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The Clinicobacterial Characteristics of Pediatric Patients With Upper Urinary Tract Infections Having ESBL-producing *Escherichia coli* in One Japanese Local Hospital, 2016–2022

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Urinary tract infections caused by extended-spectrum beta-lactamase（ESBL）-producing bacteria are increasing worldwide. However, since the start of the SARS-CoV-2 pandemic in 2020, the proportion of ESBL-producing *E. coli* has changed. This retrospective study included patients who were hospitalized in the pediatric department of Matsue Red Cross Hospital with UUTI caused by *E. coli*. Medical and hospital records were reviewed to assess patient characteristics, antimicrobial use density, and days of antibiotic therapy at the hospital from January 1, 2016, to December 31, 2022. Urine sample analyses showed that the proportion of ESBL-producing *E. coli* decreased significantly in 2020 to 2022. Antimicrobial use density and days of therapy of oral third-generation cephems was significantly correlated with the proportion of UUTI caused by ESBL-producing *E. coli* in pediatric patients. Effective hygiene measures and appropriate use of antibiotics especially, oral third-generation cephems, are effective for reducing the incidence of ESBL-producing bacterial infections.

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INTRODUCTION

Antimicrobial resistance（AMR）complicates treatment of infectious disease and is a serious threat to human health. The prevalence of extended-spectrum beta-lactamase（ESBL）-producing bacteria has increased dramatically worldwide［1］.

Previously, ESBL-producing bacteria caused nosocomial infections, but now they cause community-acquired infections worldwide; moreover, reports of urinary tract infections caused by ESBL-producing bacteria in children have increased［2］. Upper urinary tract infections（UUTI）are caused primarily by enterobacteria that colonize in the rectum which indicates a fecal-perineal-urethral route of infection［3］.

In 2016, the number of children hospitalized with UUTI caused by ESBL-producing *Escherichia coli* dramatically increased in Shimane in western Japan［4］. Since 2016, ESBL-producing *E. coli* infections have become a community-acquired UUTI in this area.

The World Health Organization（WHO）and Japan declared National Action Plan on Antimicrobial Resistance 2016–2020 to try to eradicate multidrug-resistant bacteria [5, 6]. Appropriate use of antimicrobial drugs was an important part of the plan. An antimicrobial stewardship team (AST) responsible for coordinating interventions to improve and measure the appropriate use of antimicrobial agents was established in each hospital.

In Japan, coronavirus disease (COVID-19) rapidly spread during early 2020 and the Japanese government declared a state of emergency in April 2020. The SARS-CoV-2 pandemic influenced the whole of society and resulted in major changes of lifestyle. After the start of the pandemic, hospital admissions for non-COVID reasons decreased in all age groups [7, 8], and the incidence of some diseases transmitted through contact decreased because of protective measures such as school closure, mask use, social distancing, and adherence to hygiene measures.

E. coli is the major cause of UUTI [9]. However, during this study period, the proportion of ESBL-producing *E. coli* decreased from 42% from 2016 to 2019, to 13% in 2022. Such a large decrease in the incidence of community-acquired ESBL-producing *E. coli* has not been reported previously in Japan. Therefore, we aimed to describe the clinical characteristics of ESBL-producing *E. coli* that cause community-acquired UUTI in children, and the effects of antimicrobial stewardship measures.

MATERIALS AND METHODS

Data used for this study were retrospectively collected from medical records in an electronic database at Matsue Red Cross Hospital. We collected medical records of patients who were admitted to the pediatric department with UUTI between January 1, 2016, and December 31, 2022. Their medical records were reviewed, and data were extracted on age at hospitalization, sex, hospitalization history, degree of vesicoureteral reflux (VUR) detected by voiding cystogram, white blood cell (WBC) count, and C-reactive protein (CRP) and procalcitonin (PCT) levels at the time of hospitalization.

The bacterial profile was determined using urine culture results, blood culture results, and antibiotic treatment. UUTI was diagnosed based on the clinical symptoms and the finding of more than 10^4 CFU/mL bacteria in urine caught by a catheter. Infection relapse was defined as the presence of bacteria in urine and associated clinical symptoms within 1 month after the completion of the primary treatment.

The exclusion criteria were treatment with immunosuppressive drugs, history of previous UUTI, and major congenital anomalies.

