American Journal of Epidemiology and Infectious Disease, 2017, Vol. 5, No. 1, 14-20
Available online at http://pubs.sciepub.com/ajeid/5/1/3

DOI:10.12691/ajeid-5-1-3

Beta-lactamase Producing Bacteria in Community and Hospital Setting in Riyadh: Occurrence, and Susceptibility to Antibiotics

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Abstract *Background:* Extended-spectrum β-lactamase producing bacteria (ESBL) poses an increasing challenge to both public health and hospital infection control services. *Objective:* To determine the prevalence of ESBL producing bacteria, types of infection they cause and their susceptibility patterns to antibiotics in hospital and community settings. *Settings and Design:* This is a cross-sectional study that was conducted at a Medical City in Riyadh. *Methods:* All clinical specimens with positive culture for Gram-negative bacteria were collected from the microbiology laboratory for the year 2013. When bacteria are identified as ESBL strain, the antimicrobial susceptibility is analyzed. Demographic data were collected from patients' records. *Results:* Overall, 763/6993 (10.9%) were ESBL producing strains from all gram negative bacteria. The highest detection of ESBL bacteria were from specimens of patients over sixty years (34.2%), and 23.7% were from 0-<15 year old. The most frequently detected bacteria was *E.coli* (76.5%) (Significantly higher among outpatients 54.5%) with highest detection from urine, skin swab, blood, wound and ulcer specimens, followed by *K .pneumonia* (23.1%) (Significantly higher among inpatients 69.3%) with highest detection from respiratory specimens including sputum. The resistance pattern to antimicrobials was (75.5%, 81.3%) to trimethoprim/sulfamethoxazole, (69.7%, 42.6%) to ciprofloxacin, (38.9%, 58.5%) to gentamicin and (8.7%, 30.7) to piperacillin/tazobactam (*E.coli, K. pneumonia* respectively). However, very high sensitivity to imipenem and meropenem was reported for both bacteria. Generally, ESBL bacteria isolated from outpatients showed significantly higher resistance to ciprofloxacin than the isolates from inpatients (p=0.02), conversely is detected with piperacillin/tazobactam (p<0.0001). *Conclusion:* Currently, carbapenems and amikacin are the first line antibiotics that can be used for the treatment of ESBL bacterial infections in both settings. Since ESBL bacterial resistance pattern is increasing, periodical monitoring of antimicrobial susceptibility of isolated ESBL bacteria, and rotating the use of the effective antimicrobial drugs according to guidelines of antimicrobial stewardship programs should always be considered.

Keywords: *ESBL bacterial infections, hospital setting, community setting, antimicrobial susceptibility*

Cite This Article: Najwa Al-Mously, Lamiaa Z. Abu Zaid, and Shazia Mukaddam, "Beta-lactamase Producing Bacteria in Community and Hospital Setting in Riyadh: Occurrence, and Susceptibility to Antibiotics." *American Journal of Epidemiology and Infectious Disease*, vol. 5, no. 1 (2017): 14-20. doi: 10.12691/ajeid-5-1-3.

1. Introduction

The global dissemination of extended-spectrum β-lactamase producing Enterobacteriaceae (ESBL) poses an increasing challenge to both public health and hospital infection control services [1]. ESBL producing bacteria are frequently resistant to multiple antimicrobial agents due to their ability to produce plasmid-mediated β-lactamases which are capable of hydrolyzing a wide range of expanded-spectrum β-lactams including monobactams and third-generation cephalosporins, but they are inactive against cephamycins and carbapenems [1,2,3]. Resistance to additional classes of antibiotics such as trimethoprim-sulfamethoxazole, aminoglycosides and quinolones has also been documented, and this complicates therapy and limit treatment options [4,5]. In addition to the increase in the incidence of hospital acquired infections, in many parts of the world community acquisition of ESBL-producing Enterobacteriaceae infection appears to be responsible for a proportion of these infections [5,6,7,8]. It was shown that the community could be a reservoir of these ESBL-producing bacteria and enzymes [9].

The most common ESBL-positive species are *Klebsiella pneumoniae* and *Escherichia coli*, but all enterobacteria can harbor plasmid-mediated resistant

ESBL genes [10]. ESBL-positive isolates of *Proteus mirabilis* have been also reported from different countries in the world [11]. ESBL producing organisms cause a wide spectrum of clinical diseases ranging from colonization to wide variety of infections such as urinary tract infections, bacteremia, and other sites of infections [4,9,12]. It has been reported that previous exposure to antibiotic use, residence in a long term care facility, recent hospitalization, age ≥65 years were found to be factors associated with ESBL gram negative bacterial infection. [13]. Patients infected with ESBL-producing bacteria may have a higher mortality rate and may require significantly longer hospital stays and increased hospital charges [14].

