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PREVALENCE OF ESBL-PRODUCING ENTEROBACTERIACEAE AMONG LEBANESE PATIENTS WITH URINARY TRACT INFECTIONS

Rasha Abdallah
Resident in Laboratory Medicine, Faculty of Medicine, Beirut Arab University, Beirut, Lebanon, raa195@gme.bau.edu.lb

Bassel Abdallah
Resident in Nephrology, Rayak Hospital, Rayak, Bekaa, Lebanon, dr.bassel.abdallah@hotmail.com

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PREVALENCE OF ESBL-PRODUCING ENTEROBACTERIACEAE AMONG LEBANESE PATIENTS WITH URINARY TRACT INFECTIONS

Abstract

Being the most common infections worldwide, Urinary Tract Infections (UTIs) represent a major public health problem. Gram negative bacteria are the main pathogens causing UTIs where Extended spectrum β–lactamase (ESBL)-Producing Enterobacteriaceae, mainly the multi-drug resistant species, such as E. coli sequence type 131 and klebsiella.pneumoniae, account for serious health problems and high economic burden. In Lebanon, data about prevalence of antibiotic resistant pathogens during UTIs are still scarce. In this study we examined the prevalence of ESBL-producing pathogens among Lebanese patients mainly located at Bekaa governorate. This retrospective study included 7241 urine tests that were collected from all the out- and in-patients, presented to Rayak Hospital from 1-1-2019 till 31-12-2019. Among the 7241 urine tests performed, 7.54% were positive. Among the positive samples, 59%, 17.5% and 1% were caused by E. coli, Klebsiella and Proteus, respectively. Other infections (22%) were caused by other types of pathogens. Among the E. coli-positive samples, Klebsiella-positive samples and Proteus-positive samples 45%, 26% and 17% were ESBL producing, respectively. The ESBL- producing pathogens corresponded to 31% of the total positive UTIs. The distribution of these infection-causing pathogens according to age, gender and hospitality condition was also determined. This study shows for the first time the frequency and distribution of ESBL-producing pathogens among Lebanese UTI-patients in Bekaa region.

Keywords

Urine, Infection, ESBL, pathogen

1. INTRODUCTION

Urinary tract infections (UTIs) represent the most common infections worldwide, among both genders and both ambulatory and hospital admitted patients. In the united-states, UTIs are responsible for more than 7 million physician visits annually (Susan M Schappert, 2011) and underlies 15% of all community-prescribed antibiotics, with comparable phenomena in Europe (Susan M Schappert, 2011). It is well established that nearly 1 in 3 women will have at least 1 episode of UTI requiring antimicrobial therapy by the age of 24 years and almost half of all women will experience UTI during their lifetime. The risk of UTI is higher in infants, pregnant women, and elderly patients. UTIs represent therefore a major public health problem (de Kraker, Stewardson, & Harbarth, 2016) with a substantial economic burden (de Kraker et al., 2016; Esteve-Palau et al., 2015; François et al., 2016; Susan M Schappert, 2011) due to their recurrence, the increasing hospitalization rate and the increasing prevalence of antibiotic resistance among pathogens especially gram negative bacteria (Susan M Schappert, 2011). Gram negative bacteria are the main pathogens causing UTIs with highest prevalence for E. coli that is responsible for 70-95% of both upper and lower UTIs, followed by other gram negative enteriobacteriacea such as klebsiella species and Proteus species (Mazzariol, Bazaj, & Cornaglia, 2017). Antibiotics are vitally used to prevent and treat common infections, but their overuse and misuse have contributed to an increase in antibiotic resistance. Anti-microbial resistance among UTI pathogens, especially gram negative bacteria, has reached an alarming level posing challenges for choosing effective antibiotics (Susan M Schappert, 2011). Extended spectrum β–lactamase (ESBL) are enzymes that confer bacterial resistance to Penicillin; first-, second- and third-generation Cephalosporins and Aztreonam; with no resistance to Cephamycins (as Cefoxitin) or Carbapenems (Bidell, Palchak, Mohr, & Lodise, 2016). Hence, only few antibiotic options are available for treatment of ESBL producing UTIs, which may require hospital admission or Intravenous administration of antibiotics in many case.