Microbiological identification of *E. coli* was performed using the VITEK 2 GN identification card. Screening for ESBL production was performed using an assumed ceftriaxone (CTRX)-resistant strain of ESBL-producing bacteria and an identification test disk (AmpC/ESBL differentiation disk; Kanto Chemical Co., Inc., Japan). Differentiation of ESBL-producing bacteria was based on the Clinical and Laboratory Standards Institute (CLSI) criteria. Antibiotic susceptibility was evaluated according to the CLSI definitive method. The test for drug sensitivity was examined by performing agar plate diffusion, based on the CLSI method [10].

All patients included in this study were hospitalized for UUTI caused by *E. coli*. The patients were divided into two groups based on whether they were admitted during 2016 to 2019 or 2020 to 2022.

During study period, the antimicrobial use density (AUD) and days of therapy (DOT) of intravenous broad-spectrum antibiotics and overall oral antibiotic use were evaluated by the AST of the hospital. To assess the appropriate use of antimicrobials, we collected medical records on the AUD and DOT of oral and intravenous antibiotics in the hospital between January 1, 2017, and December 31, 2022. The AUD and DOT were calculated as follows using the defined daily dose (DDD) value recommended by WHO [11]:

AUD (DDD/1,000 patient-days) =
[Total dose (g) of antimicrobial used / DDD × Total days of hospital stay] × 1000

DOT (DOT/1,000 patient-days) =
[Total days (day) antimicrobials were used / Total days of hospital stay] × 1000

STATISTICAL ANALYSIS

Continuous variables were reported as the mean ± standard deviation. The Kruskal-Wallis H-test and Mann-Whitney U-test were used to compare age, WBC, CRP, and PCT. The Chi-squared test was used to assess the association between number of children admitted with *E. coli* and ESBL-producing *E. coli*, sex, history of hospitalization, VUR greater than grade 2, blood cultures, and relapse. Spearman's rank correlation coefficient (ρ) was used to assess the correlations between proportion of UUTI caused by ESBL-producing *E. coli* and AUD and DOT of antibiotics.

All analyses were performed using Microsoft Excel (Microsoft Corporation, WA, USA) and the Ystat 2000 statistical software package (Igakuto-sho-Shuppan Co., Ltd., Saitama, Japan). For all analyses, two-tailed p-values < 0.05 were considered statistically significant.

RESULTS

Participant characteristics

Eighty children with UUTI who were admitted to the department of pediatrics at the hospital and met the inclusion criteria were included in the analysis. The secular trend in the number of UUTI admissions in children is shown in Figure 1. The total number of patients hospitalized in the department of pediatrics decreased over the study period. However, the proportion of UUTI cases among hospitalized children did not show an obvious change (1.0% in 2016–2019, and 1.9% in 2020–2022).

Among the 38 cases of UUTI caused by *E. coli* in 2016–2019, 21 (55%) were caused by ESBL-nonproducing *E. coli*, and 17 (45%) were caused by ESBL-producing *E. coli*. Among the 31 cases of UUTI caused by *E. coli* in 2020–2022, 20 (65%) were caused by ESBL-nonproducing *E. coli* and 11 (35%) were caused by ESBL-producing *E. coli*. The proportion of UUTI cases caused by

