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Original article

PREVALENCE AND RISK FACTORS OF EXTENDED SPECTRUM BETA LACTAMASE ORGANISMS IN COMMUNITY-ACQUIRED URINARY TRACT INFECTIONS IN LEBANON: A CASE CONTROL STUDY

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Summary

In Lebanon, clinical information about community-acquired urinary tract infections (CAUTI) caused by extended-spectrum beta-lactamase (ESBL)-producing Gram negative bacteria (GNB), is scarce. A population based case-control study was conducted-whereby42 cases were matched to 42 controls. The prevalence of ESBL producing strains was 14.15%. Univariate analysis showed two statistically significant independent risk factors for ESBL producing strains: antibiotic use during the last three months ($p<0.0001$), and urinary catheterization during the last six months ($p=0.0034$); and one protective factor: age group 18-50 years ($p=0.011$). Multivariate analysis showed antibiotic use as the strongest predictor for CAUTI due to ESBL-producing GNB. Co-resistance of ESBL producing strains to antibiotics was significantly higher compared with non ESBL strains: ciprofloxacin (75% vs 21.4%), trimethropin-sulfamethoxazole (71.1% vs 35.7%) and amoxicillin-clavulanate (77.7% vs 9.5%).This study confirms that ESBL-producing GNB strains constitute a notable cause of CAUTI in Lebanon. These results can be used to guide appropriate treatment of CAUTI and targeted infection control measures.

Introduction

The incidence of community-acquired urinary tract infections (CAUTIs) due to extended-spectrum beta-lactamase (ESBL)-producing pathogens has increased worldwide. Besides their capacity for rapid and widespread dissemination, ESBL-producing

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strains are increasingly associated with resistance to non-β-lactam antimicrobials, and can cause therapeutic difficulties for inpatients as well as for outpatients. Studies evaluating clinical outcomes in patients with ESBL infections have shown a trend toward higher mortality, longer hospital stay, greater hospital expenses, and reduced rates of clinical and microbiologic responses[1].

ESBL-producing Enterobacteriaceae have been reported worldwide, most often in hospital specimens and in samples from the community [2, 3]. E. coli producing a CTX-M type ESBL is an emerging cause of community-acquired urinary tract infection (CAUTI) in young women in the United States [4], Europe [5], Hong Kong [6], and elsewhere. The prevalence of such strains was high, around 45% in Asia and the Middle East, compared to European countries like Norway (around 1-2%) [7].These isolates showed high resistance rates to most of the currently used oral antimicrobial agents, including β-lactam antibiotics (amoxicillin-clavulanic acid, 69.6%), quinolones (ciprofloxacin: 84.8%; norfloxacin: 83.9%), and trimethoprim-sulfamethoxazole (75.9%), except for nitrofurantoin (15%) and fosfomycin (0%) [8].

CAUTI is the most common infection caused by ESBL-producing bacteria in non-hospitalized patients, however, the knowledge regarding the clinical epidemiology of these infections is limited [2, 3].Most studies conducted have focused on health care related infections and associated risk factors, while information on possible risk factors that elucidate mechanisms and routes for dissemination of these pathogens to the community is sparse. Among the identified risk factors: prior administration of any antibiotic, prior residence in a long-term care facility (e.g,. nursing home), presence of a urinary catheter, undergoing hemodialysis, travel to endemic regions, urinary incontinence, heart disease, diabetes, hepatitis C infection, prostatic disease, immunosuppression, male gender and age above 65 among others [9-19].

In Lebanon, so far, there are no reported epidemiological surveys to evaluate these risk factors in outpatients. Most of the studies which were conducted involved only inpatients and they focused on molecular characterization and the susceptibility pattern of ESBL producer strains to antibiotics [20-23].The aim of this study is to determine the prevalence and the possible major risk factors for ESBL positivity in community-acquired uropathogenic Gram negative bacteria, in Lebanon. These risk factors when identified can be used to guide appropriate treatment of CAUTI and form the basis for targeted infection control measures.

Methods

Design and Study Population

This case-control prospective study was conducted at the Sacre-Coeur Hospital laboratory situated in a mixed suburban and rural area in the southern suburbs of the capital Beirut. This laboratory serves around 250.000 inhabitants. The inclusion period was from February 2012 to February 2013.

