Prolonged Carriage of ESBL-producing Enterobacteriaceae and Potential Cross-transmission among Residents in Geriatric Long-term Care Facilities

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Research Article

Keywords: Extended-spectrum β -lactamase-producing Enterobacteriaceae (ESBL-E), older adult, geriatric long-term care facility, infection control and prevention

Posted Date: February 3rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-148809/v1>

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Abstract

Background: Previous studies indicated residents in geriatric long-term care facilities (LTCFs) had much higher prevalence of extended-spectrum β -lactamase-producing Enterobacteriaceae (ESBL-E) carriage than the general population. Most ESBL-E carriers are asymptomatic. The study tested the hypothesis that residents with ESBL-E carriage may accumulate inside geriatric LTCFs through potential cross-transmission after exposure to residents with prolonged ESBL-E carriage.

Methods: We evaluated 260 residents receiving long-term care in four LTCFs in Japan. All residents underwent initial ESBL-E testing of fecal specimens and were divided into two cohorts: Cohort 1, 95 patients with ≥ 2 months residence at study onset; Cohort 2, 165 patients with < 2 months residence at study onset or new admission during the study period. Among the 260 residents with continuous LTCF residence, 126 underwent second testing 3–12 months after the first testing and 36 residents underwent third testing ≥ 12 months after the second testing. Three analyses were performed: (1) ESBL-E carriage statuses in Cohort 1 and Cohort 2; (2) changes in ESBL-E carriage statuses in the second testing and third testing; and (3) lengths of positive ESBL-E carriage statuses in patients who underwent the second testing and third testing.

Results: Among all 260 residents, 95 (36.5%) were positive for ESBL-E carriage in the first testing. The prevalence of ESBL-E carriage was significantly higher in Cohort 2 than in Cohort 1 (40% vs. 28%; $p < 0.01$). In the subsequent testing results, 18.3% of residents who were negative in the first testing showed positive conversion to ESBL-E carriage in the second testing, while no patients who were negative in the second testing showed positive conversion in the third testing. The maximum length of ESBL-E carriage was 17 months.

Conclusions: ESBL-E was most likely to be carried into LTCFs through admission of new residents. Some residents acquired ESBL-E through potential cross-transmission within 3–12 months after admission. Despite possible ESBL-E carriage for > 1 year, no residents showed positive conversion > 12 months after admission, which suggests that residents with ESBL-E carriage may not accumulate inside LTCFs. Practical infection control and prevention measures against ESBL-E by care providers could improve the ESBL-E prevalence in geriatric LTCFs.

Background

With the rapid aging of populations worldwide, the number of older adults requiring residence in geriatric long-term care facilities (LTCFs) is increasing. For older residents in geriatric LTCFs, outbreaks of specific infectious diseases inside their facilities can greatly affect their mortality and morbidity [1–8]. Therefore, appropriate infection prevention and control is a critical challenge for care providers in geriatric LTCFs [1–8].

Multidrug-resistant Gram-negative organisms represent an ongoing threat to global public health and necessitate the implementation of practical infection prevention and control guidelines in daily practice

and caregiving [9–13]. Among these organisms, extended-spectrum β -lactamase-producing Enterobacteriaceae (ESBL-E) has become widespread in hospital settings as well as geriatric LTCFs worldwide [13–20]. The intestinal tract provides an ideal reservoir for ESBL-E, and carriers of ESBL-E are typically asymptomatic [21–25]. Several studies have indicated that asymptomatic carriers of ESBL-E may require effective surveillance and specific control programs to prevent the infection becoming widespread [24, 25].

The present study focused on asymptomatic LTCF residents with carriage of ESBL-E identified in their feces. In previous studies, LTCF residents had much higher prevalence of ESBL-E carriage than the general population [15, 16]. We hypothesized that in geriatric LTCFs, asymptomatic residents with ESBL-E carriage may accumulate through potential cross-transmission after exposure to residents with prolonged ESBL-E carriage. To test this hypothesis, we performed multiple ESBL-E testing with long-term follow-up for continuous residents in LTCFs to assess (1) the proportion of residents who acquired ESBL-E through potential cross-transmission inside the facilities and (2) the length of ESBL-E carriage among ESBL-E-positive residents.

Methods

Study settings and participants

We conducted a cohort study among residents receiving long-term care in 4 geriatric LTCFs in Japan. The facilities were selected because they had secure linkage with their own specific back-up hospitals where residents were typically transferred for any medical needs. All 4 LTCFs were anonymized in accordance with the ethics protocol of the study. Brief profiles of the facilities are shown in Table 1.

