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Original Article

Prevalence of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* among clinical isolates in Turaif general hospital, northern borders- Saudi Arabia

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Abstract

Introduction: *Enterobacteriaceae* that produce extended-spectrum beta-lactamase (ESBL) are quickly spreading, posing a threat to world healthcare.

Methodology: 138 gram-negative bacteria were collected from different samples (stool, urine, wound, blood, tracheal aspirate, catheter tip, vaginal swab, sputum, and tracheal aspirate) from hospitalized patients. Samples were subcultured and identified in accordance with their biochemical reactions and culture characteristics. Against all the isolated *Enterobacteriaceae*, an antimicrobial susceptibility test was performed. VITEK®2 system, phenotypic confirmation, and Double-Disk Synergy Test (DDST) had been utilized to identify the ESBLs.

Results: Of the 138 samples studied, the prevalence of ESBL-producing infections among the clinical samples of the present study was 26.8 % (n = 37). *E. coli* was the commonest ESBL producer at 51.4% (n = 19) followed by *K. pneumoniae* at 27% (n = 10). The potential risk factors for the ESBL development that produces bacteria were as follows, patients with the presence of indwelling devices, previous history of hospital admission, and usage of antibiotics. ESBL is statistically ($p \leq 0.05$) higher among the patients with indwelling devices, ICU admission, who had a previous hospital admission in the last 6 months as well as who was given antibiotics (quinolones and/or cephalosporins) in the last 6 months. One hundred thirty-two (95.7%) of ESBL isolates were resistant to amoxicillin, while the lowest resistance was for fosfomycin (15.2%).

Conclusions: ESBL-producing *Enterobacteriaceae* are highly prevalent in Turaif General Hospital setting with some potential risk factors. A strict policy to be made available on the usage of antimicrobials in hospitals and clinics should be established.

Key words: ESBL; beta-lactam antibiotics; *Enterobacteriaceae*; antibiotic resistance.

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Introduction

Bacterial antimicrobial resistance (AMR) is a serious threat to public health. Several reports about the increasing risk of infection caused by antibiotic-resistant bacteria could increase the mortality rate by 2050 worldwide [1,2].

A high level of bacterial resistance which is responsible for different and frequent types of infections in several countries had been reported by The World Health Organization (WHO) Global Antimicrobial Surveillance System (GLASS) [3]. A group of bacteria recently identified and reported by the WHO including AMR bacteria are divided into three main categories according to the impact of these bacteria on the health of human beings and the urgent need for new antimicrobials to face this problem. These categories are critical, high, and medium priority [4-6].

Extended-spectrum β lactamase (ESBL) producing *Enterobacteriaceae* are a bacteria group that lies under the critical category. Their infection is associated with severe infections and even may be fatal [2]. ESBL-producing *Enterobacteriaceae* spread rapidly, which poses a challenge to global healthcare. ESBL has over three hundred variants, making it easy to spread to many world regions with a continued upward trend [7,8]. Healthcare workers are highly concerned with the significant upward trend of ESBL organisms caused by gene mutation [9].

The ESBL-producing feature is the ability of the microorganism to synthesize a B- lactamases. This is a family of enzymes that have efficient hydrolytic activity against B lactam class of antibiotics such as penicillin and cephalosporins. This resistance is acquired by plasmid-mediated mutation encoding for

the parent enzymes, either by amino acid substitution in the active site such as the case for Temonieara (*TEM*; named after patient Temoniera) or sulfhydryl reagent variable (*SHV*; class A) enzymes or by inter bacteria gene transfer like the case of cephalosporinases (class C enzymes) [10,11].

The *Enterobacteriaceae* family's *TEM-1*, *TEM-2*, and *SHV-1* genes are highly mutant, altering the configuration of amino acids [12]. Thus, this confines the enzyme's capability to hydrolyze a wider spectrum of beta-lactam antibiotics, such as penicillin monobactams and oxyimino cephalosporins. Additionally, the enzymes mediated by plasmids are susceptible to beta-lactamase inhibitors. [13].