Outpatients with a positive urine culture yielding >10,000 CFU/ml mainly Gram-negative bacteria that belongs to the family Enterobacteriaceae among other pathogens (Pseudomonas, Staphylococcus epidermidis…), were included in this study. The following demographic characteristics were recorded: Date of birth, gender of the patient, date of isolation, specimen number, organisms isolated, ESBL-production, and susceptibility results of isolates.

The following risk factors were assessed using a questionnaire: Age group, gender, hospital admission during last 3 months back from urine collection date, antibiotics use during last 3 months, Foley catheters insertion during last 6 months, resident in a nursing home or nursery (daycare) for patients less than 5 years old, patient who is a health care worker and history of previous UTIs defined as > 4 life-time infections.

The study population consisted of all patients willing to participate with ESBL-positive UTI (case group) and selected (sex and age matching) patients with ESBL-negative UTI 1:1 (control group) (Figure 1).

Ethics statement

The study was approved by the Sacre-Coeur Hospital Ethics Committee for Medical and Health Research. Patients were also informed upon sample collection that they may be involved in a study concerning UTIs and, if selected, they will be contacted by a health worker working in collaboration with the hospital's lab. Upon contact, objectives and approaches concerning the study were explained and, if verbal consent is granted, the health worker could proceed with the questionnaire. Patients with health care associated UTI (i.e., hospitalized including emergency department), and patients who refused to grant us an interview or answer our questionnaire were excluded from the study.

Data Collection

Urine cultivation was performed using Cystine-Lactose-Electrolyte Deficient (CLED) agar [24] and Eosin-Methylene-Blue (EMB) agar. Bacterial identification was performed using the VITEK-2 system (BioMerieux, France). Antimicrobial susceptibility testing and interpretations, including ESBL screening, were performed using the disc diffusion method on Müller -Hinton agar, following the recommendations and clinical breakpoints of the Comité De l'Antibiogramme, Société Française de Microbiologie (CA-SFM) (www.sfm-microbiologie.org) (2012 edition).

The following antibiotic discs were used: Ampicillin (10µg); Ticarcillin (75 µg); Piperacillin (75µg); Amoxicillin – Clavulanic acid (20/10µg); Cefalotin (30 µg); Ce-furoxime (30µg); Cefoxitin (30µg); Cefotaxime (30µg); Ceftazidime (30µg); Imipenem (10µg); Aztreonam (30µg); Trimethoprim - Sulfamethoxazole (1,25 / 23,75µg); Gentamicin (15µg); Amikacin (30µg); Nitrofurantoin (300µg); Ciprofloxacin (5µg).

Phenotypic confirmation was performed using the double-disk synergy test (DDST) according to CA-SFM recommen-