Table 1
Background characteristics of the study settings

	Geriatric long-term care facilities (anonymized)			
Characteristics	A	B	C	D
Facility type	HSF	HSF	SNH	HSF
Resident capacity	100	50	60	150
Male : Female residents	47 : 53	11 : 32	19 : 50	33 : 67
Age of residents, median (range), year	84 (59–106)	91 (77–105)	87 (70–106)	85 (53–105)
Proportions of residents requiring diapers for excretion	52%	84%	46%	96%
Population density of municipality where facility is located (persons/km ²) ^a	389	54	389	13370
Region of Japan	Eastern	Eastern	Eastern	Western
Number of beds in the back-up hospital	90	100	90	327
Abbreviations: HSF, health services facility; SNH, special nursing home				
^a Calculated using the populations of the municipalities in 2019 or 2020				

The study participants were 260 older adults residing in the 4 LTCFs who underwent ESBL-E carriage testing during the study period (August 2018 through March 2020). Residents who did not undergo ESBL-E testing were excluded from the study. Background data for the 260 residents, such as age, sex, and general condition, were not obtained because of the ethics protocol employed in the study.

In Japan, geriatric LTCFs are classified into two main types: (1) geriatric health services facilities and (2) geriatric special nursing homes. The former are intermediate facilities between hospitals and nursing homes, with a primary focus on rehabilitation. These facilities typically have a goal of returning patients to home-based care, although some residents may require long-term care for years. The latter provide daily life support, including end-of-life care. [26–28] The study included three geriatric health services facilities and one geriatric special nursing home.

Microbiology and ESBL-E isolates

Small amounts (0.05–0.1 g) of freshly voided feces from the residents were obtained from paper diapers or papers for self-collection of stool samples (AS ONE Corporation, Osaka, Japan) using stool collection tubes with agar medium (FECES COLLECTING TUBE™; Eiken Chemical Co. Ltd., Tokyo, Japan). To avoid contamination, facility staff performed standard preventive measures during sample collection. Each fecal sample was harvested on selective screening agar plates using sterile cotton swabs. CHROMagar™

ESBL/CHROMagar™ mSuperCARBA bi-plate medium (Kanto Chemical Co. Inc., Tokyo, Japan) was used for identification of ESBL-E carriage [29]. This medium was able to grow ESBL-E simultaneously with carbapenem-resistant Enterobacteriaceae (CRE) and/or AmpC β -lactamase-producing bacteria. Following aerobic incubation at 37°C for 18–24 hours, colonies growing on either side of the adapted screening agar were regarded as suspect for any of the above bacteria, and underwent further analysis. ESBL-E and AmpC β -lactamase-producing bacteria were identified using an ESBL + AmpC Detection Set™ (MAST Group, Bootle, Merseyside, UK). CRE was identified using a Vitek™ 2 automated instrument for infectious disease testing (bioMérieux SA, Marcy l'Etoile, France) for its resistance against imipenem and meropenem. Bacterial species were identified by the Vitek™ 2 automated instrument (bioMérieux).

Study design and statistical analysis

The first ESBL-E testing was performed on all 260 residents < 1 month after study onset or initiation of residence. The 260 residents who underwent the first ESBL-E testing were classified into two cohorts (Fig. 1A): Cohort 1 contained residents who had been residing in an LTCF for ≥ 2 months at study onset, and Cohort 2 contained residents who had been residing in an LTCF for < 2 months at study onset or initiated residence in an LTCF during the study period. First, we compared the ESBL-E carriage statuses (positive/negative) between residents in Cohort 1 and Cohort 2 (Fig. 1A, **Analysis Part 1**).

Second, we assessed the changes in ESBL-E carriage statuses in residents from the first testing who subsequently underwent a second testing and/or a third testing (Fig. 1B, **Analysis Part 2**). The second testing was performed 3–12 months after the first testing and the third testing was conducted ≥ 12 months after the second testing for residents who had been continuously residing in the LTCFs. The second testing and third testing were not performed in residents who had been discharged from the LTCFs at the time of each testing. In this analysis, we identified the proportions of residents who had changed from negative to positive for ESBL-E carriage status in the results for the second testing and third testing.

