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ORIGINAL RESEARCH

High Magnitude of Fecal Carriage of Extended-Spectrum Beta-Lactamase-Producing *Enterobacteriaceae* at Debre Berhan Comprehensive Specialized Hospital, Ethiopia

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Background: Gastrointestinal colonization rate of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE) is the major risk factor for infection and dissemination of resistance clones in healthcare facilities. This study aimed to investigate the magnitude of the fecal carriage of ESBL-PE and associated factors among hospitalized patients at Debre Berhan Comprehensive Specialized Hospital, North Shoa, Amhara Regional State, Ethiopia.

Methods: A hospital-based cross-sectional study was conducted among 383 hospitalized patients from November 2020 to March 2021. Stool sample or rectal swab was aseptically collected and cultured on different culture media for isolation of *Enterobacteriaceae*. Identification was done by conventional biochemical tests. Screening of extended-spectrum beta-lactamase (ESBL) production was done by using cefotaxime and ceftazidime and confirmed by the combination disk method. Data analysis was performed by Statistical Package for Social Sciences software version 25 and a P-value ≤0.05 was considered as statistically significant.

Results: From the total of 383 hospitalized patients, a total of 347 *Enterobacteriaceae* were isolated. The overall gastrointestinal colonization rate of ESBL-PE was 47.3% (164/347). The predominant ESBL-PE were *E. coli* 54.9% (90/164) and *K. pneumoniae* 33.5% (55/164). The overall multi-drug resistance rate (MDR) was 87.8% (305/347). The highest resistance was observed to ampicillin (98.3%), followed by gentamicin (80.7%), and tetracycline (73.3%), respectively. ESBL-PE were highly susceptible to meropenem (90.2%) and imipenem (89.0%). History of antibiotic use in the past 3 months (p<0.001), admission in the neonatal intensive care unit (p=0.023), and presence of chronic disease (p<0.001) were independently associated with fecal carriage of ESBL-PE.

Conclusion: The magnitude of ESBL-PE and MDR was high in the study area. Meropenem and imipenem were active against ESBL-PE. Therefore, strict infection control measure is needed in the study area to limit the infection and dissemination of ESBL-PE.

Keywords: fecal carriage, extended-spectrum beta-lactamase, *Enterobacteriaceae*, Ethiopia, hospitalized patients, associated factors

Introduction

The *Enterobacteriaceae* family is a large and diverse collection of Gram-negative rods and is the most common cause of both community and hospital-acquired infections. They are associated with a variety of syndromes including gastritis, urinary tract infections (UTIs), bloodstream infections, pneumonia, peritonitis, meningitis, and device-associated infections.[1]

Antibacterial agents of the beta-lactam group are the commonly prescribed antibiotics for the treatment of infections caused by multi-drug resistant *Enterobacteriaceae* (MDR-E). However, the emergence of resistance to beta-lactam antibiotics has become a major challenge in the treatment of severe nosocomial infection.[2] The production of beta-lactamases is the main mechanism of resistance to beta-lactam antibiotics in *Enterobacteriaceae*. Among the beta-

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lactamases, the production of extended-spectrum beta-lactamases (ESBLs) are the most common. ESBL enzymes can break or hydrolyze many beta-lactam antibiotics including penicillins, cephalosporins, and monobactam except for cephamycins, clavulanate, and carbapenems.[3]

The emergence phenomenon of ESBL-PE has consequently increased the consumption of carbapenems. These antibacterial agents are a crucial treatment option for life-threatening nosocomial or hospital-acquired infections. The rise of carbapenem resistance may imperil or halt the advancement of current medical treatments. It is clear that very few novel antibiotics will be discovered in the near future, making the issue of carbapenem-resistant *Enterobacteriaceae* of primary importance worldwide.[1]

Fecal carriage of ESBL-PE is the major risk factor for infection with antibiotic-resistant bacteria for hospitalized patients since the bacteria can spread from colonized persons to others by hand carriage as well as contaminated food and water.[4–6] The problem is worrying because ESBL enzymes can hydrolyze almost all beta-lactams except carbapenems and cephamycins. In addition, these enzymes are usually encoded by genes found on highly mobile genetic elements such as plasmids, providing the ability for clonal and horizontal transfer. These plasmids can also confer resistance genes to other classes of antibiotics including aminoglycosides, trimethoprim, sulphonamides, tetracyclines, and chloramphenicol.[7]

The gastrointestinal tract is the principal reservoir for *Enterobacteriaceae* infections, whether they are acquired in the hospital or the community. Additionally, the gastrointestinal tract is the place where the exchange of resistance genes between bacteria happens, and antibiotic treatment selects the over-growth of resistant bacteria. Consequently, colonization by ESBL-PE is one of the most important risk factors for antibiotic-resistant bacterium infection.[8] These infections pose a great challenge which increases hospital stay, and cost and leads to increased morbidity and mortality rates due to the limited therapeutic options.[9] It has been reported that infections caused by ESBL-PE have a fatality rate that ranges from 42% to 100.[10]

Fecal carriage of ESBL-PE has been increasingly reported worldwide over the last decade. The highest carriage prevalence has been described in Asia whereas prevalence rates are lower in Europe and North America.[11,12] However, data on ESBL-PE in Eastern Africa including Ethiopia is scarce.[13]

Although antimicrobial resistance (AMR) is a global threat; the burden is higher in low-income countries like Sub-Saharan Africa (SSA) where, widespread self-medication, overcrowding of hospitals, absence of antibiotic prescription guidelines, poor infection control practices, and poor hygiene and antibiotic misuse is common.[14]

Researches have been undertaken in the context of infection caused by ESBL-PE in Ethiopia.[15] However, little is known regarding the gastrointestinal carriage rate of ESBL-PE in hospitalized patients.[16,17] Local epidemiological data on the carriage of ESBL-PE is very important to prevent and control nosocomial infection and the spread of antimicrobial resistance in hospitals. Hence, this study aimed to investigate the fecal carriage of ESBL-PE and associated factors among hospitalized patients in Debre Berhan Comprehensive Specialized Hospital (DBCSH), North Shoa, Amhara Regional State, Ethiopia.

