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High Levels of Extended-Spectrum Beta-Lactamases in a Major Teaching Hospital in Ghana: The Need for Regular Monitoring and Evaluation of Antibiotic Resistance

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Abstract.

Infections with bacteria producing extended-spectrum beta-lactamases (ESBLs) are increasing across Africa. This study reports on ESBL-producing *Enterobacteriaceae* as significant causes of infections and antibiotic resistance at Korle-Bu Teaching Hospital in Accra, Ghana. Of 300 isolates examined, 49.3% produced ESBLs. The prevalence of ESBLs was significantly high among isolates from neonates (28 of 43, 65.1%; relative risk = 1.62, 95% confidence interval = 1.33–2.13, $P = 0.002$) and adult patients > 65 years of age (36 of 51, 70.5%; relative risk = 1.89, 95% confidence interval = 1.41–2.40, $P = 0.001$). A marked increase in minimum inhibitory concentrations of ESBL-positive species was noticed compared with those for the other strains. Using these concentrations, we found that 26 (17%) ESBL producers were resistant to two or more antibiotics (aminoglycosides, fluoroquinolones, sulfonamide, and carbapenems) whereas 5 (3.2%) non–ESBL producers were multidrug resistant. Regular ESBL detection and evaluation of antibiotic resistance may help reduce the spread of ESBLs and antibiotic resistance in Ghana.

INTRODUCTION

Favored by their comparatively high effectiveness, low toxicity, and low cost, beta-lactams are prescribed more often than any other antibiotic.[1,2] Heavy use of this antibiotic has resulted in selection of drug-resistant bacteria caused by the production of beta-lactamases, and is now an increasing problem, especially in *Enterobacteriaceae*. Extended-spectrum beta-lactamase (ESBL)–producing *Enterobacteriaceae* are resistant to penicillins, narrow-spectrum and extended-spectrum cephalosporins, except the cephamycins, and aztreonam.[3–5]

Most importantly, in a large prospective study of consecutive patients with bacteremia, treatment failure was observed although the strains were susceptible *in vitro* to the antibiotics used. This failure of beta-lactam antibiotics was attributed to inoculum effect, under-dosing, and failure to achieve pharmacodynamic targets.[4,6] Despite these public health concerns, few studies have reported on the problem of ESBLs in Africa in general and Ghana in particular. In Africa, outbreaks of infection with ESBL-producing enterobacteria have been reported in South Africa,[7–9] Egypt,[10,11] Tunisia,[12] Morocco,[13] Tanzania,[14] and Nigeria.[15] In Ghana, routine ESBL detection is absent. Moreover, no systematic survey of ESBL-producing bacteria has been conducted, and the extent of the ESBL problem remains unclear.

To investigate the extent of the ESBL problem, we examined clinical isolates of *Enterobacteriaceae* collected at Korle-Bu Teaching Hospital (KBTH) in Accra, Ghana. The aim of this study was to determine the occurrence of ESBLs in the hospital and report on the resistance of ESBL-producing and non-producing strains to potentially useful antimicrobial agents.

MATHERIALS AND METHODS

Settings and study design.

Korle-Bu Teaching Hospital has 1,600 beds and intensive care units that are used for surgical, medical, and trauma emergencies. It serves a pediatric and adult population > 3 million in the Greater Accra region, and acts as a major referral health facility for an estimated population of 22 million Ghanaians. The Central Microbiology Laboratory of KBTH processes > 40,000 clinical cultures annually.

Specimens, culture, and identification.

During a three-month period (February–April 2008), 6,105 clinical samples were submitted to the microbiology laboratory of KBTH for bacteriologic investigations. All enterobacterial isolates cultured within the study period as causes of clinical infection were prospectively included in the study. A total of 1,815 samples were culture-positive for various infections. From these samples, 300 non-duplicate isolates of *Enterobacteriaceae* implicated as causative agents of infections were prospectively collected. The isolates were cultured from urine (n = 105), blood cultures (n = 57), wound swabs (n = 40), respiratory specimens (n = 28), high vaginal swabs (n = 59), and aspirates from various anatomic sites (n = 5). All isolates were speciated by using standard bacteriologic procedures[16] and API-20E® rapid test kits (BioMerieux, Marcy l'Etoile, France). Isolates were stored in trypticase soy broth containing 10% glycerol at –20°C until further workup.

