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A cross-sectional study of the antibiotic resistant prevalence of ESBL-producing Enterobacteriaceae in Vietnam

Hung Do Tran[1], Binh Trung Nguyen[2], Hien Quang Tran[3], Hung Gia Tran[4]*

[1]Department of Medical Technology, Faculty of Nursing and Medical Technology, Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam, [2]An Giang Central Hospital, Long Xuyên, Vietnam, [3]An Giang Department of Health, Long Xuyên, Vietnam, [4]Department of Dermato-Venereology, Faculty of Medicine, Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam

ABSTRACT

Introduction: Antibiotic resistance in Enterobacteriaceae producing extended spectrum beta-lactamase (ESBL) is increasing. Accurate evaluation of antibiotic resistance rates in various categories of bacteria assists medical physicians in recommending suitable indications for their medical problems, improving treatment efficiency, and minimizing dangers for patients. As a result, we undertook this research to assess the prevalence of ESBL-producing Enterobacteriaceae as well as the rate of antibiotic resistance in ESBL-producing Enterobacteriaceae.

Methods: A cross-sectional study was conducted on 2716 patients at the An Giang Central General Hospital from June 2020 to June 2021. Data collection was based on interviews and used SPSS 18.0 and GraphPad Prism 9 for data analysis and presentation. Samples included urine, blood, sputum, and pus. Samples were treated with the Phoenix 100 automated machine to separate and identify samples.

Results: The highest rate was 64.8% for *Escherichia coli*, followed by 30.2% for *Klebsiella pneumoniae*. *Proteus mirabilis* and *Klebsiella oxytoca* were found in 4.5% and 0.6% of the samples, respectively. Ampicillin resistance was greatest in *E. coli* (96.5%), *K. pneumonia* (92.4%), and *K oxytoca* (83.3%). The frequency of resistance to the other antibiotics was likewise extremely high, approaching 60%. Tobramycin, Amoxicillin/Clavulanate, Cefoxitin, and Nitrofurantoin were totally resistant to *K. oxytoca* in the ESBL-producing group. *E. coli* and *K. pneumoniae* with ESBL-producing genes also have a high antibiotic resistance rate of more than 50%.

Conclusion: *E. coli* was the most common pathogenic bacteria. Most of the species of bacteria resisted Ampicillin.

Keywords: Antibiotic resistance; extended-spectrum b-lactamase; Enterobacteriaceae

INTRODUCTION

Antibiotic resistance has been a worldwide issue, particularly in developing countries where infectious diseases such as respiratory infections, sexually transmitted diseases, and hospital-acquired infections are common (1). The rise in antibiotic resistance necessitates the development of a new generation of antibiotics, which is costly. According to European Center for Disease Prevention and Control research, extended-spectrum beta-lactamases increased six-fold between 2005 and 2009 (2,3).

Gram-negative bacilli are Enterobacteriaceae rod-shaped bacteria that are 1–5 mm long, have flagella, do not produce spores, and are oxidase negative. *Escherichia coli*, *Klebsiella* spp., *Enterobacteria* spp., and *Proteus* spp. are the most common Gram-negative bacilli that cause sickness in people (4-6). When a bacterium produces extended-spectrum b-lactamases (ESBLs), it develops resistance to a variety of medications, most notably cephalosporins. This is the true cost of Gram-negative bacilli infection treatment. Person-to-person transmission or antibiotic selection can both lead to the acquisition of ESBL-producing bacteria (7). Resistance to quinolone antibiotics such as nalidixic acid, chloramphenicol, and ciprofloxacin has recently been linked to the expression of the blaTEM, blaSHV, qnrA, qnrB, and qnrS genes (8,9). The carbapenem class of antibiotics, which includes imipenem, meropenem, and ertapenem, has remained effective against ESBL-producing bacteria. In contrast, the OXA-48 and NDM-1 genes were linked to increased carbapenem resistance in Turkey in 2016 (10).

The incidence of ESBL-producing Enterobacteriaceae varied by region in Vietnam. Cho Ray Hospital in Ho Chi Minh City, which is the largest general hospital in the

*Corresponding author: Hung Gia Tran, Department of Dermato-Venereology, Faculty of Medicine, Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam E-mail: tghung@ctump.edu.vn

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FACULTY OF HEALTH STUDIES

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south of Vietnam, indicated that the percentage of ESBL-producing strains was 61% for *K. pneumoniae* and 52.6% for *E. coli*. However, we still need an overview of the ESBL-production scenario with a large enough sample size, as well as the reaction to antibiotics presently in use in Vietnam. As a result, our research aimed at determining the prevalence of ESBL-producing gut bacteria strains and their antibiotic resistance rates.

