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ORIGINAL ARTICLE

Molecular Characterization of Carbapenem-Resistant NDM-Producing *Escherichia Coli* from Recurrent Urinary Tract Infection Patients

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SUMMARY

Background: **This study aimed to clarify the microbiological characteristics of carbapenem-resistant *Escherichia coli* (CRECO) due to New Delhi metallo-β-lactamase (NDM)-producing from recurrent urinary tract infection (RUTI) patients.**

Methods: **CRECO isolates were isolated from the urine of RUTI patients, identified with VITEK 2 compact system, and confirmed by MALDI-TOF MS. Antimicrobial susceptibility testing (AST) was performed with VITEK 2 compact system and Kirby-Bauer (K-B) method. Disk diffusion was used for extended spectrum beta-lactamase (ESBL) test. Phenotypic assays, including modified Hodge test (MHT), EDTA-modified carbapenem inactivation method (eCIM), and modified carbapenem inactivation method (mCIM), were performed to screen the carbapenemase. The antibiotic resistance genes were detected by polymerase chain reaction (PCR). Multilocus sequence typing (MLST) was performed for molecular typing of the strains.**

Results: **Among 63 CRECO strains, 22 (34.9%) strains were NDM-positive, in which NDM-5 accounted for 68.2% (15/22), NDM-1 accounted for 22.7% (5/22), and NDM-3 accounted for 9.1% (2/22). Among the 22 strains, 20 (90.9%) strains were co-carrying ESBLs genes, 12 (54.6%) strains were co-carrying *bla*$_{CTX}$ and *bla*$_{TEM}$, 8 (36.4%) strains were co-carrying *bla*$_{CTX}$ or *bla*$_{TEM}$, and 5 strains were co-carrying AmpC genes. *Bla*$_{CMY-6}$ and *bla*$_{CMY-156}$ accounted for 9.1% (2/22) and *bla*$_{CMY-42}$ and *bla*$_{DHA-1}$ accounted for 4.5% (1/22). Ten (45.5%) strains were co-carrying quinolone resistance genes. Three (13.6%) strains were co-carrying colistin resistance genes *mcr-1*. Six (27.3%) strains showed OmpF-expressed loss. Fourteen strains were positive and 8 strains were negative in the MHT, but mCIM and eCIM were both positive; the results of double-disc synergy method for detection of ESBLs were all negative in NDM-positive CRECO strains. The NDM-producing CRECO strains showed high-resistant rate to most antibiotics.**

Conclusions: **The antibiotic resistance mechanisms of NDM-positive CRECO are the coexistence of multiple resistance genes and/or the loss of or lesser expression of OMP. The emergence of *mcr-1* gene in CRECO should be paid more attention by clinicians and microbiologists. Further surveillance should be strengthened to study the microbiological characteristics in order to control infection caused by NDM-positive CRECO better.**

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INTRODUCTION

Urinary tract infections (UTIs), including cystitis (lower urinary tract/bladder) and pyelonephritis (upper urinary tract/kidney), are some of the most common diseases, can cause urosepsis, and lead to multiorgan dysfunction, failure, and even death [1-2]. A UTI begins with colonization of the urethral meatus or vaginal introitus by either uropathogens or fecal flora that ascends via the urethra to the bladder. The most common pathogen causing UTIs is *Escherichia coli* (50%) [3]. Over the last few decades, the emergence of multi-drug-resistant *Escherichia coli* causing UTIs has been increasing, making treatment more complicated, even ending in failure. There is growing concern regarding the overprescription of antibiotics for suspected UTIs, as this practice exerts selective pressure that promotes the emergence and propagation of antibiotic resistance genes [4].

In 2009, NDM was detected for the first time in a Swedish patient hospitalized in New Delhi [5]. Since then, with more and more NDM detections all over the world, the research on NDM also gradually deepened. Yet, the mechanism of drug resistance and microbiological characteristics of the NDM-positive CRECO strains from RUTI patients remain unknown. Therefore, we conducted this study to clarify these issues as listed below.