There are extensive reports of ESBL-producing organisms globally. A 1983 report by Haller *et al.* [5] confirmed the first outbreak of ESBL made in Europe, particularly Germany, the United Kingdom, and Sweden. The role of ESBL-producing organisms as primary agents in transmitting nosocomial infections has been demonstrated by statistics. The widespread of the ESBL enzymes like *CTX-M* beta-lactamases had resulted in an endemic situation in the Middle East, South America, and Europe. Confirmed by evidence that ESBL causes primary infections in Saudi Arabia associated with high mortality and morbidity rates [6,7].

In Saudi Arabia, ESBL-producing bacteria are spreading at an alarming rate. Statistics show that ESBL has a 38% upward projection yearly of ESBL-producing *Enterobacteriaceae* in Saudi Arabia. The central region reported a high frequency of ESBL, and the eastern region reported the lowest frequency rate [9]. A study by Alqasim *et al.* indicates that ESBL-producing *E coli* in Riyadh resulted in a high spread of urinary tract infections (UTIs) at the rate of 7% in 2020 [9]. Sfeir *et al.* added that 20% of *Enterobacteriaceae* resist beta-lactam antibiotics when treating ESBL infections. Ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole are the least effective drugs in treating ESBL. It is necessary to change ESBL treatment because of the highly resistant nature of ESBL-producing *Enterobacteriaceae* . This report provides an in-depth analysis of the prevalence of ESBL-producing *Enterobacteriaceae* and recommends efficient control measures for its prevention [14]. This study aimed to determine the prevalence of *Enterobacteriaceae* in clinical samples obtained from Turaif General Hospital in Northern Saudi Arabia, screening the antibiotics profile against the most used antimicrobials, and calculating the prevalence rates of ESBL among isolated samples.

Methodology

Design and setting

This cross-sectional study was conducted in the microbiology lab of the clinical analysis department at Turaif General Hospital in Northern Saudi Arabia from the period between January to June 2021.

Subjects

A non-probability sequential sample was taken from various clinical sites of infection from hospitalized patients in various wards considering the following measures; age, sex sample types, infection clinical signs, hospital admission duration, antibiotic therapy history) in the last 6 months (cephalosporins and quinolones), indwelling devices, such as an intravenous catheter(IV), urinary catheter, wound drains, orthopedic prosthesis, central venous pressure(CVP) catheter and endotracheal tubes (ventilator), causes of disturbed systemic or local immune status, such as old age (> 50 years), malignancy, diabetes mellitus, burn, presence of surgical sutures or pressure ulcers, ICU admission and previous hospital admission in the last six months.

Inclusion criteria

The infection signs and symptoms became apparent after > 48 hours following hospital admission, such as purulent discharge, turbid urine, and Chest X-ray (CXR) consolidation; especially for patients who had indwelling medical devices, such as an IV catheter, urinary catheter, wound drains, orthopedic prosthesis, central venous pressure (CVP) catheter and endotracheal tubes (Ventilator); with local or systemic manifestations of infections associated with the indwelling devices.

Exclusion criteria

1. Pre-admission infection presence (proved by the history and clinical examination on admission).
2. Infection symptoms appeared within the first 48 hours after the hospital admission.
3. Patients who were not willing to cooperate.

Ethical approval

Bioethical approval was obtained from the local committee of bioethics (LCBE) of Jouf University, Saudi Arabia, (LCBE No: 02-07-42), and from the Saudi Ministry of Health, National Ethics Committee, Northern Borders Region No (H-09-A-51).

Sample collection and transport

Several samples were collected from different clinical sites of infection, such as mid-stream urine, suction tip, pus, and blood specimens.

All the participants provided written consent. In accordance with the standard microbiological methods in the microbiology laboratory of Turaif General Hospital, all the samples were collected, and in accordance with the manufacturer's instructions, all the media included in this study were prepared.