ESBL screening.

All isolates were screened for presumptive presence of ESBLs with cefpodoxime (10 μg), ceftazidime (30 μg), and cefotaxime (30 μg) antibiotic disks (MAST Group Ltd., Bootle, United Kingdom) according to the guidelines of the Clinical and Laboratory Standard Institute (CLSI).[17] Antibiotic disk diffusion tests were performed with 0.5 McFarland standard inoculum on Mueller Hinton agar (bioMerieux). Using CLSI screening guidelines, we reported *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* with zone inhibition diameters ≤ 22 mm for ceftazidime and ≤ 27 mm for cefotaxime as positive for ESBL screening. As recommended by the CLSI, a cefpodoxime disk was included in the ESBL screening with breakpoints of ≤ 22 mm for *P. mirabilis* and ≤ 17 mm for *E. coli*, *K. pneumoniae*, and *K. oxytoca* strains. Isolates resistant at these breakpoints were reported as positive for ESBL screening. ESBL screening for other enterobacteria was performed as for *E. coli and Klebsiella* spp. All isolates with a positive result in the ESBL screening test with at least one of three screening agents were selected for ESBL confirmation.

ESBL confirmation.

Screen-positive enterobacteria isolates were confirmed for ESBL production by the combined-disk method according to CLSI guidelines.[17] Zones of inhibition were determined for each isolate to antibiotic disks containing 30 μg of cefotaxime, 30 μg of ceftazidime, and 10 μg of cefpodoxime either alone or in combination with 10 μg of clavulanic acid (MAST Group Ltd.). An isolate was classified as having an ESBL-producer phenotype if the inhibition zone differed by ≥ 5 mm between at least one of the standard antibiotic disks and its corresponding clavulanate combination disk. All the study isolates including *Citrobacter freundii* and

Enterobacter cloacae were tested for ESBL expression as determined by CLSI. *Escherichia coli* control strain ATCC 25922 was used to monitor the performance of ESBL detection agents.

Antibiogram.

The susceptibilities of isolates to the antibiotics ampicillin (10 μg), cefuroxime (30 μg), cefotaxime (30 μg), meropenem (10 μg), tetracycline (30 μg), chloramphenicol (30 μg), cotrimoxazole (25 μg), gentamicin (30 μg), amikacin (30 μg), and ciprofloxacin (5 μg) (Oxoid, Basingstoke, United Kingdom) were determined by using agar disk diffusion according to CLSI reference guidelines and breakpoints.[17] Minimum inhibitory concentrations (MICs) were determined by using the standard microbroth dilution method[18] for meropenem (0.015–32 μg/mL), ciprofloxacin (0.06–128 μg/mL), amikacin (0.125–256 μg/mL), and sulfamethoxazole (4–8,192 μg/mL). Minimum inhibitory concentrations were interpreted according to CLSI guidelines.[17] Reference strains *E. coli* NCTC 10418 and *E. coli* ATCC 25922 were included as quality controls in each susceptibility test.

Statistical analyses.

All statistical analyses were conducted by using SPSS version 16(SPSS Inc., Chicago, IL). Associations between demographic variables (sex, site of infection, and age) and ESBL infections were analyzed by using relative risk and a multinomial logistic regression model when appropriate. Minimum inhibitory concentrations of ESBL-producing isolates were compared with ESBL-negative study isolates by using the chi-square test. *P* values < 0.05 were considered significant.

Ethical considerations.

Isolates recovered from patient specimens were assigned arbitrary numbers. This study was approved by the Ethical and Protocol Review Committee of University of Ghana Medical School College of Health Sciences (Protocol identification no. MSEt/M.3P.7/20072008).

