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Original Article

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Change in the Antimicrobial Resistance Profile of Extended-Spectrum β-Lactamase-Producing *Escherichia coli*

Motoyasu Miyazaki[a, f, g], Yota Yamada[a, f], Koichi Matsuo[a], Yukie Komiya[b], Masanobu Uchiyama[a], Nobuhiko Nagata[c], Tohru Takata[d], Shiro Jimi[e], Osamu Imakyure[a]

Abstract

Background: This study aimed to investigate the trends and antimicrobial resistance profile of extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) clinical isolates.

Methods: A total of 1,303 *E. coli* isolates from January 2012 to December 2017 at Fukuoka University Chikushi Hospital, Japan, were analyzed. The rate of resistance to cefmetazole (CMZ), flomoxef (FMOX), imipenem (IPM), meropenem (MEPM), amikacin (AMK), gentamicin (GM), minocycline (MINO), ciprofloxacin (CPFX), and levofloxacin (LVFX) was compared between non-ESBL-producing *E. coli* (non-ESBL-EC) and ESBL-EC.

Results: The proportion of ESBL-EC among all the *E. coli* isolates was 24.6% (320/1,303), and the proportion remained stable throughout the study period. There was no difference in the rate of resistance to CMZ, FMOX, IPM, MEPM, and AMK between non-ESBL-EC and ESBL-EC; however, the rate of resistance to GM, MINO, CPFX, and LVFX was higher in ESBL-EC than in non-ESBL-EC (17.5% vs. 10.0%, 19.1% vs. 7.7%, 87.5% vs. 24.2%, and 87.5% vs. 23.5%, respectively; $P < 0.01$). The rate of resistance to CPFX and LVFX in ESBL-EC increased throughout the study course. The rate of *E. coli* isolates susceptible to all the antibiotics was significantly higher in non-ESBL-EC than in ESBL-EC (68.2% vs. 7.5%; $P < 0.01$), and this rate decreased significantly from 10.0% in 2012 to 3.8% in 2017 in ESBL-EC ($P < 0.01$).

Conclusions: Our findings indicate a changing antimicrobial resistance profile of ESBL-EC, particularly to fluoroquinolones. Determination of the prevalence and antimicrobial resistance of ESBL-EC will help physicians in selecting the initial empirical treatment for patients with ESBL-EC infections.

Keywords: *Escherichia coli*; Extended-spectrum β-lactamase; Antimicrobial resistance profile; Fluoroquinolone resistance

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[a]Department of Pharmacy, Fukuoka University Chikushi Hospital, 1-1-1 Zokumyoin, Chikushino-shi, Fukuoka 818-8502, Japan
[b]Department of Clinical Laboratory, Fukuoka University Chikushi Hospital, 1-1-1 Zokumyoin, Chikushino-shi, Fukuoka 818-8502, Japan
[c]Department of Respiratory Medicine, Fukuoka University Chikushi Hospital, 1-1-1 Zokumyoin, Chikushino-shi, Fukuoka 818-8502, Japan
[d]Department of Infection Control, Fukuoka University Hospital, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan
[e]Central Laboratory for Pathology and Morphology, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan
[f]These authors contributed equally to this work.
[g]Corresponding Author: Motoyasu Miyazaki, Department of Pharmacy, Fukuoka University Chikushi Hospital, 1-1-1 Zokumyoin, Chikushino-shi, Fukuoka 818-8502, Japan. Email: motoyasu@fukuoka-u.ac.jp

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Introduction

Extended-spectrum β-lactamases (ESBLs) can hydrolyze penicillins and oxyimino-cephalosporins, such as ceftazidime (CAZ), cefotaxime (CTX), and ceftriaxone, which have reportedly played important roles in the treatment of infections caused by *Enterobacteriaceae*, including *Escherichia coli* [1]. Recently, the prevalence of ESBL-producing *E. coli* (ESBL-EC) has been dramatically increasing worldwide [2-4]. In Japan, CTX-M-type ESBL-EC, which exhibits co-resistance to fluoroquinolones, has been detected more frequently than TEM- or SHV-type ESBL-EC [5, 6]. Infections caused by ESBL-EC are reportedly associated with poor clinical outcomes, inappropriate empirical antibiotic therapy, longer hospital stays, and greater hospital expenses [7-9].

