Infection and Drug Resistance

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ORIGINAL RESEARCH

High Prevalence of Multi-Drug Resistance and Extended-Spectrum Beta-Lactamase-Producing *Enterobacteriaceae* Among Hospitalized Patients Presumptive for Bacterial Infection at Debre Berhan Comprehensive Specialized Hospital, Ethiopia

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Background: Multi-drug resistant *Enterobacteriaceae* (MDR-E), primarily extended-spectrum beta-lactamase producers (ESBLs), have emerged as a major public health concern. This study aimed to determine the prevalence of multi-drug resistance and extended-spectrum beta-lactamase-producing *Enterobacteriaceae* among hospitalized patients presumptive for bacterial infections at Debre Berhan Comprehensive Specialized Hospital, Ethiopia.

Methods: A hospital-based cross-sectional study was conducted from January to May 2021. A total of 384 hospitalized patients presumptive for bacterial infections were included in the study. Urine, wound, blood, stool, and sputum samples were collected and cultured on MacConkey agar, Cysteine Lactose Electrolyte Deficient medium, and Blood agar. Identification was done using a panel of biochemical tests. The antimicrobial susceptibility test was done by disc diffusion. Screening of ESBL production was done by using cefotaxime and ceftazidime and confirmed by the combination disk method per clinical laboratory standard institute guidelines. 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: Out of 384 study participants, a total of 164 *Enterobacteriaceae* were isolated. The overall multi-drug resistance rate (MDR) was 92.1%. The overall prevalence of ESBL-PE was 104 (63.4%). *E. coli* 50 (30.5%) and *K. pneumoniae* 24 (14.6%) were the predominant ESBL producers. The highest ESBL producers *E. coli* (13.4%) and *K. pneumoniae* (6.1%) were isolated from urine sample. History of antibiotic use for the last three months (P-value=0.01), admission in neonatal intensive care unit (P-value=0.02), history of hospital stays (P-value=0.01), and chronic disease (P-value=0.04) showed statistically significant association with ESBL-PE infection.

Conclusion: The prevalence of MDR-E and ESBL-PE was high. Therefore, strong infection prevention and control measures and careful selection of antibiotics are needed in the study area to block the transmission and infection in the healthcare setting.

Keywords: bacterial infection, extended-spectrum beta-lactamase *Enterobacteriaceae*, hospitalized patients, Debre Berhan, Ethiopia

Background

Enterobacteriaceae are a large family of gram-negative, facultative anaerobes and non-spore-forming Bacilli. The family includes enteric bacteria that are both natural and incidentally pathogenic, such as *Escherichia* spp., *Klebsiella* spp, *Proteus* spp, *Enterobacter* spp., *Citrobacter* spp., *Providencia* spp, *Serratia* spp, *Salmonella* spp, and *Shigella* spp.[1]

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Antimicrobial resistance (AMR) is a major public health concern around the world. Higher mortality rates, extended hospitalization, medication failure, and health costs are linked to infections caused by resistant species. Infections caused by MDR bacteria have been declared an emerging public health epidemic by the World Health Organization (WHO).[2]

The widely used antibiotics for the treatment of infections caused by multi-drug resistant *Enterobacteriaceae* (MDR-E) are antibacterial agents of the beta-lactam category. However, these bacteria can hydrolyze certain beta-lactam antibiotics by the synthesis of beta-lactamase such as ESBLs and carbapenemase.[3]

The main mechanism of resistance to beta-lactam antibiotics in *Enterobacteriaceae* is the synthesis of beta-lactamases. Among the beta-lactamases, the production of ESBLs is the most common. These enzymes can break or hydrolyse many beta-lactam antibiotics.[4]

Extended-spectrum beta-lactamase (ESBLs)-producing pathogenic *Enterobacteriaceae* cause a serious antibiotic management problem, as the enzyme-encoding genes are easily transferred from one organism to the other via plasmids.[5] Since ESBL-PE are also resistant to other antibiotic families, advanced procedures like surgeries, cancer treatment, and organ transplantation could become increasingly risky. Inability to treat these patients would increase morbidity and mortality. This problem is more pronounced in areas where there is no adequate infection control program, periodic surveillance, and multidrug-resistant bacteria detection laboratory facility.[6]

The effect of antibiotic resistance is not only on the individual patient but also on the entire health system. Infected patients require more complex therapy, take longer to recover, and are more likely to experience treatment failure and mortality. This will result in devastating financial, social, and psychological effects. Furthermore, AMR also imposes enormous financial burdens on society as a whole.[7]

In sub-Saharan Africa, although estimations of the magnitude of the problem of antibacterial resistance are difficult and there is limited capacity for antibiotic resistance detection and surveillance, the existing reports showed a high antibiotic resistance rate to commonly used antibiotics. This condition is aggravated by lack of good hygiene, lack of safe water, civil conflicts, lack of strong infection control strategy and increasing numbers of immune-compromised people.[8]

In East Africa, gram-negative bacteria exhibited relatively high levels of resistance to antibiotics commonly used (50–100% to ampicillin and cotrimoxazole). They cause different infections including bloodstream infection (BSI), urinary tract infection (UTI), lower respiratory tract infections (LRTIs), and wound infection. Such infections are primarily treated with beta-lactam class of antibiotics such as penicillins, cephalosporins, monobactams, and carbapenems.[9]

Knowing the current status on the prevalence of MDR-E such as ESBL-PE infection is very important to understand their epidemiology and disease burden, to implement hospital infection control strategy and to prevent the spread of these bacteria. Although ESBL-PE causes significant and devastating public health problems, little is known about the prevalence of ESBL-PE infection in Ethiopia. Only a few studies have been conducted in Ethiopia regarding the prevalence of ESBL-PE infection.[10,11] Furthermore, to the best of our knowledge, most microbiology laboratories in Ethiopia do not perform ESBLs detection tests both for diagnostic and for infection control or surveillance purpose. Hence, this study aimed to determine the prevalence of multi-drug-resistant *Enterobacteriaceae*, ESBL-PE and associated factors suspected for bacterial infection at Debre Berhan Comprehensive Specialized Hospital, Amhara Region, Ethiopia.