Third, we assessed the lengths of ESBL-E carriage from one testing to the next testing among residents who underwent the second testing and third testing (Fig. 1B, **Analysis Part 3**). In this analysis, we measured the durations of positive test results in the same residents. If all three tests revealed positive results, the lengths of ESBL-E carriage were measured from the first testing through third testing. The median and range (minimum to maximum) for the lengths of ESBL-E carriage were determined.

All analyses were performed using IBM SPSS Statistics for Windows, Version 25 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as number and percentage, while numerical variables were presented as median and range unless otherwise indicated. The chi-square test was used to compare ESBL-E carriage statuses between residents in Cohort 1 and Cohort 2 (Analysis Part 1) with a significance threshold of $p < 0.05$. The study was approved by the Jichi Medical University Bioethics Committee for Medical Research (Approval ID: 20–058).

Results

Analysis Part 1

Cohort 1 and Cohort 2 contained 75 and 185 residents, respectively (**Table 2**). Among all 260 residents, 95 (36.5%) were positive for ESBL-E carriage in the first testing. Compared with the residents in Cohort 1, a significantly larger proportion of residents in Cohort 2 were positive for ESBL-E carriage (28.0% in Cohort 1 vs 40.0% in Cohort 2, $p < 0.01$). The ESBL-E strains identified in the first testing had considerable diversity (Table 3).

Table 2
ESBL-E carriage statuses among residents in Cohort 1 and Cohort 2 (N=260; Analysis Part 1)

	First ESBL-E test result ^a				Total	
	Positive		Negative			
	n	(%)	n	(%)	n	(%)
Cohort 1	21	(28.0) ^b	54	(72.0)	75	(100)
Cohort 2	74	(40.0) ^b	111	(60.0)	185	(100)
Total	95	(36.5)	165	(63.5)	260	(100)
Abbreviation: ESBL-E, extended-spectrum β-lactamase-producing Enterobacteriaceae						
^a Performed <1 month after study onset or initiation of residence						
^b Chi-square test: $p < 0.01$						

Table 3

Classification of ESBL-producing bacteria detected in fecal specimens from residents

Bacteriological classification of ESBL-producing bacteria	n	(%)
Carriage of a single strain		
<i>Escherichia coli</i> ^a	74	(77.9)
AmpC β -lactamase co-producing <i>Escherichia coli</i>	3	(3.2)
<i>Citrobacter freundii</i>	1	(1.1)
<i>Enterobacter cloacae</i>	1	(1.1)
<i>Proteus mirabilis</i>	1	(1.1)
Carriage of a multiple strains		
<i>Escherichia coli</i> + <i>Klebsiella pneumoniae</i>	7	(7.4)
<i>Escherichia coli</i> + <i>Klebsiella oxytoca</i>	2	(2.1)
Two strains of <i>Escherichia coli</i>	2	(2.1)
Three strains of <i>Escherichia coli</i>	1	(1.1)
<i>Escherichia coli</i> + AmpC β -lactamase co-producing <i>Escherichia coli</i> ^b	2	(1.1)
<i>Escherichia coli</i> + AmpC β -lactamase co-producing <i>Enterobacter cloacae</i>	1	(1.1)
Total	94	(100)
Abbreviation: ESBL, extended-spectrum β -lactamase		
^a One strain was detected for AmpC β -lactamase-producing <i>Enterobacter cloacae</i>		
^b One strain met the definition of carbapenem-resistant Enterobacteriaceae (CRE)		

Analysis Part 2

Of the 126 residents who underwent both the first testing and second testing (Table 4), 48 (38.1%) were positive for ESBL-E carriage in the second testing. Among the 44 residents positive for ESBL-E carriage in the first testing, 33 (75.0%) remained positive in the second testing. However, among the 82 residents negative for ESBL-E carriage in the first testing, 15 (18.3%) showed positive conversion in the second testing.

Table 4
Changes in ESBL-E carriage statuses from the first testing to second testing (n = 126;
Analysis Part 2)

Second ESBL-E test result ^a					Total	
Positive		Negative			(n = 126)	
(n = 48)		(n = 78)				
n	(%)	n	(%)		n	(%)
First ESBL-E test result						
Positive	33	(75.0)	11	(25.0)	44	(100)
Negative	15	(18.3)	67	(81.7)	82	(100)
Abbreviation: ESBL-E, extended-spectrum β -lactamase-producing Enterobacteriaceae						
^a Performed 3–12 months after the first ESBL-E testing						

Of the 36 residents who underwent both the second testing and third testing (Table 5), 6 (16.7%) were positive for ESBL-E carriage in the third testing. Among the 11 residents positive for ESBL-E carriage in the second testing, 6 (54.4%) remained positive in the third testing. Furthermore, among the 25 residents negative for ESBL-E carriage in the second testing, no residents showed positive conversion in the third testing.