MATERIALS AND METHODS

Bacterial isolation and identification

A total of 63 nonrepetitive carbapenem insensitive *E. coli* were collected out of 3,500 *E. coli* strains isolated from the urine of RUTI patients, and 27 strains were isolated from female patient samples. All strains were identified with VITEK 2 compact system (bioMerieux, France) and confirmed by MALDI-TOF MS (Bruker Biotyper, Germany).

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing (AST) was performed *in vitro* with VITEK 2 compact system (bioMerieux, France) and Kirby-Bauer (K-B) disk diffusion method. *Escherichia coli* (ATCC®25922 and ATCC®35218) and *Klebsiella pneumoniae* (ATCC®700603, ATCC®BAA-1705, and ATCC®BAA-1706) were used for quality control (QC). The interpretation criteria for tested antibiotics followed the Clinical Laboratory and Standard Institute (CLSI) M100-S30 [6] and European Committee on Antimicrobial Susceptibility Testing (EUCAST) [7]. The following four carbapenems were used in the study: imipenem, meropenem, doripenem, and ertapenem. Carbapenem-resistant *Escherichia coli* (CRECO) was defined as resistance to any one of the four carbapenems.

DNA extraction

The fresh, purely colony of the tested bacteria was suspended in 500 μL of sterile distilled water in a microcentrifuge tube and was boiled in order to prepare the DNA templates for polymerase chain reaction (PCR).

Drug resistance gene detection

Drug resistance gene was screened by PCR, and the positive products were validated with Sanger sequencing. Resistance genes include AmpC (*bla*$_{CMY}$, *bla*$_{DHA}$, *bla*$_{ACC}$, *bla*$_{EBC}$, *bla*$_{FOX}$, and *bla*$_{MOX}$), ESBL (*bla*$_{TEM}$, *bla*$_{CTX}$, and *bla*$_{SHV}$), quinolone resistance gene (*aac(6)-Ib-cr*, *qnrA*, *qnrB*, *qnrC*, *qnrD*, and *qnrS*), aminoglycoside resistance genes (*aac(6)- Ib*, *armA*, and *rmtB*), colistin resistance genes (*mcr1 ,mcr2, mcr3, mcr4, and mcr5*), carbapenemase genes; Ambler A (*bla*$_{NMC}$, *bla*$_{IMI}$, *bla*$_{SME}$, *bla*$_{KPC}$, and *bla*$_{GES}$), Ambler B (*bla*$_{IMP}$, *bla*$_{VIM}$, *bla*$_{NDM}$, *bla*$_{SIM}$, *bla*$_{SPM}$, and *bla*$_{GIM}$), and Ambler D (*bla*$_{OXA48}$), and the loss of outer membrane prion gene (OmpA, OmpC, and OmpF).

Molecular typing

Multilocus sequence typing (MLST) was performed with eight housekeeping genes, including *icdA*, *pabB*, *polB*, *putP*, *trpA*, *trpB*, and *uidA*. The types of sequences were determined using the MLST database (http://www.pasteur.fr/mlst.).

Phenotypic detection of ESBL and carbapenemase

The method of disk diffusion was performed to detect the ESBLs following the CLSI M100-S30 [6]. A ≥ 5-mm increase in a zone diameter for either Ceftazidime-clavulanate vs. Ceftazidime or Cefotaxime-clavulanate vs. Cefotaxime was considered ESBLs-positive. Modified carbapenem inactivation method (mCIM) and EDTA-modified carbapenem inactivation method (eCIM) were used for carbapenemase detection, and the result interpretation followed the CLSI M100-S30 [6]. The eCIM results could only be interpreted when the mCIM result was positive. A ≥ 5 mm increase in zone diameter for eCIM vs. for mCIM indicates Metallo-β-lactamase positivity.

RESULTS

Detection rate of the carbapenem-resistant *Escherichia coli*

Among 3,500 strains of *Escherichia coli*, 63 strains were found resistant to at least one of carbapenems, with the detection rate of 1.8%, defined as CRECO. Forty-six (73.02%) isolates showed resistance to all of the four carbapenems. Two (3.17%) isolates showed resistance, except to imipenem. One (1.59%) isolate showed resistance except to meropenem. One (1.59%) isolate showed resistance to imipenem and ertapenem. One (1.59%) isolate showed resistance to doripenem and ertapenem. One (1.59%) isolate showed resistance to ertapenem and intermediate resistance to doripenem.