Materials and Methods

Study Setting

A hospital-based cross-sectional study was conducted from November 2020 to March 2021. The study was conducted at DBCSH in Amhara Regional State, Central Ethiopia, Debre Berhan town which is located 130 Km far from the capital city of the country, Addis Ababa. The hospital provides health services for over two million people of Amhara, Afar, and two woredas of Oromia regions with more than 200 beds.

Study Population

All patients including neonates, infants, children, and adults who were admitted for ≥ 48 hours at DBCSH during the study period were the study population. All patients who were admitted for less than 48 hours, critically ill patients, and those unable to give a specimen were excluded from the study.

Data Collection

Sociodemographic Data

Sociodemographic and clinical data were collected using pre-tested structured questionnaires after obtaining informed consent from adult participants or consent from parents/guardians and assent from participants for those who were younger than 18 years. Clinical data of the patients such as the history of hospitalization in the past 12 months, history of antibiotic use in the past 3 months, and other clinical data were collected from their medical records.

Sample Collection

Stool sample was collected using a clean stool container. After collection, the stool was immediately taken to the Microbiology laboratory for analysis. A rectal swab was collected from neonates and participants that cannot give stool by an experienced nurse. Then the swab was put in a test tube with Cary-Blair transport media and transported to the Microbiology laboratory for further bacteriological analysis.

Isolation and Identification

Each stool sample/rectal swab was first inoculated onto MacConkey agar (SRL. Pvt. Ltd. India) and incubated aerobically at 37°C for 18 to 24 hrs. Then, each culture plate was examined for the growth of *Enterobacteriaceae*. Lactose fermenters and non-lactose fermenters were characterized on MacConkey agar and then non-lactose fermenter colonies were inoculated on Xylose-Lysine Deoxycholate (XLD) agar (HiMedia. India) to observe further characteristics. Finally, pure colonies were taken for identification. All isolated *Enterobacteriaceae* were characterized by colony characteristics and identified by conventional biochemical tests namely, indole, citrate utilization, triple sugar iron, lysine decarboxylase, urea hydrolysis, motility, and mannitol fermentation.

Antimicrobial Susceptibility Test

Antimicrobial susceptibility testing was performed by the Kirby-Bauer disk diffusion method per Clinical Laboratory Standard Institute (CLSI) guidelines on Mueller Hinton agar (MHA) (Hi-Media: India).[18] The zones of inhibition were interpreted according to CLSI guidelines. The antibiotic disks used in this study were ampicillin (AM:10μg), cefoxitin (FOX:10μg), gentamicin (GM: 10μg), ciprofloxacin (CIP: 5μg), trimethoprim-sulfamethoxazole (STX: 1.25/23.75 μg), imipenem (IPM: 10μg), meropenem (MEP: 10 μg), amoxicillin-clavulanic acid (AMC: 30μg), cefotaxime (CTX:30 μg), ceftazidime (CAZ:30μg), ceftriaxone (CRO:30μg), tetracycline (TE:30μg), cefepime (FEP:30μg), and chloramphenicol (C:30μg). All antibiotics were (Oxoid, United Kingdom).

Multi-Drug-Resistance Isolates

The isolates that were resistant to one or more antibiotics in three or more classes of antimicrobials agents were considered as multi-drug resistance *Enterobacteriaceae*.[19]

Screening for Potential ESBL Producing *Enterobacteriaceae*

Enterobacteriaceae that showed an inhibition zone size of ≤ 22 mm with ceftazidime (30 μg), and/or ≤ 27mm with cefotaxime (30 μg) were considered as potential ESBL producers CLSI guidelines.[18]

Phenotypic Confirmation of ESBL Production

Ceftazidime (30 μg) and cefotaxime (30 μg) alone, as well as their combination with Clavulanic acid (30 μg g/10 μg) acid, were placed at an appropriate distance on the MHA plate that was inoculated with a bacterial suspension of 0.5 McFarland turbidity standard and incubated overnight (18–24 hrs) at 37°C. *Enterobacteriaceae* that showed an increase in the inhibition zone diameter of ≥ 5mm for combination disks versus ceftazidime or cefotaxime disk alone were confirmed as ESBL producers.[18]

Quality Control

Standard Operating Procedures (SOP) were strictly followed for each procedure. The stool specimen was processed and transported soon after receipt as possible. If there is a delay in processing the specimen, it was placed in the refrigerator.

Before using the media, reagents, and antibiotic disks, the expiration dates were checked. Following sterility testing, the culture media was visually evaluated for cracks and thickness, as well as the presence of freezing, bubbles, and contaminants. For ESBLs confirmatory test, ESBLs positive *K. pneumoniae* ATCC 700603 and ESBLs negative *E. coli* ATCC 25922 control strains were used. The data collection form was checked for its completeness and accuracy before recording the data. Culture and antibiotics susceptibility test results were recorded carefully before entering.