The prevalence of bacterial isolates expressing the ESBL phenotype varies across different geographical regions with low rates range of 3-8 % reported in Sweden, Japan and Singapore compared to higher prevalence rates range of 34-60% in Portugal, Italy, New York, Latin American countries, and Turkey [15]. In the Arabian Peninsula, reported ESBL prevalence range from 8.9-41% in Saudi Arabia, Kuwait, and United Arab Emirates [16,17,18,19].

At king Fahad Medical City hospitals (KFMC) an increasing number of infections caused by ESBL bacteria have been identified over the years but no clear data regarding characteristics of these infections are available. Monitoring the ESBL prevalence and type in enterobacteria of clinical interest may contribute to delineating the breadth of the problem and to defining appropriate therapeutic options [20]. We previously reported on antimicrobial susceptibility patterns of ESBL *E. coli* causing urinary tract infections isolated from community and hospital settings from 2011 to 2012 [4]. In the present study we seek to determine the incidence of all ESBL producing bacteria in hospital and community settings (inpatients and outpatients), and to identify the types of infection they cause and their susceptibility patterns to antibiotics.

2. Materials and Methods

2.1. Study Design

A prospective observational study.

2.2. Setting

This study was conducted at King Fahad Medical City Hospital (KFMC), which is an academic and tertiary health care facility that includes four hospitals and four medical centers in Riyadh, Saudi Arabia.

2.3. Ethical Approval

Ethical approval was obtained from Institutional Review Board-IRB at KFMC (IRB Number: 12-213).

2.4. Data Collection

Data of all isolated Gram-negative bacteria from clinical specimens were collected from the microbiology laboratory for the period from January 2013 to end of December 2013. The in vitro susceptibility for antimicrobial drugs was collected only for the ESBL bacteria isolated. All patients who have positive cultures with SEBL infections were included in this study, and their data were collected from patients' records. Repeated samples for the same patient were excluded.

Bacteria were identified to the species level, and antimicrobial susceptibility testing was done with an automated microbiology system (Phoenix; BD). The results of the antimicrobial susceptibility tests were interpreted according to the guidelines of the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards) [21]. The most common method of testing for ESBL was used which is screening for reduced susceptibility to cefoxitin, ceftazidime, ceftriaxone, and cefepime. The phenotypic confirmatory testing was carried out by demonstrating a synergistic effect between an indicator cephalosporin and β-lactamases inhibitor that is clavulanic acid [22,23].

3. Results

From January 2013 to end of December 2013, a total of 6993 patients reported to have positive cultures with gram-negative. Overall, 763/6993 (10.9%) non-replicate isolates were confirmed to be ESBL producing strains. The distribution according to settings showed that 5.3% (372/6993) of them were outpatients and 5.6% (391/6993) were inpatients (Figure 1).

Out of the 763 confirmed infections with ESBL producing strains, 60.2% of them were females, 23.7% were less than 15 years old, and more than one third (34.2%) were 60 years or above (Table 1).

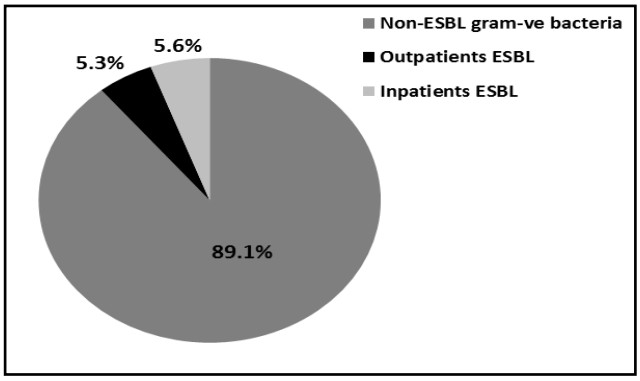


Figure 1. Incidence of ESBLs producers in the year 2013 at KFMC

Table 1. Demographic characteristics of the study sample

Variable	No.	(%)
Gender:		
Female	459	-60.2
Male	304	-39.8
Age (years):		
0-<15	181	-23.7
15-<30	96	-12.6
30-<45	99	-13
45-<60	126	-16.5
60+	261	-34.2
Total	763	-100

The most frequent bacteria were *Escherichia coli* (76.5%). *K. pneumonia* represented 23.1%, and *Proteus* was identified in three patients only (0.4%) from the inpatients, *E. coli* was significantly higher among isolates from the outpatients (54.5%), while *K. pneumonia* was significantly higher (69.3%) in inpatients (nosocomial infection) (Table 2).

