twice daily and decreased to 750 mg twice daily at 2 weeks after transplantation. Prednisone was tapered to 30 mg/day during the hospitalization, to 10 mg/day by 3 months post-transplantation, and to 5 mg/day by 6 months post-transplantation.

Strains Isolation

A total of 64 isolates of *E. coli* were collected from these patients, and only the first strain from each patient was included in the study. Each urine sample were first incubated on nutrient agar, and if pathogen was identified growing in the agar, the single colony was subcultured on new nutrient agar to obtain the pure colony. After obtaining the pure colony of *E. coli*, identification, DNA

extraction, and antimicrobial susceptibility testing were performed.

***E. coli* Identification**

Semi-quantitative urine culture using a 0.01-mL calibrated loop was performed to isolate bacterial pathogens on nutrient agar plates. Culture plates were incubated at 37°C for 24 h. *E. coli* was identified by IMViC tests and confirmed by 16S ribosomal RNA (rRNA) gene polymerase chain reaction (PCR) amplification as described previously.¹² The isolates were stored at –70°C for further analysis.

Uropathogen Identification

As above, semi-quantitative urine culture using a 0.01-mL calibrated loop was performed to isolate bacterial pathogens on nutrient agar plates. Culture plates were incubated at 37°C for 24 h, and then isolates were identified by conventional methods such as Gram staining, motility test, catalase test, coagulase test, and BBL Crystal Enteric/NF 4.0 identification kits (Becton Dickinson, NY, USA) when needed. Isolated and characterized uropathogens were stored at –70°C for further analysis.

DNA Extraction

Identified *E. coli* isolates were streaked on nutrient agar plates and incubated at 36°C for 24 h. Each single distinct colony was picked from the nutrient agar and transferred to 50 mL nutrient broth for incubation at 37 °C on a rotary shaker at 180 rpm for 9 h. Thereafter, the suspension was transferred to sterilized 1.5-mL Eppendorf tubes and used for DNA extraction. DNA extraction was performed according to the manufacturer's protocol (Transgen, Beijing, China). Extracted DNA was stored at –20°C until required for assays.

Antibiotic Susceptibility Testing

Antibiotic susceptibility was tested using the Kirby–Bauer disc diffusion method on Mueller–Hinton agar (Difco, Detroit, MI, USA), based on the Clinical and Laboratory Standards Institute (CLSI) guidelines.¹³ The susceptibility of the *E. coli* isolates to each antibiotic agent was assessed by using different antibiotic-loaded discs, and the results were interpreted in accordance with CLSI guidelines. The following antibiotics were used at the indicated concentrations: ampicillin (10 mg/disk), cefalotin (30 mg/disk), carbenicillin (100 mg/disk), ciprofloxacin (5 mg/disk), gentamicin (10 mg/disk), levofloxacin (5mg/disk),

norfloxacin (10 mg/disk), pefloxacin (5 mg/disk), trimethoprim-sulfamethoxazole (25 mg/disk), and amikacin (30 mg/disk). The *E. coli* ATCC 25922 strain was used as the control strain for all the tests.

Detection of Virulence Genes

PCR was performed for amplification of the following genes: (1) genes related to adhesions: *pap*, *papGI*, *papGII*, *papGIII*, *fim* and *sfa*; (2) genes related to iron acquisition systems: *irp2*, *iroN* and *iuc*; (3) genes related to toxins: *hly* and *cnf*. The oligonucleotide primers (Invitrogen, Shanghai, China) used for the amplification of virulence genes are listed in Table 1. PCR was performed in a PE 9600 real-time PCR System (ABI, Foster City, CA, USA). Each PCR mixture consisted of 5.0 µL of 10 Taq DNA polymerase buffer (TaKaRa, Shuzo, Japan), 4.0 µL of dNTPs (TaKaRa), 0.5 µL of each PCR primer (20 mM), 0.4 µL Taq DNA polymerase (TaKaRa), 3.1 µL of nuclease-free water and 2.0 µL DNA template.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined by a two-tailed P value <0.05. The Kolmogorov–Smirnov test was employed to test the normality of the data for continuous variables in each group. Data for continuous variables that followed a normal distribution are expressed as mean ± standard deviation (SD) and were compared using Student's *t* test. Categorical data are expressed as numbers and percentages and were compared using the Chi square test. A P value <0.05 was considered to be statistically significant.