Statistical Analysis

The data were entered into Epi Data version 3.1 and double-checked and cleaned before analysis. Then the data was exported to Statistical Package for Social Sciences (SPSS) version 25 for analysis. The descriptive statistics (median, percentages, or frequency) were calculated. Bivariant logistic regression analysis was used to observe the relationship between the dependent variable and independent variables. Variables that showed P-value ≤ 0.25 in bivariant logistic regression analysis were selected for further analysis using multivariable logistic regression models. Variables that showed a p-value ≤ 0.05 by multivariable logistic regression models were considered as statistically significant.

Ethical Considerations

The study was reviewed and approved by the Departmental Research and Ethics Review Committee (DRERC) of Microbiology, Parasitology, and Immunology, School of Medicine, College of Health Sciences; Addis Ababa University (Ref. no. DRERC /005/2020). A written permission letter was also obtained from the Debre Berhan Comprehensive Specialized Hospital. The purpose and procedures of the study were explained to the study participants and parents or guardians during the study period by providing all information about the study in an information sheet. For participants who cannot read and write, the information sheet was read to them, and a witness signed that the process had been conducted appropriately. The confidentiality of all study participants was maintained This manuscript is prepared from the MSc thesis.[20] This study also was conducted per the Declaration of Helsinki.

Results

Sociodemographic Characteristics of the Study Participants

A total of 383 study participants were included in the study. Out of these 72.8% (n=265/383) were adults (median age =41 years old, interquartile range =30 to 55 years), 17% (n=65/383) were children (median age=1.25 years, interquartile range=1 to 2.5 years) and 10.2% (n=39/383) were neonates (median age =7 days, interquartile range =4 to 11 days). Nearly half of the study participants (50.4%) were females. The majority of (61.9%) of the study participants were living in rural areas (Table 1).

Clinical Profile of the Study Participants

Of the total of 383 study participants, 27.9% (n=107/383) had a history of antibiotic usage in the past 3 months while 23.8% (n=91/383) had a history of hospitalization in the past twelve months. It was found that 8.9% (n=34/383) were admitted due to sepsis. More than one-fourth of the participants 27.2% (n=104/383) were admitted to the medical ward (Table 2).

Bacterial Identification and Antimicrobial Resistance Pattern

A total of 347 *Enterobacteriaceae* were isolated in this study. The most predominant isolates were *E. coli* 63.7% (n=221/347) followed by *K. pneumoniae* 26.5% (n=92/347), and *E. cloacae* 3.5% (n=12/347) respectively (Figure 1).

Antimicrobial susceptibility testing was done for all *Enterobacteriaceae* isolates against fourteen selected antibiotics. The highest level of resistance was observed to ampicillin (98.3%) followed by gentamicin (80.7%), tetracycline (73.3%), and trimethoprim-sulfamethoxazole (64.8%) respectively. A low level of resistance was recorded against carbapenems (imipenem (6.3%) and meropenem (6.9%)) followed by chloramphenicol (15.9%) (Table 3).

Table 1 Sociodemographic Characteristics of Study Participants at Debre Berhan Comprehensive Specialized Hospital from November 2020 to March 2021

Variables	Categories	Number (n=383)	Percent (%)
Sex	Male	190	49.6
	Female	193	50.4
Age group	Neonate	39	10.2
	Children	65	17.0
	Adults	279	72.8
Residence	Rural	237	61.9
	Urban	146	38.1
Adults Marital status	Married	245	64.0
	Single	31	8.1
	Divorced	3	0.8
Educational status	Illiterate	245	64.0
	Primary	69	18.0
	Secondary	36	9.4
	Higher and above	33	8.6
Adults occupational status	Unemployed	7	28.7
	Government employed	33	8.6
	Daily labour	3	0.8
	Farmer	65	17.0
	Housewife	82	21.4
	Others	90	23.5

E. coli isolates showed the highest resistance to ampicillin (97.3%) followed by gentamicin (73.3%), tetracycline (67.9%), and trimethoprim-sulfamethoxazole (54.8%). Among *K. pneumoniae* isolates (15.2%) were resistant to meropenem (Table 3).

Multi-drug resistance (resistance to at least 3 antibiotics in a different class) was observed in 87.6% (n=305/347). *K. oxytoca, E. cloacae, Citrobacter* spp, *M. morganii, K. ozaenae, and C. diversus* showed 100% MDR level (Table 4).

The Magnitude of Extended-Spectrum Beta-Lactamase-Producing *Enterobacteriaceae*

The overall magnitude of ESBL-PE was 47.3% (n=164/347) which accounts for *E. coli* 25.9% (n=90/347) followed by *K. pneumoniae* 15.9% (n=55/347) and other *Enterobacteriaceae* 5.5% (n=19/347).

The distribution of ESBL-PE and non- ESPL-PE was varied among *Enterobacteriaceae* species. The highest ESBL-PE was observed in *K. oxytoca* (88.9%,8) followed by *K. pneumoniae (*59.8%,55) and *E. cloacae* (50.0%,6) respectively (Figure 2).

Non-ESBL producing *Enterobacteriaceae* were more sensitive to antibiotics than ESBL-PE. Meropenem, imipenem, and chloramphenicol were active antibiotics for ESBL-PE with a sensitivity of 90.2%, 89.0%, and 76.2% respectively (Figure 3).

