Fecal carriage of ESBL-producing gut flora isolated from patients and families: Molecular pattern and risk factor

Rosantia Sarassari[ab], Dian Neni[c], Kuntaman Kuntaman[d], Usman Hadi[e], Itaru Hirai[f]

[a] santisarassari@yahoo.com
[a] Study Program of Clinical Microbiology, Faculty of Medicine, Universitas Airlangga, Surabaya and 60286, Indonesia
[b]National Research and Innovation Agency of Indonesia, Jakarta 10340, Indonesia
[c] Departemant of Basic Medical Science, Faculty of Medicine, Universitas Airlangga, Surabaya 60131, Indonesia
[d] Department of Medical Microbiology, Faculty of Medicine, Universitas Airlangga, Surabaya 60293, Indonesia
[e] Departemt of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya 60131, Indonesia
[f]Laboratory of Microbiology, School of Health Sciences, University of the Ryukyus, Japan

Abstract

Antimicrobial resistance (AMR) is considered a global public health threat. The prevalence of fecal carriage of ESBL-producing gut flora is increasing in healthcare facilities and communities. Antibiotic usage is believed as one of the major drivers of AMR both in healthcare facilities and communities. However, few data analyze fecal carriage of ESBL-producing gut flora in patients and healthy individuals simultaneously in Indonesia. Detection of fecal carriage of ESBL-producing gut flora is important to prevent the outbreak and suppress the spread. This study's aim is to analyze the molecular patterns and antibiotic use as risk factors for fecal carriage of ESBL-producing gut flora isolated from patients and their families.

One hundred rectal swabs were collected from ICU and medical ward patients and their families. The samples were then cultivated in MacConkey agar containing cefotaxime 2 g/ml. Colonies grew on MacConkey agar and were then confirmed as ESBL producers using a modified double-disk diffusion method. The genes of ESBL-producing isolates were detected using PCR. Antibiotic usage history was taken from medical records and questionnaires. Statistical analysis was performed to detect the correlation between antibiotic use and ESBL-producing gut flora carriage.

The total carriage rate was 82 (82%) of 100 participants. The highest rate was among ICU patients (n=19/29, 95%). Mostly detected gene was bla_{CTX-M} (n=62/90, 68.9%). There was no significant correlation between antibiotic use and carriage of ESBL-producing gut flora among patients and families.

Keywords: Type your keywords here, separated by semicolons ; antibiotic, carrier, ESBL, family, patient.

1. Introduction

Antimicrobial resistance (AMR) bacteria are growing public health threat, which has a significant concern to countries and affect humans, animals, and environment. AMR causing prolonged hospital stay, high cost of therapy, and increased mortality [1]. The resistance happens because of the selective pressure of antibiotics and transfer of resistance genes among bacteria using mobile genetic elements such as plasmid, transposon and phages [2] (CDC,2022).

ESBL-producing bacteria is one of AMR bacteria, that spreads worldwide [3] (Bush et al, 2018). Clonal [4] (Mohajeri et al, 2015) and nonclonal [5] (Canton et al, 2012) spreading of ESBL-producing bacteria was

reported in previous studies. ESBL are coded by three genes, bla_{CTX-M}, bla_{TEM}, and $bla_{SHV,}$ which determined resistance to expanded spectrum cephalosporins and monobactam. ESBL-producing bacteria was also reported resistant to quinolone [6] (Farajzedehsheikh et al, 2019).

Many risk factors for fecal carriage of ESBL-producing gut flora in patient and community were reported in previous studies, such as antibiotic usage, hospitalized history in ICU or medical ward, travel history, age more than 60 years old [7,8] (Karanika, 2016; Otter et al, 2019).

Gut flora is a complex community of microorganism in human intestines. The gut flora is also a reservoir of antimicrobial resistance genes [9] (Carlet et al, 2012). The changes in the composition of the gut flora, due to the particular use of antibiotics and critical illness, can happen silently, leading to the selection of highly resistant bacteria including ESBL-producing bacteria, which can remain for months in the gut of the carrier without causing any symptoms. The resistant bacteria would translocate through the gut epithelium, induce healthcare-associated infections, undergo cross transmission to other individuals, and cause an outbreak [10] (Sabitti et al, 2021). Detection of fecal carriage ESBL-producing gut flora is important to prevent the outbreaks and suppress the ESBL spread.