Results

Baseline Clinical Characteristics of the Study Participants

In the study period, a total of 510 patients received kidney transplants from deceased donors at our institution. Ninety patients developed UTIs after kidney transplantation, of whom 64 patients experienced UTIs due to *E. coli* and were included in the present study. Sixty-four non-repetitive UPEC isolates were obtained from the eligible patients. Based on the timing of symptom onset, 46 (71.9%) infections due to *E. coli* were considered CA-UTIs and 18 (28.1%) were considered HA-UTIs. Patients' clinical data are summarized in Table 2. The number of patients who received rATG as induction therapy as well

Table 1 PCR Primers Used to Detect Virulence Genes

Gene	Primer Sequence (5' to 3')	Amplicon Size (bp)
Adhesions		
<i>pap</i>	GACGGCTGACTGCAGGGTGTGGCG ATATCCTTTCTGCAGGGATGCAATA	328
<i>pap GI</i>	TCGTGCTGAGGTCCGGAATTT TGGCATCCCCCAACATTATCG	461
<i>pap GII</i>	GGGATGAGCGGGCCTTTGAT CGGGCCCCCAAGTAACCTCG	190
<i>pap GIII</i>	GTGGCAGTAGAGTAATGACCGTTA ATATCCTTTCTGCAGGGATGCATA	258
<i>fim</i>	GAGAAGAGGTTTGATTAACTTATTG AGAGCCGCTGTAGAACTGAGG	559
<i>sfa</i>	CTCCGGAGAACTGGGTGCATCTTAC CATCAAGCTGTTTGTTCTGCCGCCG	410
Iron acquisition systems		
<i>irp2</i>	AAGGATTCGCTGTTACCGGAC AACTCCTGATACAGGTGGC'	413
<i>iroN</i>	AAGTCAAAGCAGGGGTTGCCCCG GACGCCGACATTAAGACGCAG	665
<i>iuc</i>	ATGAGAATCATTATTGACATAATTG CTCACGGGTGAAAATATTTT	1482
Toxins		
<i>hly</i>	AACAAGGATAAGCACTGTTCTGGCT ACCATATAAGCGGTCATTCCCGTCA	1177
<i>cnf</i>	AAGATGGAGTTTCCTATGCAGGAG CATTGAGAGTCCTGCCCTCATTATT	498

as the number of patients who were positive for ESBL were statistically higher among patients with HA-UTIs than among patients with CA-UTIs. In addition, the mean hospital stay and catheter retention time were significantly longer in patients with HA-UTIs than in patients with CA-UTIs.

Antibiotic Resistance Among *E. coli* Strains Isolated from Kidney Recipients with UTIs

The antimicrobial resistance profiles of HA and CA *E. coli* are compared in Table 3. All antibiotic resistance rates were higher among HA *E. coli* than among CA *E. coli*. The rates of resistance to ciprofloxacin, cotrimoxazole, trimethoprim/sulfamethoxazole, and amikacin specifically were higher among HA *E. coli* than among CA *E. coli* (all

$P < 0.05$), whereas no significant differences in the rates of resistance to ampicillin, cefalotin, carbenicillin, gentamicin, levofloxacin, norfloxacin, and pefloxacin were observed between the HA and AC *E. coli* strains (Table 3).

Distribution of Virulence Genes in Isolated *E. coli* Strains

The genotypic virulence markers detected among the HA and CA *E. coli* isolates are presented in Table 4. Among the 64 *E. coli* isolates, the predominant adhesions-coding gene was *fim* (64.1%), and a majority of isolates expressed the iron acquisition system-coding gene *ipr2* (56.3%). The target toxins-coding genes were detected in less than 10% of the isolates. Only the iron acquisition system-coding genes *irp2* and *iroN* genes were differentially expressed

Table 2 Comparative Analysis of Clinical Data from CA-UTIs and HA-UTIs in Kidney Transplantation