The prevalence of ESBLs is increasing worldwide (Mazzariol et al., 2017). ESBL outspread is typically driven by international Multi-Drug Resistant (MDR) high-risk clones, mainly E. coli sequence type 131 (ST131) and K. pneumoniae ST258 (Mazzariol et al., 2017). Besides their medical impact, the economic burden of infections caused by ESBL-producing E. coli is high where an ESBL-producing infection costs more than a non-ESBL-producing E. coli infection (de Kraker et al., 2016; Esteve-Palau et al., 2015; François et al., 2016; Susan M Schappert, 2011; Vallejo-Torres et al., 2018). Looking at hospital expenses separately, the total pharmacy costs and antibiotic costs of ESBL infections were considerably higher than for non-ESBL infections, as was the need for outpatient parenteral antibiotic therapy and its related costs (Susan M Schappert, 2011). In Lebanon, as in many other developing countries, more than 30 % of antibiotics are dispensed without a prescription, and almost half of the population self-medicates with antibiotics (Susan M Schappert, 2011) and despite the high prevalence of antibiotic-resistance among pathogens, data in this regard remain scarce. The aim of this study was therefore to assess the current status of ESBL producing pathogens among Lebanese patients mainly located at Bekaa governorate.

2. METHODS

IRB approval for this study was received from the medical committee of Rayak hospital. This is a retrospective study that was conducted at Rayak hospital laboratory department (situated in the Bekaa governorate of Lebanon) from 1-1-2019 till 31-12-2019. The study included 7241 urine samples that were collected from inpatients and outpatients that were performing urine cultures. Patients' demographic data concerning age, gender and way of hospital admission were recorded.

Positive cultures yielding > 10^5 CFU/ml, were considered as positive. For positive cultures, isolated bacteria, antibiotic resistance and sensitivity were tested. Urine cultures for bacterial isolation, were carried out on Blood agar (enriched, bacterial growth medium) and Macconkey agar (selective and differential for gram negative pathogens). Subcultures included chapman agar (selective medium for the isolation of staphylococcus aureus), bile esculin agar (selective medium for streptococcus group D) and sabouraud agar (selective for fungal growth). Differential tests were also used (urea, indol , oxydase , catalase ,coagulase, API strep). Anti-microbial susceptibility testing and interpretations were determined using two methods: disc diffusion method on Muller Hinton agar (by following the instructions of the ministry of public health) and the VITEK 2 system (BIOMERIEUX ,france). The following antibiotic