Antimicrobial resistance patterns are often available for monitoring the endemicity of specific clones. In small- and medium-sized hospitals, antimicrobial resistance patterns are particularly useful for empiric therapy because it is difficult to routinely conduct genotyping in clinical laboratories. However, only few studies have been reported on trends and antimicrobial resistance patterns of ESBL-EC in limited regions. Because of the increasing clinical importance of ESBL-EC, we should carefully monitor the prevalence and antimicrobial resistance profile of ESBL-EC at our facility. Thus, the aim of this study was to investigate the trends of the rate of detection and antimicrobial resistance of ESBL-EC at our hospital.

Methods

Setting

Fukuoka University Chikushi Hospital is a 310-bed university-

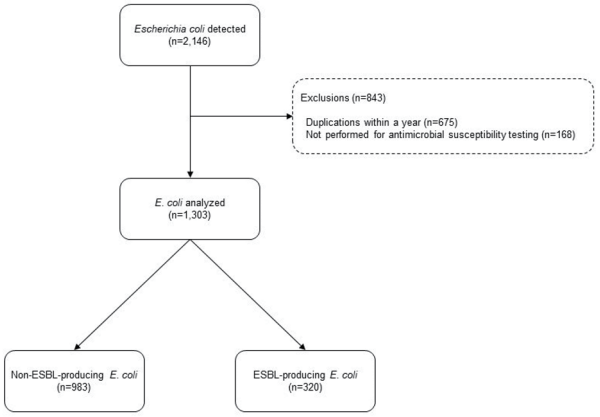

Figure 1. Samples analyzed in the present study.

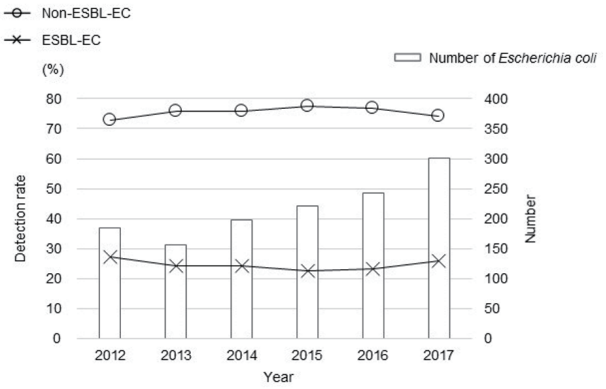

Figure 2. Yearly rate of detection of ESBL-EC among all the *E. coli* isolates.

affiliated hospital located in the southwestern district of Japan. This study was approved by the Fukuoka University Medical Ethics Review Board (R18-014). This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Collection and identification of isolates

E. coli clinical isolates were recovered from inpatients and outpatients who visited Fukuoka University Chikushi Hospital between January 2012 and December 2017. Only one isolate per patient per year was included in this study. For those patients from whom more than one isolate was recovered, only the first isolate for which the results of antimicrobial susceptibility testing were available was included. The isolates were identified using the automated Vitek-2 system (Sysmex bioMerieux, Tokyo, Japan).

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed using the automated Vitek-2 system, following the manufacturer's instructions. The breakpoint (susceptible, intermediate, or resistant) was determined according to the M100-S27 performance standards established by the Clinical and Laboratory Standards Institute (CLSI) [10]. Nine antimicrobial agents were used for susceptibility testing: cefmetazole (CMZ), flomoxef (FMOX), imipenem (IPM), meropenem (MEPM), amikacin (AMK), gentamicin (GM), minocycline (MINO), ciprofloxacin (CPFX), and levofloxacin (LVFX).

ESBL detection

ESBL detection was performed by the double disk diffusion using both CTX, CAZ, and cefpodoxime (CPDX) alone and in combination with clavulanic acid. An increase in zone size of greater than or equal to 5 mm for CTX, CAZ, and CPDX with and without clavulanic acid was taken as an indication of ESBL production.

Statistical analysis

Categorical variables were compared using the Chi-squared test or Fisher's exact test, as appropriate. Temporal trends of antimicrobial resistance were evaluated using linear regression analysis. The JMP software program (version 10, SAS Institute Inc., Cary, NC, USA) was used for all the statistical analyses. $P < 0.05$ was considered statistically significant.