Materials and Methods

Study Design, Period and Setting

A hospital-based cross-sectional study was conducted from January 2021 to May 2021. The study was conducted at Debre Berhan Comprehensive Specialized Hospital (DBCSH), which is found in Debre Berhan town, North Shoa, Amhara Region, Ethiopia. Debre Berhan is located 130 Km far from the capital city of the country, Addis Ababa. According to the 2007 population and housing census of Ethiopia, the town has a total of 160,847 people. Debre Berhan is situated at an altitude of 2840 m above sea level with a mean annual temperature that ranges from 10 to 16°C. The weather condition of the town and surrounding areas is relatively cold, dry, and windy with two distinctive seasons: summer and winter.[12] DBCSH was first established as a health facility in 1937 by Italians to serve their soldiers during the 2nd Italian attempt to colonize Ethiopia. It has 162 beds and provides services including paediatrics, emergency,

surgical, medical gynaecology, psychiatry, ophthalmology, anti-retroviral treatment (ART) services, neonatal intensive care unit, microbiological laboratories, viral load, and other health care services.

Population

All patients who sought and got medical services at DBCSH were the source population, while all hospitalized patients who were suspected of bacterial infections for ≥48 hours during the study period were the study population. All hospitalized patients suspected of bacterial infection who were given informed consent or assent were included in the study.

Sample Size Determination and Sampling Technique

The sample size was determined using a single population proportion formula as follows:

$$n = \frac{z^2 p\ (1 - p)}{d^2}$$

Where: n = the minimum required sample size; z = Standard normal distribution value at 95% CI, which is 1.96; P = the prevalence, d = the margin of error taken as 5%.

$$n = \frac{z^2 p\ (1 - p)}{d^2} = \frac{1.96^2 (0.5)\ (0.5)}{(0.05)^2} = 384$$

All hospitalized patients who were clinically presumptive for different bacterial infections were included conveniently, and study participants who did not provide complete data and appropriate specimen (saliva and/or contaminated sputum), insufficient volume of all specimens, monitored for less than 48 hours, critically ill patients, and unable to give a specimen were excluded.

Data Collection

Sociodemographic and clinical data were collected using a structured questionnaire after obtaining informed consent or assent from their guardians/parents for each study participant. For participants who cannot read and write, the information sheet was read to them, and a witness was signed before data collection.

Clinical Specimen Collection and Processing

Blood samples: 10 mL of venous whole blood from adults, 5mL from the paediatrics and 2mL from neonates were collected aseptically. Then, blood samples were inoculated in tryptic soya broth (Oxoid, LTD) and incubated immediately at 35–37°C and inspected daily for the signs of bacterial growth until 7 days. Bottles that showed positive for growth were subcultured on blood agar (Sisco Research Laboratories Pvt. Ltd, Mumbai, India) and MacConkey agar (Oxoid, LTD). Those blood culture bottles which showed no growth were continuously monitored for the potential growth of pathogens until 7 days, and if there was no growth after 7 days, the blood culture was reported as negative. A minimum blood-to-broth ratio of 1:10 was maintained.[11]

Urine sample: About 10mL freshly voided midstream urine samples were collected with sterile, wide-mouthed, and leak-proof containers. A10µl (0.01mL) well-mixed urine sample was inoculated using calibrated wire loop into Cysteine Lactose Electrolyte Deficient medium (HiMedia, India) and sub-cultured into MacConkey agar and then incubated at 37°C for 24 hr under aerobic condition. The samples with significant bacteriuria (≥10^5 CFU/mL) were further processed, whereas specimens that produced <10^5CFU/mL were considered insignificant.

Sputum sample: after briefly instructing the patients to rinse their mouths with water, a sterile wide-mouth container was used to collect 2 mL purulent sputum. Sputum specimens with much watery saliva were excluded from being processed using microbiological procedures. The sputum was immediately smeared and examined for appropriateness for culturing. Specimens that had more than 25 polymorphonuclear leukocytes and less than 10 epithelial cells were inoculated into MacConkey agar and blood agar plate and incubated for 24 hr at 37°C.

Wound sample: purulent exudates, pus, and discharges were collected aseptically from the depth of the wound using a syringe or sterile cotton swab. The cotton swab was immersed in a tube of brain heart infusion transport medium. The

brain-heart infusion culture was incubated for 24 hr and then sub-cultured onto MacConkey agar and blood agar plates and re incubated for 24 hr at 37°C.

Stool sample: Proper instruction was given to study participants about fresh stool sample collection. For each study participant, a sterile clean cup container was given to collect stool. A pea-sized stool was collected from each patient and inoculated onto MacConkey agar and incubated aerobically at 37°C for 18 to 24 hrs.[11]

Identification of Bacterial Isolates

Each culture plate was examined for the growth of *Enterobacteriaceae*. Lactose fermenters and non-lactose fermenters were characterized on MacConkey agar. Finally, pure colonies were taken for identification. *Enterobacteriaceae* was identified to species levels using triple sugar iron, indole, citrate, urea, lysine decarboxylase, H_2S production, and motility.[13]

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was performed using the Kirby-Bauer disk diffusion method as per Clinical Laboratory Standard Institute (CLSI) guidelines. Bacterial suspensions were prepared by suspending the freshly grown bacteria in 3–5 mL normal saline, and turbidity was adjusted to 0.5 McFarland standards. A sterile cotton swab was dipped and rotated several times and was pressed against the wall of the test tube. It was then swabbed over the entire surface of the Mueller Hinton agar (HiMedia, India). Antimicrobial susceptibility testing for all *Enterobacteriaceae* was performed using disk diffusion method against ampicillin (10µg), cefoxitin (30µg), gentamicin (10µg), ciprofloxacin (5µg), trimethoprim-sulfamethoxazole (1.25/23.75µg), imipenem (10µg), meropenem (10µg), amoxicillin-clavulanic acid (20/10 µg), cefotaxime (30 µg), ceftazidime (30µg), ceftriaxone (30µg), tetracycline (30µg), cefepime (30µg), and Chloramphenicol (30µg).

Screening of ESBLs

Enterobacteriaceae isolates which showed an inhibition zone size of ≤22 mm with ceftazidime (30 µg) and/or ≤27mm with cefotaxime (30 µg) considered as potential ESBL producers.[14]

Phenotypic Confirmation of ESBLs

A disk of ceftazidime (30 µg) and cefotaxime (30 µg) alone and their combination with Clavulanic acid (30 µg/10 µg) were placed 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.[14]

Data and Laboratory Quality Control

Standard operating procedures (SOP) were strictly followed verifying that media meet expiration date and quality control parameters. Culture media was prepared according to the manufacturer's instruction, and the sterility test was performed before use. Visual inspections of crack freezing, bubbles, and contaminations in media were checked before use.