On nutrient, blood, MacConkey's medium, and Cystine–lactose–electrolyte-deficient agar (CLED) agar (Oxoid Ltd, Basingstoke, Hampshire, UK), all the samples were directly cultured. Media were prepared according to the manufacturer's instructions. Blood samples were cultured overnight at 37 °C in brain heart infusion broth (Oxoid Ltd Basingstoke, Hampshire, UK). A drop of the inoculated broth was then cultured on MacConkey and blood agar and incubated at 37 °C. Colony morphology, gram-stained films, and biochemical reactions had been utilized to identify grown colonies.

Identification and susceptibility tests

By the usage of the automated biomérieux VITEK® 2 compact system, identification, and susceptibility had been carried out. For the identification of gram-negative bacteria, GN cards with different substrates had been utilized. For detection of antimicrobial susceptibility, antibiotic susceptibility card AST-N91 containing antibiotics for detection of ESBL (cefotaxime, cefotaxime with clavulanic acid, ceftazidime, and ceftazidime with clavulanic acid) had been utilized.

ESBL-producing *Enterobacteriaceae* detection involves two steps, the first is a screening cephalosporin test that looks for resistance or decreased sensitivity, hence identifying isolates that are likely to host ESBLs, and the second is a confirmation test that evaluates the synergy between an oxyimino cephalosporin and clavulanic acid, allowing isolates with ESBLs to be distinguished from those that are resistant for other reasons.

ESBL Screening

Susceptibility of *Enterobacteriaceae* isolates to different antimicrobial agents was tested by the method of disk diffusion which was also had been utilized as a screening test for the ESBLs production by noting specific zone diameters (around B lactam disks) that indicate a high level of suspicion for ESBL production (for ceftazidime and cefotaxime zone diameter ≤ 14mm while for aztreonam ≤ 15mm) according to the CLSI guidelines [15].

ESBL disk confirmation tests

Phenotypic confirmatory test

For phenotypic confirmation of the presence of ESBL ceftazidime (30 µg) and cefotaxime (30 µg) alone or in combination with clavulanic acid (10 µg) were used. If the increase in zone diameter ≥ 5 mm for either of the cephalosporin discs and their respective cephalosporin / clavulanic acid disc were interpreted as ESBL producers [15].

The Double-Disc Synergy Test (DDST)

Disk containing cephalosporins cefotaxime (30µg) and ceftazidime (30µg) was placed next to a disk containing clavulanic acid (amoxicillin/ clavulanic acid). After overnight incubation at 37 °C isolates were considered as ESBL producing bacteria when the inhibition zone of the disk of the 3rd generation cephalosporins is increased towards the amoxicillin /clavulanic acid disk or when the single antibiotic disc is not inhibitory but inhibitory in case of the two antibiotics are combined [16].

Statistical analysis

On a compatible personal computer, the SPSS program (Computer Statistical Package for Social Scientists) (SPSS, Version 22.0. Inc., Chicago, IL, USA) in Windows 10.0 had been utilized. Descriptive variables were presented as frequency and percentages. To identify the potential risk factors for ESBL organism development, a regression analysis was performed. An odds ratio (OR) that does not include a null value and a *p* value is considered statistically significant when it measures less than 0.05.

Results

This study lasted six months, from January to June 2021. During the six months, different samples were collected from 138 patients with clinically suspected nosocomial infections, from different departments of Turaif General Hospital, Northern Borders-Saudi Arabia.

During this period, a total of 138 clinical samples were collected. 35 (25.4%) were urine samples, and 32 (23.2%%) were wound samples. Blood samples were 21(15.2%). Sputum, catheter tip, vaginal swap, and stool were 20 (14.5%), 18 (13.0%), 7 (5.1%), and 5(3.6%), respectively. After being processed and cultured on suitable media under optimal incubation

Table 1. Distribution of ESBL among different samples (N = 138).

Sample	No (%)	ESβL Producing isolates (N = 37)
Urine	35 (25.4)	16 (43.2)
Wound and/or Pus	32 (23.2)	9 (24.3)
Blood	21 (15.2)	4 (10.8)
Sputum & Endotracheal aspirate	20 (14.5)	4 (10.8)
Catheter tip	18 (13.0)	2 (5.4)
Vaginal swap	7 (5.1)	2 (5.4)
Stool	5 (3.6)	0
Total	**138**	**37 (28.8)**

conditions, samples were examined in the microbiology laboratory of Turaif General Hospital (Table 1).

