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The role of early use of Carbapenems perioperatively for urolithiasis with ESBL-producing Escherichia coli

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Abstract

Background Urolithiasis combined with ESBL-producing *E. coli* is often difficult to control and leads to higher postoperative infection-related complications. This study was aim to explore the efficacy and necessity for early use of carbapenem antibiotics perioperatively in urolithiasis patients with urinary tract infections caused by ESBL-producing *E. coli*.

Methods The study included a total of 626 patients who were separated into two groups: Group I (the ESBL-producing *E. coli* group) and Group II (the non-ESBL-producing *E. coli* group). Antibiotic susceptibility testing was performed and the two groups induced postoperative infection-related events were recorded. the efficacy of perioperative antibiotics was evaluated.

Results All strains of *E. coli* in our research were sensitive to Carbapenems antibiotics. In addition to Carbapenems, the resistance rates of ESBL-producing *E. coli* to 6 other commonly used antibiotics were higher than those of non-ESBL-producing strains. Based on the preoperative antibiotic susceptibility test for the ESBL-producing *E. coli* group and the qSOFA score, the Carbapenems were more effective than the β-lactamase inhibitors ($p=0.08$), while for the non-ESBL-producing *E. coli* group, there was no difference in the treatment effects between Carbapenems, β-lactamase inhibitors, Ceftazidime and Quinolones ($p=0.975$).

Conclusions Carbapenem antibiotics significantly reduced the incidence of postoperative infection-related events compared with other types of antibiotics for ESBL-producing *E. coli* infections in patient with urolithiasis.

Keywords Urinary tract infections, Escherichia coli, Urolithiasis

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Introduction

Urinary tract infection (UTI) is one of the most common bacterial infections, which is closely associated with urinary tract calculi. With excessive and unreasonable antibiotics applied, UTI caused by ESBL (extended-spectrum β-lactamase)-producing *E. coli* has increased year by year [1, 2]. The infection is more difficult to manage since the organisms are resistant to most antibiotics. Urolithiasis is a substantial health problem with a prevalence of 6.4% and a 10-year recurrence rate of approximately 50% [3, 4]. At present, surgical intervention is the most effective treatment for stones > 1 cm and stone-free rates have increased considerably with new developments in instruments and techniques. However, the incidence of postoperative infection-related events in urolithiasis patients with ESBL-producing *E. coli* infection is still high, resulting in various complications, such as fever, bleeding, uremia and even death.

The treatment for UTI caused by ESBL-producing *E. coli* requires empiric antibiotic therapy. To be able to select safe, effective, and preferable antibiotics for the first line therapy, it is crucial that the antimicrobial susceptibility and resistance patterns of the drugs are determined [5]. Studies have shown that the risk factors for greater susceptibility to UTI are older age, female gender, urinary abnormalities, urinary tract obstructions, impaired immune response, urinary catheter inserted, and surgical procedures of the urinary tract [6]. In clinical practice, the effect of selecting perioperative antibiotics based on antimicrobial sensitivity has been found to be unsatisfactory, sometimes even with the occurrence of postoperative urosepsis. To the best of our knowledge, the incidence and characteristics of ESBL-producing *E. coli* bacteria in urolithiasis patients have not yet been discussed in detail. A previous report stated that 15–45% ESBL-producing *E. coli* infections were not appropriately treated [7]. Some studies in literature have shown that Carbapenem has a higher clinical success rate in patients with biological infection caused by ESBL [8, 9]. However, the indiscriminate use of Carbapenem is not without consequences. The increased use of carbapenem drugs has promoted the emergence of Carbapenem-resistant Enterobacteriaceae. Moreover, the role of β-lactamase inhibitors in patients infected with ESBL-producing pathogens is unclear.

The aim of the present study was to explore the efficacy of various antibiotics on ESBL-producing *E. coli* and non-ESBL-producing *E. coli* infections in patients with urinary stones and to determine the efficacy and necessary of Carbapenems for the treatment of ESBL-producing *E. coli*. Moreover, we also analyzed the incidence rate of postoperative infection-related events to provide a theoretical rationale for the proper use of perioperative antibiotics.

Methods

This retrospective study included 626 patients, comprising 136 males and 490 females with a mean age of 53.1 ± 12.3 years. All the patients were diagnosed with UTI caused by *E. coli* and underwent surgery such as ureteroscope lithotripsy, retrograde intrarenal surgery or percutaneous nephrolithotomy for urinary stones in the First Affiliated Hospital of Guangzhou Medical University from 2013 to 2017. The inclusion criteria were as follows: in a good nutrition condition, no other infections, no obstructive uropathy, body mass index < 35, operation time < 2 h, stable renal function and having received antibiotic treatment at least 3 days before the surgery. Patients were categorized into two groups according to the outcomes of preoperative midstream urine culture: Group I (ESBL-producing *E. coli*), Group II (non-ESBL-producing *E. coli*). This study abided by the ethical requirements. Because of the retrospective nature of the study, written informed consent was not required.