Quality control strain was used to check the quality of the medium. Each new lot was checked before use by testing the growth E. *coli* ATCC 25922 control strains. During ESBLs detection, ESBLs positive *K. pneumoniae* ATCC 700603 and ESBLs negative *E. coli* ATCC 25922 control strains were used. The clinical sample was collected following SOPs and immediately brought to the microbiology laboratory for bacteriological analysis. Culture results were recorded carefully before data entry, and the data were double-checked before analysis.

Data Analysis

Data were entered using Epi Data software version 3.1 and exported to SPSS 23 for analysis. The descriptive statistics such as frequency and percentage were presented with tables and graphs. Binary logistic regression was used to observe the association between dependent variables and independent variables. The variables that showed p-value less than or equal to 0.2 in bivariate logistic regression analysis were further selected for multivariate logistic regression analysis for

final confirmation of statistical significance. P-value ≤0.05 with a 95% confidence interval was considered as statistically significant.

Ethical Consideration

The study was reviewed and approved by the Research and Ethics Review committee of College of Medicine and Health Sciences, Wollo University. A written permission letter was also obtained from the DBCSH. The purpose and procedures of the study were explained to the study participants and parents or guardians within the study period. Those patients and parents or guardians who gave informed consent were selected and enrolled in this study. The confidentiality of all study participants was maintained via study participant secret code and locking. For participants who cannot read and write, the information sheets were read to them, and a witness was signed that the process had been conducted appropriately. This research was carried out in accordance with the Helsinki Declaration.

Results

Sociodemographic Characteristics of Study Participants

A total of 384 study participants were enrolled in the study. Among 384 study participants, 230 (59.9%) were female and 149 (38.8%) were children aged less than 15 years, with a mean age of 2.3 ±1.23. The majority of the study participants were rural dwellers, 240 (62.5%) (Table 1).

Clinical Profile of the Study Participants

Of the total 384 study participants, 106 (27.6%) had a previous history of antibiotic use for the last 3 months and 76 (19.8%) had a history of hospital stays (Table 2).

Distribution of *Enterobacteriaceae* Isolates and Antimicrobial Resistance Pattern

A total of 164 *Enterobacteriaceae* were isolated. Among these, the highest ESBL producers *E coli* (13.4%) and *K. pneumoniae* (6.1%) were isolated from urine sample (Table 3).

In this study, fourteen antibiotics from different classes were used. The highest level of susceptibility was observed in meropenem (77.4%) followed by imipenem (70.4%). The highest level of resistance was observed to ampicillin (100%) followed by tetracycline (97.6%) (Table 4).

From the total 164 isolated *Enterobacteriaceae*, 151 (92.1%) were MDR (resistance to at least 3 antibiotics in a different class). The highest rate of MDR was seen in *K. pneumoniae* and *E. coli,* accounting for average resistance of 46 (97.9%) and 68 (91.9%), respectively (Table 5).

Magnitude of ESBL-PE

Of the total 164 *Enterobacteriaceae* isolates, 134 (81.7%) were suspected for ESBL production. Out of the 134 suspected *Enterobacteriaceae* isolates, ESBL production was confirmed in 104 (77.6%) using a combination disc test. The overall prevalence of ESBL-PE was 104 (63.4%) (Figure 1).

Non-ESBL-producing *Enterobacteriaceae* were more sensitive to antibiotics than ESBL-PE. Ampicillin and tetracycline were (100%) resistant for ESBL-PE (Figure 2).

From the total 151 (92.1%) MDR-E isolates, 104 (68.9%) were ESBL producers. From the total of 68 (91.9%) multidrug resistant *E. coli* isolates, 50 (73.5%) were ESBL producers (Table 6).

Associated Risk Factors for ESBL-PE Infection

In a multivariate logistic regression model, history of hospital stays, the previous history of antibiotic use for the last three months, underlying diseases and admission in neonatal intensive care unit (NICU) ward showed statistical significance for ESBL-PE infection (Table 7).

Table 1 Sociodemographic Characteristics of Study Participants at Debre Berhan Comprehensive Specialized Hospital from January to May 2021

Sociodemographic Characteristics	Categories	n (%)
Sex	Male	154(40.1)
	Female	230(59.9)
Age	0–15	149(38.8)
	16–25	62(16.1)
	26–40	96(25)
	41–60	64(16.7)
	>60	13(3.4)
Place of residence	Rural	240(62.5)
	Urban	144(37.5)
Adult marital status	Married	170(75.5)
	Single	22(9.6)
	Divorced	30(13.5)
	Widowed	3(1.3)
Educational status	Illiterate	17(4.4)
	Read and write	79(20.6)
	Primary	158(41.1)
	Secondary	22(5.7)
	Diploma and above	28(7.3)
	Not applicable	80(20.8)
Adult occupational status	Governmental employed	13(5.7)
	Merchant	23(10.4)
	Housewife	56(24.7)
	Daily labour	13(5.7)
	Farmer	105(46.6)
	Other	15(6.8)
Average family income	<1000ETB	276(71.9)
	1000–2000ETB	80(20.8)
	>2000ETB	28(7.3)
Hand washing habit before meal	Yes	321(83.6)
	No	63(16.4)
Habit of eating uncooked vegetable	Yes	38(9.9)
	No	346(90.1)
Habit of eat uncooked animal product	Yes	21(5.5)
	No	363(94.5)

Note: Not applicable for educational status indicates: under age.
Abbreviation: ETB, Ethiopian birr.