The distribution of ESBLs producing E. coli and K. pneumonia according to the type of specimen was shown in Figure 2. High percentages of *E. coli* were isolated from urine (83.7%), blood (67.4%), wound and ulcer swab (65.5%), sterile body fluids and CSF (62.5%), skin swab (73.3%), and abdominal drain (60%). While, *K. pneumonia* was isolated more frequently from respiratory sample (65.2%) and sputum (58.3%). Other specimen included eye and ear swabs, pelvic aspiration, abscess, prosthetic device, and tissue biopsy.

Urine was the major source of ESBL producing strains in both outpatients (83.1%; 309/372) and inpatients (54.7%; 214/391) (data not shown). Figure 3 shows that; 59.1% of urine specimens were originating from the outpatients. However, two thirds (66.3%) of the blood specimen and 67.2% of the wound & ulcer swabs were inpatients. It is worthy of note that all the respiratory samples (23 cases) and the abdominal drains (10 cases) were inpatients. Similarly, over 80% of "sterile body fluid and CSF" and sputum were also from inpatients.

Table 2. Types of extended-spectrum beta-lactamase producing bacteria isolated from outpatients and inpatients

ESBLs	Outpatients (Total=372)		Inpatients (Total=391)		Total		P-value
	No.	(%)	No.	(%)	No.	(%)	
E. Coli	318	(54.5)	266	(45.5)	584	(76.5)	
K. pneumoniae	54	(30.7)	122	(69.3)	176	(23.1)	<0.0001
Proteus	0	(0)	3	(100.0)	3	(0.4)	

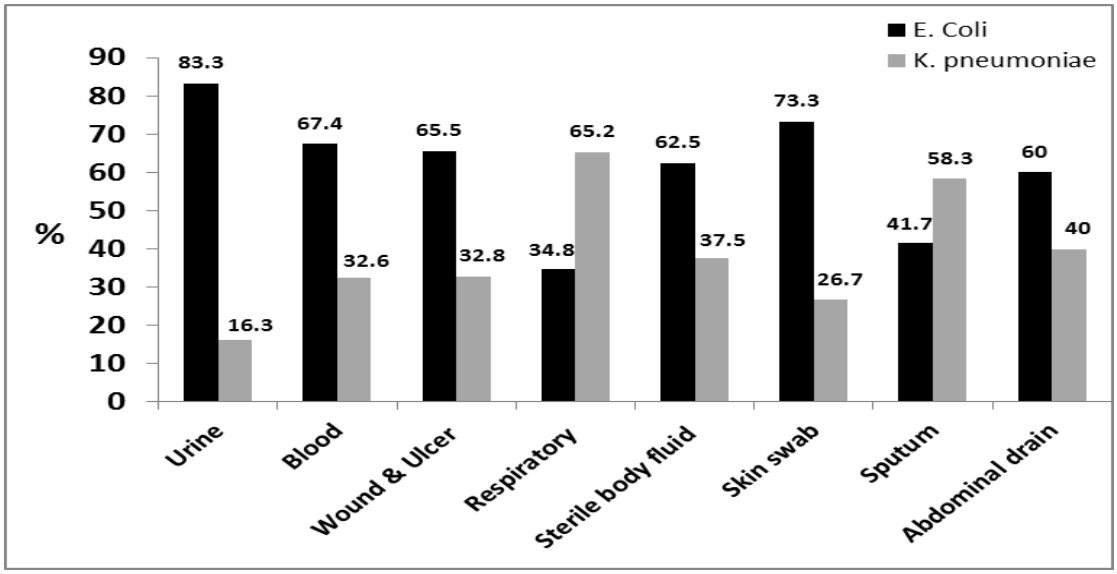


Figure 2. Distribution of ESBLs isolates among different types of specimens in percentage (%)