Results

Prevalence of ESBL-EC

A total of 2,146 *E. coli* clinical isolates were recovered between January 2012 and December 2017. Of those, 1,303 (60.7%) isolates were included in this study (Fig. 1). Further, 983 (75.4%) of the included 1,303 were non-ESBL-EC and 320 (24.6%) were ESBL-EC. The proportion of ESBL-EC among all the *E. coli* isolates was relatively stable throughout the study period (22.6-27.2%) (Fig. 2).

Antimicrobial resistance profile of non-ESBL-EC and ESBL-EC

Almost all the *E. coli* isolates were susceptible to CMZ, FMOX, IPM, MEPM, and AMK, and there was no difference between non-ESBL-EC and ESBL-EC in the rate of resistance to these antibiotics. However, the rate of resistance to GM, MINO, CPFX, and LVFX was significantly higher in ESBL-EC than in non-ESBL-EC (17.5% vs. 10.0%, 19.1% vs. 7.7%, 87.5% vs. 24.2%, and 87.5% vs. 23.5%, respectively; $P < 0.01$) (Fig. 3). In ESBL-EC, the rate of resistance to GM and MINO was stable throughout the study period, whereas that to CPFX and LVFX increased over the study period ($P = 0.048$ and $P =$

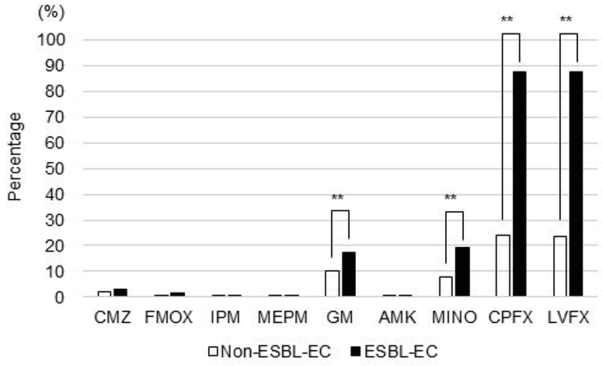

Figure 3. Antimicrobial resistance profiles of non-ESBL-EC and ESBL-EC (**P < 0.01).

0.062, respectively) (Fig. 4).

Change in the antimicrobial resistance pattern of ESBL-EC

A total of 34 resistance patterns were identified based on the resistance profile of the nine antibiotics in the *E. coli* isolates (pattern IDs: Null, I-a-f, II-a-h, III-a-i, IV-a-f, V-a-c, and VII) (Table 1). Of the 983 non-ESBL-EC isolates, the pattern ID Null (susceptible to all nine antibiotics) was the predominant resistance pattern (68.2%), followed by ID II-h (resistance to CPFX and LVFX), ID III-h (resistance to GM, CPFX, and LVFX), and ID I-e (resistance to MINO). Of the 320 ESBL-EC isolates, ID II-h (resistance to CPFX and LVFX) was the predominant resistance pattern (57.2%), followed by ID III-i (resistance to MINO, CPFX, and LVFX), ID III-h (resistance to GM, CPFX, and LVFX), and ID Null (susceptible to all antibiotics).

The yearly rates of detection of these predominant patterns in non-ESBL-EC and ESBL-EC are shown in Figure 5. There was no change in the rate of isolates with pattern ID in non-ESBL-EC. In ESBL-EC, the rate of isolates with ID Null (susceptible to all antibiotics) decreased significantly from 10.0% in 2012 to 3.8% in 2017 (P < 0.01), and the rate of isolates with ID III-h (resistance to GM, CPFX, and LVFX) increased from 4.0% in 2012 to 20.5% in 2017 (P < 0.01).

Discussion

In this study, we examined the trends of the rate of detection and antimicrobial resistance of ESBL-EC. The rate of detection of ESBL-EC has been 24.6% in the recent 6 years, which is in line with that reported by previous studies conducted in Japan [11-13]. However, at our hospital, the rate of detection of ESBL-EC exceeded 20% in 2012, and this value was higher than that during the same period at other facilities [3, 11, 14, 15]. A study reported that of 135 Japanese travelers, 55 (40.7%) carried ESBL after returning to Japan and that the majority of these carriers were returning from eastern and central Asia [16]. The Fukuoka Prefecture receives many immigrants and travelers from Southeast Asian countries with high carrier rates of ESBL-producing bacteria, which may contribute to the higher rate of detection of ESBL-EC at our hospital.