Table 2 Clinical Profile of the Study Participants at Debre Berhan Comprehensive Specialized Hospital from January to May 2021

Variables	Categories	n (%)
History of antibiotic use for last 3 months	Yes	106(27.6)
	No	278(72.4)
Discontinuing of antibiotics	Yes	3(0.8)
	No	103(26.8)
History of hospitalization in the last three months	Yes	76(19.8)
	No	308(80.2)
Previous history of ICU stays	Yes	1(0.3)
	No	383(99.7)
History of invasive procedure	Yes	21(5.5)
	No	363(94.5)
Types of invasive procedure	Catherization	11(2.9)
	Surgery	8(2.1)
	Other	2(0.5)
Admission ward	Neonatal ICU	68(17.7)
	Paediatric	80(20.8)
	Medical	91(23.7)
	Surgery	53(13.8)
	Adult ICU	24(6.3)
	Gynaecology and obstetrics	57(14.8)
	Ophthalmology	11(2.9)
Duration in the ward in days	3–7	357(93.0)
	8–15	27(7.0)
Chronic underlying disease	Yes	42(10.9)
	No	342(89.1)
Types of chronic disease	Diabetes mellitus	18(4.7)
	HIV	14(3.6)
	Hypertension	4(1.0)
	Other	6(1.5)
Previous history of UTI	Yes	10(2.6)
	No	374(97.4)
Number of patients per room	2–4	165(43.0)
	5–8	219(57.0)
Number of beds per room	2–4	79(20.6)
	2–8	305(79.4)

Abbreviation: ICU, intensive care unit.

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Table 3 ESBL-PE Isolates Against Clinical Specimen Types at Debre Berhan Comprehensive Specialized Hospital from January to May 2021

Isolates	Clinical Sample	ESBL Production (n=164)		Total n (%)
		Positive n (%)	Negative n (%)	
E. coli	Blood	14(8.5)	3(1.8)	17(10.4)
	Urine	22(13.4)	9(5.5)	31(18.9)
	Wound	9(5.5)	5(3.0)	14 (8.5)
	Sputum	–	2(1.2)	2(1.2)
	Stool	5(3.0)	5(3.0)	10(6.1)
	Total	50(30.4)	24(14.6)	74(45.1)
K. pneumoniae	Blood	8(4.9)	5(3.0)	13(7.9)
	Stool	2(1.2)	1(0.6)	3(1.8)
	Urine	10(6.1)	13(7.9)	23(14.0)
	Wound	4(2.4)	4(2.4)	8(4.9)
	Total	24(14.6)	23(14.0)	47(28.7)
K. oxytoca	Blood	2(1.2)	2(1.2)	4(2.4)
	Stool	3(1.8)	–	3(1.8)
	Total	5(3.0)	2(1.2)	7(4.3)
C. divresus	Wound	1(0.6)	–	1(0.6)
	Stool	1(0.6)	–	1(0.6)
	Blood	5(3.0)	1(0.6)	6(3.7)
	Urine	–	2(1.2)	2(1.2)
	Total	7(4.3)	3(1.8)	11(6.7)
E. aerogenes	Wound	1(0.6)	–	1(0.6)
	Urine	1(0.6)	2(1.2)	3(1.8)
	Stool	1(0.6)	2(1.2)	3(1.8)
	Total	3(1.8)	4(2.4)	7(4.3)
M. morganii	Urine	–	1(0.6)	1(0.6)
	Stool	1(0.6)	–	1(0.6)
	Total	1(0.6)	1(0.6)	2(1.2)
K. ozaenae	Blood	3(1.8)	–	3(1.8)
	Urine	1(0.6)	–	1(0.6)
	Total	4(2.4)	–	4(2.4)

(*Continued*)

Table 3 (Continued).

Isolates	Clinical Sample	ESBL Production (n=164)		Total n (%)
		Positive n (%)	Negative n (%)	
P. stuartii	Urine	3(1.8)	–	3(1.8)
	Blood	1(0.6)	–	1(0.6)
	Stool	–	1(0.6)	1(0.6)
	Total	4(2.4)	1(0.6)	4(2.4)
E. cloacae	Urine	3(1.8)	1(0.6)	4(2.4)
	Stool	1(0.6)	1(0.6)	2(1.2)
	Total	4(2.4)	2(1.2)	6(3.7)
Citrobacter spp	Wound	1(0.6)	–	1(0.6)
	Total	1(0.6)	–	1(0.6)
C. freundii	Stool	1(0.6)	–	1(0.6)
	Total	1(0.6)	–	1(0.6)
Total		104(63.4)	60(36.6)	164(100)

Discussion

ESBL-PE has become currently a global problem. ESBL dissemination compromises the activity of broad-spectrum antibiotics, creating major therapeutic difficulties with a significant impact on patient outcomes.

A total of 164 *Enterobacteriaceae* isolates were isolated that comprise, the predominant isolate, *E. coli* 45.1% followed by *K. pneumoniae* 28.7%. This finding was comparable with the study done in Bahir Dar, reported as *E. coli (*58.1%) and *K. pneumoniae (*23.3%),[11] and in Northwest Ethiopia, reported as *E. coli* (61.2%) and *K. pneumoniae (*22.8%).[15] Similar findings were also reported from other countries like in Sudan, *E. coli* (54.4%) and *K. pneumoniae* (29.5%),[16] in Uganda, *E. coli* (53.9%) and *K. pneumoniae* (28.7%),[17] and in Tanzania, *E. coli* (48.9%).[18]

Our study revealed that *E. coli* (45.1%) was the predominant pathogen among isolated *Enterobacteriaceae*. A similar finding was also reported in Uganda (44%).[3] Like other studies, our study indicated that many types of infectious diseases caused by *Enterobacteriaceae* were predominantly by *E. coli and K. pneumoniae*.[10,11,19]

The overall prevalence of ESBL-PE was (63.4%) which is supported by various study done in Addis Ababa (58%),[20] Bahir Dar (57.6%),[21] Jimma (63.4%),[22] Burkina Faso (58%),[23] and India (62.7%).[24]

The prevalence of ESBL-PE in this study was lower compared to studies done in Addis Ababa (78%),[10] Bahir Dar (85.5%)[11] and Uganda (89%).[3] This wide variation might be attributable to discrepancies in the study demographic, sample size, the patient's isolation, and the type of antibiotics used. Furthermore, the variation might be due to the difference in local antibiotic prescribing habits and infection control programs in different health facilities.

The prevalence of ESBL-PE in our study was higher compared to studies reported in Adama (25%),[13] Burkina Faso (42%),[23] Bahir Dar (46%),[21] Jimma (38%),[25] and Nepal (34%).[26] This might be anticipated due to the good infection control strategy of the countries, study participants, variation in drug management policies, and study methodology difference.