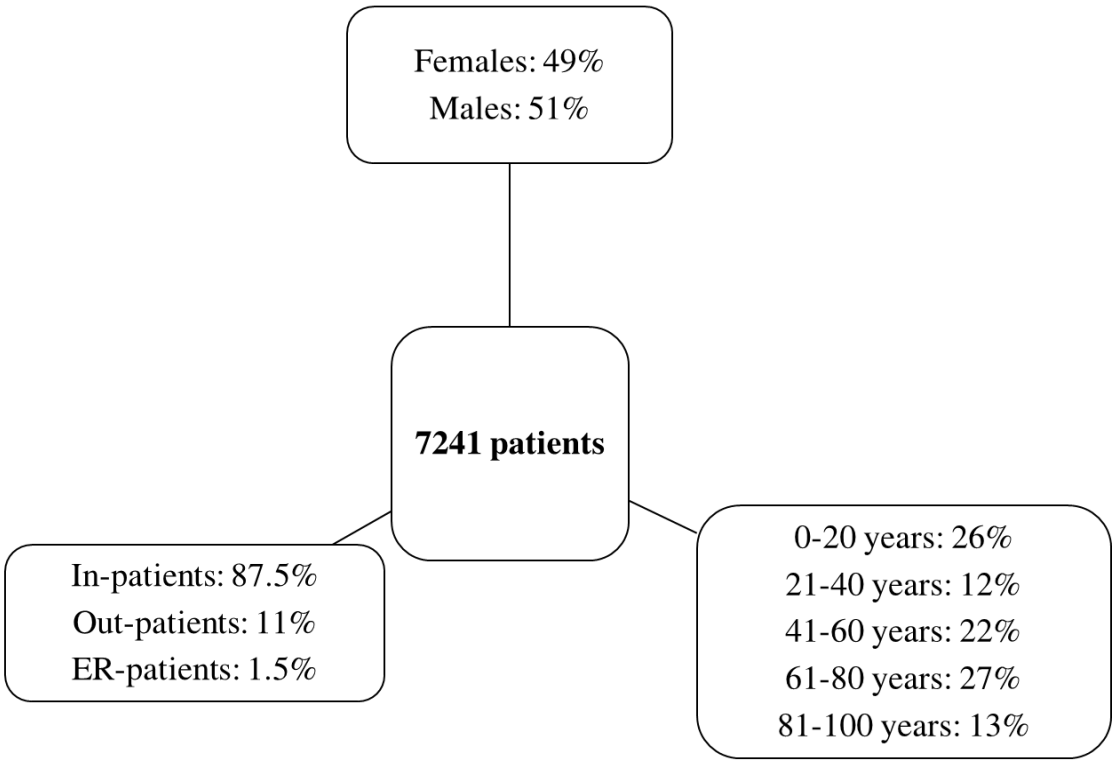
disks were used: Ampicillin (10 µg) ; Amoxicillin/Clavulanic acid (20/10 µg) ; Piperacillin/tazobactam (100/10 µg) ; Cefuroxime (30 µg) ; Cefepime (30 µg); Cefoxitin (30 µg) ; Cefotaxime (30 µg) ; Ceftazidime (30 µg) ; Cefixime (5 µg) ; Imipenem (10 µg) ; Gentamicin (10 µg) ; Amikacin (30 µg) ; Ciprofloxacin (5 µg) ; Trimethroprim-sulfamethoxazole (1,25-23.75 µg) ; Nitrofurantoin (300 µg) ; Aztreonam (30 µg) ; Ertapenem (10 µg) ; Fosfomycin+ (200 µg) ; Tigecycline (15 µg) ; Tetracycline (30 µg). In suspected ESBL isolates, we examined the main antibiotics before reporting. It should be showing R or I for Aztreonam, Ceftazidime, Cefotaxime, and/or Ceftriaxone On the other hand, it shows S to Cefoxitin and Imipenem, irrespective of the remaining antibiotics. This has been validated and reflects a cost effective and accurate method in the determination of ESBL.

For the statistical analysis, we reported percentages, means, and frequencies. Data were processed using SPSS program (version 23).

3. RESULTS

This study included 7241 urine tests that were collected from all the out- and in-patients, presented to Rayak Hospital from 1-1-2019 till 31-12-2019. Among those: 3561 (49%) were females and 3680 (51%) were males; 6342 (87.5%) were in-patients, 796 (11%) were out-patients, whereas 103 (1.5%) were in the Emergency department (ER) (as shown as Fig.1). Those patients belonged to different age groups: (0-20 years) (1824; 26%), (21-40 years) (865; 12%), (41-60 years) (1610; 22%), (61-80 years) (1978; 27%), (81-100 years) (964; 13%) (as shown as Fig. 1).

Fig.1: Distribution of the patients who performed urine test according to their age range, sex and hospitality condition.



Among the total 7241 urine tests performed, 546 (7.54%) tests were positive (as shown as Fig. 2). Out of the 546 positive urine cultures, 395 (72.3%) belonged to females patients whereas 151 (27.7%) belonged to male patients. Those positively diagnosed patients corresponded to 378 (69%) in-patients, 139 (25.5%) out-patients and 29 (5.5%) ER-patients (as shown as Fig. 2). Those patients were distributed among different age groups: (0-20 years) (124; 22.7%), (21-40 years) (82; 15%), (41-60 years) (65; 12%), (61-80 years) (174; 32%), (81-100 years) (100; 18.3%) (as shown as Fig. 2).