Of 305 MDR-E (53.3%) were ESBL mediated MDR. Among the total 181 MDR *E. coli (*49.2%) were ESBL producers (Table 5).

Factors Associated with Fecal Carriage of ESBL-PE

In bivariate logistic regressions analysis, all independent variables including socio-demographic and clinical data were assessed to determine whether they were contributing factors or not for fecal carriage of ESBL-PE. Admission in NICU ward [AOR= 4.86, 95% CI: (1.24–18.96)], history of antibiotic use in the past 3 months [AOR= 4.68, 95% CI: (2.28–9.58)]

Table 2 Clinical Profile of the Study Participants at Debre Berhan Comprehensive Specialized Hospital from November 2020 to March 2021

Variables	Categories	Frequency	Percent (%)
History of antibiotic use in the past 3 months	Yes	107	27.9
	No	276	72.1
History of hospitalization in the past 12 months	Yes	91	23.8
	No	292	76.2
Previous history of hospital stays	3–7 days	22	5.7
	8–14 days	48	12.5
	>14 days	21	5.5
Previous ICU stay	Yes	1	0.3
	No	382	99.7
Number of bed/rooms	2–4	48	12.5
	5–8	335	87.5
Number of patient/rooms	2–4	140	36.6
	5–8	243	63.4
Reason for admission	Sepsis	34	8.9
	UTI	13	3.4
	Pneumonia	22	5.7
	Meningitis	10	2.6
	Malnutrition	21	5.5
	Heart failure	28	7.3
	Peptic ulcer disease	16	4.2
	Others	239	62.4
History of invasive procedure in the past 3 months	Yes	46	12.0
	No	337	88.0
Types of invasive procedure	Catherization	32	8.4
	Surgery	14	3.6
Admission ward	Neonatal ICU	39	10.2
	Paediatric	63	16.4
	Medical	104	27.2
	Surgery	92	24.0
	Adult ICU	7	1.8
	Gynaecology and obstetrics	53	13.8
	Ophthalmology	25	6.5
Ward stays	3–7 days	326	85.1
	8–14 days	44	11.5
	>15 days	13	3.4
Chronic disease	Yes	85	22.2
	No	298	77.8
Types of chronic disease	Diabetes	23	6.0
	HIV	20	5.2
	Hypertension	31	8.1
	Haematological malignancy	1	0.3
	Tuberculosis	6	1.5
	Kidney disease	1	0.3
	Heart disease	3	0.8

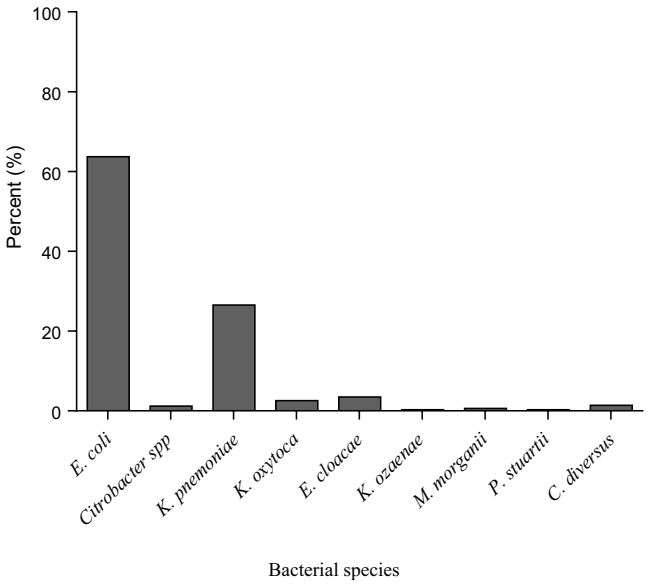

Figure 1 *Enterobacteriaceae* isolated from the fecal specimen of Debre Berhan Comprehensive Specialized Hospital from November 2020 to March 2021.

and presence of chronic disease [AOR= 3.65, 95% CI: (1.87–7.13)] showed statistical significance for fecal carriage of ESBL-PE (Table 6).

Discussions

Gastrointestinal carriage of ESBL-PE become a major challenge for hospitalized patients worldwide. Infections caused by ESBL-PE are usually multi-drug resistant making the treatment option challenging.[21] Colonization with ESBL-PE is the main threat that can lead to cross-transmission and self-infection among hospitalized patients.[22] This research addresses the fecal carriage of ESBL-PE and associated factors among hospitalized patients.

A total of 347 *Enterobacteriaceae* were isolated in this study. Out of these, the highest proportion was *E. coli* (63.6%) followed by *K. pneumoniae* (26.5%,) accounting for the two most common normal flora of the gastrointestinal tract. The result was comparable with the previous study done in Addis Ababa, Ethiopia which showed that *E. coli* (79.7%) was the most common isolate followed by *K. pneumoniae* (19.7%).[17] Similarly, a study from Gondar, Ethiopia showed that *E.coli* (59.7%) and *K. pneumoniae* (16.1%) were frequently identified *Enterobacteriaceae*.[23] Additionally, a report from Turkey also showed *E. coli* (94.5%), and *K. pneumoniae* (5.1%)[24] as predominant isolates. Other species commonly isolated following *E. coli* and *K. pneumoniae* in this study were *E. cloacae.*

Among the fourteen antibiotics tested in this study, the highest level of resistance was observed to ampicillin (98.3%) followed by gentamicin (80.7%), tetracycline (73.3%), and trimethoprim-sulfamethoxazole (64.8%), respectively. A low level of resistance rate was recorded against the last-resort antibiotics, imipenem (6.3%) and meropenem (6.9%). Comparable results were also reported from Arba Minch, Ethiopia,[16] Tanzania,[22] Egypt,[21] and Morocco.[25] The reason for the high level of resistance to ampicillin might be being cheap and the first line of treatment and thus highly misused. In the hospital, there was no antibiotic susceptibility screening service for isolates from patients and therefore the observed high resistance prevalence against these antibiotics could also be associated with empirical treatment. The finding highlights the importance of the implementation of an antimicrobial stewardship program in healthcare facilities to mitigate the spread of antimicrobial resistance and limit the consumption of antibiotics.