RESULTS

A total of 300 *Enterobacteriaceae* isolates were identified during the study period. *Escherichia coli* and *Klebsiella* species were the most commonly isolated bacteria (n = 231, 77.0%).

Occurrence of ESBL-producing *Enterobacteriaceae*.

Of the 300 enterobacterial isolates, the combined-disk method showed that 148 (49.3%) were characterized by synergy between clavulanate and at least one of the standard antibiotic disks (Table 1). When data were expressed as prevalence within each species, ESBL phenotype was highest among *Enterobacter cloacae* (18 of 24, 75.0%), followed by *K. pneumoniae* (59 of 96, 661.5%), *C. freundii* (6/12, 50.0%), *K. oxytoca* (n = 5 of 11, 45.0%) (high beta-lactamase producers of this species may mimic ESBLs), and *E. coli* (55 of 126, 43.0%,).

Distribution of ESBL-producing *Enterobacteriaceae*.

The urinary tract was the most abundant source (70 of 105, 66.70%) of ESBL producers. When the distribution of ESBL-producing isolates was compared across age groups, ESBL

prevalence was significantly high ($P = 0.001$) among isolates from patients at extremes of ages, specifically neonates (28 of 43, 65.1%; relative risk [RR] = 1.62. 95% confidence interval [CI] = 1.33–2.13, $P = 0.002$) and adult patients > 65 years of age (36 of 51, 70.5%; RR = 1.89, 95% CI = (1.41–2.40, $P = 0.001$).

Susceptibility patterns of isolates.

The susceptibility pattern of *Enterobacteriaceae* to potentially useful antimicrobial agents for ESBL producers and non–ESBL producers by disk diffusion method of sensitivity testing is shown in Figure 1. The ESBL producers comprised a large proportion of the isolates resistant to various antibiotic classes. The ESBL-producing isolates (n = 148) significantly ($P < 0.05$) had increased resistance compared with non–ESBL producers (n = 158) to cotrimoxazole (92.6%, 57.2%), gentamicin (91.2%, 50.6%), amikacin (44.8%, 20.5%), and ciprofloxacin (41.1%, 21.1%), respectively. All isolates were susceptible to meropenem.

Results of MICs in evaluating the burden of resistance attributable to ESBLs against amikacin, ciprofloxacin, meropenem, and sulfonamide are shown in Table 2. The ESBL–non-producing isolates were used to evaluate the impact of ESBLs on antimicrobial drug resistance. The particularly high MICs for the isolates in this study were caused mainly by contributions of ESBL-producing isolates. The ESBL producers had significantly decreased susceptibilities compared with the non–ESBL producers. The MIC_{50} and MIC_{90} values of all antibiotics, except meropenem, were significantly higher for ESBL-positive isolates compared with those for other strains. Meropenem was the most active agent, with an MIC_{90} (mode = 0.5 μg/mL) two-fold lower than that for susceptibility breakpoint.

Some strains expressed resistance (by broth microdilution) to two or more antibiotics (aminoglycosides, fluoroquinolones, sulfonamide, and carbapenems), and were defined as multidrug resistant (MDR). Of the ESBL producers, 26 (17%) were MDR strains, whereas only 5 (3.2%) of the non–ESBL producers were MDR strains. The difference was statistically significant ($P < 0.05$).

DISCUSSION

In the present study, we report an overall high ESBL prevalence of 49.3% during a three-month period. Approximately half of all the isolates from urinary or respiratory tract infections were ESBL producers. The high prevalence may have been caused by the fact that the ESBL problem has existed in our institution for a long time, and lack of awareness may have increased the burden. The prevalence of ESBLs differed considerably between isolates from pediatric and adult patients (Table 3). The ESBL prevalence was significantly higher in isolates from patients at the extremes of ages: neonates (28 of 43, 65.1%; RR = 1.62, 95% CI = 1.33–2.13, $P = 0.002$) and adult patients > 65 years of age (36 of 51, 70.5%; RR = 1.89. 95% CI = 1.41–2.40, $P = 0.001$). In these groups of patients, empirical antimicrobial use is likely to be higher because of responsive medical attention and greater antibiotic pressure, especially in the elderly. Our finding of ESBL producers among *Enterobactericeae* in hospitals is higher compared with that documented in some ESBL-affected institutions in South Africa (36.1%),[9] Tunisia (38.5%)[12] Tanzania (15%),[14] Nigeria (40%),[15] and in many other reviews for Europe (5.4–25%)[19] and the United States (1–25%).[20]

