Acta Translational Medicine *An International Scientific Journal*	ISSN: 2521-8662	Volume 4	Issue 1	Pp.1-9	March 2021

EVOLUTION OF IMIPENEM RESISTANCE IN ESCHERICHIA COLI : A 9-YEAR RETROSPECTIVE SURVEILLANCE REPORT IN A HOSPITAL POPULATION OF SOUTHERN CHINA

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Abstract: *Escherichia coli* (*E. coli*) is one of the most common causes of hospital-acquired infection. Our aim was to assess the evolution of Imipenem Resistance in *Escherichia coli* at the First Affiliated Hospital of Jinan University (Guangzhou, China) from 2010 to 2018. 3412 non-duplicate strains of *E. coli* were isolated from inpatients and outpatients during the researched period. The majority of isolates appeared in the urine sample (57.68%) were derived from Urology(33.76%). With an average imipenem resistance rate of 0.61%, 27 strains of *E. coli* were detected. From 2010 to 2018, the resistance rates of the 3412 strains of *E. coli* to imipenem were 0, 0.00%, 0.35%, 0.30%, 0.26%, 0.44%, 1.08%, 0.70%, 2.33%, respectively. The overall imipenem resistant rate of *E. coli* was gradually increased in recent years. Moreover, the imipenem-resistant *E. coli* was multi-drug resistant to the antibiotics used clinically.. Therefore, restraining the use of antibiotics is extremely urgent to avoid severe infection by resistant pathogens.

Key words: *Escherichia coli*; Imipenem; Antibiotic resistance.

INTRODUCTION

Escherichia coli (*E. coli*), is a Gram-negative bacillus belonging to the normal intestinal flora of humans and other mammals. Depending on its conditional pathogenicity, Various intestinal and extra-intestinal infections are caused by *E. coli*. It has also occupied the first in the detection rate of pathogenic bacteria in clinical specimens, mainly isolated from urine samples [1, 2].

Carbapenems, including imipenem, possess broad spectrum antibacterial activity and have a unique structure that is defined by a carbapenem coupled to a β-lactam ring which confers protection against most β lactamases such as metallo-β-lactamase (MBL) as well as extended spectrum β-lactamases. Consequently, carbapenems are considered as one of the most reliable drugs for treating bacterial infections [3]. However, with the widespread use of carbapenems, carbapenem-resistant *Enterobacteriaceae* (CRE) has gradually emerged in clinical practice all over the world. In 2017, the European Centre for Disease Prevention and Control (ECDC) published the bacterial resistance monitoring of 30 European countries, it showed that the drug-resistant rate of CRE gradually increased from 6.0% (2012) to 8.1% (2015) [4]. Meanwhile, the China Antimicrobial Resistance Surveillance System(CARSS) reported the similar increasing resistance rate of *E. coli* to imipenem, which was elevated from 0.3% (2005) to 1.9% (2017) [5].

The mechanisms of resistance of *Enterobacteriaceae* to carbapenems are complex including the productions of carbapenemase, the changes of penicillin-binding protein targets, the overexpression of Amp C or ESBLs combined with mutations and deletions of outer porin channel proteins, the activation of external Enhancement of the exhaust system [6-9], the above mechanisms can mediate resistance to carbapenems through individual or synergistic effects [10]. Amble classification divides this enzyme into type A (KPC, SME, NMC-A, IMI), type B (NDM, VIM, IMP) and type D (OXA) , in which type A and type D are serine enzymes, and their active sites have serine structure, while type B is metalloenzyme, which needs metal ion Zn^{2+} to play the activity and can be inhibited by EDTA [11].

CRE-induced drug resistance is often characterized by multiple drug resistance, which makes clinical treatment of patients with CRE infection very difficult [12, 13]. The aim of this study was to evaluated the drug-resistance changes of *E. coli* to imipenem at the First Affiliated Hospital of Jinan University (Guangzhou, China) from 2010 to 2018.

MATERIALS AND METHODS

Hospital setting and strains collection

The *E. coli* isolates were collected at the First Affiliated Hospital of Jinan University (Guangzhou, China) from 2010 to 2018. Only the first pathogens isolated from the patients were selected, the strains with unclear clinical information were excluded. The samples included urine, blood, sputum, ascites and wound secretions. Bacterial identification to the species level on all tested strains was performed by standard procedures reported previously [14, 15].