The rate of resistance of ESBL-EC to fluoroquinolones, such as CPFX and LVFX, was significantly higher than that of non-ESBL-EC, and this is consistent with the findings of a recent study conducted in Japan [13]. The resistance of ESBL-EC to fluoroquinolones is closely related to the genotype. There are three ESBL types: CTX-M, TEM, and SHV [1]. The CTX-M type is classified into five major groups: CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9, and CTX-M-25 [17]. CTX-M-9 has been the predominant group in Japan since 2000 [6,

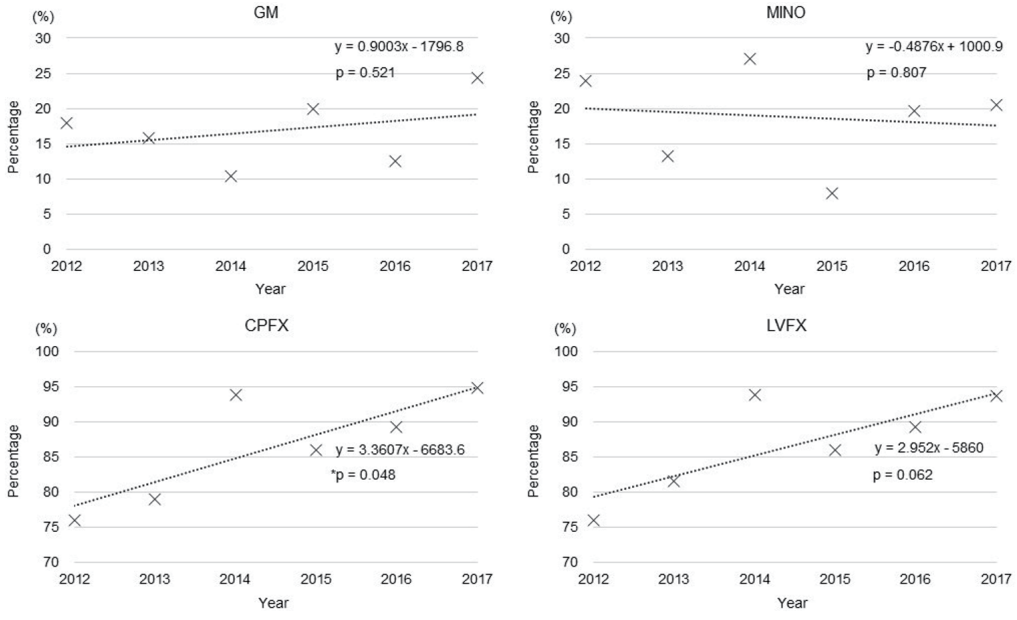

Figure 4. Trends in the rates of resistance of ESBL-EC for GM, MINO, CPFX, and LVFX (*P < 0.05).

Table 1. Antimicrobial Resistance Pattern of Non-Extended-Spectrum β-Lactamase-Producing *Escherichia coli* and Extended-Spectrum β-Lactamase-Producing *Escherichia coli*