Our findings revealed that the highest ESBL production was observed in *E. coli* (30.5%) followed by *K*. pneumoniae (14.6%). The result was comparable to those reported in Arba Minch, *E. coli* (44%);[27] in India, *E. coli* (44%);[24] in Burkina Faso, *K. pneumoniae* (26%) (71); in Adama, *K. pneumonia* (11.5%).[13]

Our result was lower compared to findings from Tanzania, reported as *E. coli* (68%),[28] and Burkina Faso, reported as *E. coli* (78%).[23] However, our finding was higher compared to the study done in Gondar, reported as *E. coli* (16.2%),[29] and Morocco,

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Table 4 Antimicrobial Resistance Pattern of *Enterobacteriaceae* Isolates at Debre Berhan Comprehensive Specialized Hospital from January to May 2021

Isolates	AST	Antibacterial Agents Level n (%) (n = 164)													
		AMP	**FOX**	**GEN**	**CIP**	**STX**	**AMC**	**MER**	**IMP**	**CTX**	**CAZ**	**CRO**	**TET**	**FEP**	**C**
E. coli (74)	S	–	46(62.1)	42(56.8	7(9.5)	16(21.6)	20(27.0)	56(75.7)	60(81.1)	12(16.2)	12(16.2)	15(20.3)	–	14(29.7)	42(56.8)
	I	–	–	5(6.7)	25(33.7		7(9.5)	2(2.7)	–	–	–	3(4.1)	–	–	1(1.4)
	R	74(100)	28(38.0)	27(36.5)	42(56.8)	58(85.4)	47(63.5)	16(21.6	14(18.9)	62(83.2)	62(83.8)	56(75.7)	74(100)	52(70.3)	31(41.8)
K. pneumoniae (47)	S	–	20(42.6)	26(55.3	2(4.3)	8(17.0)	8(17.00)	31(66.0)	37(78.7)	10(21.3)	10(21.3)	14(29.8)	3(6.4)	14(29.8)	22(46.8)
	I	–		2(4.3)	15(31.9)		3(6.40)	1(2.1)	–	–	2(4.3)	1(2.1)	–	–	–
	R	47(100	27(57.4)	19(40.4)	30(63.8)	39(83.0)	36(76.6)	15(31.9)	10(21.3)	37(78.7)	37(78.7)	32(68.1)	44(93.6)	33(70.2)	25(53.2)
K. oxytoca (7)	S	–	1(14.2)	1(14.3)	–	1(14.3)	–	3(42.90	4(57.1)	–	–	1(14.3)	–	–	2(28.6)
	I	–	–	–	1(14.3)		–	–	–	–	–	–	–	–	–
	R	7(100)	6(85.8)	6(85.7)	6(85.7)	6(85.7)	7(100)	4(57.1)	3(42.9)	7(100)	7(100)	6(86.7)	7(100)	7(100)	5(71.4)
Citrobacter spp *(1)*	S	–	1(100)	–			–	1(100)	1(100)	–	–		–	–	–
	I	–		–	–		–		–	–	–	–	–	–	–
	R	1(100)	–	1(100)	1(1000	1(100)	1(100)		–	1(00)	1(100)	1(100)	1(100)	1(100)	1(100)
E. aerogens (7)	S	–	5(71.4)	4(57.1)	1(14.3)	29(28.6)	4(57.1)	6985.7)	7(100)	2(28.6)	4(57.1)	4(57.1)	–	4(57.1)	4(57.1)
	I	–	–	–	5(71.4)		1(14.3)	–	–	2(28.6)	–	–	–	–	–
	R	7(100)	2(28.6)	3(42.9)	1(14.3)	5(71.4)	2(28.6)	1(14.3)	–	3(42.8)	3(42.9)	4(42.9	7(100)	4(42.9)	3(42.9)
P. stuartii (5)	S	–	1(20.0)	2(40.0)	1(20.0)		–	1(20.0)	1(20.0)	1(20.0)	–	1(20.0)	–	–	1(14.3)
	I	–		–	–		–	–	–	–	–	–	–	–	–
	R	5(100)	4(80.0)	3(60.0)	4(80.0)	5(100)	5(100)	4(80.0)	4(80.0)	4(80.0)	5(100)	4(80.0)	5(100)	5(100)	4(80.0)
M. morganii (2)	S	–	–	1(50.0)	–			2(100)	2(100)	1(100)	1(50.0)	–	–	–	1(50.0)
	I	–		(50.0)	950.0)			–		–	–	–	–	–	–
	R	2(100)	2(100)	–	1(50.0)	2(100)	2(100)			1(50.0)	1(50.0)	2(100)	2(100)	2(100)	1(50.0)

E. cloacae (6)	S	–	3(50.0)	1(16.7)	–	1(16.7)	2(33.3)	5(83.3)	1(16.7)	1(16.7)	1(16.7)	2(33.3)	–	1(16.7)	2(33.3)
	I	–		2(33.3)	2(33.3)		–	1(16.7)	–	–	–	–	–	–	–
	R	6(100)	3(50.0)	3(50.0)	4(66.7)	5(83.3)	4(66.7)	–	5(83.3)	5(83.7)	5(83.3)	4(66.7)	6(100)	5(83.3)	4(66.7)
C. diverus (10)	S	–	3(30.0)	4(40.0)	2(20.0)	3(30.0)	1(10.0)	7(70.0)	6(60.0)	3(30.0)	1(10.0)	3(30.0)	–	1(10.0)	5(50.0)
	I	–	–	–	1(10.0)		–		–	–	–	–	–	–	–
	R	10(100)	7(70.0)	6(60.0)	7(70.0)	7(70.0	9(90.0)	3(30.00	4(40.00	7(70.0)	9(90.0)	7(70.0)	10(100)	9(90.0)	5(50.0)
C. freundii (1)	S	–	1(100)	1(100)	–		–	1(100)	1(100)	–	–	–	–	–	1(50.0)
	I	–	–	–	–		–	–	–	–	–	–	–	–	–
	R	1(100)	–	–	1(100)	1(100)	1(100)	–	–	1(100)	1(100)	1(100	1(100)	1(100)	1(50.0)
K. ozaenae (4)	S	–	3(75.0)	1(25.0)	–	1(25.0)	1(25.0)	3(75.0)	3(75.0)	1(25.0)	–	–	–	–	2(50.0)
	I	–	–	–	–	–		–	–	–	–	–	–	–	–
	R	4(100)	1(25.0	3(75.0)	4(100)	3(75.)	3(75.0)	1(25.0	1(25.0	4(75.0)	4(100)	4(100)	4(100)	4(100)	2(50.0)
Total (164)	S	–	85(51.8)	84(51.2)	17(10.4)	34(20.7)	127(77.4)	116(70.7)	38(23.2)	33(2.1)	30(18.3)	42(25.6)	4(2.4)	43(26.2)	81(49.4)
	I	–	–	9(5.5)	47(28.8)	–	3(1.8)	4(2.4)	3(4.4))	5(3.0)	2(1.2)	4(2.4)	–	–	1(0.6)
	R	164(100)	79(48.2)	71(43.3	100(61.0)	130(85)	34(20.7)	44(26.8)	115(70.7)	126(76.8)	132(80.5)	118(72.0)	160(97.6)	121(73.8)	82(50.0)