The general antibiotic susceptibility of the study isolates shows an overall high drug resistance prevalence to many routinely tested drugs. It has been the experience at KBTH that

resistance to these drugs among clinical isolates of *Enterobacteriaceae* is high (e.g., tetracycline = 82%, chloramphenicol = 75%, cotrimoxazole = 73%) and the prevalence is increasing.[19] Using MICs, we found that 26 (17%), of the ESBL producers were resistant to two or more antibiotics (aminoglycosides, fluoroquinolones, sulfonamide, and carbapenems, whereas 5 (3.2%) of non–ESBL producers were MDR strains. In this study, the resistance levels in non–ESBL-producing *Enterobacteriacae* (cefotaxime = 29.1%, ceftazidime = 21.9%, gentamicin = 57.2%, cotrimoxazole = 52.6%, and ciprofloxacin = 21.1%) would still be considered high compared with such isolates reported from the European Antibiotic Resistance Surveillance Network.[21] Meropenem was the only antibiotic active against all the study strains and, perhaps, the best choice for empiric treatment. Meropenem has been on the Ghanaian market for a relatively short period of time since 2002. However, systemic meropenem therapy over a period may also favor the selection of meropenem-resistant strains.

Korle-Bu Teaching Hospital acts as a major referral health facility for an estimated population of 22 million Ghanaians. Although the high prevalence and drug resistance levels may be biased by the referral policy of this main hospital in Ghana, the antibiotic resistance levels in these pathogens are extremely worrisome and indicative of heavy antibiotic selection pressure in primary care and in Ghanaian hospitals. In recent years, enterobacteria producing ESBLs have emerged as major pathogens in our institution. In 2007, 39 of 50 blood stream isolates of *Enterobactericeae* involved in an outbreak of septicemia in the neonatal intensive care unit of KBTH were cephalosporin resistant (Codjoe FS, unpublished data). We are unable to determine if the high ESBL prevalence was part of a nosocomial outbreak because of insufficient data on inpatient and outpatient status in relation to culture dates.

Regular ESBL detection, rational antibiotic drug monitoring, and evaluation of drug resistance may help reduce the spread of ESBLs and antibiotic resistance in KBTH. There is a need to strengthen the clinical microbiologic research and diagnostic capacity of health professionals for surveillance of antibiotic resistance, antibiotic consumption, and the quality of antibiotics on the Ghanaian market. The judicious use of antibiotics, especially meropenem, for improved human health should be urgently promoted in Ghana.

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*outlegends*f1*Figure 1. Prevalence of antimicrobial resistance among extended-spectrum beta-lactamase (ESBL)–producing and non-ESBL–producing Enterobacteriaceae at Korle-Bu Teaching Hospital, Accra, Ghana. [a,b,c] indicate significant difference ($P < 0.05$, by chi-square test) in antibiotic susceptibility between ESBL producers and ESBL non-producers for all antibiotics, except ampicillin, tetracycline, chloramphenicol, and meropenem.