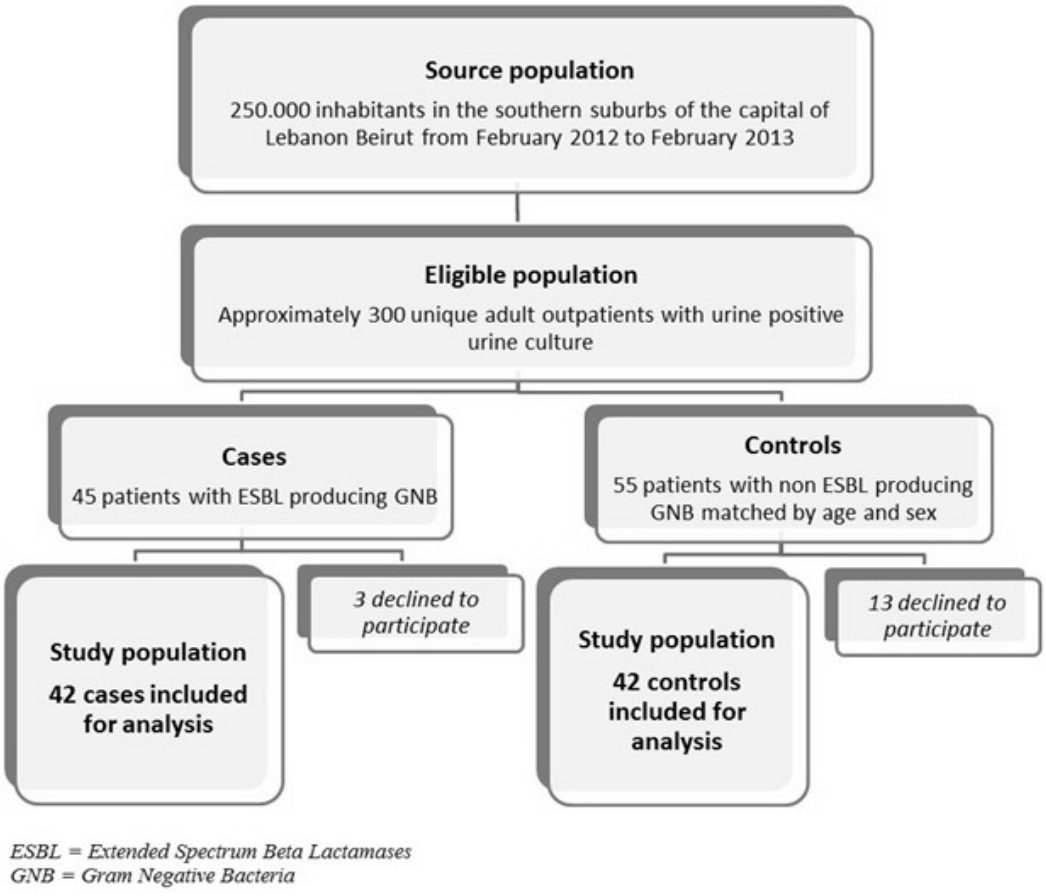

Figure 1: Selection of study population.

dations (qualitative method). DDST was done on a Mueller-Hinton agar plate inoculated with a bacterial suspension (density of 0.5 McFarland). Disks containing cephalosporins (cefotaxime or ceftriaxone, ceftazidime, cefepime) were applied next to a disk with clavulanic acid (amoxicillin-clavulanic acid or ticarcillin-clavulanic acid). Positive result was indicated when the inhibition zones around any of the cephalosporin disks were augmented in the direction of the disk containing clavulanic acid resulting in a characteristically shaped zone referred to as a "champagne-cork," "keyhole," "ellipsis," or "phantom image". The distance between the disks was critical and a 30mm distance center-to-center, has been found to be optimal for cephalosporin 30µg disks [25].

Statistical Analysis

Univariate analyses were performed using Pearson's chi-square test or Fisher's exact test when appropriate (for small numbers). The association between potential risk factors and infection caused by ESBL-producing E. coli, K. pneumonia or Proteus was quantified by odds ratio (OR) with 95% confidence interval (CI).
Multivariate analysis using a manual backward stepwise elimination procedure by a multivariate logistic regression model was performed to identify independent risk factors. Variables introduced into the multivariate analysis were those with a crude p value <0.1. All statistical analyses were conducted using SPSS statistics software, version 17.0 and P value less than 0.05 was considered statistically significant.

Results

From February 2012 to February 2013, 318 positive urine cultures were identified from approximately 1000 consecutive urine samples obtained from outpatients. E. coli was isolated from229 (72%), Klebsiella spp. from 34 (10.7%), Proteus spp. from 13 (4%), other gram negative pathogens (Citrobacter, Enterobacter, Pseudomonas…) from 26 (8.1 %) and gram positive pathogens (mostly are Enterococcus feacalis) from16 samples (5%).
Most isolates were obtained from female patients, 251 (78.9%), and from patients of the age group >50 years, 193 (60.6%). The overall incidence of ESBL producing strains was 14.15% (45/318). By considering only gram negative pathogens the incidence goes up to 14.9% (45/302). Among these patients, the mean age was 52.7 years, 11.9% (8/67) were males and 14.7% (37/251) were females. The prevalence of ESBL producing strains among isolated E.coli was 18.3% (42/229), Klebsiella 5.8% (2/34), and among Proteus spp. 7.6% (1/13).
Among the ESBL producing bacteria, E.coli was predominant, 93.3% (42/45), followed by Klebsiella4.4 (2/45), and Proteus 2.2% (1/45).The highest number of ESBL producers was noted in the age groups 0-18 and >50 years, 21.6% (8/37) and 16.5% (32/193), respectively.

1. Antibiotic resistance

In general, ESBL-producing isolates expressed more co-resistances compared to non-ESBL strains in several antibiotics (Table 1).

