Journal of Infectious Diseases & Preventive Medicine

Taha et al., J Infect Dis Preve Med 2018, 6:2
DOI: 10.4172/2329-8731.1000183

Research article Open Access

Prevalence and Risk Factors of Extended Spectrum Beta-Lactamase-Producing Uropathogens among UTI Patients in the Governmental Hospitals of North West Bank: A Cross-Sectional Study

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Received date: October 07, 2018; **Accepted date:** October 16, 2018; **Published date**: October 22, 2018

Abstract

Background: Urinary tract infections caused by Extended Spectrum Beta-Lactamase producing organisms (UTI-ESBL) are increasing in incidence and pose a great threat to modern medicine. The objective of this study was to assess the prevalence and risk factors of Extended Spectrum Beta-Lactamase (ESBL)-producing uropathogens among patients with urinary tract infections in the north of West Bank and to determine the antimicrobial susceptibility profile of the isolated bacteria.

Methods: A total of 427 patients who were attending the governmental hospitals in the northern cities of the West Bank were included in the study. They were older than 12 years and diagnosed with UTI in the period from June 2017 to September 2017. Isolated bacteria was collected from the microbiology labs of the respective hospitals and tested for the ESBL production and their antibiotic susceptibilities were determined. Information regarding the risk factors was collected from the patient's medical records. Univariate analyses were performed for potential risk factors for the development of UTI-ESBL, and then multivariate analyses were performed for all significant variables.

Results: Out of the 427 urine cultures screened for ESBL, 163 (38.4%) were confirmed to be ESBL producers. *E. coli* was the most frequent uropathogen. K. *pneumoniae* produced the highest rate of ESBL (54.9%), followed by *E. coli* (42.5%), and *Proteus mirabilis* (7.14%). Patients with recurrent UTI had 5 times relative risk of having ESBL producing uropathogens (odd ratio (OR), 4.7) followed by previous antibiotic use (OR, 3.07), hemodialysis (OR, 2.92), chronic kidney disease (OR, 2.69) and finally diabetes mellitus (OR, 1.87). ESBL isolates were susceptible to fosfomycin (100%), nitrofurantoin (93.9%), pipracillin/tazobactam (94.5%), ertapenem (98.2%), meropenem (98.8%), and amikacin (93.9%).

Conclusion: The prevalence of ESBL-producing uropathogens was 38.4%. Recurrent UTI appeared to be the strongest risk factor for ESBL-UTI. ESBL–producing uropathogens were highly susceptible to amikacin, nitrofurantoin, and much more to fosfomycin and piperacillin/tazobactam in addition to carbapenems.

Keywords: ESBL; UTI; *E. coli*; *K. pneumonia*; Risk factors; Antimicrobial resistance; Antibiotics

Abbreviations: ESBL: Extended-Spectrumβ-Lactamase; HIS: Health Information System; UTI: Urinary Tract Infection; O-UTI: Out-patient Urinary Tract Infection; I-UTI: In-patient Urinary Tract Infection; OR: Odd Ratio; CI: Confidence Interval; IRB: Institutional Review Board; CFU: Colony Forming Unit; SD: Standard Deviation; DDST: Double-Disc Synergy Test.

Background

Infection caused by multidrug-resistant bacteria are emerging is a global threat to modern medicine and pose serious challenges for clinicians with respect to antimicrobial treatment options and infection control [1].

Urinary tract infection (UTI) remains the most common infections affecting outpatients as well as hospitalized patients [2]. Worldwide data show that resistance among uropathogens to conventional drugs is increasing [3].

Extended-spectrum B-lactamases (ESBL), which are produced by many gram negative bacilli such as *Enterobacteriaceae* family mainly, *E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis*, hydrolyze the -lactam ring in -lactam antibiotics rendering them inactive. Doing so, these enzymes confer resistance to all -lactam antibiotics such as cephalospornins which are used in the treatment of UTI [4]. Additionally, ESBL-producing organisms bear co-resistance to other antimicrobial agent's classes, such as aminoglycosides, sulfonamide and fluoroquinolones. Therefore, these multi-drug resistant organisms make treatment options and infection control challenging, and initial empiric therapy is often ineffective and associated with increased morbidities, hospitalization period, and rising medical costs [5].

Overuse of extended spectrum antibiotics, contribute to the high prevalence of ESBL [6]. The prevalence and phenotypic characteristics of clinical isolates vary among different regions due to differences in prescribing practices and use of antibiotics [7].

Consequently, early identification of patients who are at risk for infection with ESBL-producing uropathogens is necessary to prescribe the most effective empirical therapy and to apply preventive measures to limit the dissemination of infection [8].

This can minimize the complications associated with UTI, reduce the burden of medical expenses, halt the development of antibiotic resistance, and enhance the clinical outcome among the patients [9].

The main objectives of the study were: 1) to determine the prevalence of ESBL-producing uropathogens 2) to investigate the risk factors that give rise to this resistance and 3) to determine the antibiotic susceptibility profile of ESBL-producing uropathogens.