TABLE 1

Prevalence of ESBL-producing isolates among members of the family *Enterobacteriaceae*, Ghana*

Species	Distribution of ESBL-producing isolates in specimens (%)									
	Within species	Total	Urine, n = 105	Blood, n =577	Wound, n = 40	Sputum, n = 28	HVS, n = 59	CSF, n = 2	ASP, n = 5	Other, n = 4
Escherichia coli	55/126 (43.7)	55/148 (37.2)	37/67 (56.1)	5/17 (29.4)	4/16 (25)	6/10 (60)	3/14 (21.4)	0/1	0/1	0
Klebsiella pneumoniae	59/96 (61.5)	59/148 (39.8)	24/27 (88.9)	13/26 (50)	6/11 (54.5)	10/23 (43.4)	3/6 (50)	0/1	1/1 (100)	0/1
Klebsiella oxytoca	5/11 (45.5)	5/148 (3.4)	3/3 (100)	0/3	0/2	2/2 (100)	0/1	0	0	0
Enterobacter cloacae	18/24 (75.0)	18/148 (2.2)	2/2 (100)	7/9 (77.8)	4/8 (50)	3/3 (100)	2/2 (100)	0	0	0
Enterobacter aerogenes	2/7 (28.5)	2/148 (1.4)	0	1/1 (100)	1/4 (25)	0	0/1	0	0/1	0
Proteus mirabilis	3/17 (17.0)	3/148 (2.0)	2/3 (66.6)	0	1/10 (10)	0	0/2	0	0/1	0/1
Proteus vulgaris	0/4	0	0/1	0	0/3	0	0	0	0	0
Citrobacter freundii	6/12 (50.0)	4/148 (4.0)	2/2 (100)	0/1	2/4 (50)	1/1 (100)	1/2 (50)	0	0/1	0/1
Citrobacter koseri	0/3	0	0	0/1	0/1	0	0	0	0	0/1
Total (%)	148/300 (49.3)	(100)	70/105 (66.7)	26/57 (45.6)	19/40 (22.5)	22/28 (78.5)	10/59 (16.9)	0	1/5 (20)	0

* ESBL = extended-spectrum beta-lactamase; Total = overall number of ESBL producers in a particular species expressed as a percentage (in parentheses) of the total number of ESBL producers (148) in the study; HVS = high vaginal specimen; CSF = cerebrospinal fluid; Asp = Aspirate; Other = bacteria isolated from specimens not indicated (e.g., ear swab, pus).

TABLE 2

Minimum inhibitory concentrations (MICs) of non-beta-lactams and meropenem for ESBL-producing and ESBL-non-producing enterobacteria strains, Ghana*

Antibiotic/organism	Phenotype†	No. strains resistant at MIC (µg/mL)																MIC_{50}‡	MIC_{90}‡	% Res§
		< 0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	> 1,024			
Amikacin																				
Escherichia. coli	ESBL+	0	0	0	1	2	3	5	3	17	7	2	3	5	3	2	2	8	256	27.2
	ESBL–	2	3	2	8	13	19	4	5	4	5	4	2	0	0	0	0	1	16	8.5
Klebsiella spp.	ESBL+	0	0	1	3	5	5	5	12	12	5	2	5	2	5	2	0	8	256	25.0
	ESBL–	0	2	3	3	11	5	3	3	5	2	1	2	1	0	0	0	1	16	9.7
Other	ESBL+	0	1	1	2	2	1	1	4	2	4	2	1	2	3	2	1	16	512	37.9
	ESBL–	0	1	2	4	9	4	3	5	1	2	2	2	1	2	0	0	1	64	18.4
Ciprofloxacin																				
E. coli	ESBL+	0	1	13	6	6	16	0	4	1	2	3	2	1	0	0	0	1	32	23.6
	ESBL–	0	11	22	12	9	5	6	5	1	0	0	0	0	0	0	0	0.25	2	16.9
Klebsiella spp.	ESBL+	1	4	11	8	13	10	1	6	2	2	4	2	0	0	0	0	0.5	16	26.5
	ESBL–	1	3	13	10	5	3	3	1	1	1	0	0	0	0	0	0	0.25	2	14.6
Other	ESBL+	1	1	3	2	6	8	3	2	3	0	0	0	0	0	0	0	1	8	27.5
	ESBL–	1	3	10	9	5	4	4	2	0	0	0	0	0	0	0	0	0.25	2	15.3
Sulfonamide																				
E. coli	ESBL+	0	0	0	0	0	0	0	0	0	0	0	0	4	8	22	21	512	> 1,024	78.2
	ESBL–	0	0	0	0	0	0	0	0	0	2	8	12	28	10	5	8	128	1,024	18.3
Klebsiella spp.	ESBL+	0	0	0	0	0	0	0	0	0	0	0	0	6	6	31	21	256	> 1,024	81.2
	ESBL–	0	0	0	0	0	0	0	0	0	0	3	3	12	7	10	6	256	1,024	39.0
Other	ESBL+	0	0	0	0	0	0	0	0	0	0	0	1	3	6	12	7	512	1,024	65.5
	ESBL–	0	0	0	0	0	0	0	0	0	1	3	4	16	4	5	5	64	1,024	26.3
Meropenem																				
E. coli	ESBL+	1	4	15	20	10	4	0	0	0	0	0	0	0	0	0	0	0.25	0.5	0
	ESBL–	0	4	20	27	14	5	0	0	0	0	0	0	0	0	0	0	0.25	0.5	0
Klebsiella spp.	ESBL+	2	6	7	23	19	7	0	0	0	0	0	0	0	0	0	0	0.25	1	0
	ESBL–	3	2	21	10	7	0	0	0	0	0	0	0	0	0	0	0	0.125	0.25	0
Other	ESBL+	1	3	8	14	3	0	0	0	0	0	0	0	0	0	0	0	0.25	0.5	0
	ESBL–	0	6	12	18	2	0	0	0	0	0	0	0	0	0	0	0	0.25	0.5	0