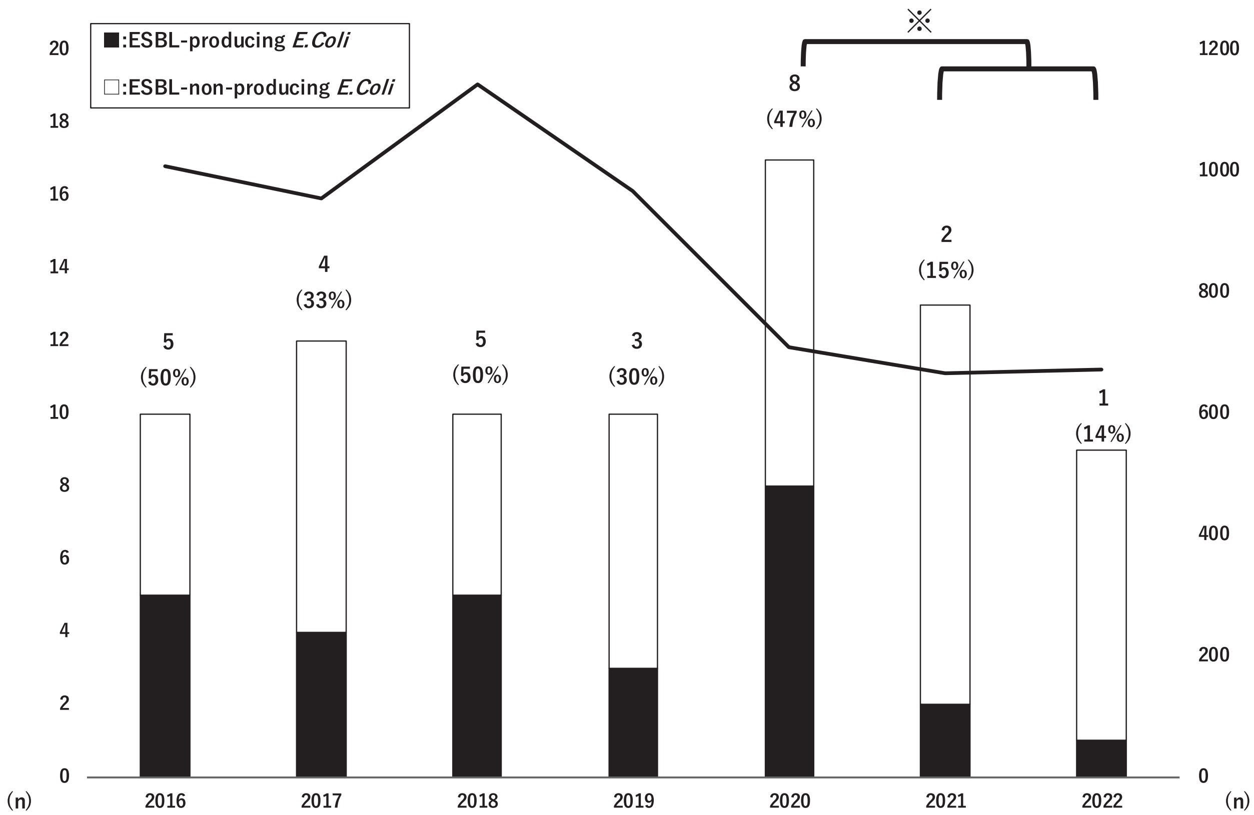

Fig. 1. Incidence and cause of upper urinary tract infections
Patients hospitalized with an upper urinary tract infection (white bars and left Y-axis); patients hospitalized with an upper urinary tract infection caused by ESBL-producing *Escherichia coli* (black bars and left Y-axes); and the total number of patients hospitalized in the pediatric department (line chart and right Y-axes) are shown. * $p < 0.05$
ESBL, extended-spectrum beta-lactamase

ESBL-producing *E. coli* decreased significantly from 47% in 2020 to 13% in 2022 (p = 0.036). Similarly, the proportion of ESBL-producing *E. coli* is confirmed in whole urine and blood culture samples in hospitalized patients decreased from 2020 to 2022. (Fig.2).

Patient demographics and clinical characteristics are summarized in Table 1, and the antibiotic susceptibility of ESBL-producing *E. coli* detected in pediatric urine samples is shown in Table 2. There were no significant differences in antibiotic susceptibility, sex, age at the time of hospitalization, history of hospitalization, number of relapses, incidence of bacteremia, proportion of patients born in the hospital, WBC count, or CRP and PCT levels among children hospitalized in 2016–2019 and 2020–2022.