The colonization rate of ESBL-producing gut flora in patients and healthy individuals was reported increased in some countries because of extensive usage of antibacterial in hospital and community [11,7,12] (Desta et al., 2016; Karanika et al., 2016; Ríos et al., 2017). However, few data exist on the current fecal carriage of ESBL-producing gut flora among patients and their families in Indonesia. Family who directly contact to patients has more risk for acquired ESBL-producing gut flora, which might be a source for community transmission. The objectives of this study were: 1) to explore the ESBL resistance genes gut flora among hospitalized patients and families; and 2) to identify the risk factor of ESBL-producing gut flora carriage in patients and families

2. Material and method

2.1. Sample collection and settings

The rectal swabs were voluntary provided after taking informed consent from 50 patients and 50 families, from April to July 2017. Patients were 48 hours patients who hospitalized in ICU and internal medicine wards. Families are family member who were living in the same house and accompanying patients during hospitalization in the hospital. Sample was collected using consecutive sampling method which collected all of participant who hospitalized more than 48 hours in ICU and internal medicine ward during study period. Minimum sample size was followed formula

$$n1 = n2 = \left[\frac{z\alpha\sqrt{2PQ} + z\beta\sqrt{P1Q1 + P2Q2}}{P1 - P2}\right]2$$

$$= \left[\frac{1{,}96x\sqrt{2x0{,}12x0{,}88} + 0{,}842\sqrt{0{,}2x0{,}8 + 0{,}04x0{,}96}}{0{,}2 - 0{,}04}\right]2$$

$$= 55$$

N = Sample size
P1=Proporsion of E.coli fecal carriage in hospitalized patient (20% from Xu et al, 2016)
P2 = Fecal carriage of ESBL in community (4% from Chong et al, 2013)

Q1= 1-P1 = 0.8
Q2= 1-P2 = 0.96
P = P1+P2/2 = 0.12
Q = Q1+Q2/2 = 0.88

This hospital is a tertiary care facility and national referral hospital in Indonesia. The ICU ward has 25 beds that provide care to patients who have acute or potentially life-threatening medical conditions. The internal medicine ward has 35 beds which is a sharing room unit that provide care to patients who have infectious disease. A rigid removable curtain separates the two beds in both ICU and internal medicine wards. The study was ethically approved by ethical committee no (#386/Panke.KKE/V/2017).

2.2. Questionnaires

Questionnaires were administrated to patients and their families to identify the antibiotic use among patients and their families. The questionnaires had 2 sections, namely demographic information and the antibiotic use history in the last 3 months including the antibiotic's categories. The Questionnaires was made by author according to guideline of ethics and research department in our hospital.

2.3. Isolation of ESBL-producing gut flora

Rectal swabs were taken using amies swab (Copan, USA) and inoculated on MacConkey (Oxoid, UK) agar supplemented with 2µg/ml of cefotaxime sodium salt (Wako, Japan) incubated at 37°C, overnight. All colonies grew on MacConkey (Oxoid, UK) agar were picked up from each sample. Bacterial species identification was conducted by conventional biochemical tests using TSI agar (Oxoid, UK), SIM agar (Oxoid, UK), MRVP agar (Oxoid, UK).

2.4. Phenotypic detection of ESBL production

The ESBL producer were confirmed by modified double disc synergy test (DDST) using antibiotic discs (Oxoid, UK) containing Amoxcicillin clavulanat (AMC) 30/10 µg in the center of plate, and astreonam (ATM) 30 µg, ceftazidime (CAZ) 30 µg, ceftriaxone (CRO) 30 µg, cefotaxime (CTX) 30 µg around AMC with distance 20 mm from AMC disc, referred to the previous study [13]. E. coli ATCC 25922 was used as quality control in this study.

2.5. Detection of gene encoding ESBL-producing gut flora

The bla_{CTX-M}, bla_{SHV} and bla_{TEM} were detected by Polymerase Chain Reaction (PCR) using GoTaq® Green Master Mix (Promega, USA). The four primer sets (table 1) were used to amplify bla_{CTX-M}, bla_{SHV} and bla_{TEM} as described previously. The amplicon then visualized in 1.5% agarose in electrophoresis gel. Electrophoresis was performed in 100 Volt for 30 minutes. The positive control of each gene was using our previous studies.