METHODS

We conducted a cross-sectional study of 2716 patients with infectious diseases treated at An Giang Central General Hospital in Vietnam. The sample size was determined using data from a previous study in Vietnam, which found that 53.5% of Enterobacteriaceae produced ESBLs (11). An Giang Central General Hospital is a second-class facility with 900 beds, 28 departments, and a specialized team of over 300 college staff including medical professionals and pharmacists, as well as advanced technology.

Patients over the age of 16 who were diagnosed with an infectious disease and admitted to the hospital for treatment were eligible. The patients gave their consent to participate in the research. Individuals who had received antibiotics before hospitalization were excluded, and the samples did not meet guidelines. Sociodemographic and clinical data (age, gender, admission date, and specimen collection date) and samples were collected by infectious disease physicians. Urine, blood, sputum, and pus samples were collected to determine pathogen identification and antibiotic resistance rates (Figure 1). We followed the sampling protocol to ensure the quality of the samples as follows:

1. Blood samples: Blood samples for the research must be from 8 to 10 mL. To ensure the quality, it was required to transfer to the microbiology laboratory as soon as possible. Samples were kept at room temperature not over than 4 h. Storing in refrigerator was not permitted.
2. us samples: Pus samples included pus of closed lesions (abscesses, pleural fluid, peritoneal cavity, and joints) and pus of opened lesions. These samples would be immediately transferred to the laboratory for culturing or preserved in Stuart or Armies medium for later experiments.

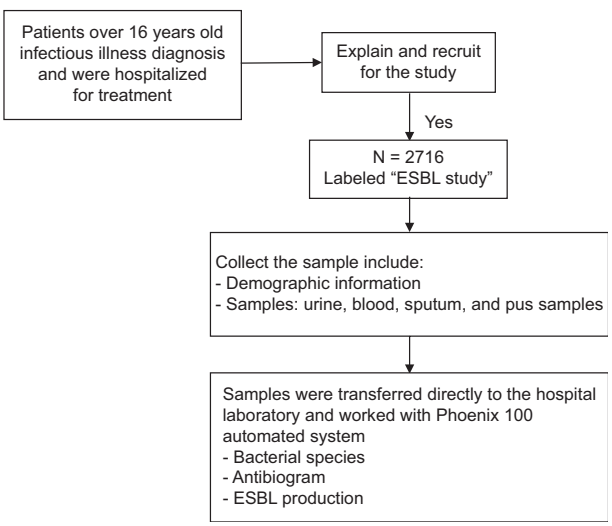

FIGURE 1. Schema of data collection.

3. Sputum samples: Sputum at 1–5 mL was stored in a sterile plastic bottle with a screw cap, avoid mixing with saliva. It was required to transport immediately to the laboratory as soon as possible, because pathogens in the sputum can be overwhelmed by the microflora. Furthermore, it could be stored at 2–4°C but not over than 4 h.
4. Urine samples: Samples had to be the midstream urine in the morning, at this time, bacteria had enough time to multiply during the night in the bladder. It was necessary to discard (approximately 30 mL) of the first urine as this part is often contaminated with bacteria residing in the urogenital region. A 30 mL urine volume was then collected into a wide-mouth sterile vial (approximately 50 mL volume). The urine sample should be brought to the laboratory within 2 h for culture or stored at 4°C for 18 h.

Following inoculation onto blood and MacConkey agar plates, the specimen was smeared onto a clean glass slide, heat fixed, and stained with Gram's stain. The stained smear was examined using an ordinary light microscope's oil immersion lens (×1000).

On blood agar and MacConkey agar, each specimen was inoculated. Blood agar plates were incubated overnight at 37°C with the samples. The bacteria were identified and their antibiotic susceptibility was determined using an Automated Microbiology System (BD Phoenix, Becton Dickinson).

The isolates resistant to ceftriaxone, ceftazidime, and cefotaxime were suspected of producing ESBLs and phenotypic confirmatory tests for ESBL production were performed. According to the CLSI, (2019) guideline, the breakpoints of the minimum inhibitory concentration of ceftazidime, ceftriaxone, and cefotaxime were 2 g/mL.