There were distinct resistance patterns among the different bacterial species. *E. coli* isolates showed the highest resistance to ampicillin (97.3%) followed by gentamicin (73.3%), tetracycline (67.9%), and trimethoprim-sulfamethoxazole (54.8%). This was in close agreement with the study conducted in Addis Ababa, Ethiopia,[17] Gondar, Ethiopia[23]) and Tanzania.[22] In *K. pneumoniae* the highest rate of resistance was recorded against ampicillin (100%), followed by gentamicin (95.7%), trimethoprim-sulfamethoxazole (84.8%), and tetracycline (80.4%). This was

Table 3 Antimicrobial Resistance Pattern of *Enterobacteriaceae* Isolated at Debre Berhan Comprehensive Specialized from November 2020 to March 2021

Isolates	Antimicrobial resistance level in n (%)													
	AMP	FOX	GM	CIP	STX	IPM	MEP	AMC	CTX	CAZ	CRO	TE	FEP	C
E. coli (n=221)	215(97.3)	42(19.0)	162(73.3)	66(29.9)	121(54.8)	6(2.7)	6(2.7)	103(46.6)	94(42.5	66(29.9)	93(42.)	150(67.9)	35(15.8)	19(8.6)
Citrobacter spp (n=4)	4(100.0)	2(50.0)	4(100.0)	1(25.0)	3(75.0)	0(0.0)	0 (0.0)	2(50.0)	3(75.0)	2(50.0)	3(75.0)	4(100.0)	0(0.0)	0(0.0)
K. pneumoniae (n=92)	92(100.0)	3(38.0)	88(95.7)	54(58.7)	78(84.8)	12(13.0)	14 (15.2)	68(73.9)	63(68.5)	50(54.3)	65(70.7)	74(80.4)	34(37.0)	25(27.2)
E. cloacae (n=12)	12(100.0)	6(50.0)	10(83.3)	5(41.7)	11(91.7)	0(0.0)	0(0.0)	8(66.8)	8(66.7)	7(58.3)	8(66.7)	12(100.0)	4(33.3)	7(58.3
K. oxytoca (n=9)	9(100.0)	4(44.4)	8(88.9)	6(66.7)	7(77.8)	4(44.4)	4(44.4)	7(77.8)	9(100.0)	9(100.0)	9(100)	7(77.8)	5(55.6)	2(22.2)
C. diversus (n=5)	5(100.0)	1(20.0)	5(100.0)	0(0.0)	3(60.0)	0(0.0)	0(0.0)	5(100.0)	4(100.0)	3(60.0)	2(40.0)	5(100.0)	0(0.0)	0(0.0)
M. morganii (n=2	2(100.0)	2(100.0)	2(100.0)	0(0.0)	1(50.0)	0(0.0)	0(0.0)	2(100.0)	2(100.0)	2(100.0)	0(0.0)	2(100.0)	0(0.0)	2(100).0)
P. stuartii (n=1)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
K. ozaenae (n=1)	1(100.0)	0(0.0)	1(100.0)	1(100.0)	1(100.0)	0(0.0)	0(0.0)	1(100.0)	1(100.0	1(100.0)	1(100.0)	1(100.0)	0(0.0)	0(0.0)
Total resistance (n=347)	341(98.3)	92(26.5)	280(80.7)	133(38.3)	225(64.8)	22(6.3)	24(6.9)	196(56.5)	184(53.0)	140(40.3)	181(52.2)	255(73.3)	78(22.5)	55(15.9)

Abbreviations: AMP, ampicillin; FOX, cefoxitin; GM, gentamicin; CIP, ciprofloxacin; STX, trimethoprim-sulfamethoxazole; IPM, imipenem; MEP, meropenem; AMC, amoxicillin-clavulanic acid; CTX, cefotaxime; CAZ, ceftazidime; CRO, ceftriaxone; TE, tetracycline; FEP, cefepime; C, chloramphenicol.