Table 1. Primer sequences used in this study

Target gene	Nucleotide sequences (5'-3')	Amplicon (bp)
bla_{CTX-M}	F: TTTGCGATGCAGTACCAGTAA	593
	R: CGTATATCGTTGGTGGTGCCATA	
bla_{SHV}	F: GGGTAATTCTTATTTGTCGC	867
	R: TTAGCGTTGCCAGTGCTC	
bla_{TEM}	F: ATAAAATTCTTGAAGACGAAA	867
	R: GACAGTTACCAATGCTTAATCA	

2.6. Data analysis

Data from questionnaires, laboratory including phenotypic and genotypic results than put on SPSS 23 to further statistic analysis. The data were consisted nominal data for sex, age, wards, antibiotic use, antibiotic class usage, bacterial species, ESBL carriage.

The correlation of ESBL-carriage and sex, ESBL-carriage and location, ESBL-carriage and age, ESBL-carriage and antibiotic use, ESBL-carriage and antibiotic class among patient and family groups were assessed using the Chi-square test using SPSS 23. 2x2 table was made for analysed the correlation automatically using SPSS 23. P-value <0.05 was considered as statistically significant. The descriptive data such as demographic data was shown in table and figure.

3. Results

3.1. Demographic data of patients and families

Total 100 participants were enrolled in this study, consisted of 20 ICU patients, 20 ICU families, 30 medical ward patients, 30 medical ward families. The distribution of sex, ages of the participants were showed in table 2.

Table 2. Demographic data of the participants

Variables	Sample Categories				Total (n=100)
	ICU patient (n=20)	ICU family (n=20)	Medical ward patient (n=30)	Medical ward family (n=30)	
Sex					
Male, n (%)	12 (46.16)	9 (34.61)	5 (19.23)	0(0)	26 (100)
Female, n (%)	8 (10.81)	11 (14.86)	25 (33.79)	30 (40.54)	74 (100)

Age (years)					
0-14, n (%)	2 (100)	0 (0)	0 (0)	0 (0)	2 (100)
15-64, n (%)	14 (16.3)	19 (22.10)	24 (27.9)	29 (33.72)	86 (100)
65-70, n (%)	2 (25.00)	1 (12.50)	4 (50.00)	1 (12.50)	8 (100)
>71, n (%)	2 (50.00)	0 (0)	2 (50.00)	0 (0)	4 (100)

3.2. Isolation of ESBL-producing gut flora

Total 90 ESBL-producing gut flora were isolated from 100 participants with distributions as follows: 8 (8%) participants carried two strain isolates; and 74 (74%) persons carried one strain isolate and 18 participants (18%) did not carry ESBL producing gut flora. Among 90 ESBL-producing gut flora, 9 (10%) were non-Enterobacteriaceae and 81 (90%) were Enterobacteriaceae. Among 9 non-Enterobacteriaceae isolates, 8 (88.9%) were Pseudomonas aeruginosa and 1 (12.1%) was Acinetobacter spp. Distribution among ICU patients, ICU families, medical ward patients and medical ward families were showed in fig.1.

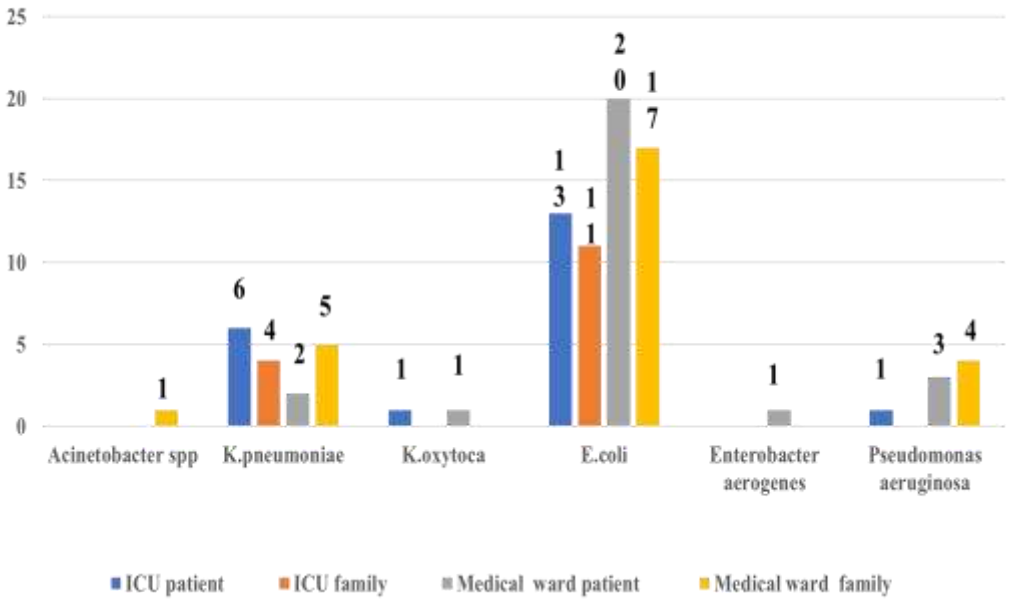

Fig.1. Distribution of ESBL-producing gut flora isolated from ICU patient, ICU families, medical ward patient and medical ward family. X axis is species of ESBL-producing gut flora; Y axis is the absolute number of ESBL-producing gut flora.