Table 5
Changes in ESBL-E carriage statuses from the second testing to third testing (n = 36;
Analysis Part 2)

Third ESBL-E test result ^a					Total	
Positive		Negative			(n = 36)	
(n = 6)		(n = 30)				
n	(%)	n	(%)		n	(%)
Second ESBL-E test result						
Positive	6	(54.5)	5	(45.5)	11	(100)
Negative	0	(0)	25	(100)	25	(100)
Abbreviation: ESBL-E, extended-spectrum β -lactamase-producing Enterobacteriaceae						
^a Performed $\geq$ 12 months after the second ESBL-E testing						

Analysis Part 3

The lengths of ESBL-E carriage in the residents who underwent the second testing and third testing are shown in Fig. 2. The lengths of carriage were measured for 4, 30, and 2 residents for the first testing to third testing, first testing to second testing, and second testing to third testing, respectively. The maximum length of ESBL-E carriage was 17 months. The median length of carriage for all evaluated residents was 4 months.

Discussion

The present study had three key findings. First, the prevalence of ESBL-E carriage was significantly higher in Cohort 2 than in Cohort 1 (40% vs 28%), which indicates that ESBL-E was most likely to be carried into LTCFs through admission of new residents, who provided a large contribution to the increased total prevalence of ESBL-E carriage among LTCF residents. Second, 18% (15/82) of residents showed positive conversion to ESBL-E carriage in the second testing, which indicates that some residents may have acquired ESBL-E through potential cross-transmission inside the LTCFs after short-term residence (3–12 months after admission). Third, some residents maintained ESBL-E carriage for > 1 year (maximum, 17 months), which indicates that these residents may be high-risk triggers for outbreaks inside LTCFs through resident-to-resident transmission as a potential ESBL-E reservoir. However, we subsequently found that no residents exhibited positive conversion to ESBL-E carriage after long-term residence (> 12 months after admission). This finding indicated that, from the long-term perspective, residents with ESBL-E carriage were less likely to accumulate inside LTCFs. Thus, the present findings highlight the importance for appropriate implementation of practical ESBL-E infection control and prevention measures by care providers in geriatric LTCFs, with the expectation of disappearing ESBL-E from the facilities.

Using the exact same LTCF settings employed in the present study, we recently reported that the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the nasal cavity of LTCF residents was approximately 10% [26]. However, the prevalence of ESBL-E carriage among residents was much higher in the present study (36.5%; 95/260 residents). We further reported that MRSA may be imported into LTCFs via transfer of residents rather than spread by potential cross-transmission inside LTCFs [26]. Similar to MRSA, the present study indicated that ESBL-E were most likely to be carried into LTCFs through admission of new residents. However, major differences between MRSA and ESBL-E may be the frequency of potential cross-transmission and the length of carriage. Compared with MRSA [26], ESBL-E was more likely to become widespread inside geriatric LTCFs through potential cross-transmission among residents and less likely to disappear spontaneously after short-term residence. These differences may contribute to the higher prevalence of ESBL-E compared with MRSA. Given that ESBL-E can be transmitted during the excrement disposal process or fecal contamination, care providers in geriatric LTCFs should pay thorough attention to adherence for infection prevention, especially for residents requiring diaper disposal.

The present results indicated that residents with ESBL-E carriage may diminish during long-term residence. This finding was supported by a previous study. Overdevest et al. [14] conducted a surveillance study and suggested that ESBL-E could be predicted to disappear from LTCFs over time. They also reported that the lengths of ESBL-E carriage differed in accordance with the strain types, with ESBL-*Escherichia coli* of sequence type O25:ST131 having the longest carriage period before its disappearance from LTCFs [14]. In the present study, ESBL-*Escherichia coli* was only identified in residents with prolonged ESBL-E carriage for > 12 months (data not shown), although we did not identify any other sequence types. We further found that 17% of residents had acquired ESBL-E through potential cross-transmission inside the LTCFs within short-term residence after admission. Although there are no previous studies to support this finding, some possible hypotheses can be proposed. First, new residents admitted to LTCFs may have had multiple risk factors for ESBL-E acquisition, such as episodes of recent antibiotic use and/or previous hospitalization [15–18, 21, 22, 30, 31]. Our selected LTCFs had their own linkages with specific back-up hospitals. Second, ESBL-E may have been most infectious immediately after being carried into the facilities, and then gradually become less infectious. This may be associated with the duration from previous antibiotics use. Importantly, our findings highlight that the risk of ESBL-E acquisition inside geriatric LTCFs may further increase with admission of large numbers of new residents.