Abbreviations: AMP, ampicillin; FOX, cefoxitin; GM, gentamycin; CIP, ciprofloxacin; COT, cotrimoxazole; IMP, imipenem; MER, meropenem; AMC, amoxicillin–clavulanic acid; CTX, cefotaxime; CAZ, ceftazidime; CRO, ceftriaxone; TE, tetracycline; FEP, cefepime; C, chloramphenicol; S, susceptible; R, resistance; I, intermediate.

Table 5 Multi-Drug Resistance Patterns of Enterobacteriaceae Isolates at Debre Berhan Comprehensive Specialized Hospital from January to May 2021

Level of Antibiotic Resistance n (%)									
Isolates (Number)	**R0**	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**≥R7**	**Total MDR R≥3**
E. coli (n = 74)	0(0.0)	1(1.4)	5(6.8)	2(2.7)	2(2.7)	7(9.1)	5(6.8)	52(70.3)	68(91.9)
K. pneumoniae (n = 47)	0(0.0)	0(0.0)	1(2.1)	4(8.5)	4(8.5)	2(4.3)	2(4.3)	34(72.3)	46(97.9)
E. cloacae (n = 7)	0(0.0)	0(0.0)	0(0.0)	1(14.3)	1(14.3)	0(0.0)	0(0.0)	4(57.1)	6(85.7)
E. aerogens (n = 7)	0(0.0)	0(0.0)	2(33.3)	1(16.7)	1(16.7)	0(0.0)	0(0.0)	3(42.3)	5(71.4)
K. oxytoca (n = 7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(14.3)	0(0.0)	0(0.0)	6(85.7)	7(100)
M. morganii (n = 2)	0(0.0)	0(0.0)	1(50.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(50.0)	1(50.0)
C. diverus (n = 10)	0(0.0)	1(10.0)	1(10.0)	1(10.0)	0(0.0)	0(0.0)	1(10.0)	6(60.0)	8(80.0)
C. freundii (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)	1(100)
P. stuartii (n = 5)	0(0.0)	1(20.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(80.0)	4(80.0)
Citrobacter spp (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)	1(100)
K. ozaenae (n = 4)	0(0.0	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(100)	4(100)
Total (n = 164)	0(0.0)	2(1.2)	9(5.5)	9(5.5)	9(5.5)	9(5.5)	8(4.9)	116(70.1)	151(92.1)

Abbreviations: 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 (resistant to one or more antibiotics in three or more classes).

reported as *E. coli* (19.4%).[30] The potential reason for the difference in the prevalence of ESBL-PE among *Enterobacteriaceae* could be variation in type and frequency of isolates, sample size, study participants and geographical location.

The recent study revealed that higher resistance to ampicillin (100%), followed by tetracycline (97.0%), sulfamethoxazole-trimethoprim (85%), ceftazidime (80.0%) and cefotaxime (79%). This could be due to the overuse of the drug for many years.

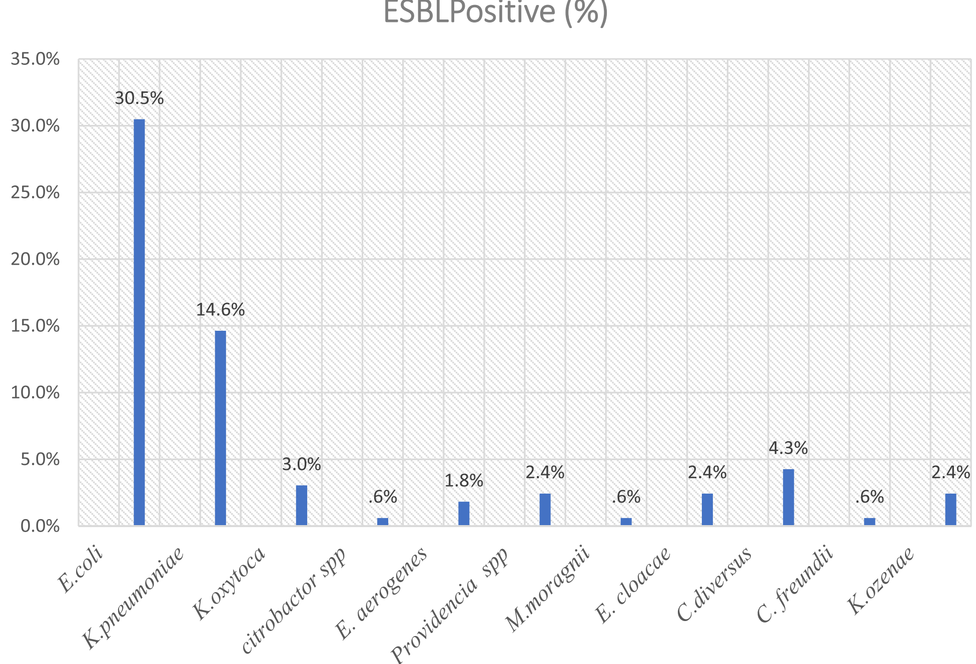
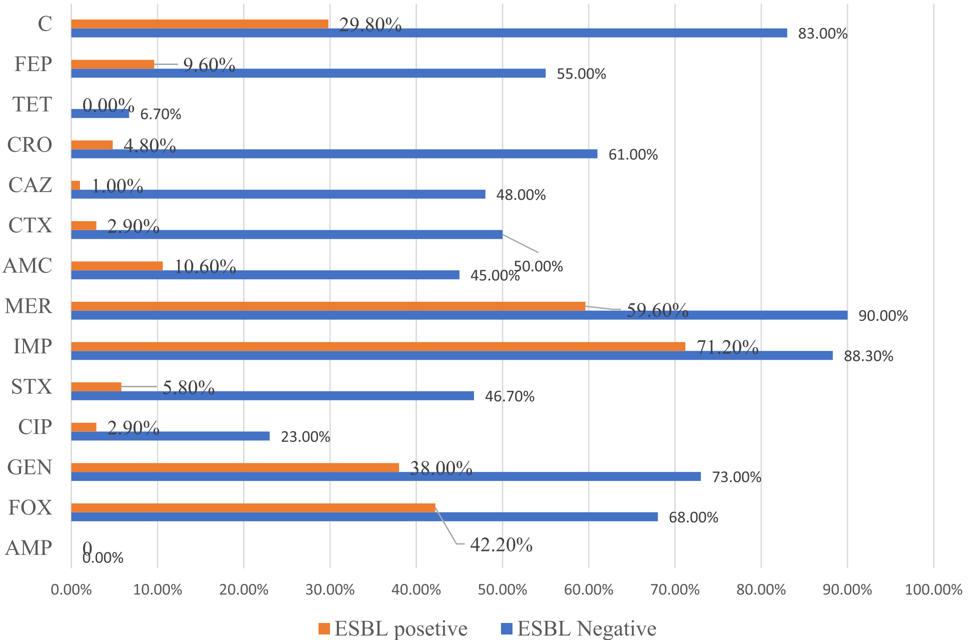