Susceptibility testing

The MIC (Minimum Inhibitory Concentration) concentration was automatically tested by a VITEK 2 Compact automatic microorganisms analyzer. The Drug susceptibility cards (VITEK 2 AST-N335, Merrier diagnostics (Shanghai) co., LTD) were used to absorb the pure bacterial colony suspension of the positive samples with McKessler's unit turbidity required by the drug sensitivity test. The results were interpreted according to the 2018 criteria of Clinical and Laboratory Standards Institute (CLSI). The ATCC25922 *E. coli* from the Guangdong Center for Clinical Laboratory was used as control.

Statistical analysis

Antimicrobial susceptibility results and organization were managed by WHONET (version 5.6). A chi-square test or Fisher's exact test was performed to exam the difference between the resistance rates of inpatients and outpatients. A $p < 0.05$ was defined as statistically significant.

RESULTS

Detection quantity and detection rate of E. coli

A total of 3412 strains were isolated from January 2010 to December 2018, including 176 strains in 2010, 198 strains in 2011, 283 strains in 2012, 328 strains in 2013, 389 strains in 2014, 451 strains in 2015, 462 strains in 2016, 568 strains in 2017 and 557 strains in 2018. The average detection rate of *E. Coli* nosocomial infection in the study years was 13.78%. The specific numbers were 13.84%, 12.32%, 14.40%, 15.12%, 14.47%, 14.67%, 12.35%, 11.44% and 17.01%, from 2010 to 2018, respectively (Figure 1).

Detection time distribution of E. coli

The third quarter (July to September) showed the highest detection rate (27.67%) and the first quarter (January to March) showed the lowest (19.7%) of E. coli during the study period (Figure 2).

Departments distribution and source of specimens of E. coli

The urology department had the highest detection rate of *E. coli* (33.76%), followed by obstetrics and gynecology (8.65%) and pediatrics (8.03%) (Table 1). E. coli was mainly detected from urine (57.68%), blood (12.57%) and sputum (8.70%) (Table 2).

Age distribution of E. coli

The study cohort was grouped as infant (<1 year), youth (1-40 years), middle-aged (40-60 years) and agedness (>60 years) according to the World Health Organization (WHO) age classification standard. Most of the patients diagnosed with E. coli infection were agedness (44.61%), followed by the middle-aged group (24.97%), and the infant group had the lowest detection rate (5.80%) (Figure 3).

Imipenem-resistance rates of E. coli

A total of 27 non-repeat E. coli strains were resistant to imipenem. The average resistance rate was 0.61%. The specific numbers were 0.00%, 0.00%, 0.35%, 0.30%, 0.26%, 0.44%, 1.08%, 0.70% and 2.33%, from 2010 to 2018, respectively (Figure 4).

By the year of 2011, the sensitivity rate of *E. coli* to imipenem was still 100.00%. The imipenem resistant began to appear in 2012. There was a significantly increasing of resistant strains since 2015. The highest number of resistant strains was detected in 2018 (Figure 5).

The total number of strains is the number of positive strains isolated and cultured in the hospital within one year, including all common and uncommon gram-positive bacteria and gram-negative bacteria. The number of *E. coli* strains is the number of *E. coli* strains isolated and cultured in the hospital within one year.

Composition ratio: The number of *E. coli* strains/ The total number of strains.

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Composition ratio: The number of *E. coli* strains/ The total number of strains