* ESBL = extended-spectrum beta-lactamase; *Klebsiella* spp. = *K. pneumoniae, K. oxytoca*; Other = *Enterobacter aerogenes, Enterobacter cloacae, Proteus mirabilis, P. vulgaris, Citrobacter freundii, C. koseri.*

† ESBL+ = strains producing ESBL; *ESBL*– = non–ESBL-producing strains.

‡ $MIC_{50/90}$ = minimum inhibitory concentrations for 50% and 90% of the organisms, respectively, in µg/mL.

§ % Res = percentage resistance.

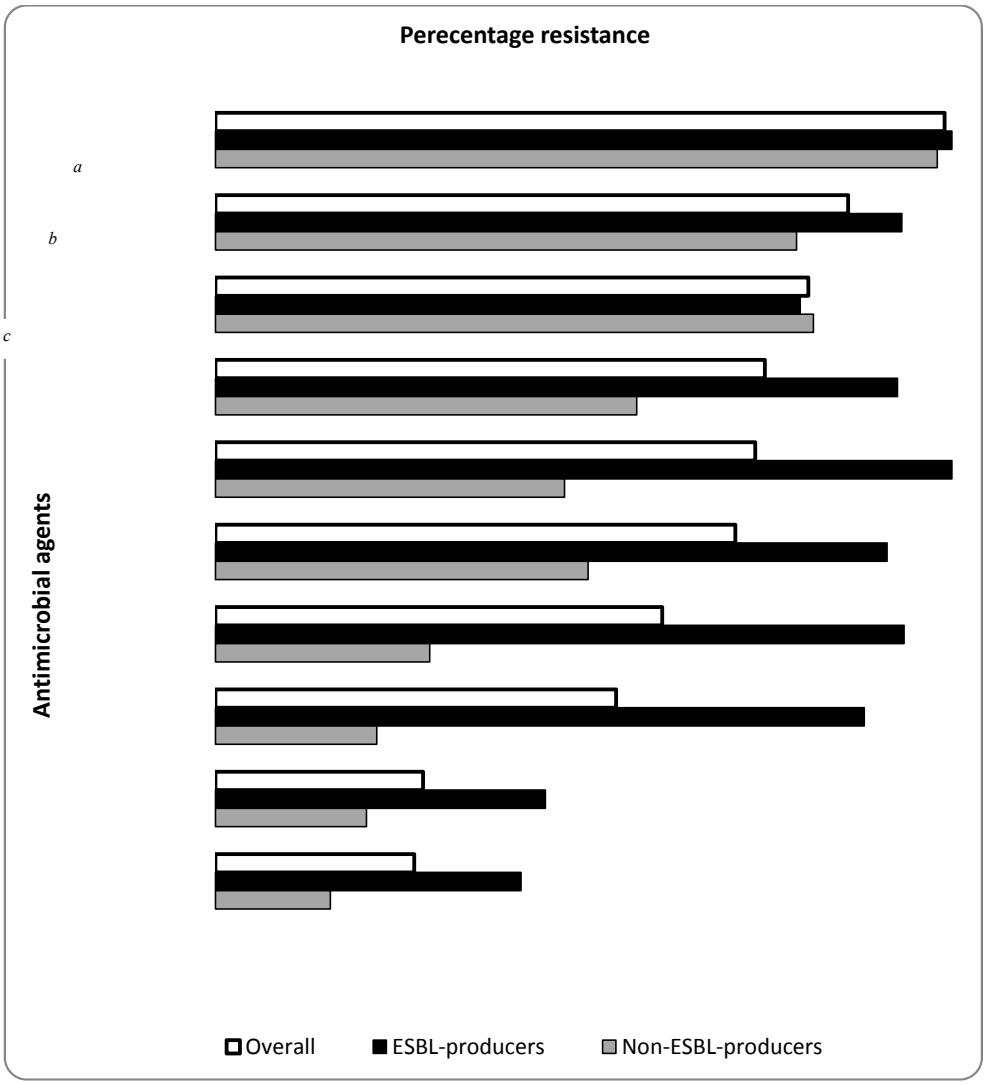
TABLE 3

Demographic factors associated with ESBL infections in Korle-Bu Teaching Hospital, Ghana*

Variable	ESBL (n = 148)		Non-ESBL (n = 152)		Relative risk (95% CI)	*P*
	No.	%	No.	%		
Sex						
M (n = 162)	78	48.1	84	51.8	0.93 (0.75–1.17)	
F (n = 138)	70	50.7	68	49.2	0.93 (0.75–1.17)	0.569
Source of infection						
Urinary tract (n = 105)	70	66.7	35	33.3	1.69 (1.36–2.100)	0.001
Blood (n = 57)	26	45.6	31	54.4	0.89 (0.57–1.42)	0.643
Respiratory specimen (n = 40)	22	55.0	18	45.0	1.23 (0.93–1.62)	0.177
HVS (n = 28)	9	32.1	19	67.9	0.643 (0.38–1.07)	0.53