Midstream urine was collected after proper perineal cleaning. Fresh urine samples were delivered to the laboratory for bacterial cultures and antimicrobial susceptibility tests. ESBL-producing strains of *E. coli* were identified using a Vitek2 automatic bacteria identification instrument (BioMerieux Vitek, Hazelwood, MO). The antibiotic susceptibility of clinical isolates was tested with the Kirby-Bauer diffusion method. Other laboratory tests were routine blood test and blood biochemistry examinations. Postoperative complications were recorded and classified as simple fever, sepsis and severe sepsis.

The diagnosis of urosepsis was made according to the European diagnostic criteria for sepsis as follows [10]: Criteria I: proof of bacteremia or clinical suspicion of sepsis; Criteria II: systemic inflammatory response syndrome (SIRS), including body temperature ≥ 38℃ or ≤ 36℃, tachycardia ≥ 90 beats /min, tachypnoea ≥ 20 breaths/min, PaCO2 ≤ 32 mmHg and leukocytes ≥ 12 000/μL or ≤ 4000/μL; Criteria III: multiple organ dysfunction syndrome, manifested as arterial systolic blood pressure ≤ 90 mmHg or mean arterial blood pressure ≤ 70 mmHg for ≥ 1 h despite adequate fluid or vasopressure agents resuscitation; Production of urine < 0.5 mL kg − 1 body weight/hour despite adequate fluid resuscitation; PaO2 ≤ 75 mm Hg (breathing room air) or PaO2/FiO2 ≤ 250 (assisted respiration); platelets < 80,000 / μL or decrease ≥ 50% in 3 days; blood-pH ≤ 7.30 or base excess ≥ 5 mmol /L or plasma-lactate ≥ 1.5-fold of normal; somnolence, agitation, confusion, coma. The diagnostic criteria for sepsis were criteria I + criteria II, and severe sepsis were criteria I + criteria II + criteria III.

As there has been controversy about whether quick sequential organ failure assessment (qSOFA) can replace SIRS in the determination of sepsis [11–13], for this study the sepsis patients were grouped according to the

Table 1 The outcomes of susceptibility test in 2 groups ESBL-producing strains of *E. Coli* to 10 antibiotics (*N* = 626)

Antibiotics	Group I (*N* = 350), n (%)			Group II (*N* = 276), n (%)		
	S	I	*R*	S	I	*R*
Meropenem	350 (100)	0 (0)	0 (0)	276 (100)	0 (0)	0 (0)
Imipenem	350 (100)	0 (0)	0 (0)	276 (100)	0 (0)	0 (0)
Cefoperazone/Sulbactam	209 (60)	102 (29)	39(11)	258 (93)*	11 (4)	7 (3)#
Piperacillin/Sulbactam	332 (94)	13 (4)	5 (2)	268 (97)	4 (1.5)	4 (1.5)
Amikacin	330 (94)	3 (1)	17 (5)	268 (97)	4 (1.5)	4 (1.5)#
Cefepime Hydrochloride	167 (48)	64 (18)	119 (34)	268 (97)*	0 (0)	8 (3)#
Ceftazidime	161(46)	38 (11)	151 (43)	255 (92)*	8 (3)	13 (5)#
Cefazolin Pentahydrate	7 (2)	0 (0)	343 (98)	177 (64)*	23 (8)	76 (28)#
Levofloxacin	87 (25)	7 (2)	256 (73)	185 (67)*	12 (4)	79 (29)#
Ciprofloxacin	83 (24)	7 (2)	260 (74)	171 (62)*	9 (3)	96 (35)#

Group I (ESBL-producing *E. coli*); Group II (non-ESBL-producing *E. coli*); S (susceptible), I (intermediary), R (resistance); *Susceptibility rate of Group I to the drugs was significantly lower than that of Group II ($P<0.01$); #resistance rate of Group I to the drugs was significantly higher than that of Group II ($P<0.01$

Table 2 Patient's demographics and clinical characteristics in the two study groups (*N* = 626)