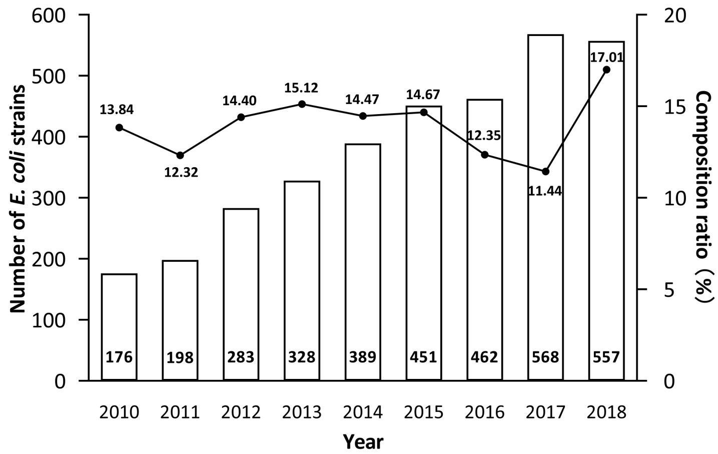

Figure 1 Statistics of detected *E. coli* strains from 2010 to 2018

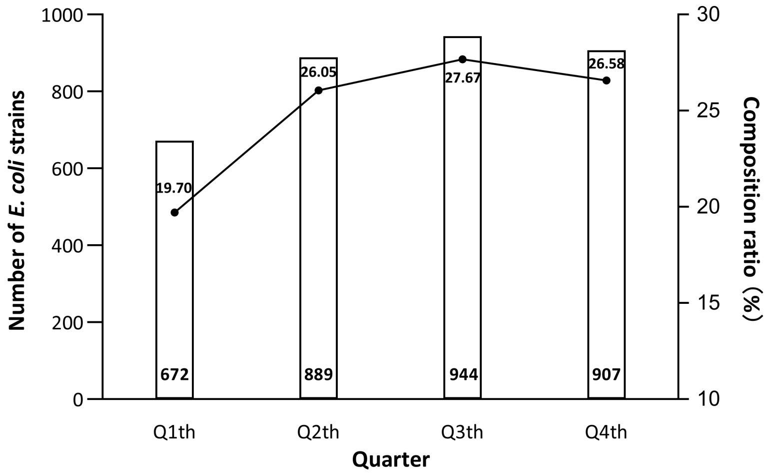

Figure 2 Time distribution of detection of *E. coli* strains from 2010 to 2018

Table 1 Department distribution of detection of *E. coli* strains from 2010 to 2018

Department	Number of *E. coli* strains (n)	Composition ratio(%)
Urology	1152	33.76
Obstetricand Gynecology	295	8.65
Pediatrics	274	8.03
orthopedics	177	5.19
Hepatobiliary surgery	164	4.81
Respiratory	163	4.78
Digestion	153	4.48
Cardiovascular	133	3.90
Neurology	127	3.72
ICU	107	3.14
Others	667	19.55

Table 2 Specimen sources of *E. coli* strains from 2010 to 2018

Specimen sources	Number of *E. coli* strains (n)	Composition ratio(%)
Urine	1968	57.68
Blood	429	12.57

Sputum	297	8.70
Others	189	5.54
Secretions	112	3.28
Purulence	78	2.29
Amniotic fluid	45	1.32
Cerebrospinal fluid, pleural fluid, joint	44	1.29
Bile, gastric juices	250	7.33

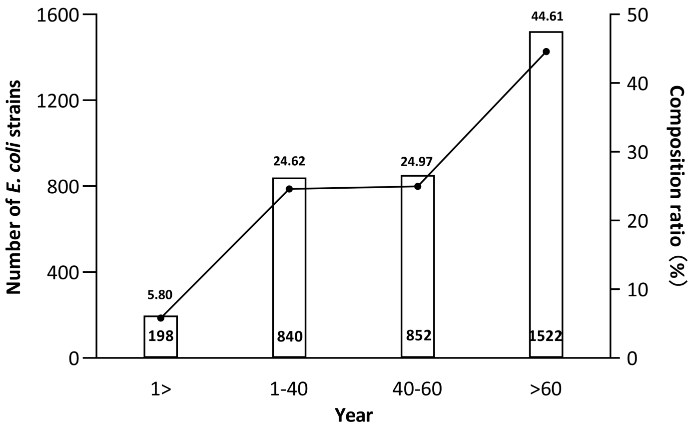

Figure 3 The age distribution of patients with *E. coli* detected from 2010 to 2018

The total number of strains is the number of positive strains isolated and cultured in the hospital within one age group, including all common and uncommon gram-positive bacteria and gram-negative bacteria. The number of *E. coli* strains is the number of *E. coli* strains isolated and cultured in the hospital within one age group.

Composition ratio: The number of *E. coli* strains/ The total number of strain

The total number of strains is the number of positive strains isolated and cultured in the hospital within one year, including all common and uncommon gram-positive bacteria and gram-negative bacteria. The number of imipenem resistant *E. coli* strains is the number of imipenem resistant *E. coli* strains isolated and cultured in the hospital within a year.

Antiboitic resistance rates: The number of imipenem resistance *E. coli* strains/ The total number of strains

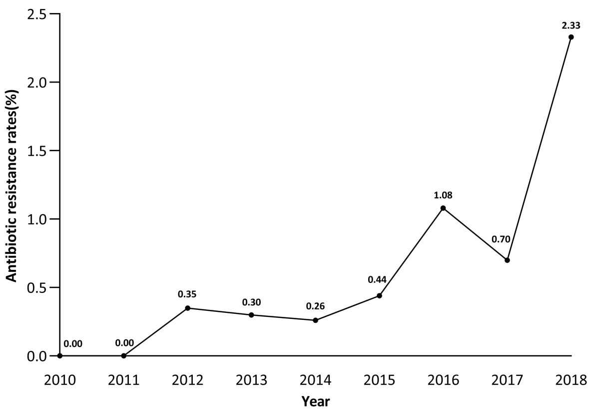

Figure 4 The antibiotic resistance rate of *E. coli* to imipenem from 2010 to 2018