Antimicrobial use density and days of antibiotic therapy

The AUD and DOT of intravenous broad-spectrum

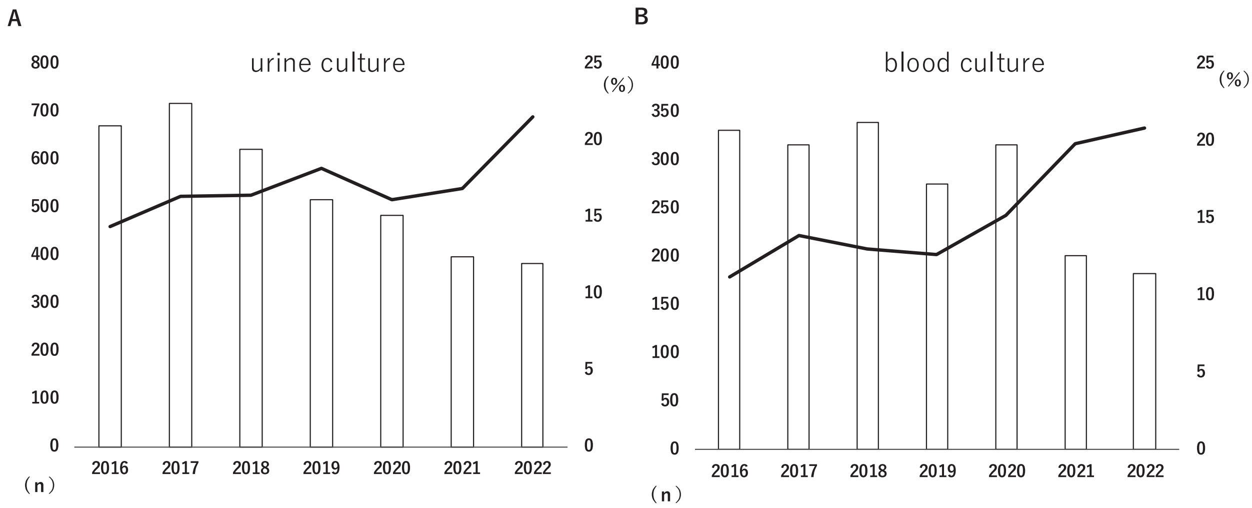

Fig. 2. Samples of urine and blood culture in our hospital and proportion of ESBL-producing *Escherichia coli*
A: Samples of urine culture in our hospital (line chart and left Y-axes) and proportion of ESBL-producing *E. coli* (white bars and right Y-axis)
B: Samples of blood culture in our hospital (line chart and left Y-axes) and proportion of ESBL-producing *E. coli* (white bars and right Y-axis)

Table 1. Demographics, clinical characteristics, and examination data of pediatric patients with UUTI caused by *E. coli*

period	2016-2019	2020-2022			P value
n (ESBL-producing *E.Coli*)	42 (17)	38 (11)			
		2020	**2021**	**2022**	
		17 (8)	13 (2)	8 (1)	
Male	30	26			0.76
Age (month)	2 – 96 (Median 5)	0-168 (Median 3)			0.61
Born at our hospital	13	6			0.18
VUR (greater than Grade 2)	6/25	4/10			0.59
History of hospitalization	5 (11.9%)	5 (13.2%)			0.86
WBC (/µl)	17746 ± 6222	16750 ± 6212			0.46
CRP (mg/dl)	7.69 ± 5.99	7.52 ± 6.21			0.83
PCT (mg/dl)	5.58 ± 10.79	3.64 ± 5.76			0.32
Case of bacteremia	2 (4.7%)	2 (5.3%)			0.68
Case of relapse	1	4			0.18

WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; VUR, vesicoureteral reflux.

Table 2. Antimicrobial resistance profiles of ESBL-producing *E. coli* detected in pediatric urine samples each year

	ESBL-producing ***E.Coli***						
year	2016	2017	2018	2019	2020	2021	2022
n	5	4	5	3	8	2	1
Antibiotic susceptibility (%)							
ABPC	0	0	0	0	0	0	0
PIPC	0	0	0	0	0	0	0
SBT/ABPC	60	100	100	100	100	100	0
CEZ	0	0	0	0	0	0	0
CAZ	0	0	0	0	0	0	0
CTRX	0	0	0	0	0	0	0
CFPM	0	0	0	0	0	0	0
CMZ	100	100	100	100	100	100	100
FMOX	100	100	100	100	100	100	100
IPM	100	100	100	100	100	100	100
MEPM	100	100	100	100	100	100	100
AZT	0	0	0	0	0	0	0
GM	60	100	100	100	100	100	0
AMK	100	100	100	100	100	100	100
MINO	80	100	100	100	100	100	100
CPFX	80	100	100	100	100	100	0
LVFX	80	100	100	100	100	100	0
CP	100	100	100	100	100	100	100

Ampicillin (ABPC), piperacillin (PIPC), sulbactam/ampicillin (SBT/ABPC), cefazolin (CEZ), ceftazidime (CAZ), ceftriaxone (CTRX), cefepime (CFPN), cefmetazole (CMZ), flomoxef (FMOX), imipenem (IPM), meropenem (MEPM), aztreonam (AZT), gentamicin (GM), amikacin (AMK), minocycline (MINO), ciprofloxacin (CPFX), levofloxacin (LVFX), chloramphenicol (CP)

antibiotics such as quinolone, carbapenem, fourth-generation cephems, and piperacillin/tazobactam (TAZ/PIPC) and the AUD and DOT of oral antibiotics are shown in Figure 3. The reduction in the use of oral third-generation cephems was significant ($p = 0.0026$) and was significantly correlated with the proportion of ESBL-producing *E. coli* in UUTI cases, as shown in Figure 4 ($\rho = 0.93745$; $Y = 0.06X + 0.15$).

DISCUSSION

During this study period, the highest incidence of hospitalization due to UUTI was in infants aged less than 6 months. The age and sex profile of the children in this study was similar to that of Japanese children with UUTI in a previous study [9]. The total number of patients hospitalized in the pediatric department decreased from 2016 to 2022; however, the decrease in the number of patients with UUTIs was more gradual and less evident than the overall decrease in the number of patients.