Table 1. Phenotype, resistance genes, and MLST typing features of NDM-producing CRECO.

No.	Carbapenems resistance				MHT	mCIM	eCIM	ESBL	Resistance gene	MLST
	IMP	MEM	DOR	ETP						
E 4	R	R	R	R	P	P	P	N	*bla*$_{NDM-1}$, *la*$_{CMY-6}$	ST2
E 42	R	R	R	R	P	P	P	N	*bla*$_{NDM-1}$, *bla*$_{CTX-M-55}$, *OmpF*	ST2
E 44	R	R	R	R	P	P	P	N	*bla*$_{NDM-5}$, *bla*$_{CTX-M-14}$, *aac (6')-Ib-cr*	ST2
E52	R	S	R	R	N	P	P	N	*bla*$_{NDM-3}$, *bla*$_{CTX-M-14}$, *OmpF*	ST741
E53	R	R	R	R	P	P	P	N	*bla*$_{NDM-3}$, *bla*$_{CTX-M-14}$, *OmpF*	ST741
E54	R	R	R	R	P	P	P	N	*bla*$_{NDM-5}$, *bla*$_{TEM-1}$, *bla*$_{CTX-M-55}$	ST2
E55	R	R	R	R	P	P	P	N	*bla*$_{NDM-1}$, *bla*$_{CMY-6}$, *bla*$_{TEM-1}$, *bla*$_{CTX-M-1}$, *mcr-1*, *OmpF*	ST2
E58	R	R	R	R	P	P	P	N	*bla*$_{NDM-5}$, *bla*$_{CMY-42}$, *bla*$_{TEM-1}$, *bla*$_{CTX-M-15}$, *aac (6')-Ib-cr*	ST692
E60	R	R	R	R	N	P	P	N	*bla*$_{NDM-5}$, *bla*$_{TEM-135}$, *bla*$_{CTX-M-14}$, *aac (6')-Ib-cr*, *qnrS*	ST2
E61	R	R	R	R	P	P	P	N	*bla*$_{NDM-5}$, *bla*$_{TEM-1}$, *bla*$_{CTX-M-14}$	ST84
E68	R	R	R	R	N	P	P	N	*bla*$_{NDM-5}$, *bla*$_{TEM-1}$, *bla*$_{CTX-M-14}$	ST2
E69	R	R	R	R	P	P	P	N	*bla*$_{NDM-5}$, *bla*$_{TEM-135}$, *bla*$_{CTX-M-14}$, *aac (6')-Ib-cr*	ST2
E70	R	R	R	R	P	P	P	N	*bla*$_{NDM-5}$, *bla*$_{TEM-1}$, *bla*$_{CTX-M-14}$, *Omp F*	ST8
E72	R	R	R	R	P	P	P	N	*bla*$_{NDM-1}$, *bla*$_{TEM-1}$, *qnrS*	ST21
E74	I	R	R	R	P	P	P	N	*bla*$_{NDM-5}$, *bla*$_{TEM-1}$, *bla*$_{CTX-M-55}$	ST2
E76	R	R	R	R	N	P	P	N	*bla*$_{NDM-5}$, *bla*$_{CTX-M-55}$	ST2
E79	R	R	R	R	P	P	P	P	*bla*$_{NDM-5}$, *bla*$_{TEM-1}$, *bla*$_{CTX-M-55}$, *Omp F*, *qnrS*	ST2
E81	R	R	R	R	N	P	P	N	*bla*$_{NDM-5}$, *bla*$_{CMY-156}$, *bla*$_{DHA-1}$, *qnrB-6*	ST650
E82	R	R	R	R	N	P	P	N	*bla*$_{NDM-5}$, *bla*$_{CMY-156}$, *bla*$_{CTX-M-14}$	ST2
E84	R	R	R	R	N	P	P	N	*bla*$_{NDM-5}$, *bla*$_{TEM-1}$, *bla*$_{CTX-M-55}$, *aac (6')-Ib-cr*, *MCR-1*	ST471
E85	R	R	R	R	P	P	P	N	*bla*$_{NDM-5}$, *bla*$_{TEM-1}$, *bla*$_{CTX-M-55}$, *aac (6')-Ib-cr*, *MCR-1*	ST471
E89	R	R	R	R	N	P	P	N	*bla*$_{NDM-1}$, *bla*$_{CTX-M-15}$, *aac(6')-Ib-cr*	ST2