3.3. Fecal carriage of ESBL-producing gut flora

Total 90 ESBL-producing gut flora were carried by 82 (82%), of 100 participants. The number of ESBL-producing gut flora was more than participants because 8 (9.7%) participants carried 2 ESBL-producing gut flora isolates and 74 (90.3%) participants carried 1 ESBL-producing gut flora isolate.

The distribution carrier rates were 44 of 50 (88.0%) patients and 38 of 50 (76.0%) families. The carriage

rate of ESBL-producing Enterobacteriaceae in ICU patient was 19 (95%) patients of 20 patients, ICU family was 15 (75%) families of 20 families, medical ward patient was 25 (83.3%) patients of 30 patients, medical wards family was 23 (76.7%) families of 30 families

The distribution carrier rates were 44 of 50 (88.0%) patients and 38 of 50 (76.0%) families. The carriage rate of ESBL-producing gut flora in ICU patient was 19 (95%) patients of 20 patients, ICU family was 15 (75%) families of 20 families, medical ward patient was 25 (83.3%) patients of 30 patients, medical wards family was 23 (76.7%) families of 30 families.

3.4. Distribution of gene encoding ESBL-producing gut flora

Among 90 ESBL-producing gut flora isolates, 62 (68.9%) isolates were possessing bla_{CTX-M}, 19 (23.5%) isolates were bla_{SHV} and 39 (43.3%) isolates were bla_{TEM}. The distributions of gene encoding ESBL-producing gut flora in each participants categories were listed in table 3. There was not significant different the carrier rate of ESBL producing gut flora among wards and families ($p>0.05$).

Table 3. Distribution of gene encoding ESBL-producing gut flora

Genes	Sample Categories				P value
	ICU patient (n=20)	ICU family (n=20)	Medical ward patient (n=30)	Medical ward family (n=30)	
bla_{CTX-M}	14 (22.6)	10 (17.2)	22 (35.4)	16 (25.8)	0.31
bla_{SHV}	7 (36.8)	5 (26.3)	3 (15.8)	4 (21.1)	0.25
bla_{TEM}	11 (28.2)	5 (12.8)	10 (25.6)	13 (33.4)	0.25

3.5. Correlation between antibiotic usage and fecal carriage

Total antibiotic use among subject in this study was 35 (35%) of 100 subject. Twenty-one (70%) of 30 medica**l** ward patients, and 16 (80%) of 20 ICU patients used antibiotics during hospitalization. Among ICU patients, beta lactam antibiotic group was the most common used (n=15/20,75%) as a therapy. On the other hands, 13 of 30 (43.43%) internal medicine wards patients used non-beta lactam antibiotic as a therapy. Both ICU families and ward families were not consuming antibiotics.

Correlation between sex, age, ward, antibiotic usage and fecal carriage of ESBL-producing gut flora were not significantly corelated ($p > 0.05$), **table 4**.

Table 4. Risk factor of fecal carriage of ESBL-producing gut flora

Variables	ESBL-carriage (n =82)	No carriage of ESBL (n=18)	P value
Sex Female, n (%) Male n (%)	 63 (76.82) 19 (23.17)	 11 (61.11) 7 (16.90)	0.17
Age Children (≤18), n (%) Adult (>18), n (%)	 5 (6.10) 77 (93.90)	 0 (0) 18 (100.00)	0.58
Antibiotic Use, n (%) No use, n (%)	 31 (37.80) 51 (62.20)	 4 (22.22) 14 (77.78)	0.21

Ward ICU, n (%) Non-ICU, n (%)	 34 (41.46) 48 (58.54)	 6 (33.33) 12 (66.67)	0.53

Correlation between antibiotic use categories and fecal carriage of ESBL-producing gut flora was also not significantly different among wards. **Table 5**.