Some studies have evaluated the changes in urinary tract infection (UTI) incidence rates in children during the SARS-CoV-2 pandemic in Japan [7, 8]. In a study by Kishimoto *et al* [8], a decrease in hospitalizations due to upper respiratory infection, lower respiratory infection, and gastrointestinal infection, which are more clearly related to social distancing and viruses, was observed in the pediatric age group during the COVID-19 period compared with the pre-COVID-19 period, whereas the hospitalization rate for UTIs did not change.

The major cause of UUTI in this study was *E. coli*, as in previous studies [2, 4, 9]. Since 2016, almost 50% of all UUTI cases in Matsue City have been caused by ESBL-producing *E. coli*. However, the proportion of UUTI caused by community-acquired ESBL-producing *E. coli* decreased markedly during the period from 2020 to 2022 (Fig. 1).

In Matsue City, the number of patients with COVID-19 increased from 209 in 2020 to 136,079 in 2022 [10]. The SARS-CoV-2 pandemic led to

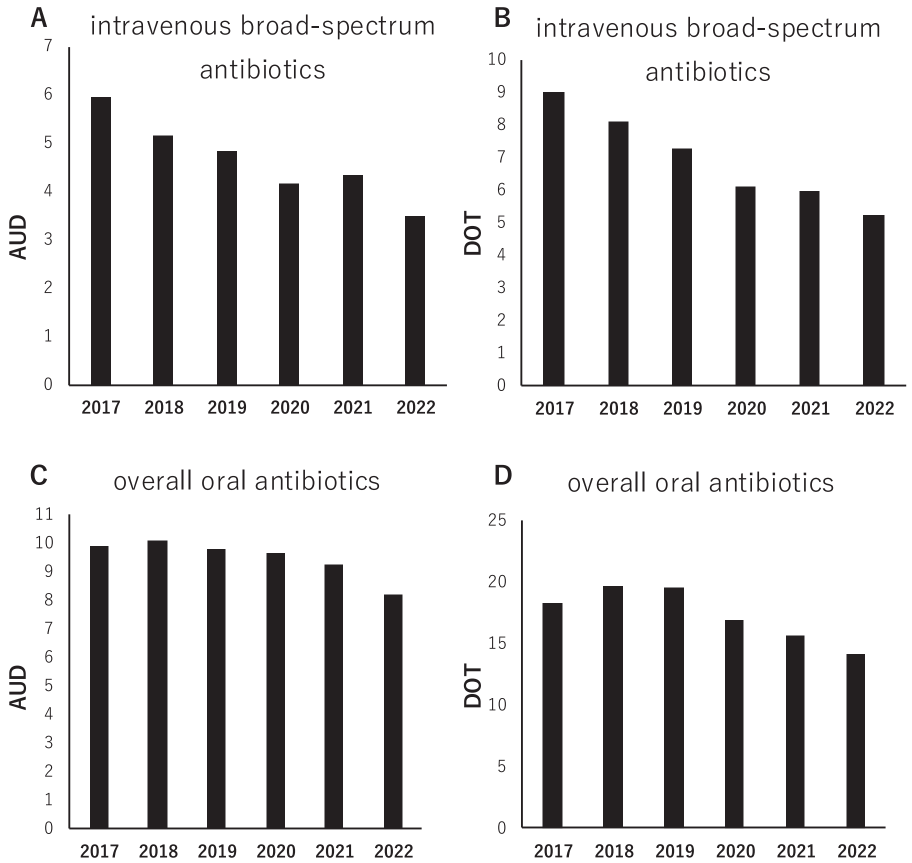

Fig. 3. Antimicrobial use density and days of therapy of antibiotics of our hospital in 2017-2022
(A) AUD of intravenous broad-spectrum antibiotics; (B) DOT/1,000 patient-days of intravenous broad-spectrum antibiotics; (C) AUD of overall oral antibiotics; (D) DOT/1,000 patient-days of overall oral antibiotics.
Broad-spectrum antibiotics include quinolones, carbapenems, fourth-generation cephems, and piperacillin/tazobactam.
AUD, antimicrobial use density (DDD/1,000 patient-days); DOT, days of therapy (DOT/1,000 patient-days)