Variable	CA-UTIs (n=46)	HA-UTIs (n=18)	P
Gender, male	10(21.7)	5(27.8)	0.608
Age (years)	42.1±13.4	41.2±10.3	0.798
BMI (kg/m ²)	22.8±3.6	23.6±3.6	0.440
Pretransplantation conditions			
Diabetes mellitus	11(23.9)	5(27.8)	0.748
Coronary heart disease	7(15.2)	4(22.2)	0.504
Chronic liver disease	4(8.7)	3(16.7)	0.358
Chronic lung disease	3(6.5)	1(5.6)	0.886
Induction therapy			0.030
Basiliximab	24(52.2)	4(22.2)	
rATG	22(47.8)	14(77.8)	
CMV mismatch (D+/R-)	6(13.0)	3(16.7)	0.708
Delayed graft function	3(6.52)	5(27.78)	0.021
ESBL positive	30(65.2)	17(94.4)	0.031
Length of hospital stay (d)	21.5±8.2	34.6±13.2	<0.001
Catheter retention time (d)	7.3±1.2	8.8±3.2	0.008

Abbreviations: rATG, rabbit anti-human thymocyte immunoglobulin; BMI, body mass index; CA-UTIs, community-acquired urinary tract infections; CMV, cytomegalovirus; D, donor; ESBL, extended spectrum β -lactamase; HA-UTIs, hospital-acquired urinary tract infections; R, recipient.

Table 3 Antibiotic Resistance Profiles of the Isolated *E. coli* Strains Causing UTIs in Kidney Transplant Recipients

Antibiotic	Total, n(%)	CA-UTIs, n(%) (n=46)	HA-UTIs, n(%) (n=18)	P*
Ampicillin	59(92.2)	42(91.3)	17(94.4)	0.674
Cefalotin	49(76.6)	33(71.7)	16(88.9)	0.145
Carbenicillin	52(81.3)	36(78.3)	16(88.9)	0.327
Ciprofloxacin	19(29.7)	10(21.7)	9(50)	0.026
Cotrimoxazole	40(62.5)	25(54.3)	15(83.3)	0.031
Gentamicin	23(35.9)	15(32.6)	8(44.4)	0.375
Levofloxacin	22(34.4)	13(28.3)	9(50)	0.100
Norfloxacin	18(28.1)	10(21.7)	8(44.4)	0.069
Pefloxacin	44(68.8)	30(65.2)	14(77.8)	0.330
Trimethoprim/sulfamethoxazole	37(57.8)	22(47.8)	15(83.3)	0.010
Amikacin	13(20.3)	6(13)	7(38.9)	0.021

Note: *P values for comparison between CA-UTI and HA-UTI *E. coli* isolates.

between the HA *E. coli* and CA *E. coli*, and both were found more frequently found in the HA *E. coli* than in the CA *E. coli*.

Discussion

Because of shortage of kidney donors and the continually increasing number of patients in need of a kidney transplantation, kidneys from deceased donors are being used more often. This approach can increase the pool of organs and reduce the number of patients on the waiting list. However, previous research has established that kidney

transplants from deceased donors have higher rates of primary non-function and delayed graft function than those from donation after brainstem death (DBD) or living donors.¹⁴ A recent meta-analysis revealed that the infection risk among deceased donor kidney recipients is 2.65 times higher than that among recipients of living donor kidney transplants.¹⁵ UTIs are the most common infectious complication in kidney transplant patients and may be associated with the high risk for graft loss and mortality.^{5,16} Approximately 70–95% of UTIs in these patients are caused by UPEC.¹⁷ Indeed, in the present

Table 4 Distribution of Virulence Genes in Isolated *E. coli* Strains [n(%)]

Virulence Genes	Total, n(%)	HA-UTIs, n (%) (n=18)	CA-UTIs, n (%) (n=46)	P*
Adhesions				
<i>pap</i>	16(25.0)	4(22.2)	12(26.1)	0.748
<i>pap GI</i>	10(15.6)	3(16.7)	6(13)	0.708
<i>pap GII</i>	29(45.3)	8(44.4)	21(45.7)	0.930
<i>pap GIII</i>	9(14.1)	2(11.1)	7(15.2)	0.671
<i>fim</i>	41(64.1)	12(66.7)	29(63.0)	0.786
<i>sfa</i>	20(31.3)	8(44.4)	12(26.1)	0.154
Iron acquisition systems				
<i>irp2</i>	36(56.3)	16(88.9)	20(43.5)	0.001
<i>iroN</i>	30(46.9)	14(77.8)	16(34.8)	0.002
<i>iuc</i>	15(23.4)	5(27.8)	10(21.7)	0.608
Toxins				
<i>hly</i>	6(9.4)	3(16.7)	3(6.5)	0.211
<i>cnf</i>	3(4.7)	1(5.6)	2(4.3)	0.837

Note: *P values for comparison between CA-UTI and HA-UTI *E. coli* isolates.

study, the prevalence of UTIs due to UPEC was 71.11% among deceased donor kidney transplant recipients. Moreover, 71.9% of the UPEC infections were community acquired, while 28.1% were hospital acquired.