The cephalosporin/clavulanate combination disk method was used to phenotypically confirm initial ESBL screening test positive isolates in this study. Ceftazidime, ceftazidime plus clavulanic acid, and cefotaxime, cefotaxime plus clavulanic acid disks were placed center to center, at least 25 mm apart, on Mueller Hinton agar. After 16–18 h of incubation at 37°C, any antimicrobial agent with a 5 mm increased zone diameter when tested in combination with clavulanic was considered positive for ESBL production.

The data were analyzed using SPSS 18.0 and all graphs were drawn using GraphPad Prism 9.0. The quantitative variable (age) is organized and presented in the same way as the qualitative variable. The data in tables and graphs are given by frequency (n) and percentage (%).

This study has been approved by the ethical committee of An Giang General Medicine Hospital and the Institutional Review Board of Can Tho University of Medicine and Pharmacy. Informed consent forms discussed and demonstrated the study's purpose, technique, risks, and benefits to patients or their legal representatives. Subjects who agreed to participate in the study completed two forms of informed consent: one for the research team and one for the participants or their representatives.

RESULTS

Females made up 58.5% of the 2716 patients who took part in the study, and the average age was 65.6. We separated the patients into four age categories, with the 61–80

groups having the greatest rate (46.8%) and the 16–40 group having the lowest (7.7%) (Table 1).

We gathered samples from the majority of the hospital departments. The Intensive Care – Emergency department received the most specimens (31.5%), followed by the Internal Medicine department and the Endocrinology department, 21.2% and 15.4%, respectively. Among the samples, urine was the most prevalent (33.2%) (Table 2).

Overall, *E. coli* had the highest rate (64.8%), followed by *Klebsiella pneumoniae* (30.2%). *Proteus mirabilis* and *Klebsiella oxytoca* made up 4.5 and 0.6% of the total, respectively. The most common bacteria found in urine were *E. coli* and *K. pneumoniae*, accounting for 78.5% and 16.8%, respectively. *E. coli* highly found in blood samples accounted for 80.9%, whereas *K. pneumoniae* found in sputum samples accounted for 69.4% (Table 3). We determined that 47.2% of 2716 specimens had ESBL production, with *E. coli* generating the highest number (53.5%) (Table 4).

We determined each strain's resistance rate based on ESBL production. The majority had a high antibiotic resistance rate, but *P. mirabilis* had a lower prevalence, <50% for most antibiotics. Ceftriaxone and Cefepime were the most resistant to by *E. coli* (85.3% for each), followed by Nitrofurantoin (82.4%). Nitrofurantoin and Ertapenem were the most resistant to *K. pneumoniae*, with 86.5% and 84.5%, respectively. Tobramycin, Amoxicillin/Clavulanate, Cefoxitin, and Nitrofurantoin were all completely resistant to *K. oxytoca* (Figure 2).

DISCUSSION

The existence of microorganisms with enhanced antibiotic resistance piques the medical community's interest the most. There was little information available to us on the presence of ESBL synthesis among Enterobacteriaceae bacteria strains. The primary goal of this research was to evaluate the infection rate of ESBL-producing Enterobacteriaceae bacteria strains and the antibiotic resistance rate of these strains in Vietnam to address this information gap. We had 2716 participants with 58.5% women at An Giang General Hospital, Vietnam. At An Giang General Hospital in Vietnam, we had 2716 participants, with 58.5% of them being women. The age group over 61–80 had the greatest rate (47%), with a mean age of 65.6 years. The majority of persons in this age range are retired, have underlying ailments, and are prone to infections, particularly infectious ones. A prior research on ESBL generating Enterobacteriaceae in orthopedic surgery found a frequent age range of 59–78 (12). Furthermore, our research included a large sample size of 2716 people drawn from all departments of a general medical hospital, while prior investigations were restricted to one department or had a lower sample size (12,13).

Sputum, blood, pustules, and urine were all collected as samples, with urine being the most prevalent in our research (33.2%). In recent years, there has also been increased worry about urinary tract infection caused by ESBL-producing Enterobacteriaceae (14,15). The most prevalent germs identified in this investigation were *E. coli* and *K. pneumoniae*. Similarly, prior research on Gram-negative bacteria that produce ESBL found that *E. coli* and *K. pneumoniae* were the most prevalent (13,16). The production of ESBL in *E. coli* has lately increased. It was 53.1% in our research. However, the rate of ESBL generation was substantially greater in other *E. coli* focus study. According to a recent study conducted in Myanmar on pediatric patients, ESBL-producing *E. coli* accounted for 76.4% of all *E. coli* isolates (17). Knaapila et al. (2018), in instance, reported 88% for fluoroquinolone-resistant infections and 62% for third-generation cephalosporin-resistant strains (18).