P - positive, N - negative, NA - not applicable.

One (1.59%) isolate showed resistance to meropenem and intermediate resistance to doripenem. One (1.59%) isolate showed intermediate resistance to both doripenem and ertapenem. Four (6.35%) isolates only showed resistance to ertapenem, and five (7.94%) isolates only showed intermediate resistance to ertapenem. The results are shown in Table 1.

Phenotypic detection of ESBL and carbapenemase

The results of MHT in 22 NDM-producing CRECO strains were positive in 14 strains (63.6%) and negative in 8 strains (36.4%), but the results of mCIM and eCIM were both positive. Different from the results of ESBL gene detection, NDM-producing strains were all negative by disk diffusion in ESBL test. The results are shown in Table 1.

Detection of NDM genes of CRECO strains by PCR

Among 63 CRECO strains, 22 strains were identified as NDM-producing CRECO (Table 1), with the detection rate of 34.9% (22/63), in which NDM-5 was the most common, accounting for 68.2% (15/22), followed by NDM-1, accounting for 22.7% (5/22), and NDM-3, accounting for 9.1% (2/22).

Detection of resistance genes

Among the 22 NDM-producing CRECO strains, 20 (90.9%) strains were co-carrying ESBLs, in which there were 8 (36.4%) strains co-carrying *bla*$_{CTX}$ or *bla*$_{TEM}$, 12 (54.6%) strains co-carrying *bla*$_{CTX}$ and *bla*$_{TEM}$, and no ESBL was detected in 2 (9.1%) strains. There were 5 strains co-carrying AmpC enzyme; *bla*$_{CMY-6}$ and *bla*$_{CMY-156}$ accounted for 9.1% (2/22), respectively, and *bla*$_{CMY-42}$ and *bla*$_{DHA-1}$ accounted for 4.5% (1/22), respectively

Table 2. Antimicrobial susceptibility profile of 22 NDM-producing CRECO strains.

Drug class	Antimicrobial agents	R (%)
Penicillins	Ampicillin	100
	Mecillinam	45.6%
Beta-lactam/Beta-lactamase inhibitor combinations	Ticacillin/Clavulanic acid	100
	Ampicillin/Sulbactam	100
	Cefoperazone/Sulbactam	100
	Piperacillin/Tazobactam	100
Cephems	Cefazolin	100
	Cefotetan	100
	Ceftriaxone	100
	Ceftazidime	100
	Cefepime	100
Aminoglycosides	Gentamicin	59.1%
	Tobramycin	59.1%
	Amikacin	22.7%
Monobactams	Aztreonam	95.5
Carbapenems	Ertapenem	100
	Doripenem	100
	Meropenem	95.5
	Imipenem	95.5
Tetracyclines	Doxycycline	90.1%
	Minocycline	50%
	Tigecycline	4.5%
Quinolones and fluoroquinolones	Ciprofloxacin	86.4%
	Levofloxacin	86.4%
Folate pathway inhibitors	Trimethoprim/Sulfamethoxazole	68.2%
Fosfomycins	Fosfomycin	31.8%
Nitrofurans	Nitrofurantoin	5%
Lipopeptides	Colistin	9.1%