Table 4 Multi-Drug Resistance Patterns of *Enterobacteriaceae* Isolates at Debre Berhan Comprehensive Specialized Hospital from November 2020 to March 2021

Isolates (Number)	Number of Antimicrobials Resisted (n (%)								
	R0	R1	R2	R3	R4	R5	R6	≥R7	Total MDR Isolates (R≥3)
E. coli (n=221)	1(0.5)	12(5.4)	27(12.2)	30(13.6)	32(14.4)	27(12.2)	21(9.5)	71(32.2)	181(81.9)
Citrobacter spp (n=4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(25.0)	1(25.0)	2(50.0)	4(100.0)
K. pneumoniae (n=92)	0(0.0)	0(0.0)	1(2.2)	7(7.6)	1(1.0)	10(9.7)	9(9.7)	64(69.5)	91(98.9)
E. cloacae (n=12)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(16.6)	2(16.6)	8(66.6)	12(100.0)
K oxytoca (n=9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(11.1)	8(88.9)	9(100.0)
C. diversus (n=5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1((20.0)	2(40.0)	2(40.0)	5(100.0)
M. morganii (n=2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(100.0)	2(100.0)
P. stuartii (n=1)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
K. ozaenae (n=1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(100.0)	1(100.0)
Total (n=347)	1(0.3)	13(3.7)	28(8.1)	37(10.6	33(9.5)	41(11.8)	36(10.3)	158(45.5)	305(87.8)

Note: R0: resistance to no antibiotics, R1-7: resistance to 1, 2, 3, 4, 5, 6, and 7 antibiotics; ≥R3: resistance to 3 or more antibiotics from different classes.

comparable with the findings done in Arba Minch, Ethiopia,[16] Tanzania,[22] and Morocco.[25] This high resistance pattern among the isolates may be due to inappropriate prescription of antibiotics, and self-medication practices. The increase of AMR is a threat for many developing countries because of the absence of detection methods due to a lack of resources and poor infrastructure. Poor personal hygiene due to different factors such as water shortage and lack of knowledge may also contribute to the increased resistance prevalence in the current study. Previously it was reported that if there are poor hand hygiene resistant bacteria can spread from one patient to another via healthcare workers' contaminated hands predisposing the patients to infection by antibiotic-resistant bacteria.[17]

The overall carriage rate of MDR-E was 87.8%. This finding was comparable with the studies reported in Arba Minch, Ethiopia (71%),[16] and Tanzania (94%).[26] However, higher than studies done in Addis Ababa, Ethiopia (43%),[17] Gondar, Ethiopia (38.7%),[23] and Morocco (42.8%).[27] This inconsistency might be due to indiscriminate use of antibiotics, poor hygienic practice in the study area, and differences in the study population.

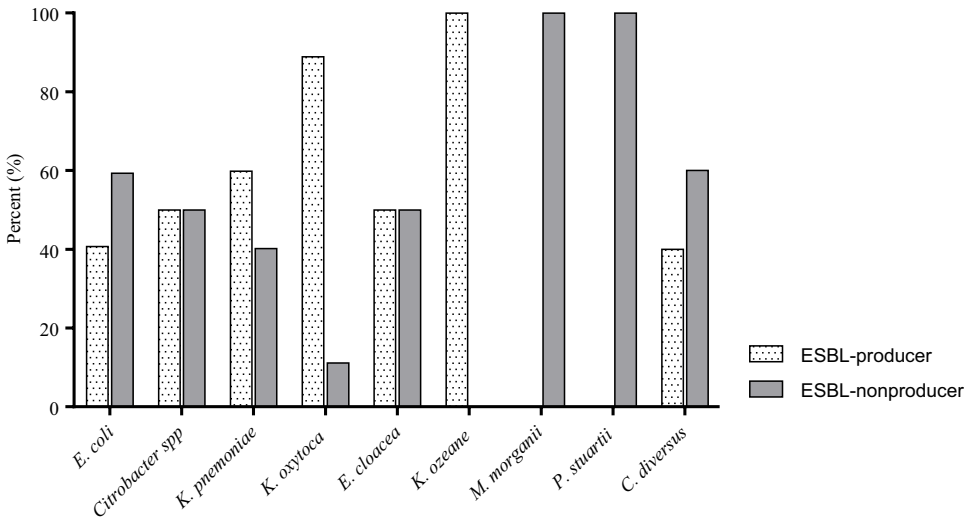

Figure 2 The magnitude of ESBL-PE and non-E ESBL-PE at Debre Berhan Comprehensive Specialized Hospital from November 2020 to March 2021.