Our primary objective was to ascertain the resistance rate of Enterobacteriaceae strains that produce ESBLs. Notable, our study was the fact that *E. coli, K. pneumoniae and K. oxytoca* had a significantly higher resistant prevalence to the majority of antibiotics, almost over 50%, including the carbapenem group. Antibiotic resistance is the most critical area of research in bacteria. Antibiotics have been used more frequently in medical treatment in Vietnam over the last decade. In comparison to the other strains, *E. coli* has the most research data. Comparing to a study published in 2019, the resistant rates of some typical antibiotics of ESBL-producing *E. coli* of Iran and Vietnam in our study were ceftriaxone (58.8% vs. 85.3%), ampicillin (73.5% vs.

TABLE 1. Characteristics of the study subjects

	N	Percentage (%)
Sex		
Male	1127	41.5
Female	1589	58.5
Age group		
16–40 years old	214	7.9
41–60 years old	757	27.9
61–80 years old	1277	47.0
>81 years old	468	17.2

TABLE 2. Characteristics of the specimens

Department	Total N	Specimen			
		Sputum *n* (%)	Blood *n* (%)	Pus *n* (%)	Urine *n* (%)
General Medicine	526	228 (43.3)	99 (18.8)	16 (3.0)	183 (34.8)
General Surgery	274	5 (1.8)	27 (9.9)	53 (19.3)	189 (69.0)
Intensive care – Emergency	855	313 (36.6)	283 (33.1)	37 (4.3)	222 (26.0)
Endocrinology	419	19 (4.5)	80 (19.1)	136 (32.5)	184 (43.9)
Operation – Anesthesia resuscitation	362	0 (0.0)	4 (1.1)	357 (98.6)	1 (0.3)
Orthopedics	76	1 (1.3)	3 (3.9)	66 (86.8)	6 (7.9)
Others	204	38 (18.6)	38 (18.6)	12 (5.9)	116 (56.9)
Total	2716	604 (22.2)	534 (19.7)	677 (24.9)	901 (33.2)

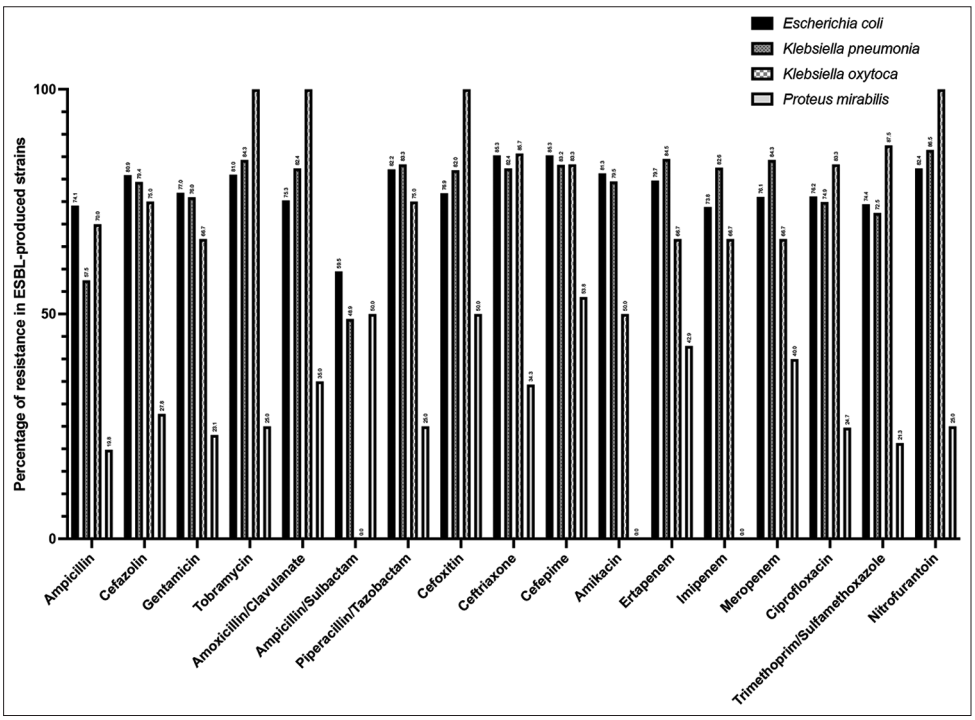

FIGURE 2. Antibiotic resistance rate among Extended Spectrum Beta-Lactamase-producing bacterium species.