Number of antibiotics[a]	Pattern ID	Antibiotics								Non-ESBL (n = 983)		ESBL (n = 320)	
		Cephamycin	Oxacephem	Carbapenems		Aminoglycosides		Tetracycline	Fluoroquinolones	n	%	n	%
0	Null									670	68.2	24	7.5
Subtotal										670	68.2	24	7.5
1	I-a	CMZ								5	0.5	0	0.0
	I-b				MEPM					1	0.1	0	0.0
	I-c					AMK				1	0.1	0	0.0
	I-d						GM			22	2.2	11	3.4
	I-e							MINO		34	3.5	0	0.0
	I-f								CPFX	5	0.5	0	0.0
Subtotal										68	6.9	11	3.4
2	II-a	CMZ	FMOX							1	0.1	1	0.3
	II-b	CMZ					GM			2	0.2	0	0.0
	II-c	CMZ						MINO		0	0.0	1	0.3
	II-d						GM	MINO		5	0.5	2	0.6
	II-e						GM		CPFX	2	0.2	1	0.3
	II-f							MINO	CPFX	2	0.2	0	0.0
	II-g							MINO	LVFX	1	0.1	0	0.0
	II-h								CPFX LVFX	131	13.3	183	57.2
Subtotal										144	14.6	188	58.8
3	III-a	CMZ	FMOX				GM			1	0.1	0	0.0
	III-b	CMZ	FMOX						LVFX	0	0.0	1	0.3
	III-c	CMZ							CPFX LVFX	3	0.3	1	0.3
	III-d	FMOX		IPM	MEPM					1	0.1	0	0.0
	III-e			IPM					CPFX LVFX	1	0.1	0	0.0
	III-f					AMK			CPFX LVFX	1	0.1	0	0.0
	III-g						GM	MINO	LVFX	1	0.1	0	0.0
	III-h						GM		CPFX LVFX	55	5.6	35	10.9
	III-i							MINO	CPFX LVFX	23	2.3	47	14.7
Subtotal										86	8.7	85	26.6
4	IV-a	CMZ	FMOX						CPFX LVFX	1	0.1	0	0.0
	IV-b	CMZ					GM		CPFX LVFX	2	0.2	1	0.3
	IV-c	CMZ						MINO	CPFX LVFX	1	0.1	2	0.6
	IV-d			IPM				MINO	CPFX LVFX	1	0.1	0	0.0

Table 1. Antimicrobial Resistance Pattern of Non-Extended-Spectrum β-Lactamase-Producing *Escherichia coli* and Extended-Spectrum β-Lactamase-Producing *Escherichia coli* - *(continued)*

Number of antibiotics[a]	Pattern ID	Antibiotics						Non-ESBL (n = 983)		ESBL (n = 320)	
		Cephamycin	Oxacephem	Carbapenems	Aminoglycosides	Tetracycline	Fluoroquinolones	n	%	n	%
	IV-e				AMK	MINO	CPFX LVFX	0	0.0	1	0.3
	IV-f				GM	MINO	CPFX LVFX	5	0.5	6	1.9
Subtotal								10	1.0	10	3.1
5	V-a	CMZ	FMOX		GM		CPFX LVFX	2	0.2	0	0.0
	V-b	CMZ	FMOX			MINO	CPFX LVFX	2	0.2	2	0.6
	V-c	CMZ			GM	MINO	CPFX LVFX	1	0.1	0	0.0
Subtotal								5	0.5	2	0.6
7	VII	CMZ	FMOX	IPM	MEPM	GM		CPFX LVFX	0	0.0	1	0.3
Subtotal								0	0.0	1	0.3

AMK: amikacin; CMZ: cefmetazole; CPFX: ciprofloxacin; ESBL: extended-spectrum beta-lactamase; ESBL-EC: ESBL-producing *Escherichia coli*; FMOX: flomoxef; GM: gentamicin; IPM: imipenem; LVFX: levofloxacin; MEPM: meropenem; MINO: minocycline. [a]The number of antibiotics to which *Escherichia coli* isolates were resistant.

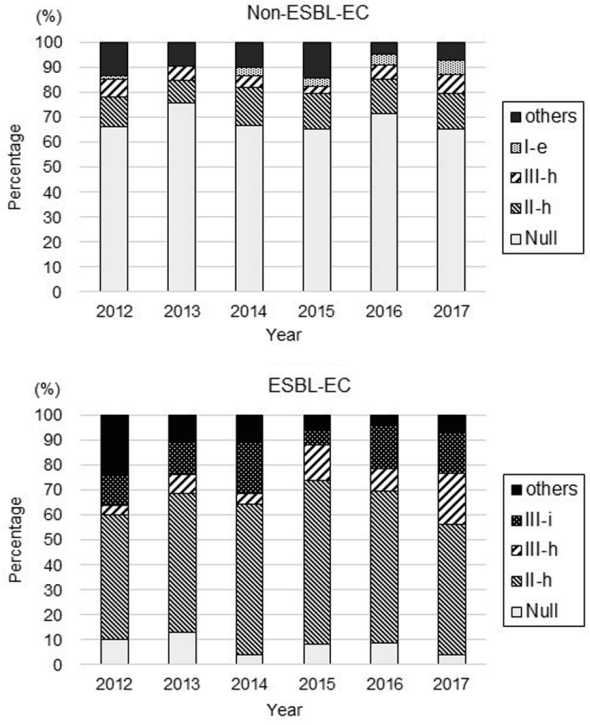

Figure 5. Changes in the antimicrobial resistance patterns of non-ESBL-EC and ESBL-EC.