Methods

Patients and data collection

Four hundred and twenty-seven patients attending the governmental hospitals in northern cities of the West Bank (Rafidia Governmental Hospital, Al-Watani governmental Hospital, Tubas Turk Devlet Hastanesi, Thabet-Thabet Hospital, Darwish Nazzal Hospital and Jenin Government Hospital) who met the inclusion criteria were included in the study. They were older than 12 yr and diagnosed with gram-negative UTI in the period from June 2017 to September 2017. Their medical records were reviewed for the demographic information, medical history and potential risk factors. The bacterial isolates were collected from the corresponding laboratories for further testing. Diagnosis of UTI was based on the presence of positive urine culture of $>10^5$ *CFU*/mL in addition to one or more of the following symptoms or signs: fever higher than 38°C, chills, tenderness in the suprapubic or flank area, painful urination, urgency, and frequency [10].

Patients were considered to have out-patient urinary tract infection (O-UTI) if they were diagnosed at outpatient clinics, emergency room or within 48 h of hospitalization. If the patients developed UTI after 48 h of hospitalization, they were classified as having in-patient urinary tract infection (I-UTI).

Demographic and clinical data were extracted from the Hospital Information System (HIS) at the participating hospitals.

Microbiological methods

The isolated bacterium was collected from the laboratories for further testing which included:

Confirmation and identification of the causative organism.

Testing of ESBL production, screening and confirmatory tests.

Assessment of antimicrobial susceptibility.

Bacteria identification was confirmed using an API 20E strip test.

ESBL screening was performed using disc diffusion method on Muller-Hinton agar using five prepared, fixed concentration, paper antibiotic discs which include (cefotaxime (30 µg), ceftriaxone (30 µg), ceftazidime (30 µg), aztreonam (10 µg) and cefpodoxime (10 µg). After an incubation period of about 18-24 h at 37°C, the zones of growth inhibition around each of the antibiotic discs were measured and interpreted according to guidelines of CLSI 2017 [11]. ESBL-production was confirmed by Double-Disc Synergy Test (DDST). Discs containing cephalosporin (cefotaxime (30 µg), ceftriaxone (30 µg), ceftazidime (30 µg) and cefepime (30 µg)) were applied next to a disc with amoxicillin (20 µg)+clavulanic acid (10 µg), a positive result is recorded when expansion of indicator cephalosporin inhibition zone toward antibiotic with clavulanic acid were observed according to guideline of CLSI 2017 [11].

ESBL positive strains were tested for antimicrobial susceptibility using 11 commercially-prepared, fixed concentration, paper antibiotic discs (piperacillin/tazobactam (100/10 µg), ertapenem (10 µg), imipenem (10 µg), meropenem (10 µg), gentamicin (10 µg), ciprofloxacin (5 µg), norfloxacin (10 µg), fosfomycin (200 µg), trimethoprim/sulfamethoxazole (23.75/1.25 µg) ,nitrofurantoin (300 µg) and amikacin (30 µg)) (Oxoid, UK). Antibiotic discs were placed on inoculated agar surface, the zones of growth inhibition around each of the antibiotic discs were measured and interpreted based on CLSI guidelines 2017 [11]. *E. coli* ATCC 25922 was used as a control throughout the study. The following risk factors were retrieved from patients' medical records: age, gender, previous hospitalization, previous antimicrobial use, recurrent UTI, in-patient, diabetes mellitus, urologic operation, Foley's catheterization, hemodialysis, chronic kidney disease, history of urolithiasis, and malignancy.

If the patient administered at least one antibiotic for more than one day before the time of the diagnosis of urinary tract infection in the past year he was considered to have previous antimicrobial use. If the patient spent more than one day in the hospital before the time of diagnosis, he was considered as having previous hospitalization. History of Foley's catheterization was defined as cases with catheterization for more than 3 days before the time of the diagnosis of urinary tract infection [12]. If the patient has ≥ 2 urinary tract infections in the past six months or 3 infections in the past year, he was considered to have recurrent UTI [13].

Statistical analysis

Statistical analysis was done using SPSS statistical software version 23. The following potential risk factors for the emergence of ESBL-producing uropathogens were examined using univariate analysis: gender, age, in-patient, previous hospitalization, recurrent UTI, chronic kidney diseases, diabetes mellitus, history of Foley's catheterization, previous antibiotics use, history of urologic operation, malignancy, urolithiasis and hemodialysis. Variables with $P<0.05$ in univariate analysis were analyzed using multivariate logistic regression. All statistical tests were 2-tailed. Statistical value of $P<0.05$ was considered to be significant.

Results

Epidemiology

The most common bacteria was *E. coli*, followed by *K. pneumoniae*, *P. aeroginosa*, *P. mirabilis*, *S. marcescens*, *A. baumannii*, *C. koseri*, and *M. morganii* as shown in Table 1.