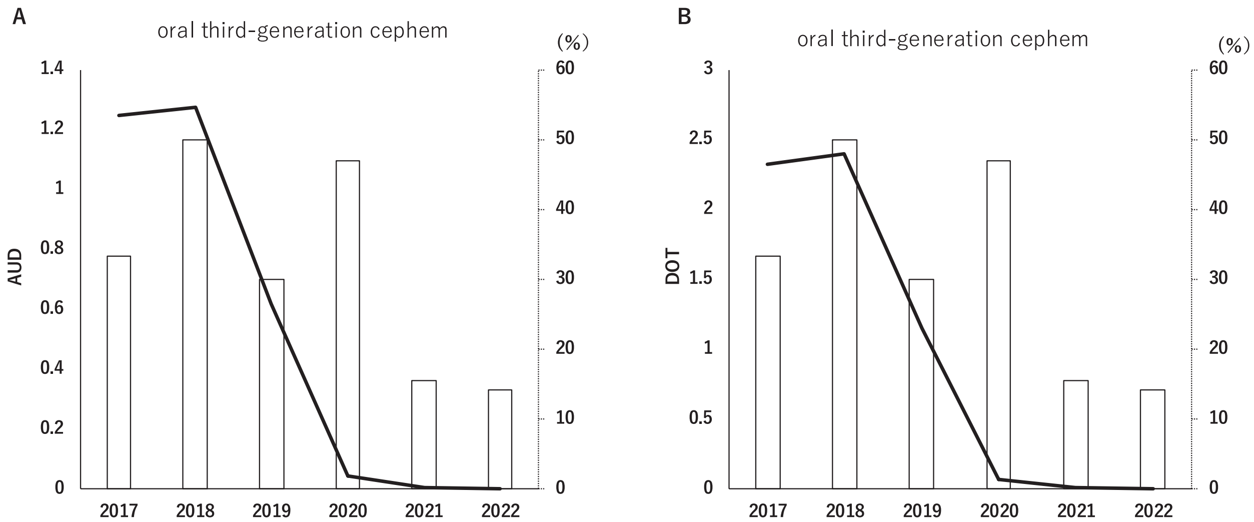

Fig. 4. Oral third-generation cephems and proportion of upper urinary tract infections caused by ESBL-producing *Escherichia coli*
(A) AUD of oral third-generation cephem (line chart and left Y-axes) and proportion of hospitalized children with UUTI caused by ESBL-producing *E. coli* (white bars and right Y-axis)
(B) DOT of oral third-generation cephem (line chart and left Y-axes) and proportion of hospitalized patients with UUTI caused by ESBL-producing *E. coli* (white bars and right Y-axis)
AUD, antimicrobial use density (DDD/1,000 patient-days); DOT, days of therapy (DOT/ 1,000 patient-days);
ESBL, extended-spectrum beta-lactamase; UUTI, upper urinary tract infection

radical changes in hygienic measures worldwide. People began wearing face masks, physical distancing from others, washing hands, disinfecting hands with alcohol, and avoiding crowded places to prevent transmission.

ESBL-producing bacteria are often multidrug resistant, and related genes are encoded by plasmids that are transferred from species to species. Previously, the digestive tract was thought to be the main reservoir from which ESBLs were derived [3]. However, Matsumoto *et al*. [13], reported that ESBL-producing *E. coli* were also isolated from respiratory samples. Traditionally, UUTI is defined as a non-communicable disease. However, it is possible that both the reduction in the number of hospital admissions and hygienic measures such as washing hands and widespread use of alcohol disinfectants in public places and home, could have reduced the transmission of ESBL plasmids from person-to-person or from the gut to the urinary tract via the hands.

One of the goals of the AMR action plan is to promote the appropriate use of antimicrobial agents by reduction of the use of broad-spectrum antimicrobial agents, such as cephalosporins, fluoroquinolones, and macrolides [6]. During the study period, even before the onset of the SARS-CoV-2 pandemic, the AUD and DOT of intravenous broad-spectrum antibiotics and overall oral antibiotics decreased, which indicates a reduction in the amount used and a shorter period of use of these antibiotics. These results indicate that the AST plays a crucial role in the surveillance of antimicrobial usage and interventions to ensure appropriate antimicrobial use.

The reduction of oral third-generation cephem use was significantly correlated with the proportion of community-acquired ESBL-producing *E. coli* detected in urine samples. Previously, several studies have shown that the cephem-containing β-lactam rings are able to induce ESBL production and that exposure to third-generation oral cephems can induce conjugative transfer of ESBL plasmids [13–16].

Furthermore, removal of antibiotic pressure results in loss of resistance plasmids and reduces the number of antibiotic-resistant bacteria because of a fitness cost in the absence of selection [17]. A natural history study of multidrug-resistant *Enterobacteriaceae* colonization rates in the community decreased during the 12-month follow-up period [18].