TABLE 3. Percentage of 4 types of Enterobacteriaceae strains isolated from 4 types of specimens

Bacteria	Specimen			
	Sputum *n* (%)	Blood *n* (%)	Pus *n* (%)	Urine *n* (%)
Escherichia coli	167 (27.6)	432 (80.9)	453 (66.9)	707 (78.5)
Klebsiella pneumoniae	419 (69.4)	87 (16.3)	163 (24.1)	151 (16.8)
Klebsiella oxytoca	5 (0.8)	2 (0.4)	3 (0.4)	6 (0.7)
Proteus mirabilis	13 (2.2)	13 (2.4)	58 (8.6)	37 (4.1)
Total	604	534	677	901

TABLE 4. ESBL production rate by Enterobacteriaceae strains

Bacteria	ESBL *n*(%)	Non-ESBL *n* (%)	Total
Escherichia coli	941 (53.5)	818 (46.5)	1759
Klebsiella pneumoniae	316 (38.5)	504 (61.5)	820
Klebsiella oxytoca	7 (43.8)	9 (56.2)	16
Proteus mirabilis	19 (15.7)	102 (84.3)	121
Total	1283	1433	2716

ESBL: Extended Spectrum Beta-Lactamase

74.5%), amikacin (50% vs. 81.3%), and amoxicillin/clavulanic acid (41.2% vs. 75.3%), respectively. Notably, the carbapenem group included imipenem (4.9% vs. 73.8%) and meropenem (11.8% vs. 76.1%) (19). Thus, the antibiotic resistance rates in our study were much higher than in the previous one. Besides, the current research found that *K. pneumoniae and K. oxytoca* were more resistant to most antibiotics than E. *coli*. Only *P. mirabilis*, which had the lowest incidence in the ESBL-producing group, exhibited a low resistance rate to popular antibiotics such as ceftriaxone (34.3%), PTZ (25%), ertapenem (42.9%), meropenem (40%), and imipenem (0%). These figures signaled the need for caution when using an antibiotic for treatment.

Our study focused on the laboratory evaluation of antibiotic resistance in ESBL-producing strains to aid physicians in clinical treatment. However, antibiotic response varies according to the disease. Seo et al. demonstrated that PTZ and ertapenem were highly effective against *E. coli*, including ESBL-producing *E. coli*, with a cure rate of 94% for each (14). Harris et al. reported that PTZ (12.3%) did not outperform meropenem (3.7%) in terms of bloodstream infection mortality rate (risk difference, 8.6% [1-sided 97.5% CI, to 14.5%]; P = 0.90 for noninferiority) (20). In addition, Popejoy et al. revealed that the cure rates for levofloxacin and meropenem remained high, with over 80% of urinary tract and intra-abdominal infections caused by ESBL-producing *E. coli* and *K. pneumoniae* being cured (21). According to these studies, the efficacy of PTZ, levofloxacin, ertapenem, and meropenem against ESBL-producing *E. coli* and *K. pneumoniae* remains significant. Meanwhile, the resistant prevalence of those antibiotics was high in our study.

With a high number of individuals, our research might reflect ESBL-producing Enterobacteriaceae infection in Vietnam. As a result, our current research may help guide future work on selecting suitable therapy as well as studies testing the effectiveness of several novel antibiotics in Vietnam, such as sitafloxacin, pivmecillinam, and ceftolozane/tazobactam. These antibiotics have been proven to be effective against ESBL-producing Enterobacteriaceae infections such acute pyelonephritis, lower urinary tract infections, and intra-abdominal infections (21-23). Despite this, empiric treatment, or the clinical response to a particular situation, may vary. This is also the purpose of our future research in Vietnam: to contribute data to aid in antibiotic selection.

CONCLUSION

Infection rates were greatest for *E. coli, K. pneumoniae, P. mirabilis*, and *K. oxytoca*, in that order. Ampicillin resistance was the most prevalent, accounting for the greatest incidence with *E. coli, K. pneumoniae,* and *K. oxytoca*.

P. mirabilis has the highest level of resistance to the antibiotic Trimethoprim-Sulfamethoxazole.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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