Antibiotic	Rate of resistance ESBL positive (n=42)	Rate of resistance ESBL negative (n=42)
Ciprofloxacin	75%	21.4%
Trimethropin-Sulfamethoxzole	71%	35.7%
Nitrofurantoin	8.8%	11.9%
Amoxicillin-Clavulanate	77.7%	9.5%

Table 1: Comparison of rates of resistance to antibiotics between ESBL positive and ESBL negative GNB.

2. Risk Factor Analysis

A total of 42 patients with positive urine cultures yielding ESBL producing gram negative enterobacteriacea were matched 1:1 with controls on the basis of sex and age (mean age was 52.7 and 53.6 in ESBL+ group and ESBL-group, respectively). Both groups yielded only gram – enterobacteriacea (E.coli in 39/45 and 37/45 of ESBL+ and ESBL- , respectively). The results of the univariate analyses on risk factors are presented in Table 2. Antibiotics use during the last 3 months and Foley catheters insertion during the last 6 months were identified as statistically significant risk factors for ESBL UTI (p<0.0001 and P=0.034, respectively). However, hospitalization during the last 3 months was of borderline significance (p=0.053).

To evaluate sex and age groups as potential risk factors, all 318 patients with positive urine culture were included. Two groups were identified: 45 patients with ESBL+ urine cultures (case group) and 273 patients with ESBL- urine cultures (control group). The results of the univariate analyses on risk factors are presented in Table 3. Age group 18 to 50 years was identified as a statistically significant protective factor (p<0.05) (Table 3).

Variables	ESBL + (n=42)	ESBL - (n=42)	Crude OR	95% CI	P value
Hospitalization last 3 months	16 (38%)	8 (19%)	2.61	0.97 - 7.04	0.053
Antibiotics use during last 3 months	33 (78%)	12 (28%)	9.17	3.38 - 24.81	<0.0001
Foley catheters insertion last 6 months	10 (23%)	3 (7%)	4.06	1.03 - 16.02	0.034
Resident of a nursing home, or nursery (daycare)	0 (0%)	2 (5%)	0	N/A	0.246
Patient or household who is a health care worker	8 (19%)	10 (24%)	0.75	0.26 - 2.15	0.596
History of UTIs	21 (50%)	20 (48%)	0.91	0.38 - 2.14	0.823

Table 2: Univariate comparison of risk factor exposition in the study population with and without ESBL-positive urinary tract infection matched by age and sex.
OR: Odds ratio; CI: Confidence Interval

Variables	ESBL + (n=45)	ESBL - (n=273)	Crude OR	95% CI	P value
Male sex	8 (17.7%)	59 (21.6%)	0.78	0.34 - 1.77	0.559
Age 0-18 years	8 (17.7%)	29 (10.6%)	1.82	0.77 - 4.28	0.165
Age 19-50 years	5 (11.1%)	83 (30.4%)	0.29	0.10 - 0.75	0.011
Age >50 years	32 (71.1%)	161 (58.9%)	1.71	0.86 - 3.4	0.122

Table 3: Univariate comparison of sex and age group as possible risk factors in the study population with and without ESBL-positive urinary tract infection.
OR: Odds ratio; CI: Confidence Interval

Multivariate analysis was also performed to identify independent risk factors. Antibiotics use during the last 3 months, Foley catheters insertion during last 6 months, and hospitalization during last 3 months were included in this analysis. Antibiotic use in the last 3 months was shown to be the strongest predictor for ESBL UTI (Table 4).

Discussion

ESBL-producing gram negative Enterobacteriacea have become the most worrisome causative agents of community-acquired UTIs. In the present study, ESBL positivity was detected in 14.15% of positive urine cultures. A similar percentage was found in Turkey (14%) [14] and Rwanda (19%) [16]. A much higher percentage of 41.15% was found in Israel [11] while a much lesser percentage was reported in Norway 1.3% [7]. These results make Lebanon a high prevalence country and indicate the need for a national policy to control the emergence of resistant bacteria. This study confirmed that E.coli is still the most common uropathogen isolated from outpatients (72%) and the most common pathogen to produce ESBLs with a proportion of 18% of producers. Additionally, 93% of ESBL + pathogens were E.coli, very similar to many studies conducted worldwide [7, 9-19].