ESBL distribution among different samples showed that it was most commonly isolated from urine samples 16 (43.2%) followed by sputum (24.3%). It was isolated from wound, blood culture, and endotracheal aspirate catheter tips, 10.8%, 10.8%, 5.4%, and 5.4%, respectively (Table 1).

Regarding the potential risk factors for infection with ESBL *Enterobacteriaceae* in our study, the risk is statistically higher ($p \leq 0.05$) among the patients with indwelling devices, ICU admission, who had a previous hospital admission in the last 6 months as well as who were given antibiotics (quinolones and /or cephalosporins) in the last 6 months (Table 2).

The prevalence of infection by ESBL-producing bacteria among the clinical samples of the present study was 26.81% (n = 37). Nineteen (51.4%) were *E. coli*, 10 (27%) were *K. pneumonia* and 8 (21.6%) were *Proteus mirabilis* (Table 3).

In accordance with the Clinical Laboratory Standard Institute (CLSI) guidelines, the total of the isolated *Enterobacteriaceae* was screened by the method, disk diffusion. Out of which, 37 (26.8%) were found to suspected ESBL produces, 101 (73.2%) gave negative results. All the isolates also were subjected to a double disk synergy test. 33 (23.9%) were positive and 105 (76.1%) were negative. 37 (26.8%) were positive by the VITEK® 2 compact system and 101

Table 3. Distribution of ESBL-producing bacteria among different species.

Species	ESBL Number (%)
Escherichia coli	19 (51.4)
K. pneumoniae	10 (27.0)
Proteus mirabilis	8 (21.6)
Total	**37**

Table 2. ESBL producing Enterobacteriaceae and its potential risk factors.

Variable	ESBL (N = 37)	Non-ESBL (N = 101)	Odds Ratio	95% Confidence interval	*p* -value
Gender					
Male	20 (25)	60 (75)	0.80	0.38-1.71	0.71
Female	17 (29.3)	41 (70.7)			
Age group					
Less than 60 years	11 (20)	44 (80)	0.55	0.24-1.23	0.20
60 and above	26 (31.3)	57 (68.7)			
Indwelling devices*					
Yes	24 (44.4)	30 (55.6)	2.78	1.28-6.04	**0.01**
No	13 (15.5)	71 (84.5)			
Duration of hospital admission					
< 7 days	18 (25.7)	52 (74.3)	0.89	0.42-1.89	0.84
>7 days	19 (27.9)	49 (72.1)			
ICU Admission					
Yes	11 (33.3)	22 (66.7)	1.47	1.08-2.02	**0.043**
No	26 (24.8)	79 (75.2)			
Previous hospital admission (last six months)					
Yes	19 (39.6)	29 (60.4)	2.62	1.21-5.69	**0.016**
No	18 (20)	72 (80)			
History of antibiotics (cephalosporins and quinolones) in the last six months					
Yes	22 (40)	33 (60)	3.02	1.39-6.57	**0.005**
No	15 (18.1)	68 (81.9)			
Disturbed systemic or local immune status**					
Yes	14 (23.7)	45 (76.3)	0.76	0.35-1.63	0.561
No	23 (29.1)	56 (70.9)			

* IV catheter, Urinary catheter, Wound drains, Orthopedic prosthesis, CVP catheter & endotracheal tubes (Ventilator) ** Malignancy, diabetes mellitus, Burn, presence of surgical sutures or pressure ulcers. N B: *p* value less than 0.05 is considered statistically significant.

(73.2%) were negative. Only 4 isolates were not detected by the double disk synergy test. The methods for ESBL detection were compared in this study. High agreement was found between VITEK® 2 system and screening by disk diffusion method with a statistically non-significant difference between the three methods used (Table 4).