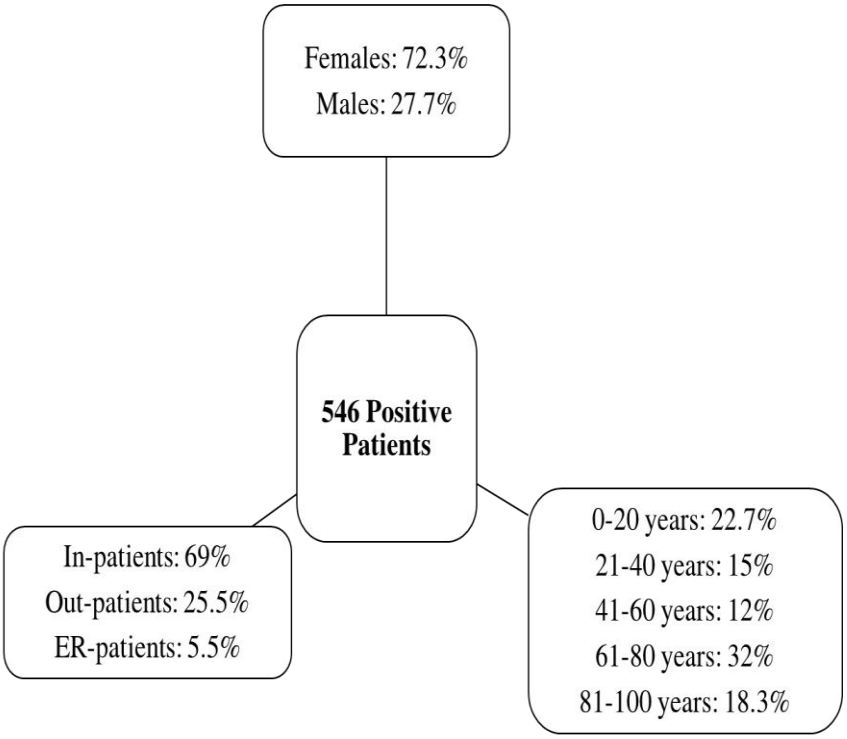


Fig.2: Distribution of the UTI-positive patients according to their age ranges, sex and hospitality condition.

Among the 546 positive urine infections, 322 (59%) were caused by *E. coli*, 96 (17.5%) were caused by *Klebsiella* and 6 (1%) were caused by *Proteus* where the other samples 122 (22%) were caused by other types of pathogens such as *pseudomonas*, *enterobacter*, *enterococci*, *staphylococcus* and *candida* (as shown as Fig. 3).

Among the 322 *E. coli*-positive samples, 165 (51%) contained non-ESBL *E. coli*, 144 (45%) contained ESBL producing *E. coli* whereas 13 (4 %) contained CRE *E. coli* (as shown as Fig. 3). Among the 96 *Klebsiella*-positive samples, 66 (69%) contained non-ESBL *Klebsiella*, 25 (26%) contained ESBL producing *Klebsiella* whereas 5 (5 %) contained CRE *Klebsiella* as shown as Fig. 3). Among the 6 *Proteus* -positive samples, 5 (83%) contained non-ESBL *Proteus* where only 1 (17%) contained ESBL producing *Proteus* (as shown as Fig. 3).