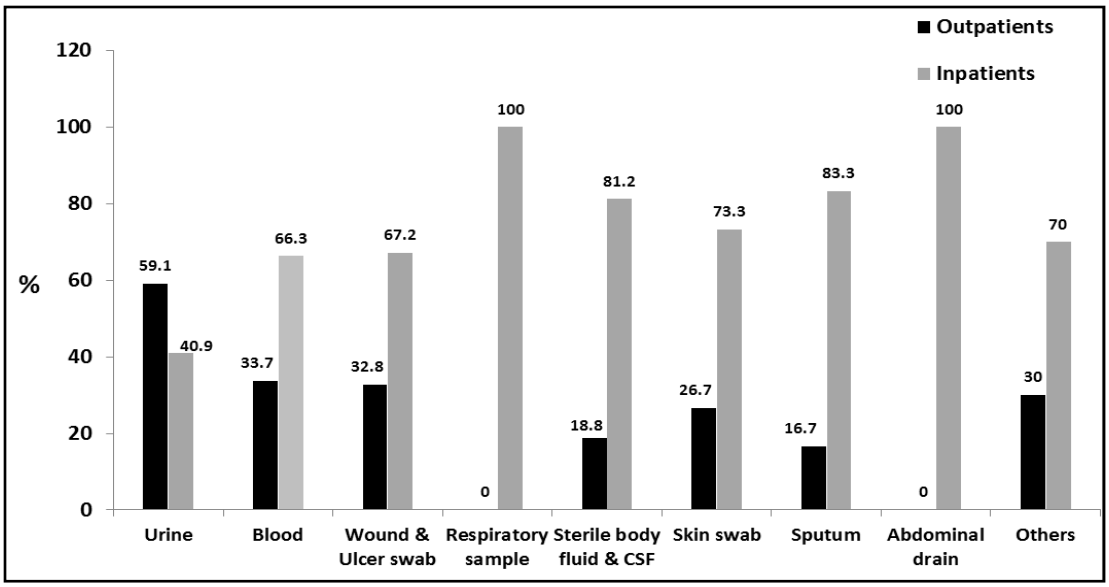


Figure 3. Types of specimen obtained from outpatients and inpatients in percentage (%)

All ESBL producing strains in both outpatients and inpatients had almost 100% resistance to a panel of antibiotics including: cephalxin, cefuroxime, cetriaxone, cefotaxime, cefepime, ceftazidime, ampicilline, and amoxyclav (data not shown). Antimicrobial resistance pattern of ESBLs producing *E. coli* and *K. pneumonia* is shown in Figure 4. Most of *E. coli* and *K. pneumonia* isolates were sensitive to amikacin, imipenem, and meropenem. The resistance pattern to antimicrobials was (75.5%, 81.3%) to trimethoprim/sulfamethaxozole, (69.7%, 42.6%) to ciprofloxacin, (38.9%, 58.5%) to gentamicin and (8.7%, 30.7) to piperacillin/tazobactam for *E.coli, K. pneumonia* respectively.

In both settings, outpatients and inpatients, almost all ESBLs isolates were sensitive to imipenem and meropenem (Figure 5). ESBLs isolates showed high resistance to trim/sulfa (75.8% and 78%) and to a lesser extent to gentamicin (40.1% and 47.1%) in outpatients and inpatients respectively. ESBL producing strains from outpatients showed a higher resistance (67.2%; 250/372) to ciprofloxacin than the isolates from inpatients (59.6%; 233/391) and this difference was statistically significant (P-value=0.02). Conversely, isolates from inpatients showed a higher resistance (20.2%; 79/391) to piperacillin/tazobactam than those from outpatients and the difference was also statistically significant (P-value<0.00).