Table 5. Antibiotic categories and fecal carriage of ESBL-producing gut flora

Location	**Antibiotic use**	**Fecal carriage**		**P value**
		Yes	No	
ICU	**Beta lactam**			
	Yes n (%)	14 (93.3)	1(6.7)	0.48
	No n (%)	7 (100)	0 (0)	
	Ceftriaxone			0.33
	Yes n (%)	7 (87.5)	1 (12.5)	
	No n (%)	7 (100)	0 (0)	
	Ceftazidime			0.68
	Yes n (%)	2 (100)	0 (0)	
	No n (%)	12 (92.3)	1 (7.7)	
	Cefazolin			0.78
	Yes n (%)	1(100)	0 (0)	
	No n (%)	12 (92.8)	1 (7.2)	
	Meropenem			0.60
	Yes n (%)	3(100)	0 (0)	
	No n (%)	10 (91.7)	1 (8.3)	
	Cefoperazone-sulbactam			0.68
	Yes n (%)	1(100)	0(0)	
	No n (%)	13 (92.8)	1 (7.2)	
	Non-beta lactam			0.73
	Yes n (%)	2 (100)	0 (0)	
	No n (%)	17 (94.4)	1 (5.6)	
	Levofloxacin			0.68
	Yes n (%)	2 (100)	0(0)	
	No n (%)	12 (92.3)	1(7.7)	
Medical ward	**Beta lactam**			0.77
	Yes n (%)	8 (88.9)	1 (11.1)	
	No n (%)	11(84.6)	2 (15.4)	
	Ceftriaxone			0.90
	Yes n (%)	7(87.5)	1(12.5)	
	No n (%)	12 (85.7)	2 (14.3)	
	Ceftazidime			0.68
	Yes n (%)	1(100)	0 (0)	
	No n (%)	18 (85.7)	3 (14.3)	

Non-beta lactam			0.73
Yes n (%)	11 (91.7)	1(8.3)	
No n (%)	7 (77.8)	2 (12.2)	
Levofloxacin			0.55
Yes n (%)	2 (66.7)	0 (0)	
No n (%)	17 (85)	3 (15)	
Ciprofloxacin			0.32
Yes n (%)	7 (77.8)	2 (12.2)	
No n (%)	12 (92.3)	1 (7.7)	

4. Discussion

Total fecal carriage of Total fecal carriage of ESBL-producing gut flora in this study was 82%. The rate of fecal carriage of this study was higher than other studies which were less than 50 % [14,10,15] (Ebrahimi et al., 2016; Sabiiti et al., 2021; Woerther et al., 2013). It was because of the fecal carriage rate of ESBL-producing gut flora was different geographically, affected by many risk factors contributed such as demographic patients, severity of the diseases, medical device use, antibiotic use, and implementation of infection prevention and control.

The fecal carriage rate of ESBL-producing gut flora in this study was higher among patients (88%) than families (76.0%). This result was higher than a study comparation of fecal carriage of ESBL-producing gut flora among patients and household contact which was 52.7% and 20% respectively [16] (Haverkate et al., 2017).

In this study fecal carriage of ESBL-producing gut flora was higher in ICU patients than internal medicine. However, another study observed similar fecal carriage of ESBL-producing Enterobacteriaceae among ICU or other ward patients [14] (Ebrahimi et al., 2016). Therefore, the distribution of fecal carriage of ESBL-producing gut flora was not affected by ward types [9] (Carlet et al, 2012).

Because of the fecal rate of ESBL-producing gut flora was higher in patients than families, we hypothesized the ESBL-producing gut flora were possibly transmitted from patients to families. Patients and families are closely contact in home and at hospital during hospitalization. Studies observed transmission of ESBL-producing Enterobacteriaceae between patient and family in hospital and household settings [16,17,18] (Haverkate et al., 2017; Hilty et al., 2012; Riccio et al., 2021). However, in this study we did not perform finger printing to decide the cross-contamination.

Moreover, compared to another studies from Indonesia, the fecal carriage rate among patients in this study was higher than medical students [19] (Rosantia et al., 2020), pregnant women [20] (Oktaviani et al., 2020) and primary health care center patients [21] (Naelasari et al., 2018). Therefore, we predicted the ESBL-producing gut flora was transmitted from hospitalized patients to another population in Indonesia.

Fecal carriage of ESBL-producing gut flora can be a reservoir of ESBL and involve in spreading of ESBL-producing bacteria in hospital and communities [22] (Bezabih et al., 2021). ESBL is transmissible through contact with humans, animals or environments Contaminated hospital environment with ESBL-producing Enterobacteriaceae was observed in a previous study [23] (Freeman et al., 2014). Because of the fecal carriage rate of ESBL-producing gut flora in this study was high, we suggested the evaluation of infection prevention and control implementation at our hospital. Moreover, cohorting, screening or treatment for patients who carried ESBL-producing gut flora need to be considered in the future.