Figure 1 Distribution of ESBL-PE at Debre Berhan Comprehensive Specialized Hospital from January to May 2021.



IMP: imipenem, MER: meropenem, AMC: Amoxicillin–clavulanic acid, CTX: Cefotaxime, CAZ: Ceftazidime, CRO: Ceftriaxone: TET: Tetracycline, FEP: Cefepime: C: Chloramphenicol

Figure 2 Antibiotics susceptibility pattern of ESBL positive and ESBL negative to different classes of antibiotics at Debre Berhan Comprehensive Hospital from January to May 2021.

Abbreviations IMP, imipenem; MER, meropenem; AMC, amoxicillin–clavulanic acid; CTX, cefotaxime; CAZ, ceftazidime; CRO, ceftriaxone; TET, tetracycline; FEP, cefepime; C, chloramphenicol.

Our results were comparable to studies conducted in Bahir Dar, resistant to ampicillin (100%), followed by ceftazidime (96.6%) and cotrimoxazole (93.2%),[11] Arab Minch, tetracycline (91.1%) and sulfamethoxazole-trimethoprim (93.84%),[27] in Nepal, ceftazidime (83.2%) and cefotaxime (74.7%),[26] in Iran, sulfamethoxazole-trimethoprim (94%) and ceftazidime (73%).[31]

However, it was higher compared to a study conducted in Debre Markos, reported as ampicillin (70.4%), sulfamethoxazole-trimethoprim (53.1%),[32] Addis Ababa, sulfamethoxazole-trimethoprim (55.6%), cefotaxime (47%), ceftazidime (44.1%).[19] The possible reason for this difference might be due to the indiscriminate use of antibiotics, patient condition, and empirical treatment.

E. coli isolates showed the highest resistance to ampicillin (100%) followed by sulfamethoxazole-trimethoprim (85%), ceftazidime (83.8%), and cefotaxime (83%). This is comparable to a study done in Addis Ababa, reported as sulfamethoxazole-trimethoprim (77%), cefotaxime (62.2%), cefepime (60.3%), and ceftazidime (60.8%),[20] and in Saudi Arabia, reported as ampicillin (96.61%), cefotaxime (76.27%) and ceftazidime (81.36%)[11]

The second most predominant *Enterobacteriaceae* isolates in our study were *K. pneumoniae* which showed the highest level of resistance to ampicillin (100%), followed by tetracycline (93.6%), sulfamethoxazole-trimethoprim (83%), ceftazidime (78.7%). Our finding was comparable to study done in Gondar, reported as Ampicillin (100%), sulfamethoxazole-trimethoprim (72.2%),[33] in Tanzania, reported as ampicillin (100%),[34] in Arba Minch, reported as tetracycline (91.7%).[27] The increased antibiotic resistance of *Enterobacteriaceae* may be due to antibiotic misuse and overuse, as well as poor infection prevention, control, personal and environmental hygiene. Furthermore, mainly due to the habit of empirical treatment, infrequent bacterial identification and absence of susceptibility testing, antimicrobial resistance among bacterial infections to the commonly used antibiotics become increasing that make clinicians left with very limited choices of drugs for the treatment of infection.

Table 6 Distribution of ESBL-PE and MDR Isolates at Debre Berhan Comprehensive Specialised Hospital from January to May 2021

Isolates	ESBL n (%)		MDR n (%)
	Positive	Negative	
E. coli (n= 74)	50(73.5)	18(26.5)	68(91.9)
K. pneumoniae (n = 47)	24(52.2)	22(47.2)	46(97.9)
E. cloacae (n = 7)	4(66.6)	2(33.3)	6(85.7)
E. aerogens (n = 7)	3(60.0)	2(40.0)	5(71.4)
K. oxytoca (n = 7)	5(71.4)	2(28.6)	7(100)
M. morganii (n = 2)	1(100)	0(0.0)	1(50.0)
C. diverus (n = 10)	7(87.5)	1(12.5)	8(80.0)
C. freundii (n = 1)	1(100)	0(0.0)	1(100)
P. stuartii (n = 5)	4(100)	0(0.0)	4(80.0)
Citrobacter spp (n = 1)	1(100)	0(0.0)	1(100)
K.ozaenae (n = 4)	4(100)	0(0.0)	4(100)
Total (n = 164)	104(68.9)	47(31.1)	151(92.1)

The overall rate of MDR-*Enterobacteriaceae* (MDR-E) was (92.1%), which is fairly similar to a study done in Gondar, reported as (93.5% and 87.4%),[15,35] Bahir Dar, reported as (93.1%)[36] and in Nepal, reported as (96.84%).[26] However, this finding was higher compared to a study done in Dessie (74.6%).[37]

The possible reason for high MDR might be repeated, inappropriate, and incorrect use of antimicrobial agents in empirical treatment and poor infection control strategies. Furthermore, this inconsistency may be due to the selection of antibiotics from a different class, study period, specimen type and differences in the study population. However, the increased proportion of MDR seen in this study was considered worrying because only a few treatment options remain for infections. Therefore, implementing strong infection control strategies is required to reduce the MDR burden.