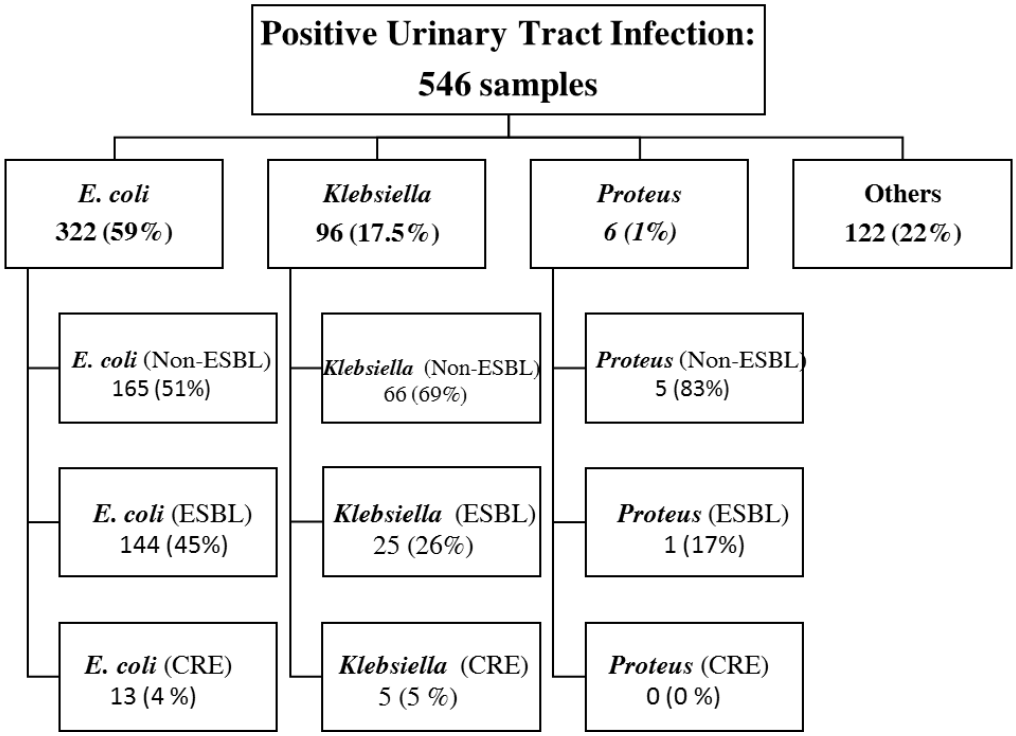


Fig.3: Distribution of *E. coli*, *Klebsiella*, *Proteus* and other pathogens among the UTI patients.

It is noteworthy that among the 546 positive urine infections, 170 samples (31%) contained ESBL- producing pathogens. Among the 170 detected ESBL pathogens, 144 (84.7%) were *E. coli*, 25 (14.7%) were *Klebsiella* species (*pneumonie and ocytoca*) and 1 (0.6%) were *Proteus* (as indicated in Table 1). Among the whole sample, the incidence of ESBL producing gram negative enterobactriaceae according to gender corresponded to 123/395 samples (31.12%) in females and 47/151 samples (27, 65%) in males. The highest incidence according to age groups was found in the age groups 0-20 years and 61-80 years, with 45/124 (36,2%) and 55/174 (31,6%), respectively. ESBL-producing pathogens incidence corresponded to 120/407 (29,4 %) among inpatients and 40/139 (28.7%) among all outpatients.

Table 1: Frequencies and Percentages of the detected ESBL producing bacteria.

ESBL-producing Bacteria	Numbers	Percentages
E.coli (ESBL)	144	84.7%
Klebsiella (ESBL)	25	14.7%
Proteus (ESBL)	1	0.6%
Total	170	100%

4. DISCUSSION

Urinary Tract Infections correspond to the most common bacterial infections among out-and in-patients, therefore represent a major health issue of modern medicine. Misuse and overuse of antibiotics have complicated further the issue leading to the highest rates of resistance among urinary pathogens, thus rendering patients' health at high risk, along with the substantial treatment costs.

Our study focused on assessing the prevalence of ESB-producing enterobacteriacea among hospital and community acquired UTIs, reported at Rayak hospital from 1-1-2019 till 31-12-2019 with distribution based on demographic variants and type of admission.

In the present study, out of 546 identified positive urine cultures, E.coli was the predominant 59%, followed by klebsiella 17,5%, and proteus 1%. On the other hand, other pathogens (including as pseudomonas, enterobacter, enterococci, staphylococcus, and candida) represented 22%. Notably, the output of this study is consistent with the results of a previous study done in the south of Lebanon in 2017 (Sokhn et al., 2020) where the prevalence of E.coli, klebsiella, proteus and other pathogens among UTIs was 67,1%, 10%, 3.7% and 19,2 % respectively (Sokhn et al., 2020). Moreover, this prevalence is comparable to that observed in other studies done in different geographic regions (Ahmed et al., 2015; Chamoun et al., 2016; Morrissey et al., 2013; Pasillas Fabian et al., 2021).