CTX-M-type ESBL was the most common ESBL type detected in this study, it was according with the widely spread of CTX-M-type ESBL in the world. The reason of widely spreads of CTX-M-type ESBL is mediated by the clonal spread such as ST 131 E. coli and mobile genetic elements such as plasmid, transposon

or insertion sequences [5] (Cantón et al., 2012).

The mechanism of ESBL-producing bacteria dissemination among patients and community is still unknown, whether by clonal or mobile genetic elements. Previous study detected no clonal transmission among ICU patients [24] (Prevel et al., 2019). Clonal transmission was observed in healthy individuals in community [19,25]. However, this study didn't perform genetic finger printing to detect the possible spreading among patients and families.

The selection pressure of inappropriate use of antibiotic is associated with MDR bacteria. Antibiotic kill the sensitive bacteria and remain resistant bacteria to grow more and become dominant in a bacterial population [26] (CDC, 2013). Correlation of antibiotic use and fecal carriage of ESBL-producing gut flora in this study was not significantly corelated ($p>0.05$). Our finding was not inline to another studies [27,28] (Hu et al., 2020; Suranadi et al., 2021). The comprehensive antibiotic use is needed for next study.

This study detected high fecal carriage rate of ESBL-producing gut flora in both of patients and families of different household, the possibility of ESBL transmission among patients and families was nosocomial acquisition. Linier to that a study suggested the main source of colonization of ESBL- producer in adult patients especially ICU patients was nosocomial acquisition [29] (Alves et al., 2016). Therefore, the infection prevention and control need to be evaluated regularly to decrease the spread of ESBL-producing bacteria and other MDR bacteria in this hospital and Indonesia at general.

The carriage rate of ESBL-producing gut flora was detected high in this study with the highest rate was among ICU patients. bla_{CTX-M} was the most commonly detected genes in this study. Infection prevention and control need to be evaluated regularly to decrease the spread of ESBL-producing bacteria

Acknowledgements

We here appreciate to all doctors, microbiology fellow, technicians of Microbiology Department, Universitas Airlangga, Dr.Soetomo Academic General Hospital, Surabaya, Indonesia for supporting this study. ICU and Medical ward of Dr. Soetomo Academic General Hospital, Surabaya, Indonesia and Institute of Tropical Diseases, Surabaya for valuable contributions in this research.

References

Alves, M., Lemire, A., Decré, D., Margetis, D., Bigé, N., Pichereau, C., Ait-Oufella, H., Baudel, J.L., Offenstadt, G., Guidet, B., Barbut, F., Maury, E., 2016. Extended-spectrum beta-lactamase - producing enterobacteriaceae in the intensive care unit: Acquisition does not mean cross-transmission. BMC Infectious Diseases 16. https://doi.org/10.1186/s12879-016-1489-z

Bezabih, Y.M., Sabiiti, W., Alamneh, E., Bezabih, A., Peterson, G.M., Bezabhe, W.M., Roujeinikova, A., 2021. The global prevalence and trend of human intestinal carriage of ESBL-producing Escherichia coli in the community. J Antimicrob Chemother 76, 22–29. https://doi.org/10.1093/jac/dkaa399

Bush, K., 2018. Past and present perspectives on β-lactamases. Antimicrobial Agents and Chemotherapy. https://doi.org/10.1128/AAC.01076-18

Cantón, R., González-Alba, J.M., Galán, J.C., 2012. CTX-M enzymes: Origin and diffusion. Frontiers in Microbiology 3. https://doi.org/10.3389/fmicb.2012.00110

Carlet, J., 2012. The gut is the epicentre of antibiotic resistance. Antimicrob Resist Infect Control 1, 39. https://doi.org/10.1186/2047-2994-1-39

CDC,2019. Antibiotic resistance threats in the United States, 2019. Atlanta, Georgia.