This study revealed that ESBL producers were high levels of resistance to third-generation cephalosporin, penicillin and sulfonamides: ceftazidime (99%), cefotaxime (97.1%), ceftriaxone (94.2%), ampicillin (100%), amoxicillin with clavulanic acid (84.6%), tetracycline (100%) sulfamethoxazole-trimethoprim (94.2%). This is supported by studies done in Nairobi, reported as sulfamethoxazole-trimethoprim (61.1%), ceftazidime (100%), ceftriaxone (100%),[38] Nepal, reported as amoxicillin with clavulanic acid (100%)[26] and Addis Ababa, reported as ampicillin (99.2%), ceftazidime (98.5%), ceftriaxone (98.5%), amoxicillin with clavulanic acid (98%) and sulfamethoxazole-trimethoprim (81%).[19] The possible justification for co-resistance to non-beta lactam antibiotics in this study could be explained by the fact that gene codes for ESBL production are usually found on mobile genetic elements: that may also carry resistance genes for non-beta-lactam antibiotics.

Our study shows that ESBL-PE was predominantly found *E. coli* (13.4%) in urine and in the blood (8.5%) followed *K. pneumoniae* by in urine (6.1%) and in the blood (4.9%). This might be due to the larger number of urine and blood samples included in this study.

The current study revealed that antibiotic use in the last 3 months, presence of chronic underlying disease, history of hospital stays, and admission in neonatal intensive care unit ward showed statistically significant association with ESBL-PE infection.

Participants who used antibiotics in the previous three months were more likely to be infected with ESBL-PE than those who had not. This is supported by the studies done in Gondar,[29] Tanzania,[28] Cyprus,[39] Algeria,[40] and Iran.[41]

Table 7 Associated Risk Factors for ESBL-PE Infection Using Bivariate and Multivariate Analysis at Debre Berhan Comprehensive Specialized Hospital from January to May 2021

Variables	Categories	ESBL Production		COR (95% CI)	P-value	AOR (95% CI)	P-value
		Positive n (%)	Negative n (%)				
Hand washing habit before the meal	Yes	92(56.1)	43(26.2)	Ref			
	No	12(7.3)	17(10.4)	3(13–6.9	0.00	2.5(0.5–11)	0.23
Habit of eating uncooked vegetable	Yes	28(17.1)	5(3.0)	4(1.5–11.2)	0.07	2.2(0.5–8.7)	0.26
	No	76(46.3)	55(33.5)	Ref			
History of antibiotic use for the last three months	Yes	54(32.9)	15(9.1)	3.2(1.6–6.5)	0.0	6.3(1.8–21.6)	0.001**
	No	50(30.5)	45(27.4)	Ref			
History of hospital stays	Yes	62(37.8)	6(3.7)	13(5.2–34)	0.00	1.9(1.4–6.9)	0.001**
	No	42(25.6)	54(32.9)	Ref			
Admission ward	Medical	26(15.9)	12(7.3)	0.7(0.2)	0.51	1.9(0.3–9.7)	0.40
	Surgical	18(11.0)	6(3.7)	0.9(0.3–3.5)	0.94	0.3(0.0–2.3)	0.28
	Paediatric	30(18.3)	15(9.1)	0.6(0.2–1.9)	0.41	1.3(0.3–5.7)	0.70
	NICU	10(6.1)	17(10.4)	0.2(0.1–0.6)	0.06	0.1(0.0–0.7)	0.02**
	Adult ICU	1(0.6)	4(2.4)	0.1(0.0–0.8)	0.04	0.4(0.0–5.4)	0.49
	G/obs	19(11.5)	6(3.7)	Ref			
Chronic diseases	Yes	21(12.8)	3(1.8)	4(1.1–14.0)	0.03	4.9(1.1–22.9)	0.04**
	No	83(50.6)	57(34.8)	Ref			

Note: **(P<0.05).
Abbreviations: COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval; Ref, Reference; NICU, neonatal intensive care unit; ICU, intensive care unit; G/obs, gynecology and obstetrics.

Another factor associated with ESBL-PE infection was the presence of chronic disease. This is similar to studies done in Arba Minch,[27] Iran[41] and Algeria.[40] This might be because participants who have chronic diseases will have frequent contact with health professionals which may lead to ESBL infection.

The third factor that contributed to ESBL-PE infection was the history of hospital stays which was comparable to the study done in Iran,[42] Mali[43] and Arba Minch.[27]

The other factor that contributed to ESBL-PE infection was admission to the neonatal intensive care unit. This is comparable to studies done in Iran[42] and Mali.[43]

The discrepancy of association with this finding could be explained by the difference in the clinical condition of the study participant, sample size, methodological difference, and study setting.

This study highlights the high magnitude of MDR-E and ESBL-PE in the study area among bacterial suspected patients that require careful selection of antibiotics following antimicrobial susceptibility test, strong infection prevention and control measures, and periodic surveillance of AMR in the study area. In addition, the finding of this study informs the need for routine screening of ESBL and especially for patients admitted to the intensive care unit and patients who had chronic diseases in the study site as well as nationwide for both diagnostic and infection control or surveillance purpose to limit the dissemination and infection caused by antimicrobial resistance strain.

Conclusions

In this study, the prevalence of MDR-E and ESBL-PE was high. The majority of ESBL-PE infections were found primarily in the urine specimen. *E. coli* and *K. pneumoniae* were the most frequent ESBL-PE. History of antibiotic use in the last 3 months, admission in NICU ward, history of hospital stays, and chronic disease showed a statistically significant association to ESBL-PE infection. Therefore, strong infection control measures should be needed to block the infection and the dissemination of antimicrobial-resistant bacteria in the study area.

Data Sharing Statement

All data that support the findings of the study are included.

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Disclosure

The authors declare that they have no competing interests.

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