It should be noted that one strain carried $bla_{\text{CMY-156}}$ and $bla_{\text{DHA-1}}$ simultaneously. There were 10 (45.5%) strains co-carrying quinolone resistance genes, in which there were seven strains co-carrying *aac (6')-Ib-cr*, accounting for 31.8% (7/22), three strains co-carrying *qnrS*, accounting for 13.6% (3/22), and one strain co-carrying *qnrB*, accounting for 4.5% (1/22). It should be noted that one strain carried *qnrS* and *aac (6')-Ib-cr* simultaneously. There were 3 (13.6%) strains co-carrying colistin resistance genes *mcr-1*. There were 6 (27.3%) strains that showed OmpF-expressed loss, accounting for 27.3% (6/22). However, no aminoglycoside resistance genes were found to co-carrying in the NDM-producing CRECO strains simultaneously. The results are summarized in Table 1.

MLST of the NDM-producing CRECO strains

Based on the MLST, the 22 NDM-producing CRECO strains belonged to 7 different sequence types (STs), ST2 and ST741 were more common, accounting for 59.1% (13/22) and 18.2% (4/22), respectively. There was only one NDM-producing CRECO strain belonging to ST21, ST692, ST84, ST8, and ST650, accounting for 4.5%, respectively. See Table 1 for details.

Antimicrobial susceptibility test of the NDM-producing CRECO strains

The NDM-producing CRECO strains showed high resistance rates to most antibiotics. The resistance rates in the study are shown in Table 2.

DISCUSSION

Urinary tract infections are among the most common bacterial infectious diseases worldwide. For patients who experience RUTI, it represents a major health hazard. *Escherichia coli* is the most common pathogen of UTI. In a study of 289 female patients with recurrent urinary tract infection from 2006 to 2014, 71% persistent and 47% reinfected recurrent urinary tract infections were caused by *Escherichia coli* [8]. Gordon et al. reported that the isolation rate of *E. coli* in UTI was as high as 47% in North America, Europe, and Latin

America in a retrospective study of SENTRY Surveillance Project in 2000 [9]. A study carried in China also showed that *E. coli* rank no. 1, accounting for 28.85% in pathogen-caused UTIs from 2016 to 2017 [10]. To ameliorate the incidence of UTIs, various antibiotics have been the mainstay of therapy, but due to the emergence of multi-resistant *E. coli*, recurrent infections continue to afflict many patients [11]. Among the major multidrug-resistant bacteria, the emergence and dissemination of CRECO is recognized as one of the most serious threats to public health worldwide due to the limited availability of therapeutic options and high mortality. The carbapenem resistance in *E. coli* was predominantly caused by bla_{NDM}, which was identified in both hospitalized patients and healthy people [12]. NDM is a type of metallo β-lactamase (MBL), which is able to hydrolyze most β-lactams, including carbapenems, except monobactams. The hydrolysis of β-lactams by NDM enzymes cannot be prevented by β-lactamase inhibitors, including avibactam, clavulanate, sulbactam, and tazobactam [13,14]. NDM-1 was first identified in 2008 in a Swedish patient hospitalized in new Delhi, India [5]. Since then, 24 NDM variants have been identified in *Enterobacteriaceae*, *Acinetobacter sp.*, and *Pseudomonas sp.*, etc. The SMART global surveillance program demonstrated that the NDM-positive detection rate in *Enterobacteriaceae* in 55 countries from 2008 through 2014 was 0.28% (290/103, 960); the prevalence of NDM-positive strains varied significantly in different countries: 5.01% in the United Arab Emirates (UAE), 6.15% in Egypt, 6.22% in India, and 6.26% in Serbia [15]. Another large-scale multinational study, INFORM, collected 38,266 *Enterobacteriaceae* isolates from 40 countries between 2012 and 2014 [16]. The proportions of NDM-positive strains were 0.19% (72/38, 266) in *Enterobacteriaceae* [16], consistent with the relatively low prevalence revealed by the SMART project. Fan [17] carried a retrospective study of bla_{NDM} in 12,858 Gram-negative bacteria in China from 2010 through 2019, and the results showed that the isolation rates of bla_{NDM}-positive strains were 0.08% (2/2,520) in 2015, 0.06% (3/5, 334) in 2016, 0.24% (1/424) in 2018, and 0.05% in total. Unlike other resistance genes that can be isolated from environment or livestock and poultry, the bla_{NDM}-positive strains were only isolated from the clinical patients. Another cross-sectional study investigated the prevalence of CRECO in healthy volunteers in 19 provinces in China and showed that the CRECO isolation rate was 2.38% (92/3, 859) [12]. Among the 92 CRECO strains, 43 (46.7%) strains were NDM-positive, 40 (93%) strains were NDM-5-positive, and 3 (7%) strains were NDM-1-positive. In our study, the isolation rate of CRECO was 1.8%; NDM-positive strains had an isolation rate of 0.6%. The detection rate of NDM in CRECO was 34.9%, in addition to NDM-5 and NDM-1 (the detection rate was 68.2% and 22.7%, respectively). Meanwhile, there were NDM-3 detected in the study, and the detection rate was 9.1%, which was similar with the study mentioned above and suggested a relatively low prevalence.