Characteristics	Group I	Group II	*P*
Patients, n	350	276	-
Age, years	54.1 ± 12.2	52.2 ± 12.6	0.795
Gender, male/female	81/269	55/221	0.380
BMI, kg/m2	23.0 ± 4.2	22.5 ± 2.9	0.690
History of urolithiasis surgery			
URL/Total, n	3/350	1/276	0.635
RIRS/Total, n	2/350	3/276	0.659
PCNL/Total, n	4/350	2/276	0.700
WBC before surgery	7.3 ± 2.3	6.9 ± 2.1	0.381
HB before surgery	120.0 ± 19.0	124.0 ± 17.6	0.257
CT value of urolithiasis, Hu	898.8 ± 232.8	919.3 ± 248.3	0.403
Stone surface area, mm^2	355.2 ± 294.3	346.1 ± 262.2	0.253
Diabetes/Total, n	42/350	39/276	0.472
Kind of the performance			
URL/Total, n	42/350	30/276	0.706
RIRS/Total, n	64/350	40/276	0.234
PCNL/Total, n	244/350	206/276	0.180

BMI, Body Mass Index; WBC, white blood cell*10^9/L; HB, hemoglobin, g/L; CT, computed tomography; URL, ureteroscope lithotripsy; RIRS, retrograde intrarenal surgery; PCNL, percutaneous nephrolithotomy

qSOFA score on the basis of SIRS criteria. The analyses were based on the third international consensus definitions for sepsis and septic shock (Sepsis-3) task force, which recently introduced a new clinical qSOFA score for identification of patients at risk of sepsis, i.e. systolic blood pressure of ≤100 mmHg, respiratory rate of ≥22/minute, and altered mental status. There were three indicators, with one point for each, and a score of ≥2 was considered as sepsis or organ dysfunction [11].

Statistical analysis

Data obtained in the study were analysed statistically using SPSS vn.16.0 software. Results were stated as mean ± standard deviation values, or number and percentage (%). Continue variables were compared using Student's t-test or Mann-Whitney u test. Counting data were applied the chi-square test. A value of $p<0.05$ was considered statistically significant.

Table 3 Infection-related complications in the two study groups after surgery

Complication	Group I (*N* = 350)	Group II (*N* = 276)	*P*
Simple Fever, n (%)	40(11.4)	15 (5.4)	0.010
Sepsis, n (%)	99 (28.3)	37 (13.4)	< 0.001
Total, n (%)	139 (39.7)	52 (18.8)	< 0.001

Results

The susceptibility and resistance rate of the two groups of ESBL-producing strains of *E. coli* to frequently-used antibiotics are shown in Table 1. ESBL-producing *E. coli* accounted for 55.9% (350/626) in all patients. The strains of Group I were significantly more resistant to most of the drugs than the Group II ($p<0.01$), except for Meropenem and Imipenem which were all strains sensitive. In terms of the drug susceptibility, the value of Group I were lower than those of Group II.

There was no significant difference between Group I and Group II strain infections in respect of the number of patients, age, gender or body mass index (Table 2). No statistically significant differences were determined between Group I and Group II in respect of other clinical characteristics such as preoperative white blood cell and hemoglobin, general characteristics of the stone (CT value, stone surface area), incidence of diabetes, or type of operation.

In the comparison of total infection-related complications, the number of patients in group I was significantly higher than group II ($p=0.01$). A statistically significantly greater number of patients developed simple fever and sepsis in Group I (n:40, 99) compared to Group II (n:15, 37) ($p<0.001$) (Table 3). Of the total number of patients with sepsis, 8 in Group I and 6 in Group II had severe sepsis.

As stated above, a qSOFA score of ≥2 was accepted as sepsis or organ dysfunction. The majority of patients had

a postoperative qSOFA score < 2, and 75 (12%) cases had a score > 2 (Group I: 52, Group II:23) ($p < 0.05$) (Table 4).

For comparison, the antibiotics were divided into Carbapenem, β-lactamase inhibitor (BLI) and Quinolone groups. The drug efficacy was compared by the incidence of non-urosepsis and urosepsis after surgery in the two patient groups (Table 5). In reducing the incidence of urosepsis, Carbapenems were much more efficacious than the other two group of antibiotics in Group I bacteria (2.2% vs. 15.1% vs. 25.7%, $p = 0.008$). However, the effects of all three types of antibiotics were not significantly different in Group II strains ($p = 0.975$).