One hundred thirty-two (95.7%) of ESBL isolates were Amoxicillin resistant, and 92.8% were Azithromycin resistant while the lowest resistance was for Fosfomycin (15.2%) (Table 5).

Discussion

The WHO celebrates "World Antimicrobial Awareness Week" every year from the 18th –the 24th of November. This celebration aimed to increase awareness about antibiotic resistance and better use of antibiotics among the public, healthcare workers, and other stakeholders [17]. Also, the WHO has initiated global integrated surveillance and approach to handle the ESBL-producing *E. coli* [18]. The above actions and approaches of the WHO reinstates the importance of managing ESBL-producing organisms in hospitals and other healthcare settings. The purpose of this study was to determine the ESBL prevalence-generating organisms and their risk factors in Turaif general hospital on the northern border of the KSA. This study also attempted to find the pattern and resistant status of commonly used antimicrobials in the same hospital.

The prevalence and incidence rate of ESBLs producing organisms has vast differences around the world [19-22]. These differences are attributed to the types of healthcare settings, availability of healthcare facilities, knowledge, attitude, and practice of antibiotics by the public and healthcare workers, and so on [23]. The lowest prevalence is reported in European and North American countries (4.6% to 7.5%), while the highest prevalence is reported in Asian countries, especially Southeast Asian countries (29% to 51.3%) [12,24].

The present study was done with clinical samples from Turaif general hospital. A total of 138 clinical samples were collected, 35 (25.4%) were urine samples, 32 (23.2%%) were wound samples, blood samples were 21 (15.2%), sputum, catheter tip, vaginal swap, and stool were 20 (14.5%), 18 (13.0%), 7 (5.1%), and 5 (3.6%), respectively.

Distribution of ESBL among different samples showed that it was most commonly isolated from urine samples 16 (43.2%) followed by sputum (24.3%). It was isolated from wound, blood culture, endotracheal aspirate, and catheter tips, 10.8%, 10.8%, 5.4%, and 5.4% respectively.

The ESBL-producing infection prevalence between the present study clinical samples was 26.81% (n = 37) Nineteen (51.4%) were *E coli*, 10 (27%) were *K. pneumonia* and 8 (21.6%) were *Proteus mirabilis*.

The present study revealed that ESBLs producing organisms were significantly higher among the patients with indwelling devices (IV catheter, urinary catheter, wound drains, orthopedic prosthesis, CVP catheter, and endotracheal tubes), ICU admission, previous history (within last 6 months) of hospital admission and usage of antibiotics (quinolones and cephalosporins). Few studies done around the world in the past also found a similar potential risk factor for the ESBL-producing organism's development [25,26]. In addition to the above risk factors and in contrast to our study, some of the authors have found increasing age, male gender, and disturbed immune status are significantly the potential risk factors [27-30]. These differences are due to various reasons such as the types of samples included in their study, settings in which the research was conducted, and so on.

In our study, the ESBL-producing organism prevalence was 26.81%. Other studies done by Alqasim *et al.* 2018 and Abu Taha *et al*. in 2018 have found a

Table 5. Resistance profile of the commonly used antimicrobials from different isolates (n = 138).

Antimicrobial	No (%)
Amoxycillin	132 (95.7)
Azithromycin	128 (92.8)
Clindamycin	110 (79.7)
Imipenem	105 (76.1)
Ciprofloxacin	98 (71.0)
Levofloxacin	91 (65.9)
Gentamycin	62 (44.9)
Trimethoprim- Sulfamethoxazole	46 (33.3)
Tetracycline	37 (26.8)
Fosfomycin	21 (15.2)
Total	138

Table 4. Comparison of disk diffusion method, Double disk test (DDT) and Vitek for detection of ESBLs among 138 *Enterobacteriaceae.*

Method	Disk diffusion	Double -Disk synergy test	VITEK® 2 compact system	*p* value
ESBL +ve	37(26.8)	33(23.9)	37(26.8)	
ESBL-ve	101(73.2)	105(76.1)	101(73.2)	> 0.05
Total	138	138	138	

$p > 0.05$ statistically non-significant.

slightly higher prevalence (33% and 38.4%) of ESBL-producing isolates [31,32]. This contrasting result is due to the types of clinical samples. In our study, we have taken all types of samples such as urine, sputum, etc., while Alqasim *et al.* analyzed only urine samples. Another study done by Reuland *et al.* in Amsterdam has found a lower proportion (8.6%) of ESBL-producing bacteria [33]. This contrast is due to the setting of the research. The present study has analyzed samples from the general hospital and Reuland *et al.* have done it from the community settings. Similar to our study, a study done by Kandeel in 2014 also stated almost the same prevalence [34].