Any antibiotic use in the previous three months period was found to be the strongest predictor of CAUTI-ESBL+ pathogens. Interestingly the history of UTIs defined as more than four lifetime infections was not a risk factor. This fact can elucidate the importance of the proximity in time from last antibiotic use to sample collection. Besides, these results demonstrate further again the lack of class restriction of oxyimino-beta-lactams antibiotics and the misuse of antibiotics in hospitals and in the community, knowing that Lebanon is a country where antibiotics can be purchased without a prescription. It is important to note that, a study performed in Spain showed a marked decrease in the number of infections caused by ESBL-producing K. pneumoniae (from 4.9 episodes to 0.6 episodes per 1000 patient-days) after institution of barrier protections and restriction of oxyiminocephalosporins [22]. A similar result was observed in a study performed in New York where the number of cases with ESBL-producing K. pneumoniae declined significantly after the institution of barrier precautions and restriction of ceftazidime use at one hospital [26].

In addition, urinary catheter insertion, at least once during the previous six months, was found to be a statistically significant risk factor. This fact was also confirmed by many other studies elsewhere [12, 18].

On the other hand, in contradistinction to most worldwide reported studies, recent hospitalization was not found to be a statistically significant risk factor nor did the fact of being a health care worker or living in the same house with one. This result can be due to efforts of barrier protection (gloves, gowns, hand hygiene…) of colonized and/or infected patients which has become standard in our hospitals, mainly in the region where the pool of patients was studied. However, this conclusion requires further studies with bigger sample size

Variables	Adjusted OR	95 % CI	P value
Hospitalization last 3 months	0.822	0.219 - 3.082	0.771
Antibiotics use during l ast 3 months	8.541	2.931 - 24.889	<0.0001
Foley catheters insertion last 6 months	2.488	0.463 - 13.379	0.288

Table 4: Results of the multivariate analysis.
OR: Odds ratio; CI: Confidence Interval

Moreover, data in this study showed that the age group 18-50 years was a protective factor. Such result can be due to the well-known clinical epidemiology that most urinary tract infections in this age group are uncomplicated cystitis in female patients. On the other hand, patients younger than 18 years (mostly infancy and childhood) and older than 50 years were associated with complicated UTIs (functional or anatomic abnormalities, poor bladder function, urinary incontinence, post menopause…) which would put them at risk of increased antibiotics use, frequent hospitalizations, leading to the emergence of antimicrobial resistant strains.

One troublesome aspect of ESBL-positive bacteria is its association with high rates of resistance to non-β-lactam antibiotics, particularly quinolones, trimethoprim–sulphamethoxazole, and aminoglycosides. The results of this study show high rates of resistance among ESBL+ E.coli isolates: 75% for ciprofloxacin, 71.1% for trimethoprim-sulfamethoxazole, and 77.7% for Amoxicillin – Clavulanic acid. However, resistance to Ciprofloxacin was reported to be 31.5% in ESBL-positive, in a study from Spain in 2006 [27]. The most important consequence of such high resistance rates is the ensuing difficulty in the management of UTI patients. The number of drugs available for use in the outpatient setting is limited. Amoxycillin–clavulanate was successful in treating patients with cystitis due to ESBL-producing *E. coli* in a Spanish study [28] where the resistance rate was 29%, but as 77.7% of our ESBL-positive isolates were found to be resistant, this does not seem to be a good choice in our country. However, Nitrofurantoinis an acceptable choice in uncomplicated cases; only four of all 45 uropathogenic *E.coli* isolates were resistant to this drug.

In brief, this study has several limitations that must be addressed. First, it is of low power, it took place only in a single outpatient laboratory setting. A bigger sample size is needed to further investigate the risk factors being targeted. Second, some information is missing and could not be taken from the patient such as the type of antibiotic given before, at what dose or was it really necessary. Third, a selection bias may have risen by the control selection for matching. Finally, some antibiotics were not tested, such as fosfomycin, which is usually effective against ESBL producer isolates.

Conclusion

Lebanon is a high prevalence country in terms of ESBL producing gram negative enterobacteriacea causing urinary tract infection. Recent antibiotics use (last three months), was found to be a significant risk factor for acquiring such infections while the age group "18-50 years" was a protective factor. Also, high rates of co-resistance to other antibiotics commonly used in our country have been identified. Lebanon definitely needs a strategy to restrict abuse of antibiotics as an essential step towards decreasing the prevalence of resistant pathogens and the resulting morbidity/mortality rates.

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