https://doi.org/10.15620/cdc:82532
CDC, 2013. Antibiotic resistance threats in the United States, 2013. Current 114. https://doi.org/CS239559-B
Chong, Y., Shimoda, S., Yakushiji, H., et al. (2013) 'Community spread of extended spectrum beta-lactamase-producing Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis: A long-term study in Japan', Journal of Medical Microbiology, 62(PART7), pp. 1038–1043. doi: 10.1099/jmm.0.059279-0.
Desta, K., Woldeamanuel, Y., Azazh, A., Mohammod, H., Desalegn, D., Shimelis, D., Gulilat, D., Lamisso, B., Makonnen, E., Worku, A., Mannerqvist, K., Struwe, J., Aspevall, O., Aklillu, E., 2016. High gastrointestinal colonization rate with extended-spectrum β-lactamase-producing Enterobacteriaceae in hospitalized patients: Emergence of carbapenemase-producing K. Pneumoniae in Ethiopia. PLoS ONE 11. https://doi.org/10.1371/journal.pone.0161685
Ebrahimi, F., Mózes, J., Monostori, J., Gorácz, O., Fésus, A., Majoros, L., Szarka, K., Kardos, G., 2016a. Comparison of rates of fecal colonization with extended-spectrum beta-lactamase-producing enterobacteria among patients in different wards, outpatients and medical students. Microbiology and Immunology 60, 285–294. https://doi.org/10.1111/1348-0421.12373
Farajzadehsheikh, A., Veisi, H., Shahin, M., Getso, M., Farahani, A., 2019. Frequency of quinolone resistance genes among extended-spectrum ?-lactamase (ESBL)-producing Escherichia coli strains isolated from urinary tract infections. Tropical Medicine and Health 47. https://doi.org/10.1186/s41182-019-0147-8
Freeman, J.T., Nimmo, J., Gregory, E., Tiong, A., de Almeida, M., McAuliffe, G.N., Roberts, S.A., 2014. Predictors of hospital surface contamination with Extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae: Patient and organism factors. Antimicrobial Resistance and Infection Control 3. https://doi.org/10.1186/2047-2994-3-5
Haverkate, M.R., Platteel, T.N., Fluit, A.C., Stuart, J.W.C., Hall, M.A.L., Thijsen, S.F.T., Scharringa, J., Kloosterman, R.C., Bonten, M.J.M., Bootsma, M.C.J., 2017. Quantifying within-household transmission of extended-spectrum b -lactamase-producing bacteria. Clinical Microbiology and Infection 23, 46.e1-46.e7. https://doi.org/10.1016/j.cmi.2016.08.021
Higa, S., Sarassari, R., Hamamoto, K., Yakabi, Y., Higa, K., Koja, Y., Hirai, I., 2019. Characterization of CTX-M type ESBL-producing Enterobacteriaceae isolated from asymptomatic healthy individuals who live in a community of the Okinawa prefecture, Japan. Journal of Infection and Chemotherapy 25. https://doi.org/10.1016/j.jiac.2018.09.005
Hilty, M., Betsch, B.Y., Bögli-Stuber, K., Heiniger, N., Stadler, M., Küffer, M., Kronenberg, A., Rohrer, C., Aebi, S., Endimiani, A., Droz, S., Mühlemann, K., 2012. Transmission dynamics of extended-spectrum -lactamase-producing enterobacteriaceae in the tertiary care hospital and the household setting. Clinical Infectious Diseases 55, 967–975. https://doi.org/10.1093/cid/cis581
Hu, Y., Matsui, Y., W. Riley, L., 2020. Risk factors for fecal carriage of drug-resistant Escherichia coli: A systematic review and meta-analysis. Antimicrobial Resistance and Infection Control 9. https://doi.org/10.1186/s13756-020-0691-3
Karanika, S., Karantanos, T., Arvanitis, M., Grigoras, C., Mylonakis, E., 2016. Fecal Colonization with Extended-spectrum Beta-lactamase-Producing Enterobacteriaceae and Risk Factors among Healthy Individuals: A Systematic Review and Metaanalysis. Clinical Infectious Diseases 63, 310–318. https://doi.org/10.1093/cid/ciw283
Mohajeri, P., Farahani, A., Feizabadi, M.M., Norozi, B., 2015. Clonal evolution multi-drug resistant Acinetobacter baumannii by pulsed-field gel electrophoresis. Indian J Med Microbiol 33, 87–91. https://doi.org/10.4103/0255-0857.148390
Naelasari, N., Koendhori, E., Dewanti, L., Sulistiawati, Kuntaman, K., 2018. The prevalence of Extended Spectrum B-lactamase (ESBL)- producing gut bacterial flora among patients in Dr. Soetomo hospital and primary health center in Surabaya. Folia Medica Indonesiana 54, 161. https://doi.org/10.20473/fmi.v54i3.10004
Oktaviani, R., Hasanah, M., Setyarini, W., Parathon, H., Kitagawa, K., Nakanishi, N., Nomoto, R., Osawa, K.,