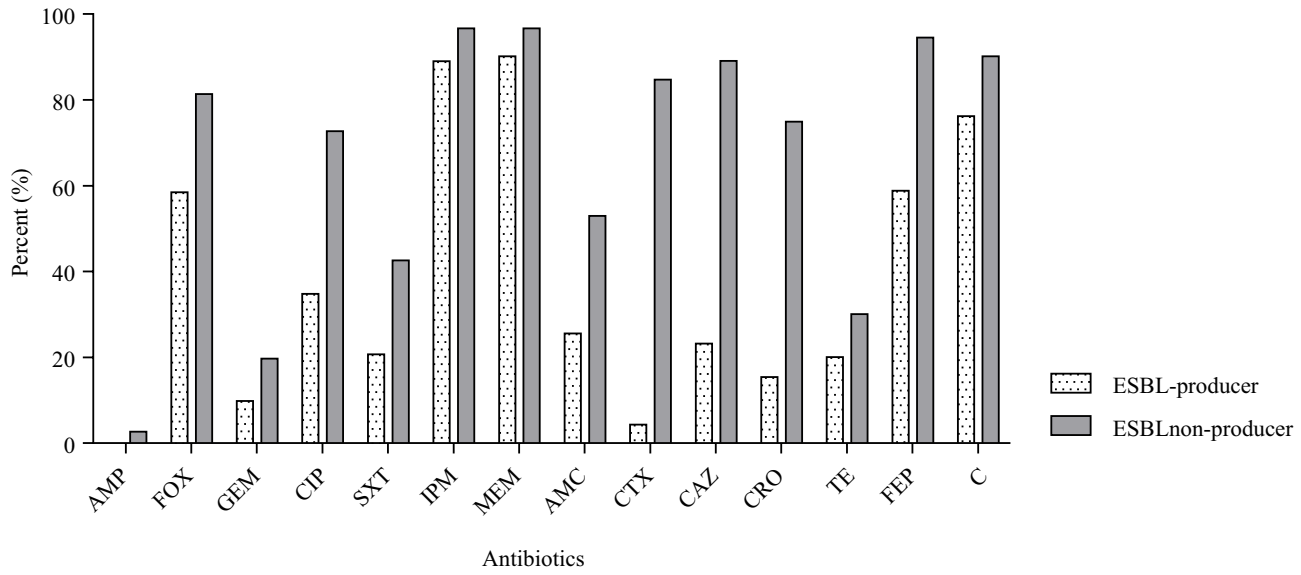

Figure 3 Antibiotics susceptibility pattern of ESBL producing and non-ESBL-producing *Enterobacteriaceae* at Debre Berhan Comprehensive Specialized Hospital from November 2020 to March 2021.

Abbreviations: AMP, ampicillin; FOX, cefoxitin; GM, gentamicin; CIP, ciprofloxacin; STX, trimethoprim-sulfamethoxazole; IPM, imipenem; MEP, meropenem; AMC, amoxicillin-clavulanic acid; CTX, cefotaxime; CAZ, ceftazidime; CRO, ceftriaxone; TE, tetracycline; FEP, cefepime; C, chloramphenicol.

In the present study, a 100% MDR carriage rate was seen in *K. oxytoca, E. cloacae, Citrobacter* spp, *M. morganii*, and *C. diversus*. Being colonized by such multidrug-resistant bacteria is recognized to be a cause of infection and cross-transmission. Therefore, good hygienic practice and careful infection prevention should be implemented in the study setting.

The overall magnitude of ESBL-PE in this study was 47.3% 95% CI (42.0–52.2%). This result was comparable with the reports in Addis Ababa, Ethiopia (52%),[17] Chad (46%),[6] Madagascar (49%),[28] Burkina Faso (42%),[29] and India (43%).[30] However, it was lower than the studies done in Egypt (65%),[21] Tanzania (60%),[22] Algeria (54%),[31] Morocco (58%),[25] and India (63%).[32] In contrast, the current finding was higher than the studies done in Gondar, Ethiopia (16%)[23] Arba Minch, Ethiopia (33%),[16] Zimbabwe (41%),[33] Spain (7.69%),[34] Cyprus (21.4%),[5] and Turkey (34%).[24] This

Table 5 Distribution of ESBL-PE and MDR Isolates at Debre Berhan Comprehensive Specialized Hospital from November 2020 to March 2021

Isolates (Number)	ESBL Positive n (%)	Total MDR n%)
E. coli (n=221)	89 (49.2)	181(59.3)
K. pneumoniae (n=92)	55 (61.1)	91(29.8)
E. cloacae (n=12)	6(50.0)	12(3.9)
K. oxytoca (n=9)	8 (88.9)	9(2.9)
C. diversus (n=5)	2(40.0)	5(1.63)
Citrobacter spp (n=4)	2(50.0)	4(1.3)
M. morganii (n=2)	0(0.0)	2(0.6)
P. stuartii (n=1)	0(0.0)	0(0.0)
K. ozaenae (n=1)	1(100.0)	1(0.0)
Total (n=347)	163(53.4)	305(87.8)

Table 6 Factors Associated with Fecal Carriage of ESBL-PE at Debre Berhan Comprehensive Specialized Hospital from November 2020 to March 2021

Variables	Categories	ESBL Carriage n (%)	COR (95% CI)	P-value	AOR (95% CI)	P-value
Age group	Neonates Children Adults	23 (6.6) 31 (8.9) 110 (31.7)	3.92 (1.69–9.09) 1.69 (0.945–3.02) 1	0.001 0.077	1.65 (0.9–4.79) 1.50 (0.28–8.09)	0.67 0.63
History of antibiotic use in the past 3 months	Yes No	80 (23.1) 84 (24.2)	7.35 (4.25–12.71) 1	0.000	4.68 (2.28–9.58)	≤0.001
History of hospitalization in the past 12 months	Yes No	62 (17.9) 102 (24.4)	4.03 (2.36–6.86) 1	0.000	1.02 (0.48–2.14)	0.960
History of invasive procedure in the past 3 months	Yes No	37 (10.7) 127 (36.6)	5.63 (2.63–12.09) 1	0.000	2.28 (0.91–5.74)	0.078
Admission ward	NICU Pediatric Medical Surgery Gynecology and obstetrics Ophthalmology	23 (6.6) 31 (8.9) 39 (11.2) 39 (11.2) 17 (4.9) 8 (2.3)	6.11 (1.91–19.55) 2.84 (1.01–7.77) 1.45 (0.57–3.69) 1.69 (0.66–34.32) 1.24 (0.44–3.49) 1	0.02 0.039 0.432 0.273 0.676	4.86 (1.24–18.96) 1.15 (0.38–3.52)	0.023 0.81
Chronic disease	Yes No	60 (17.3) 104 (30.0)	4.45 (2.55–7.75) 1	0.000	3.65 (1.87–7.13)	≤0.001

Note: 1 =reference.
Abbreviations: CI, confidence interval; COR, crude odd ratio; AOR, adjusted odd ratio; NICU, neonatal intensive care unit.

discrepancy might be due to the difference in the study population, inappropriate use of antibiotics, variation in antibiotic resistance prevention measures, and variation in the method of ESBL detection.