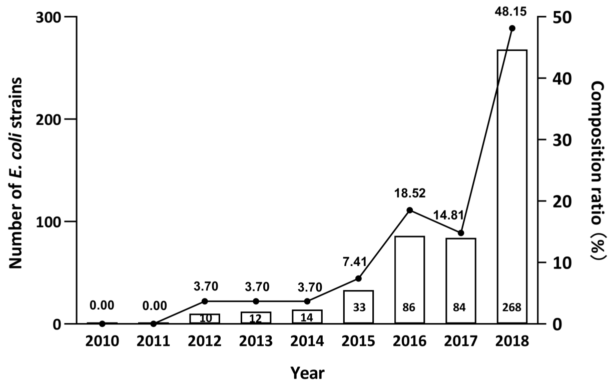

Figure 5 Detection time distribution of imipenem resistant *E. coli* strains from 2010 to 2018

The total number of *E. coli* strains is the number of positive *E. coli* strains isolated and cultured in the hospital within one year. The number of imipenem resistant *E. coli* strains is the number of imipenem resistant *E. coli* strains isolated and cultured in the hospital within one year.

Composition ratio: The number of imipenem resistant *E. coli* strains /The total number of *E. coli* strains

Department distribution and specimen source of imipenem resistant E. coli

From January 2010 to December 2018, the departments with the highest detection rate of imipene-resistant *E. Coli* were the urology department (25.93%), followed by the respiratory department (14.81%) and the gastroenterology department (11.11%), as shown in Table 3. Imipene-resistant *E. coli* was mainly detected from urine (44.44%), sputum (22.22%) and blood (18.52%), as shown in Table 4.

Table 3 Department distribution of imipenem resistant *E. coli* strains from 2010 to 2018

Department	Number of imipenem resistant *E. coli* strains (n)	Composition ratio(%)
Urology	7	35.93
Respiratory	4	14.81
Digestion	3	11.1
Pediatrics	2	7.41
Neurology	2	7.41
ICU	1	3.70
Cardiovascular	1	3.70
Hepatobiliary	1	3.70
Orthopedics	1	3.70
Others	5	18.52

Table 4 Specimen sources of imipenem resistant E. coli strains from 2010 to 2018

Specimen sources	Number of imipenem	Composition ratio(%)
Urine	12	44.44
Sputum	6	22.22
Blood	5	18.52
Wound secretion	2	7.41
Ascites	1	3.70
Others	1	3.70

Susceptibility of imipenem-resistant E. coli to other antimicrobial agents

The resistant rate of the 27 strains to other antimicrobial drugs was also evaluated. 10 antibiotics, including cephalosporins (ceftazidime and cefepime), quinolones (ciprofloxacin and ofloxacin), aminoglycosides (amikacin and tobramycin), sulfa (sulfamethoxazole), monocyclic-β-lactamases (aztreonam) and combinations of β-lactamase inhibitors (piperacillin / tazobactam and cefoperazone / sulbactam) were selected to conduct the evaluation. More than 50% of the imipenem-resistant *E. coli* showed multi-drug resistance to the tested antibiotics. β-lactamases showed the highest resistant rate of 90%, followed by tobramycin (48.15%), and amikacin showed the lowest (25.93%) (Table 5).

Table 5 Susceptibility of 27 imipenem resistant *E. coli* strains to 10 antimicrobial agents

Antibacterial drugs	Resistance		Intermediary		Sensitive	
	strains	resistance rate （%）	strains	Intermediary rate（%）	strains	Sensitivity rate （%）
Ceftazidime	25	92.59	0	0.00	2	7.41
Cefepime	25	92.59	0	0.00	2	7.41
Ciprofloxacin	19	70.37	2	7.41	6	22.22
Levofloxacin	19	70.37	2	7.41	6	22.22
Amikacin	7	25.93	0	0.00	20	74.07
Tobramycin	13	48.15	3	11.11	11	40.74
Trimethoprim/ sulfamethoxazole	17	62.96	0	0.00	10	37.04
Aztreonam	24	88.89	0	0.00	3	11.11
Piperacillin/ Tazobactam	24	88.89	0	0.00	3	11.11
Cefoperazone/ sulbactam	25	92.59	0	0.00	2	7.41