With the continued emergence of antibiotic resistance, UTI treatment has become increasingly challenging. The infecting organisms for HA-UTIs tend to be more resistant than those for CA-UTIs, and thus, HA-UTIs generally require more expensive antibacterial agents and higher treatment costs. Not surprisingly, in the present study, the HA *E. coli* strains exhibited higher resistance rates to ciprofloxacin, cotrimoxazole, trimethoprim/sulfamethoxazole, and amikacin than did the CA *E. coli* strains. Cooke et al¹⁸ also reported higher resistance rates among HA *E. coli* to ciprofloxacin and trimethoprim/sulfamethoxazole as well as to ampicillin and cefalotin. Also, consistent with our findings, Ferjani et al¹⁹ reported higher resistance rates to amikacin and cotrimoxazole among *E. coli* strains isolated from HA-UTIs. ESBL-producing bacteria can hydrolyze and confer resistance to cephalosporins, penicillins, and monobactams, and Halaji et al²⁰ found that ESBL-producing strains are significantly more frequent in kidney transplant patients (KTPs) compared with non-KTPs. In the present study, the percentage of patients positive for ESBL was statistically higher among patients with HA-UTIs than among patients with CA-UTIs. UPEC

strains employ an array of virulence factors that are related to adhesive organelles, iron acquisition/transport systems, hemolysin, and flagella to overcome host immunity, and consequently contribute to the successful bacterial colonization and invasion within the urinary tract. Adhesions promote colonization, invasion, and replication within uroepithelial cells, which are indispensable for the establishment of an infection. The most common virulence factors in UPEC are genes encoding adhesive systems, and the most prevalent adhesive genes observed in our study were *fim* (64.1%) and *pap GII* (45.3%). These findings were consistent with those reported by Zhao et al.²¹

Iron is an essential element for the survival of *E. coli*, but its availability in the urinary tract is extremely limited. In order to survive in the host, UPEC has evolved to harbor genes encoding iron acquisition systems, which allow them to more efficiently obtain iron. Of the iron acquisition systems genes tested in the present study, *irp2* was the most prevalent gene among the *E. coli* isolates, followed by *iroN* and then *iuc*. These findings are in agreement with those of Paniagua-Contreras et al²² who reported that *irp2* was the most frequent iron acquisition systems gene expressed by UPEC isolated from patients with UTIs. Moreover, we found that the prevalence rates of *irp2* and *iroN* expression were higher in the HA-UTI isolates than in the CA-UTI isolates. Further large-scale studies with in vitro bacterial culture and in vivo animal experiments are warranted to explore the functions of *irp2* and *iroN* in the uropathogenicity of *E. coli* and its association with HA-UTIs.

Toxins help a pathogen survive in the host by killing immune cells, helping the pathogen gain access to nutrients inside the host cell, and allowing the pathogen to disseminate into deeper tissues to cause severe invasive infections. Previous studies showed that the prevalence of toxins-associated virulence genes varies significantly by geographical location, ranging from 0–44% for *hly* and from 0–30% for *cnf*.^{23,24} The percentage of isolates expressing the toxins-encoding genes *hly* and *cnf* in the present study were 9.4% and 4.7%, respectively.

In conclusion, this study showed that *E. coli* strains, especially HA *E. coli* strains, isolated from patients with UTI after kidney transplantation from deceased donors tends to exhibit high rates of antibiotic resistance and harbor numerous virulence genes. These findings provide evidence for genetic characterization and epidemiological studies of *E. coli* strains causing UTIs in kidney transplant recipients and suggest that timely UTI prevention and

intervention strategies should be applied in patients after kidney transplantation from deceased donors.

Data Sharing Statement

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Ethical Approval

This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (Qingdao, China; no. QYFY WZLL 26484). All procedures involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethics standards. Written informed consent was obtained from all individual participants included in this study.

Funding

There is no funding to report.

Disclosure

The authors declare that they have no competing interests.

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