The predominant ESBL-PE were *E. coli* 54.9% (n=90/164) and *K. pneumoniae* 33.5% (n=55/164). This result was lower than the previous findings from Addis Ababa, Ethiopia *E. coli* (70%),[17] Tanzania *E. coli* (68%),[22] Burkina Faso: *E. coli* (78%)[29] Cyprus *E. coli* (94.4%),[5] and Spain *E. coli* (77.7%).[34] However, our finding was higher than the studies done in Gondar, Ethiopia *E. coli* (16.2%)[23] Morocco *E. coli* (19.4%),[25] and Korea *E. coli* (14.4%).[35] The potential reason for the difference in magnitude of ESBL among *Enterobacteriaceae* could be several factors such as variation in type and frequency of isolates, sample size, study participants, and geographical location.

ESBL-PE were highly susceptible to meropenem (90.2%) and imipenem (89.0%). The highest susceptibility of carbapenems was in close agreement with the studies conducted in Addis Ababa, Ethiopia,[17] Zimbabwe,[36] and India[32] where all reported a 100% sensitivity of carbapenems drugs. This highest susceptibility of ESBL-PE to carbapenems might be unavailability and high cost of carbapenems in healthcare settings and pharmacies of developing countries like Ethiopia and being last resort drug, limit the overuse and misuse of such antibiotics. ESBL-PE was also resistant to multiple antibiotics including aminoglycosides, sulfonamides, tetracycline, and other class antibiotics used. Similar findings were reported in Chad and Burkina Faso.[29,37]

ESBL producers showed the highest resistance to gentamicin (91.2%) followed by tetracycline (79.9%) and trimethoprim-sulfamethoxazole (79.3%). ESBL producers also showed significant resistance to amoxicillin-clavulanic acid (74.4%), ciprofloxacin (65.2%), and cefoxitin (41.5%). This result was fairly similar to the findings reported in Arba Minch, Ethiopia[16] Morocco,[25] Egypt,[21] and Tanzania[22] which all revealed ESBL-PE showed the highest resistance to gentamicin, tetracycline, and trimethoprim-sulfamethoxazole. The possible justification for the high co-resistance to other classes of antibiotics could be explained by the fact that gene codes for ESBL production are usually found on the same

mobile genetic elements: that may also carry resistance genes for non-beta-lactam antibiotics.[38] This finding indicates high fecal carriage ESBL-PE that were also resistant to most antibiotics which poses a high risk for nosocomial infection, dissemination of resistance genes and thus resistant pathogen in the hospital.

Socio-demographic and clinical data were analyzed as independent risk factors for ESBL-PE carriage. Multivariable logistic regression identified 3 variables as contributing factors for ESBL-PE carriage. Antibiotic use in the past 3 months, presence of chronic diseases, and admission in the neonatal intensive care unit showed statistically significant association with fecal carriage of ESBL-PE.

Participants who had a history of antibiotic use in the past 3 months were 4.68 times more likely carriers for ESBL-PE than those who had not used (AOR 4.68, 95% CI (2.28–9.58). This was similar to the studies conducted in Gondar, Ethiopia,[23] Tanzania,[22] Algeria,[31] Burkina Faso,[29] and Cyprus.[5] This might indicate inappropriate use of antibiotics by the study participants which may result in selective pressure in the bacteria. This finally could have a role for ESBL carriage.

Another factor associated with the fecal carriage of ESBL-PE was the presence of chronic disease, consistent with the previous studies done in Arba Minch, Ethiopia,[16] and Algeria.[31] This might be due to participants with chronic diseases will have more exposure to antibiotics, and frequent hospital visits, which may lead to ESBL-PE carriage.

The third factor that contributed to the carriage of ESBL-PE was admission to a neonatal intensive care unit. Participants who had been admitted to NICU were 4.86 times more likely carriers for ESBL-PE than those who had been admitted to other wards. This finding is supported by the previous study conducted in Korea[35] and Turkey.[39] This could be due to the overuse of broad-spectrum antibiotics in the neonatal intensive care unit (NICU) to treat serious infections. Eventually, patients with ESBL-PE carriage might be sources for self and cross-transmission of resistance genes among other patients that could result in untreatable nosocomial infection in the study area.

This study indicates a high fecal carriage of ESBL-PE and MDR-E in the study area that needs strong infection prevention measures, careful selection of antibiotics after antimicrobial susceptibility test, and periodic surveillance of AMR at the study site. In addition, the finding informs the need for routine screening of ESBL, especially for patients admitted to the intensive care unit and patients who had chronic diseases in the study area for diagnostic and infection control or surveillance purpose which is not practiced yet in Ethiopia.

Conclusions

In this study, the fecal carriage of ESBL-PE and MDR-E was high among hospitalized patients. ESBL-PE showed a high level of resistance to many commonly used antibiotics. However, meropenem and imipenem were active against ESBL-PE. Antibiotic use in the past 3 months, admission in the neonatal intensive care unit, and presence of chronic disease showed statistically significant association with fecal carriage of ESBL-PE. Therefore, strict infection prevention measures should be implemented to limit infection and the spread of antimicrobial resistance strains in the study area.

Data Sharing Statement

Data that support the findings of the study are included.

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Disclosure

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