These results suggest that there is a close relationship between reduction of oral third-generation cephem use and infections with ESBL-producing bacteria.

However, some types of ESBL-producing plasmids require little fitness cost for the host bacterium despite an absence of antibiotic pressure [19]. Further studies focusing on the effect costs of ESBL-producing bacteria and antibiotic pressure are required to investigate the decrease in the prevalence of AMR bacteria after reduction in the use of third-generation cephems.

Pathogen resistance in UTI varies according to geographic location. The incidence rate of infections cause by ESBL-producing bacteria has been relatively low in Japan [1, 20], but has increased in neighboring countries [1]. The hospital is in an area of Japan that has a has experienced a major influx of foreign-born residents from South American and other Asian countries [21]. ESBL-producing bacteria have been detected not only at medical centers, but also in food, animals, and travelers [1, 22]. Previous studies conducted in America and Europe have shown that ESBL-producing bacteria in the stool are strongly correlated with international travel, especially in travelers returning from Asian and African countries. [16, 22].

After the start of the SARS-CoV-2 pandemic in 2020, restrictions were placed on travel to other countries, and the number of foreign individuals living in Matsue City decreased [21]. Limitations of international travel might have reduced the transfer of regional antibiotic resistance genes. Therefore, as the world emerges from the SARS-CoV-2 pandemic, and the movement of people, foods, goods, and animals resumes, and the number of ESBL-producing bacterial outbreaks might increase.

This study has several limitations. We conducted a retrospective review of patient medical records; therefore, in pediatric patients who were born in other hospitals, the neonatal medical records and the obstetric records of their mothers were not available for review. Medications prescribed at other hospitals and other factors preceding the child's UUTI hospitalization were not assessed. Prior exposure to antibiotics might have affected the results. Furthermore, we did not have data regarding the onset of the UUTI before hospitalization. Therefore, further prospective studies are necessary to explore the factors associated with ESBL-producing *E. coli* and UUTI in children.

CONCLUSIONS

The study results suggest that hygienic measures and appropriate use of antimicrobials, especially reduction of the use of oral third-generation cephems are effective for reducing the incidence of ESBL-producing bacterial infections such as UUTI. However, as the world emerges from the SARS-CoV-2 pandemic, and the movement of people, foods, goods, and animals resumes and the incidence of ESBL-producing bacterial infections might increase. Therefore, it is necessary for the AST in each hospital to focus on use of antibiotics and maintain ongoing surveillance of the prevalence of ESBL-producing bacteria.

Ethics approval and informed consent

The study was approved by the Ethics Committee of Matsue Red Cross Hospital of Japan, (IRB approval number: 554). All potential personal identifiers were removed to maintain confidentiality. All procedures performed were carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and the institutional ethics guidelines. The requirement for informed consent to participate was waived by the Ethics Committee of Matsue Red Cross Hospital of Japan because the study was retrospective.

Author contributions

AH contributed to the study conception and design, performed material preparation, data collection, and analysis, and wrote the first draft of the manuscript. MS, MN, SH, YM, YH, TF, MM, and AN contributed to the study conception and design, performed material preparation, data collection, and analysis, and provided comments on drafts of the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

The authors declare no conflict of interest.

REFERENCES

1) Woerther PL, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum β-lactamases in the community: Toward the globalization of CTX-M. *Clin Microbiol Rev*. 2013;26:744-58. doi: 10.1128/CMR.00023-13.

2) Dayan N, Dabbah H, Weissman I, Aga I, Even L, Glikman D. Urinary tract infections caused by community-acquired extended-spectrum β-lactamase-producing and nonproducing bacteria: a comparative study. *J Pediatr*. 2013;163:1417-21. doi: 10.1016/j.jpeds.2013.06.078.

3) Yamamoto S, Tsukamoto T, Terai A, Kurazono H, Takeda Y, Yoshida O. Genetic evidence supporting the fecal-perineal-urethral hypothesis in cystitis caused by *Escherichia coli*. *J Urol*. 1997;157:1127-9.

4) Horie A, Nariai A, Katou F, *et al*. Increased community-acquired upper urinary tract infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* in children and the efficacy of flomoxef and cefmetazole. *Clin Exp Nephrol*. 2019;23:1306-14. doi: 10.1007/s10157-019-01775-w.

5) World Health Organization. Global Action Plan on Antimicrobial Resistance. World Health Organization. 2015 [cited 2023 May 1]. Available from: https://www.who.int/publications/i/item/9789241509763.