The present study revealed *E. coli* was the commonest ESBLs- producing organism (51.4%) followed by *K. pneumoniae* (27.0%). Most of the studies around the world also revealed that *E. coli* is the most common ESBL-producing organism and consist of more than half of all ESBL-producing organism [15,17,18,35,36]. In a study by Hameed *et al.*, a high prevalence rate of B lactamase-producing *K. pneumoniae* was observed [37]. Different studies reinstate the importance of the WHO's initiation of the global integrated surveillance and approach to handling the ESBL-producing *E. coli* [11].

The methods for ESBL detection were compared in this study. High agreement was found between VITEK® 2 compact system and screening by disk diffusion method with a statistically non-significant difference between the three methods used. We recommend that screening for ESBL production by disk diffusion should be joined to routine culture and susceptibility testing especially when rapid results and low costs are needed.

Antimicrobial resistance is one of the biggest global challenges for the healthcare system. More than 2.8 million people get antibiotic-resistant infections and about 35 thousand people due to antibiotic-resistant infections in the USA alone, stated by the Centers for Disease Prevention and Control (CDC), USA [38]. This states the importance of the prevention and control of antimicrobial resistance. The present study found that highly resistant bacterial strains were found against a majority of the commonly used antibiotics. The highest resistance was present with amoxicillin (95.7%), while the lowest resistance was present with Fosfomycin (15.2%). Several studies done in the hospital setting around the world and KSA found similar findings [39,40]. But the studies done by some of the authors in the community settings have found lower levels of resistance against these commonly used antibiotics [41,42].

Despite the best efforts and with the use of the standard methodology in the present study, certain limitations need to be considered while interpreting the results. Firstly, this study was a cross-section study design, and it finds only the association between potential risk factors, not the causations. Secondly, some of the details were self-reported. Hence, the limitations related to self-reported data are to be considered such as time distortion, recall bias, and subjective base. Finally, this study was done in a single center (Turaif general hospital) of one province (northern border region) of the KSA. Hence, the findings of this study may not reflect the entire region of the KSA.

The high prevalence and distribution of ESBLs among different strains reflect the rapid dissemination of plasmids encoding ESBLs among distinct strains and genera, which is generated by antibiotic selection pressure. This prevalence poses a problem that requires urgent application of strict infection control measures, restriction of the use of oxyimino-cephalosporins, and antibiotic cycling and /or switching to different classes of antibiotics

Conclusion and Recommendations

Our study results suggest that ESBL-producing organisms are highly prevalent in Turaif general hospital setting. The potential risk factors for the development of ESBL-producing organisms were patients with the presence of indwelling devices, ICU admission, previous history of hospital admission, and usage of antibiotics. Also, highly resistant bacterial strains were found against the majority of the commonly used antibiotics. Hence, effective programs such as the formation of an active surveillance team, diagnostic, and antibiotic stewardship are to be activated in the hospital.

A strict policy to be made available on the usage of antimicrobials in hospitals and clinics should be established. Continuous review of the progress of the newly instituted programs to be done. This can be done through regular auditing from internal and external stakeholders. Furthermore, a multicentric study should be done in the KSA to find the national-level prevalence of ESBLs producing organisms and their risk factors.

This high prevalence of ESBL-producing *Enterobacteriaceae* poses a problem that requires the urgent application of strict infection control measures restriction of the use of oxyimino-cephalosporines and antibiotic cycling and /or switching to different classes of antibiotics

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