Table 4 Postoperative qSOFA score in the two study groups

	Group I (*N* = 350)	Group II (*N* = 276)	Total	*P*
qSOFA<2, n (%)	298 (85.1)	253 (91.7)	551(88.0)	0.013
qSOFA ≥ 2, n (%)	52 (14.9)	23 (8.3)	75(12.0)	0.013

Table 5 The postoperative incidence of non-urosepsis and urosepsis after perioperative treatment with Carbapenem and BLI in the two study groups

		Carbapenem, *n* (%)	BLI, *n* (%)	Quinolone, *n* (%)	*P*
Group I	Non-urosepsis	46 (97.8)	107 (84.9)	26 (74.3)	0.008
	Urosepsis	1 (2.2)	19 (15.1)	9 (25.7)	
Group II	Non-urosepsis	11 (91.7)	76 (92.7)	56 (93.3)	0.975
	Urosepsis	1 (8.3)	6 (7.3)	4 (6.7)	

BLI (β-lactamase inhibitors)

Discussion

The spread of extended-spectrum β-lactamase producing organisms has gradually increased in hospitals and long-term care facilities [2, 14]. Patients infected with ESBL-producing *E. coli* can have poor outcomes due to delays in receiving appropriate antimicrobial therapy, especially urolithiasis patients with ESBL-producing *E. coli* infections. Carbapenems are well accepted as the antibiotics of first choice for ESBL-producing *E. coli* infection, and inadequate antibiotherapy is an isolated mortality risk factor, which is why the early empirical use of Carbapenems is extremely important [15]. Postoperative infection is a common complication of endoluminal surgery, with increasing incidence. The perfusion of normal saline, the increase of intrapelvic pressure and the reflux of fluid can all cause the occurrence of postoperative infection-related events in endoscopic surgery [16]. In the 626 UTI patients in the present study, there were no significant differences between the two groups in respect of patient demographics and clinical characteristics, while 350 (55.9%) cases with ESBL-producing *E. coli* infections were detected. This incidence rate of ESBL-producing *E. coli* organisms in urine culture was higher than those of other reports [2, 7, 17]. This discrepancy might be due to the fact that the selected cases were urolithiasis patients with UTI who underwent surgery, which added another high-risk factor for the development of ESBL- producing *E. coli* infections.

Mortality following bacteraemic infection caused by ESBL-producing *E. coli* was significantly higher than non-ESBL-producing *E. coli* [18]. In our research, the incidence of infection-related events during laparoscopic surgery is higher for ESBL-producing *E. coli* infections than for non-ESBL-*E. coli* infections, so clinicians must pay attention to this. Carbapenems are generally considered the drug of choice for ESBL-producing *E. coli* infections due to their stable effect against this organism. However, it has been reported [19] that the extensive use of carbapenem drugs is not without disadvantages, and may lead to the emergence of bacterial drug resistance. Besides, the antibiotic management in most country is so strict so the use of carbapenems in ordinary wards is restricted. In such situation, alternative antibiotics are often chosen because of a lack of carbapenems. Therefore, many medical institutions are likely to choose BLI for ESBL-producing *E. coli*. As previously stated, the incidence of infection-related events after endoluminal surgery is high, and it is therefore necessary to explore the importance of perioperative selection of carbapenem drugs for such patients. The results of this study demonstrated that *E. coli* were absolutely susceptible to Carbapenem antibiotics (Meropenem, Imipenem) with no drug resistance, whether ESBL-producing *E. coli* or non-ESBL-producing *E. coli*, while the BLI group such as Cefoperazone/Sulbactam, Piperacillin/Sulbactam were less effective in the treatment of ESBL-producing *E. coli* infections. The susceptibility rates for Cefoperazone/Sulbactam and Piperacillin/Sulbactam were determined to be 60% and 94% respectively, and resistance rates were 11% and 2%, respectively. In clinical work, Ceftazidime is usually selected as a perioperative drug for the treatment of ESBL-producing *E. coli* infections [20]. However, the resistance rate of ESBL-producing *E. coli* to this drug was found to be nearly 50%. In respect of other non-Carbapenem antibiotics, it was determined that of the ESBL-producing strains of *E. coli*, 98%, 73% and 74% were not susceptible to Cefazolin, Levofloxacin and Ciprofloxacin, respectively. This clearly demonstrates that these three antibiotics are not suitable for ESBL-producing *E. coli* infections. Nevertheless, they all had relatively lower resistance to the non-ESBL-producing *E. coli* infections, with 28%, 29%, 35% resistance rates to Cefazolin, Levofloxacin and Ciprofloxacin, respectively, similar to previous reports [21].