DISCUSSION

E. coli is the most common pathogen causing nosocomial infections and is widely found in hospital settings. When the patient's immune function is low, *E. coli*, which is a normal flora in the human intestine, will be ectopically colonized to other tissues or organs, causing urinary tract infections, respiratory infections, blood infections, and abdominal infections [16].This article showed that from 2010 to 2018, the average detection rate of *E. coli* in the First Affiliated Hospital of Jinan University was 13.78%, and the average resistance rate to imipenem was 0.61%, which was lower than the 2017 CHINET drug resistance monitoring reported rate 1.90% [17]. This might be related to the different use of antibacterial drugs in different regions and different levels of hospitals. The detection rate of the number of *E. coli* isolates from 2010 to 2017 was stabilized and had no obviously increasing trend, but the detection rate rose sharply to 17.01% in 2018, which was much higher than the average detection rate of 13.78%. Meanwhile, the number of imipenem-resistant *E. coli* isolated in 2018 was 13 isolates, accounting for 48.15% of the resistant strains isolated during the nine-year period. This might be a result of the surge in outpatients, inadequate nursing staff, and insufficient management of clinical medications in 2018.

The nine years of continual monitoring results showed that among the 3412 detected strains of *E. coli*, urine specimens (57.68%) were the most common sample, followed by blood specimens (12.57%) and sputum specimens (8.70%). *E. coli* was the main pathogen that causing urinary tract infections in our hospital, which was consistent with other domestic reports [18, 19]. It has been reported that *E. coli* is easy to cause urinary tract infection because the fimbriae of *E. coli* can adhere firmly to the epithelial cells of the urethra, thus weakening the peristalsis of the ureter, leading to ureteral dilatation, so that the urine can't wash away the bacteria in time [20]. On the perspective of department distribution, *E. coli* has the highest detection rate in the urology department (33.76%). It has more invasive procedures such as urinary catheters and cystoscopy with patients in this ward, which causes urinary tract mucosal damage and then more likely to cause *E. coli* infection. According to the age distribution, *E. coli* infection mainly occurred in the elderly group (44.61%) over 60 years old. On the one hand, with the increase of age, the patient's organs aged and atrophied, degenerative changes in the urinary tract, obstacles to urination reflexes, increased residual urine volume, and decreased body immunity, making urinary tract infections more prone. On the other hand, *E. coli* is the common pathogen of urinary infection [21].

In recent years, imipenem-resistant *E. coli* at home and abroad has been widely reported [22, 23]. In 2012, the first imipenem-resistant *E. coli* strain appeared in our hospital. Carbapenemase was the main mechanism of resistance of Enterobacter bacteria to carbapenems. According to the reports, clinically isolated carbapenem-resistant *E. coli* in

China commonly produce KPC enzymes and NDM-1 (New Delhimetallo-β-lactamase-1) enzymes [24, 25]. Because the carbapenemase gene was mostly located on a conjugable plasmid, the resistance to carbapenem can also be transmitted between different strains and different species through plasmid transfer, which may also easily cause resistant strains widespread [26]. In this study, 13 imipenem-resistant *E. coli* were detected in 2018, accounting for 48. 15% of the resistant strains isolated during the nine-year period, which was significantly higher than the number detected in 2017 and was most likely a plasmid transfer caused by the carbapenemase gene. At the same time, a statistical analysis of the susceptibility of 27 imipenem-resistant Escherichia coli strains revealed that Imipenem-resistant *E. coli* was multi-drug resistant to most commonly used antibacterials, but it had a high sensitivity rate to aminoglycosides amikacin. Aminoglycosides are one of the few drugs with in vitro resistance to carbapenem-resistant Enterobacteriaceae, which is consistent with Smith K [27]. Therefore, the clinicians should timely grasp the drug resistance characteristics of *E. coli*, try to use drugs reasonably according to the drug sensitivity results, and avoid the continuous resistance of imipenem-resistant *E. coli* to aminoglycosides increase. At the same time, more attention should be paid to the isolation of patients with multi-drug resistant bacterial infections to prevent their spread in hospitals.

CONCLUSION

During the nine years from 2010 to 2018, urine specimens were the main source of specimens for clinical isolation of *E. coli*, while Urology was the main department for sending specimens for *E. coli* infection. The results were consistent with that of imipenem-resistant *E. coli*. The overall drug resistance rate of *E. coli* to imipenem was increasing gradually, and there were multiple drug resistance to common antibiotics.

ETHICS APPROVAL

Given that this study was performed without accessing patient information, approval of the ethics committee was not required.

ACKNOWLEDGMENTS

This work was funded by the research project of Guangdong Provincial Bureau of traditional Chinese Medicine, China (No. 20191089 and No. 20201082) and Guangdong Provincial Hospital Pharmaceutical Research Fund (No.2020A27)

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