Care providers in geriatric LTCFs should consider that residents are most likely to have ESBL-E in their feces on their initial admission to the facilities, especially those admitted from hospital settings. Furthermore, residents with short-term residence should be considered as high-risk residents for ESBL-E acquisition. A patient traceability with alarm system for ESBL-E carriage between specific back-up hospitals and their receiving LTCFs may be effective in preventing ESBL-E transmission inside LTCFs. However, the standard precautions against ESBL-E transmission should be of utmost importance for all care providers in geriatric LTCFs. A previous study showed that enhanced infection control measures mainly based on thorough adherence to standard precautions led to subsidence of an outbreak of ESBL-producing bacteria inside an LTCF [32]. Several intervention programs may improve adherence to standard precautions among care providers in geriatric LTCFs [4, 5, 33]. In particular, care providers should be careful about daily care in the excrement disposal process and fecal contamination for residents requiring diapers. Such residents comprised the majority in our study settings. To our knowledge, no previous studies have focused on older adults with diapers and infections. This situation may warrant further assessment of infection control and prevention strategies against ESBL-E.

The present study had some limitations. First, we did not obtain complete information on the background characteristics of the residents, such as sex, age, general condition, and medical history because of the ethics protocol employed in the study; the ethics review board did not grant approval to obtain this information. Second, we were unable to obtain information on the prevalence of ESBL-E carriage in region-specific general populations surrounding each LTCF and among patients hospitalized in each specific back-up hospital, which may have affected our results. Third, the study participants comprised a small number of residents from a limited number of LTCFs. Finally, we did not obtain information on where the residents had been prior to their transfer to the LTCFs.

Conclusions

ESBL-E was most likely to be introduced into LTCFs through admission of new residents. Furthermore, some residents acquired ESBL-E through potential cross-transmission inside the LTCFs within a short period (3–12 months) after admission. Although ESBL-E carriage could be maintained for > 1 year, no residents exhibited positive conversion to ESBL-E carriage upon long-term residence of > 12 months after admission, which indicates that residents with ESBL-E carriage may not accumulate inside LTCFs. Practical infection control and prevention by care providers could decrease the prevalence of ESBL-E in geriatric LTCFs.

Abbreviations

ESBL-E: extended-spectrum β -lactamase-producing Enterobacteriaceae

LTCF: long-term care facility

Declarations

Ethics approval and consent to participate

All methods were performed in accordance with the Declaration of Helsinki. Jichi Medical University Bioethics Committee for Medical Research approved the study and waived the requirement for informed consent from individual participants (Approval ID: 20-058).

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the Japan Agency for Medical Research and Development (AMED) under grant number JP20dk0110030. The funding body had no role in the design of the study, the collection, analysis, and interpretation of data, or the writing of the manuscript.

Authors' contributions

RA, TS, KK, and MO conceptualized and designed the study, carried out the analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

RA, TS, DA, MO, KH, SH, and LC conceptualized and designed the study and critically reviewed the manuscript for important intellectual content.

TS, AY, and LC designed the data collection instruments, coordinated and supervised the data collection, and critically reviewed the manuscript.

KS, YK, and LC were responsible for microbiological testing and analysis.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Acknowledgments

We thank all the staff of the long-term care facilities who contributed to this study. We also thank Alison Sherwin, PhD, from Edanz Group (<https://en-author-services.edanz.com/ac>) for editing a draft of this manuscript.

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Figures

Figure 1

Study design (N=260) aAt the start of the study. bIf all three tests revealed positive results, the lengths of ESBL-E carriage were measured from the first testing through third testing. Abbreviations: LTCF, long-term care facility; ESBL-E, extended-spectrum β -lactamase-producing Enterobacteriaceae

Figure 2

Lengths of positive ESBL-E carriage statuses among residents who underwent the second testing and third testing (n=36; Analysis Part 3) aPerformed 3–12 months after the first testing. bPerformed ≥ 12 months after the second testing. cExcluding 4 residents with positive results in the third testing. Abbreviations: ESBL-E, extended-spectrum β -lactamase-producing Enterobacteriaceae