These NDM variants are highly similar to each other, with only several amino acids different; their hydrolysis activities toward carbapenem also vary. Compared with NDM-1, NDM-5 possesses stronger carbapenemase activity [18]. In China, NDM-5 has frequently been observed during surveillance of both clinical and food animal sectors [12].

In our study, bla_{TEMs} or $bla_{CTX\text{-}Ms}$ was detected in most of these *E. coli* strains, but their ESBL tests were negative. The reason why antibiotics with enzyme inhibitors show resistance is that the production of carbapenemase by bacteria cannot be inhibited by any of the beta-lactamase inhibitors.

It is noteworthy that co-carrying of antibiotic resistance genes by a single pathogenic bacterial isolate has become a major threat to public health. Particularly, co-production of multiple carbapenemase genes, especially bla_{NDM} and bla_{KPC}, brings a significant challenge for clinical treatment. Gronthal Thomas reported the first case on the transmission of carbapenemase-producing *E. coli* between dogs and humans [19]. A study demonstrated that swine waste is an important reservoir of bla_{NDM} and *mcr-1* [20]. Sekizuka reported that a strain of *E. coli* was isolated from a wastewater treatment plant producing dual β-lactamases $bla_{NDM\text{-}5}$ and $bla_{CTX\text{-}M\text{-}55}$ in Tokyo Bay in Japan [21]. It indicated an emerging potential health hazard, suggested environ-mental contamination through WWTP effluents leading to producers of NDM variants.

The results in the study showed 20 (90.9%) NDM-positive CRECO strains were co-carrying ESBLs, 5 strains were co-carrying AmpC enzyme, 10 (45.5%) strains were co-carrying quinolone resistance genes, 3 (13.6%) strains were co-carrying colistin resistance genes *mcr-1*, and 6 (27.3%) strains showed OmpF-expressed loss. These resistance mechanisms worked together so that the strains showed higher resistance rates to most antibiotics used in clinical setting. To ampicillin in penicillins, beta-lactam/beta-lactamase inhibitor combinations, cephems, ertapenem, and doripenem, the resistance rates were high, up to 100%; to aztreonam, meropenem, imipenem, and doxycycline, the resistance rates were above 95%. Only the resistance rates of tigecycline, amikacin, nitrofurantoin, and colistin were below 10% and kept a good antibacterial activity.

CONCLUSION

As the resistance mechanism of NDM-positive CRECO strain is relatively complex, it leads to clinical treatment failure, especially for RUTI patients, and increases the suffering of patients, extends the length of hospital stay, and increases the medical cost. Further surveillance and management are urgently needed to deepen the research on the NDM-positive CRECO strains, including the clinical significance and microbiological characteristics. It will help in controlling the infection, delaying the

emergence of resistant strains, and prolonging the life cycle of antibiotics.

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Ethical Approval:
This study was approved by the Ethics Committee of Shijitan Hospital, CMU. The informed consent was waived, because this study was a retrospective study with a review of related data through electronic medical records.

Declaration of Interest:
There is no conflict of interest between the authors of this study; the authors report no conflicts of interest in regard to this work, and they are responsible for the authenticity of the content.

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