6) The Government of Japan. National action plan on antimicrobial resistance (AMR) (2016–2020). Ministry of Health, Labour and Welfare. https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000138942.pdf. (accessed 2023 Feb 1).

7) Fukuda Y, Tsugawa T, Nagaoka Y, *et al*. Surveillance in hospitalized children with infectious dis-

ease in Japan: pre- and post-coronavirus disease 2019. *J Infect Chemother*. 2021;27:1639-47. doi: 10.1016/j.jiac.2021.07.024.

8) Kishimoto K, Seiko B, Shin JH, *et al*. Early impact of school closure and social distancing for COVID-19 on the number of inpatients with childhood non-COVID-19 acute infections in Japan. *Eur J Pediatr*. 2021;180:2871-8. doi: 10.1007/s00431-021-04043-w.

9) Nagata H, Furuse A, Irie S, *et al*. Clinical comparison between childhood upper urinary tract infection due to extended- and non-extended-spectrum β-lactamase-producing bacteria. *Japanese Journal of Pediatric Nephrology* 2015;28:37-42. doi: 10.3165/jjpn.28.37.（Eng Abstr）

10) Clinical and Laboratory Standards Institute. Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data: Approved Guideline. Fourth Edition. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.

11) WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health. ATC/DDD Index. Norwegian Institute of Public Health. https://www.whocc.no/atc_ddd_index/.（accessed 2023 May 1）.

12) Shimane Prefectural Infectious Disease Surveillance Center. The number of COVID-19 patients. May 30, 2025 update. Shimane Prefectural Infectious Disease Surveillance Center. https://www1.pref.shimane.lg.jp/contents/kansen/dis/zensu/703.htm.（accessed 2025 Oct 22）.（in Japanese）

13) Matsumoto H, Komiya K, Ichihara S, *et al*. Factors associated with extended-spectrum β-lactamase-producing enterobacteria isolated from respiratory samples. *Intern Med*. 2023;62:2043-50. doi: 10.2169/internalmedicine.0690-22.

14) Liu G, Bogaj K, Bortolaia V, Olsen JE, Thomsen LE. Antibiotic-induced, increased conjugative transfer is common to diverse naturally occurring ESBL plasmids in *Escherichia coli*. *Front Microbiol*. 2019;10:2119. doi: 10.3389/fmicb.2019.02119.

15) Birgy A, Cohen R, Levy C, *et al*. Community faecal carriage of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* in French children. *BMC Infect Dis*. 2012;12:315. doi: 10.1186/1471-2334-12-315.

16) Karanika S, Karantanos T, Arvanitis M, Grigoras C, Mylonakis E. Fecal colonization with extended-spectrum beta-lactamase-producing *Enterobacteriaceae* and risk factors among healthy individuals: a systematic review and meta-analysis. *Clin Infect Dis*. 2016;63:310-8. doi: 10.1093/cid/ciw283.

17) Martínez JL, Coque TM, Baquero F. What is a resistance gene? Ranking risk in resistomes. *Nat Rev Microbiol*. 2015;13:116-23. doi: 10.1038/nrmicro3399.

18) Bar-Yoseph H, Hussein K, Braun E, Paul M. Natural history and decolonization strategies for ESBL/carbapenem-resistant Enterobacteriaceae carriage: systematic review and meta-analysis. *J Antimicrob Chemother*. 2016;71:2729-39. doi: 10.1093/jac/dkw221.

19) Dimitriu T, Medaney F, Amanatidou E, Forsyth J, Ellis RJ, Raymond B. Negative frequency dependent selection on plasmid carriage and low fitness costs maintain extended spectrum β-lactamases in *Escherichia coli*. *Sci Rep*. 2019;9:17211. doi: 10.1038/s41598-019-53575-7.

20) Suzuki S, Shibata N, Yamane K, Wachino J, Ito K, Arakawa Y. Change in the prevalence of extended-spectrum-β-lactamase-producing *Escherichia coli* in Japan by clonal spread. *J Antimicrob Chemother*. 2009;63:72-9. doi: 10.1093/jac/dkn463.

21) Shimane Prefectural Government. Change in the number of foreigner residents of the prefecture. Dec 31, 2021 update [cited 2023 Feb 1]. Available from: https://www.pref.shimane.lg.jp/bunkakokusai/tabunka/sousei-tabunka.html#.

22) Lübbert C, Straube L, Stein C, *et al*. Colonization with extended-spectrum beta-lactamase-producing and carbapenemase-producing *Enterobacteriaceae* in international travelers returning to Germany. *Int J Med Microbiol*. 2015;305:148-56. doi: 10.1016/j.ijmm.2014.12.001.