It is well known that females have the highest incidence rate among positive urine cultures. This can be explained by the cross infection during sexual intercourse, and by the female anatomy characterized by a short urethra, and the short distance between the opening of the urethra and those of the anus and vagina as well as the spermicidal use in young females (Raz et al., 2000). Moreover, decrease of estrogen level, urodynamic factors especially incontinence, non-secretor status and other factors make post-menopausal women more vulnerable to infection. Consistently, in this study we observed that 72,3% of the positive UTIs belonged to females. In addition to the sex distribution, different age groups were affected by bacterial pathogens but the prevalence was the highest in age groups 0-20 years and 61-80 years representing 26% and 27 %, respectively.

Among the positively diagnosed UTIs, 170/546 (31%) contained ESBL-producing enterobatriacea. Among the detected ESBL-producing enterobatriacea, 84.7% were E. coli which constitute 26.37 % of the total reported UTIs On the other hand, 14.7% were Klebsiella species representing 4.57% of the total UTIs and 0.6% were Proteus corresponding to 0,18 % of the total UTIs. The results of this study were consistent with the Study for Monitoring Antimicrobial Resistance Trends (SMART) which evaluated the prevalence of ESBL production among enterobacteriacea (E. coli, klebsiella and proteus) isolated from UTIs between 2009 and 2011, and reported highest prevalence in Asia and Middle east with significant increase from 2009 till 2011 (Middle east $p<0,001$ and Asia $p=0,002$) and a lower prevalence in Europe 20% (Morrissey et al., 2013). Besides, a previous study done in south Lebanon in 2017 showed very similar results with 32,9% prevalence of ESBL producers among enterobacteriaceae where E. coli was the major ESBL producer with 35,2 % among total E. coli isolates and 27,7% ESBL producing klebsiella among klebsiella isolates (Sokhn et al., 2020). Moreover, a previous study done at Pakistan institute of medical sciences in 2015 confirmed the increasing trend of ESBL production, where ESBL-producing E. coli and ESBL-producing klebsiella represented 35.5 % and 2,93 % of the total UTIs, respectively (Ahmed et al., 2015). High rates of ESBL production among gram negative pathogens, were also reported in Saudi Arabia (33%) (Alqasim, Abu Jaffal, & Alyousef, 2018), in India where ESBL-producing E. coli represented 69% of E. coli and 41% of klebsiella species isolates were ESBL producers . Furthermore, a study carried out among UTIs in turkey showed that 66.2% E. coli and 64.4% K. pneumonia were ESBL-producers (Moges et al., 2019). Lower rates were reported in Danish (Hansen et al., 2012) and Canada (Simner et al., 2011) where ESBL production was 2.4 % and 5%, respectively. This could be due to the appropriate measures concerning antibiotic prescription and infections control in these advanced countries.

In our present study, incidence of ESBL producing pathogens was similar between outpatients and hospital admitted patients with 28,7% and 29,4 % respectively; similar between males and females with 31,12% and 31,13% respectively but with highest incidence in the age groups 0-20 years and 61-80 years with 36,2 % and 31,6 %, respectively. The results of this study are in line with a previous study in Lebanon that reported that ESBL production occurs almost equally between in-patients (51,1%) and out-patients(48,9%) (Sokhn et al., 2020). These results confirm that multi drug resistance which is

increasing among community patients and affecting children in an ascending pattern, constitutes an alarming concern that needs immediate control measures.

One limitation in this study corresponds the lack of molecular tests for the identification and confirmation of ESBL producing-strains. Another limitation is the absence of assessment of other risk factors for UTIs, including diabetes, prostate hypertrophy, sexually transmitted diseases (STDs), immune-suppression, foley catheter, and kidney stones.

5. CONCLUSION

This study revealed the predominance of *E. coli* among pathogens responsible of UTIs in Lebanese population with increasing incidence of ESBL producing enterobacteriaceae among both hospital-admitted and outpatients. These results are alarming since the increasing prevalence of MDR Enterobacteriaceae limits the available options for treatment of UTIs. It is therefore strongly recommended to prescribe antibiotics based on positive urine culture and antibiogram results with control of the Minimum Inhibitory Concentration (MIC). Proper counseling of patients should be necessary to monitor their compliance to proper and complete courses of medications, which can limit the evolution of resistant strains.

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