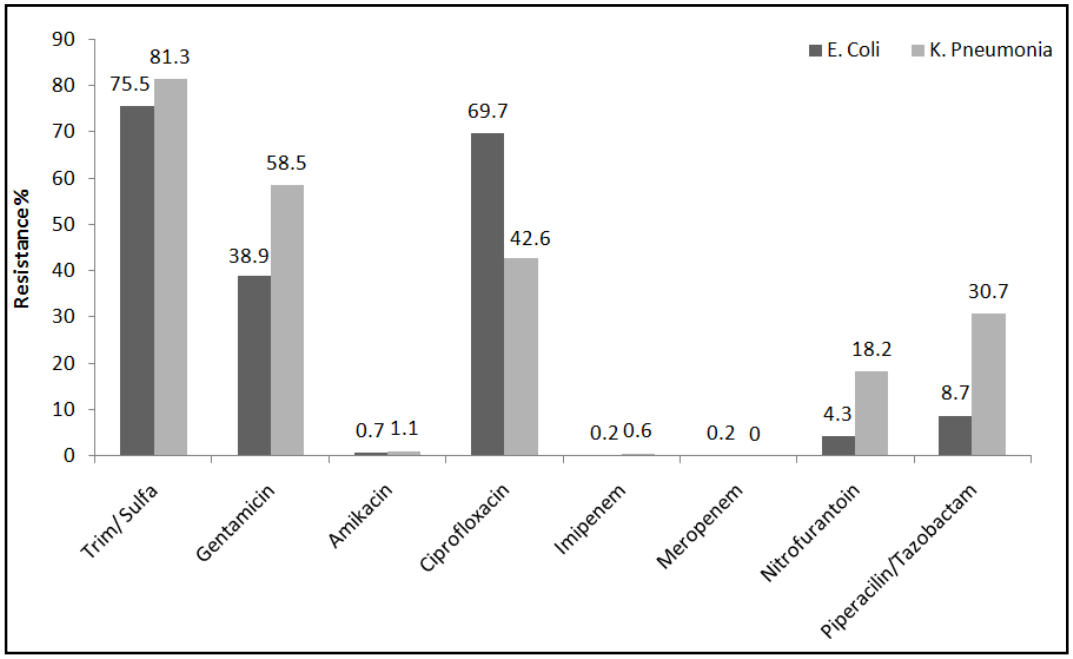
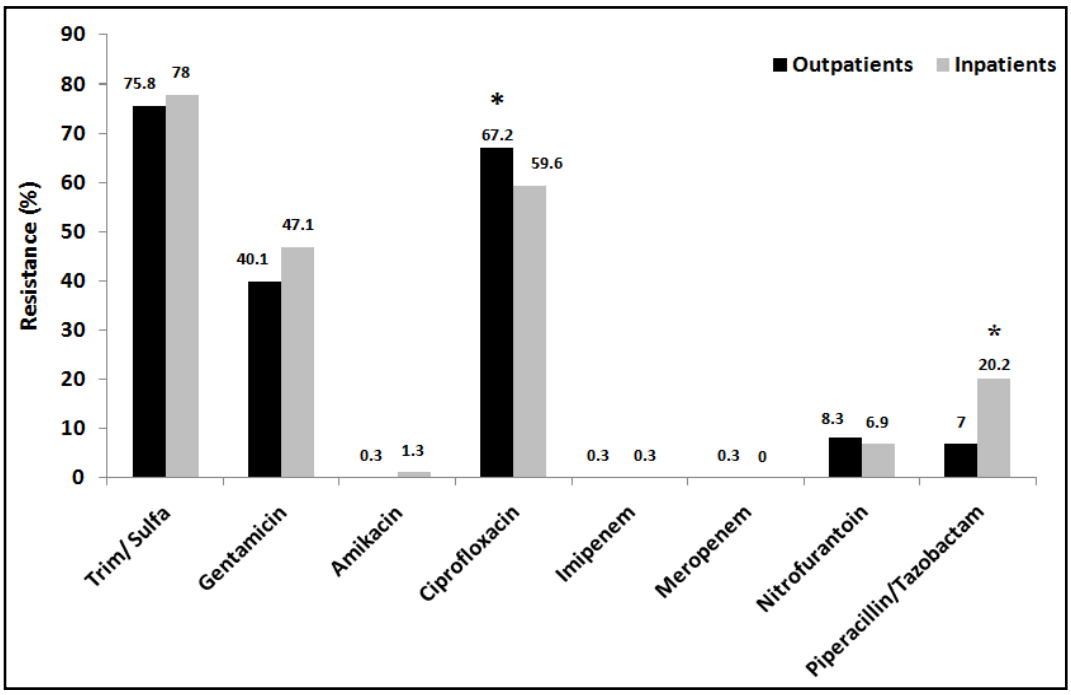


Figure 4. Antimicrobial resistance pattern of ESBLs producing *E. coli* and *K. pneumonia*



*P-value < 0.05

Figure 5. Pattern of antimicrobial resistance in ESBLs producing bacteria isolated from outpatients and inpatients