18]. A previous report has suggested that 75% of the 24 strains in the CTX-M-14 and CTX-M-27 groups, which belong to the CTX-M-9 group, are resistant to LVFX [3]. In addition, a recently disseminated lineage of *E. coli* designated sequence type ST131 according to multilocus sequence typing (MLST) is associated with CTX-M-15, which belongs to the CTX-M-1 group, that is usually fluoroquinolone resistant [19], and this type of ESBL-EC has been reported in Japan [3, 6]. In the antimicrobial resistance pattern analysis of ESBL-EC conducted in this study, the ESBL-EC pattern ID III-h, which shows resistance to GM as well as fluoroquinolones, increased from 4.0% in 2012 to 20.5% in 2017. Ender et al reported the transmission of an ESBL-EC ST131 producing CTX-M-15 strain that is resistant to GM, trimethoprim-sulfamethoxazole, and fluoroquinolones between a father and his daughter [20]. It has been suggested that specific ESBL-EC clones, such as isolates with ST131, CTX-M-14, CTX-M-15, or CTX-M-27, are transmitted in our hospital or the area surrounding our hospital.

Particularly for urinary tract infections, fluoroquinolones are still recommended as the initial treatment. However, in the present study, approximately 90% of ESBL-EC and 25% of non-ESBL-EC were resistant to fluoroquinolones, and fluoroquinolones as the initial treatment should be used with caution. Particularly in cases wherein infection with ESBL-EC is suspected, initial treatment with non-fluoroquinolone drugs should be considered. In previous studies, the use of immunosuppressive drugs or corticosteroids, the use of quinolones prior to isolation, nursing home-associated infections, and antibiotic administration within the preceding 30 days were the independent predictors associated with ESBL-EC bacteremia

[13, 21]. Carbapenems may be recommended as the initial treatment for infectious cases with these factors [22]. In the present study, the sensitivity of ESBL-EC and non-ESBL-EC to CMZ and FMOX was as high as that previously reported in Japan [13, 21]. According to a previous multicenter retrospective study conducted using a propensity score, CMZ and FMOX were not inferior to carbapenems in the empirical and definitive treatment of ESBL-EC bacteremia regarding the 30-day mortality rates and clinical success; hence, these cephems may be effective alternatives to carbapenems in the treatment of ESBL-EC bacteremia [23].

There are several limitations to this study. First, this study was conducted at a single center; hence, it is not clear if our results reflect the trend of ESBL-EC in Japan or in only the Fukuoka Prefecture. Second, we did not routinely conduct antimicrobial sensitivity tests for tazobactam/piperacillin (TAZ/PIPC) against *E. coli*. Because TAZ/PIPC, like carbapenems, is recommended for the empirical treatment of infections with suspected urosepsis, it is necessary to consider routine sensitivity testing at our hospital. Third, we have not stored the strain nor determined the ESBL type using polymerase chain reaction and the ESBL-EC strain type using MLST in the *E. coli* isolates. However, there were only few reports in Japan that compared the antimicrobial resistance profile between ESBL-EC and non-ESBL-EC, and there were no reports concerning the trends in the resistance patterns.

In conclusion, the rate of detection of ESBL-EC has been 24.6% in the recent 6 years. Almost all the *E. coli* isolates were susceptible to CMZ, FMOX, IPM, MEPM, and AMK; however, the rates of resistance to GM, MINO, CPFX, and LVFX were significantly higher in ESBL-EC than in non-ESBL-EC. In ESBL-EC, the rates of the isolates susceptible to all antibiotics decreased significantly during the study period, and the rates of the isolates resistant to GM, CPFX, and LVFX increased over the study period. ESBL-EC is an important resistant strain for infection control or infection treatment, and it is necessary to carefully monitor the trends in its resistance profile and genotype in the future.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Not applicable.

Author Contributions

MM, YY and OI contributed to the concept and design of the study; MM, YY, KM, and YK conducted the study; MM, YY, MU, and NN were involved in data analysis and interpretation of the results; MM and YY drafted the manuscript; TT, SJ, and OI supervised the entire project and reviewed the manuscript; All the authors approved the final version of the manuscript.

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