As seen in Tables 3 and 4, under the premise of preoperative regular use for 72 h of non-Carbapenem antibiotics, the rate of adverse reaction for Group I was higher than that of Group II, regardless of the incidence of sepsis

or qSOFA score. Therefore, the selection of reasonable antibiotics during the perioperative period is especially important for ESBL-producing *E. coli* infections. It has been reported that compared to non-β-lactamase/β-lactamase inhibitors, Carbapenems are only considered the drugs of choice for serious infections with ESBL-producing *E. coli* organisms [22]. A recent study showed that Carbapenem was not significantly superior to Cefepime or Piperacillin-Tazobactam for ESBL-producing *E. coli* infections in patients with hematological malignancy, but the sample size was relatively low [23]. Based on the incidence of urosepsis and susceptibility test, the results of the current study revealed that Carbapenems were significantly better than β-lactamase inhibitors in the treatment of urolithiasis patients with urinary tract ESBL-producing *E. coli* infections.

To the best of our knowledge, this is the first study to have compared the efficacy of Carbapenems and β-lactamase inhibitors in the treatment of ESBL-producing *E. coli* infections. The results demonstrated that after 72 h regular use of antibiotics preoperatively, the incidence of sepsis in the Carbapenems group was much lower than that of the β-lactamase inhibitor group. The efficacy of the two antibiotics seemed to be different in the treatment of ESBL-producing *E. coli* infections. However, the drug susceptibility test suggested that the bacteria were sensitive to both group of antibiotics. The explanations for this might be that first, the bacteria in urine culture and in stone culture were inconsistent, and the antibacterial spectrum of Carbapenems was wider than that of β-lactamase inhibitor [24]. Second, the differences in operation time and the skill of the surgeon (the perfusion of normal saline, control of intrapelvic pressure and reflux of fluid) might be influential factors. Third, it was not possible to obtain the same preoperative antibiotic dosage from each medical record because the study was retrospective. It is unclear if larger quantities of BLI exceed the capacity of ESBLs to hydrolyze them. It has been reported that some bacteria will produce other enzymes such as AmpC β-lactamases, which will further complicate the bacterial environment and reduce the efficiency of BLI [25]. Several studies have shown that the in vitro anti-ESBL activity of β-lactamase inhibitors is moderate to high [26–28], but this does not necessarily translate into clinical efficacy. Fourth, the anti-infection time before surgery might be insufficient. Therefore, it can be suggested that for UTI patients with urolithiasis infected by ESBL-producing *E. coli*, Carbapenems should be given priority in the use of perioperative antibiotics. In addition, the drugs have to be administered for at least 72 h preoperatively and adjusted according to the outcomes of routine urinalysis and drug susceptibility test.

For no-ESBL-producing *E. coli* infections, β-lactamase inhibitors, first-generation cephalosporins and Quinolones were all as effective as Carbapenems, with no statistical difference determined between them based on the incidence of postoperative sepsis and drug susceptibility test. Therefore, Quinolones or first-generation cephalosporins could be selected for perioperative anti-infection therapy when preoperative urinary culture is confirmed as non-ESBL-producing *E. coli*. However, in recent years, due to the resistance has become increasingly serious and the occurrence of adverse events, the clinical use of the quinolones or fluoroquinolones is limited [29, 30].

Limitations of this study included the retrospective nature and single center study. SOFA was not analyzed due to the lack of relevant data in our study. In additions, we couldn't avoid the potential influence of females, diabetics and kind of the surgeries on the outcome of infection complications in this study. In the future, we will conduct more high-quality research.

Conclusions

Carbapenem antibiotics significantly reduce the incidence of postoperative infection-related events compared with the β-lactamase inhibitor group of antibiotics for ESBL-producing *E. coli* infections in patients with urinary stone. Therefore, for such patients, although the urine culture drug sensitivity test indicates that other antibiotics are sensitive, Carbapenem antibiotics should be given priority in perioperative anti-infective treatment. For no-ESBL-producing *E. coli* infections, β-lactamase inhibitors, first-generation cephalosporins and Quinolones were all as effective as Carbapenems.

Abbreviations

UTI	Urinary Tract Infection
ESBL	Extended-Spectrum β-Lactamase
SIRS	Systemic Inflammatory Response Syndrome
q-SOFA	Quick Sequential Organ Failure Assessment
BLI	β-Lactamase Inhibitor

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Author contributions

YDL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: YDL. Acquisition of data: ZLL, DLC, HCZ.Analysis and interpretation of data: ZLL, DLC, HCZ. Drafting of the manuscript: ZLL, DLC, HCZ. Critical revision of the manuscript for important intellectual content: MAK, CHJ, SLZ, YDL. Statistical analysis: ZLL. Supervision: SLZ, YDL. Other: none.

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Data availability

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

Declarations

Ethics approval and consent to participate
This study met the ethical requirements by the Local Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. The Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University has waived the need of informed consent for this study. All methods were performed following the relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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