Wound (n = 59)	20	32.2	39	67.8	0.67 (0.47–0.82)	0.616
Aspirate (n = 5)	1	20.0	4	80.0	0.50 (0.15–1.70)	0.163
CSF (n = 2)	0	0	2	100.0	–	–
Other (n = 4)	0	0	4	100.0	–	–
Age						
≤ 28 days (n = 43)	28	65.1	15	34.9	1.62 (1.33–2.13	0.002
> 28 days – 1 year (n = 41)	7	17.1	15	34.9	0.33 (0.17–0.67)	0.001
> 1–5 years (n = 37)	14	37.8	34	82.9	0.83 (0.54–1.29)	0.348
> 5–15 years (n = 35)	10	28.6	25	71.4	0.62 (0.36–1.06)	0.051
> 15–65 years (n = 63)	24	38.1	39	698.2	0.83 (0.58–1.57)	0.275
> 65 years (n = 51)	36	70.5	15	29.5	1.89 (1.41–2.40)	0.001

* ESBL = extended-spectrum beta-lactamase; CI = confidence interval; HVS = high vaginal swab; CSF = cerebrospinal fluid; Other = bacteria isolated from specimens not indicated (e.g., ear swab, pus).

Figure 1



[a,b,c] Significant difference ($P < 0.05$, Chi-square test) in antibiotic susceptibility between ESBL-producers and ESBL-non-producers were noticed for all antibiotics, except for ampicillin, tetracycline, chloramphenicol and meropenem.