4. Discussion

ESBL producing enterobacteria can cause a variety of clinical infections ranging from urinary tract infections to sepsis. The incidence of infections caused by ESBL producing strains is cosmopolitan with regional and institutional variations [24]. In this study we report that 10.9% is the overall prevalence of ESBL producing bacteria among all gram negative bacteria at our healthcare facility. Sporadic reports from other countries have shown a wide range of prevalence rates of ESBL producing bacteria. For example 20.3%, 29%, 45.8% and 57.6% prevalence were reported from Venezuela, Tanzania, India, and Ethiopia respectively [25,26,27,28]. There is an increase in the prevalence of ESBL-producing Enterobacteriaceae, and this was shown from consecutive surveys conducted (few years apart) in the Netherlands and Italy [29,30]. Interestingly, this increase in the prevalence has been reported even in the same study on community associated infections in France [31], and on nosocomial UTIs in Germany [32]. Monitoring the ESBL prevalence and type in enterobacteria of clinical interest may contribute to defining appropriate therapeutic options [20].

In this study, the rates of ESBL producing infections in hospital and community settings were (51.2%, 48.8%) respectively. A lower rate has been reported from outpatients setting locally (12.7%), however, the study was conducted around a decade earlier [33]. In recent studies, reported rates of ESBL producing infections in community and hospital settings from Japan were (10.6%, 10.7%), and from Thailand were (15.6%, 68.8%) respectively [34,35]. Higher rates of these infections in hospital settings reflect the degree of implementation of infection control measures in hospitals. These studies also show that the spread of ESBL producing bacteria within the community represent an important source of acquisition of infections and their transmission among population.

Controversy exists in literature about the association of ESBL bacterial infection and gender. In this study, around 60% of all patients were females, 23.7% were less than 15 years old and 34.2% were 60 years and above. A significant association between ESBL-producing bacteria and pediatric age group patients with no significant association with patient's gender has been reported in recent studies [28,36]. Controversially, Kumar and colleagues (2015) detected a significant gender difference for the occurrence of ESBL *E.coli* in hospital and community setting (65.1% females and 34.9% males) [37]. These studies show variable gender and age factors distribution of isolated ESBL-producing bacteria. However, it appears that female and very young children groups might carry the highest incidence rates.

The highest detected ESBL-producing bacterial strain in this study was *E.coli* (being more prevalent in outpatient), followed by *K. pneumoniae* (being more prevalent in inpatients) and Proteus mirabilis (76.5%, 23.1% and 0.4% respectively). Our results differ from those reported in other countries demonstrating that ESBL *K. pneumoniae* was the highest isolated followed by *E.coli* and *Proteus mirabilis* [27,28]. However, our results are in agreement with reports from other countries showing that ESBL *E.coli* being more detected in outpatient and *K. pneumoniae* being more prevalent in inpatients [37,38,39].

Our study results clearly show high isolation rates of ESBL-producing strains from different infected body sites with the highest rates obtained from urine and respiratory samples for *E.coli* and *K. pneumoniae* respectively. The contrary was reported in an older study where the highest isolation rate of ESBL *E.coli* (28.7%) was from respiratory tract specimens and (47.1%) of *K.pneumoniae* was from urinary tract [40]. Singh et al, (2016) reported the highest isolation rate of ESBL *E.coli* in urine samples (82.6%) followed by pus (9.8%) and blood (3.4%) in a study among ICU patients [36]. Another study described the distribution of these bacteria among clinical specimens obtained from hospitalized and outpatient females and males. ESBL *E.coli* was obtained from urine in both females and males (43.1% and 34.8%). In females it is followed by genital tract specimens (26%) and pus (17.9%). In males it was followed by pus (30.4%) then blood (14.5%). The isolation rates of *K. pneumoniae* were as follows: among females, 42.9% from urine and 24.2% from pus and among males, 32.1% from pus, 26.9% from respiratory secretions and 17.9% from urine. It is worth mentioning that the isolation rate among female and male patients was significant except for pus, blood and body fluids [37]. In the KSA, the frequency of isolation of ESBL-producing strains, for both *E.coli* and *K. pneumoniae*, were: 63.2% in urine, 26.7% in skin swabs, deep wound swabs, tissues and sterile body fluids, 6.6% in respiratory samples and 3.5% in blood samples [41]. Significant isolation rates of ESBL Enterobacteriaceae from blood (84.8%) and open wound swabs (72.7%) were mentioned by Abera et al, (2016) [28]. Also, ESBL-production was high among pus samples (51.37%) followed by urine (45.63%) [37].