Kinoshita, S., Hirai, I., Shirakawa, T., Kuntaman, K., 2020. Prevalence of Carriage of Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae Among Pregnant Women in the Primary Health Care Center and Hospital Setting in Indonesia. https://doi.org/10.21203/rs.3.rs-38906/v1

Otter, J. A., Natale, A., Batra, R., Tosas Auguet, O., Dyakova, E., Goldenberg, S. D., & Edgeworth, J. D. (2019). Individual- and community-level risk factors for ESBL Enterobacteriaceae colonization identified by universal admission screening in London. Clinical Microbiology and Infection, 25(10), 1259–1265. https://doi.org/10.1016/j.cmi.2019.02.026

Prevel, R., Boyer, A., Zali, F.M., Cockenpot, T., Lasheras, A., 2019. Extended spectrum beta-lactamase producing Enterobacterales faecal carriage in a medical intensive care unit : low rates of cross-transmission and infection 9, 1–7.

Riccio, M.E., Verschuuren, T., Conzelmann, N., Martak, D., Meunier, A., Salamanca, E., Delgado, M., Guther, J., Peter, S., Paganini, J., Martischang, R., Sauser, J., de Kraker, M.E.A., Cherkaoui, A., Fluit, A.C., Cooper, B.S., Hocquet, D., Kluytmans, J.A.J.W., Tacconelli, E., Rodriguez-Baño, J., Harbarth, S., Brossier, C., von Dach, E., Renzi, G., Schrenzel, J., Bunk, S., Goepel, S., Hölzl, F., Eib, M., Autenrieth, I.B., Pascual, Á., Bertrand, X., Scharringa, J., Musicha, P., 2021. Household acquisition and transmission of extended-spectrum β-lactamase (ESBL) -producing Enterobacteriaceae after hospital discharge of ESBL-positive index patients. Clinical Microbiology and Infection. https://doi.org/10.1016/j.cmi.2020.12.024

Ríos, E., López, M.C., Rodríguez-Avial, I., Culebras, E., Picazo, J.J., 2017. Detection of Escherichia coli ST131 clonal complex (ST705) and Klebsiella pneumoniae ST15 among faecal carriage of extended-spectrum β-lactamase- and carbapenemase-producing enterobacteriaceae. Journal of Medical Microbiology 66, 169–174. https://doi.org/10.1099/jmm.0.000399

Rosantia, S., Higa, T., Yagi, N., Tokunaga, T., Higa, S., Yakabi, Y., Shirakawa, T., Kuntaman, K., Hirai, I., 2020. Characterization of CTX-M-type-extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae isolated from Indonesian undergraduate medical students of a university in Surabaya, Indonesia. Journal of Infection and Chemotherapy 26, 575–581. https://doi.org/10.1016/j.jiac.2020.01.010

Sabiiti, W., Alamneh, E., Bezabih, A., Peterson, G.M., Bezabhe, W.M., Roujeinikova, A., 2021. The global prevalence and trend of human intestinal carriage of ESBL-producing Escherichia coli in the community 22–29. https://doi.org/10.1093/jac/dkaa399

Shaikh N. K.,Mundhada S. G. , Lalngaihzuali R., I.K. v., 1Associate, 2016. Comparison of different phenotypic methods for the detection of extended spectrum β- lactamase (esbl) in bacterial isolates from tertiary care center. Int J Cur Res Rev 8, 10–14.

Suranadi, W., Fatmawati, D., Ryalino, C., Hartawan, I.G.A.G.U., Yanto, F., 2021. The influence of antibiotics usage on extended-spectrum β-lactamase-producing enterobacter colonization among intensive care unit patients. Open Access Macedonian Journal of Medical Sciences 9, 52–56. https://doi.org/10.3889/oamjms.2021.5522

WHO, 2021. Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report.

Woerther, P.L., Burdet, C., Chachaty, E., Andremont, A., 2013. Trends in human fecal carriage of extended-spectrum beta-lactamases in the community: Toward the globalization of CTX-M. Clinical Microbiology Reviews 26, 744–758. https://doi.org/10.1128/CMR.00023-13

Xu, M., Fan, Y., Wang, M. and Lu, X. (2016) 'The characteristics of extended-spectrum β-lactamases-producing Escherichia coli in hospital faecal carriage in Beijing Tongren hospita', Japanese Journal of Infectious Diseases The. doi: 10.7883/yoken.JJID.2016.023.