As per clinical specimens collected in this study from both settings, urine (59.1%) was the most frequently isolated sample from outpatients. On the other hand, more than 80% of sterile body fluids and CSF samples as well as sputum were collected from hospitalized patients. All respiratory and abdominal drain samples were collected in hospitals. The remaining types of clinical specimens were collected from both inpatients and outpatients at variable rates. Results revealed that urine is the major source ESBL producing bacteria from outpatients. Screening of the community carriage rate of ESBL- producing bacteria, among other multidrug resistant microorganisms, as well as the gastrointestinal colonization rate of such bacteria in hospitalized patients is important to decide the choice of the proper antimicrobial drug therapy [42].

Therapies for infections caused by ESBL bacteria are usually difficult, since these organisms not only are resistant to penicillins, cephalosporins, and the monobactam aztreonam but often are characterized by associated resistance to other classes of antimicrobials [3,4]. Our data revealed that ESBL positive bacteria remained almost fully susceptible to imipenem, meropenem and amikacin in both outpatients and inpatients. However, bacteria showed high resistance to trimethoprim/ sulfamethoxazole (75.8% and 78%) and to gentamicin (40.1% and 47.1%) in outpatients and inpatients respectively. ESBL bacteria from outpatients showed a significantly higher resistance to ciprofloxacin than those isolated from inpatients ($p<0.05$), and this could be explained by the higher prescription rate of oral ciprofloxacin for outpatients. Similarly, this could

explain the difference that was revealed in this study which showed that 69.7% of *E.coli* and 42.6% of *K.pneumonia* were resistant to ciprofloxacin, keeping in consideration that the majority (85%) of outpatients infections were due to *E.coli* The overuse explanation of antibiotic can be applied also for piperacillin/tazobactam since our data showed that ESBL bacteria from inpatients showed a significantly higher resistance to piperacillin/tazobactam than those isolated from outpatients ($p<0.05$). Similarly, other recent reports have also showed that imipenem, amikacin, and piperacillin/tazobactam were the most effective antimicrobial drugs against ESBL *E.coli* [4,36]. They also concluded that nitrofurantoin was the most effective drug among urinary isolates. Markovic et al, (2013) isolated ESBL *E.coli* from urine samples of outpatients and noted that all isolates were susceptible to imipenem with higher resistance rates to amikacin (79.1%) and gentamicin (76.8%) than those found in our study [43]. In another study which included hospital and community acquired cases, ESBL *E.coli* showed higher resistance rates than our study to Ciprofloxacin (89.1%), and amikacin (31.4%), and ESBL *K. pneumoniae* isolates showed higher resistance rates also to amikacin (31.4%) and imipenem (8.9%) [37]. Other studies demonstrated lower resistance rates for ESBL bacteria isolated from inpatients and outpatients were reported to quinolones and aminoglycosides, and nearly similar rates to our study for trimethoprim/sulfamethoxazole and nitrofurantoin [28,44].

Knowledge of the antimicrobial susceptibility patterns of the ESBL-producing bacteria is necessary to decide the proper empiric therapy to be used in our clinical settings. In summary, our study results confirm that the carbapenems and amikacin are the first line drugs for the treatment of both outpatients and inpatients ESBL bacterial infections. Antibiotic combination with nitrofurantoin and piperacillin/tazobactam for ESBL infections could be considered for urinary tract infections. Periodical monitoring of susceptibility to antimicrobials and the avoidance of indiscriminate use of antimicrobial drugs and using antibiotics prudently based on guidelines of antimicrobial stewardship programs is of high importance to any healthcare facility. In addition, the implementation of proper infection control policy is of major importance in order to limit the development and spread of the resistant bacteria [45].

This study has its own limitations. The design of the study did not allow us to know whether there are certain risk factors for infection in the history of all outpatients. Also, results of this study cannot be generalized, since it was conducted in one medical city in Riyadh.

5. Conclusion

This study highlights the occurrence and current antimicrobial susceptibility pattern of ESBL producing bacteria considering the source of infection in terms of being isolated from inpatient or outpatient setting. Currently, carbapenems and amikacin are the first line antibiotics that can be used for the treatment of both outpatients and inpatients ESBL bacterial infections. Since bacterial resistance pattern to antimicrobials is continuously increasing, periodical monitoring of antimicrobial susceptibility of isolated ESBL bacteria, and rotating the use of the effective antimicrobial drugs according to guidelines of antimicrobial stewardship programs should always be considered.

Statement of Competing Interests

The authors have no competing interests.

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