Out of the 427 positive urine cultures screened for ESBL, 163 (38.4%) were confirmed ESBL producers (134 *E. coli*, 28 *K. pneumoniae*, 1 *P. mirabilis*). Among ESBL producing isolate, *E. coli* was the most frequent one, but the rate of ESBL production is highest in *K. pneumoniae* (54.9%: 28 out of 51), followed by *E. coli* (42.5%; 134 out of 315) and *P. mirabilis* (7.14%: 1 out of 14) (Table 2).

Percent (%)	Number of isolates	Bacteria
Escherichia coli	315	73.8
Kelbsiella pneumoniae	51	11.9
Proteus mirabilis	14	3.3
Pseudomonas aeroginosa	32	7.5
Serratia marcescens	6	1.4
Morganella morganii	2	0.5
Citrobacter koseri	3	0.7
Acintetobacter baumannii	4	0.9

Table1: Distribution of gram negative uropathogens.

	Non-ESBL producers	ESBL producers
Organism	N (%)	N (%)
E. coli	181 (68.56)	134 (82.2)
Kelbsiella pneumoniae	23 (8.71)	28 (17.18)
Proteus mirabilis	13 (4.92)	1 (0.613)
Pseudomonas aeroginosa	32 (12.12)	-
Serratia marcescens	6 (2.27)	-
Morganella morganii	2 (0.76)	-
Citrobacter koseri	3 (1.14)	-
Acintetobacter baumannii	4 (1.52)	-
Total	264	163

Table 2: Distribution of ESBL-producing and Non-ESBL producing uropathogens.

Risk factors for ESBL-producing *Enterbacteriaeceae*

Risk factors for infection due to an ESBL-producing uropathogens, identified through univariate analysis, were age 65 yr, previous hospitalization, and previous antibiotic use, past history of Foley's catheterization, hemodialysis, diabetes mellitus, recurrent UTI, urolithiasis and chronic kidney disease (Table 3).

Multivariate analysis identified 5 variables as statistically significant predictors of infection due to an ESBL-producing uropathogens: recurrent UTI (OR,4.7:95% CI,2.68-8.27) previous use of any antibiotic (OR,3.07;95% CI,1.46-6.45), hemodialysis (OR,2.92;95% CI,1.01-8.41), chronic kidney disease (OR,2.69;95% CI,1.28-5.67) and diabetes mellitus (OR,1.87;95% CI,1.06-3.31) (Table 3).

	Univariate analysis	P-Value	Multivariate analysis	P-Value
Variable (all patient 427)	Odds Ratio (95% CI)		Odds Ratio (95% CI)	
Age 65	2.55 (1.68-3.86)	<0.001	1.41 (0.83-2.40)	0.209
Male gender	1.16 (0.77-1.75)	0.479	-	-
Inpatient	1.11 (0.68-1.83)	0.67	-	-
Previous hospitalization	3.28 (1.86-5.80)	<0.001	1.51 (0.78-2.93)	0.223
Previous antibiotic use	8.90 (4.80-16.5)	<0.001	3.07 (1.46-6.45)	0.003
Foley's catheterization	3.09 (2.01-4.73)	<0.001	0.69 (0.39-1.23)	0.205
Hemodialysis	3.97 (1.69-9.36	0.01	2.92 (1.01-8.41)	0.048
Diabetes mellitus	2.99 (1.92-4.64)	<0.001	1.87 (1.06-3.31)	0.032
Recurrent UTI	9.08 (5.76-14.32)	<0.001	4.70 (2.68-8.27)	<0.001
Urologic operation	4.97 (3.17-7.80)	0.869	-	-
Malignancy	1.067 (0.56-2.03)	0.846	-	-
Urolithiasis	3.73 (2.23-6.24)	<0.001	1.43 (0.75-2.70)	0.275
Chronic kidney disease	7.47 (4.09-3.64)	<0.001	2.69 (1.28-5.67)	0.009

Table 3: Predictors of infection with an Extended-Spectrum β-Lactamase-producing pathogenic.

Antimicrobial Susceptibility

Antimicrobial susceptibility profile for ESBL-producing uropathogens is presented in Table 4. In our study, ESBL-producing isolates were totally susceptible to *Fosfomycin* (100%), highly susceptible to nitrofurantoin (93.9%), piperacillin/tazobactam (94.5%), ertapenem (98.2%), meropenem (98.8%), and amikacin (93.9%). 59.5% of isolates were susceptible to gentamicin. On the other hand, a poor susceptibility was observed for ciprofloxacin, norfloxacin, trimethoprim/sulfamethoxazole and imipenem.

Antibiotic	Resistant (%)	Intermediate (%)	Sensitive (%)
Piperacillin/tazobactam	0	5.5	94.5
Ertapenem	0.6	1.2	98.2
Imipenem	68.1	6.7	25.2
Meropenem	0	1.2	98.8
Gentamicin	38.0	2.5	59.5
Ciprofloxacin	55.8	6.1	38.0
Norfloxacin	55.2	3.1	41.7
Fosfomycin	0	0	100
Nitrofurantoin	4.9	1.2	93.9
Trimethoprim/ sulfamethoxazole	68.1	1.8	30.1
Amikacin	4.3	1.8	93.9

Table 4: Antimicrobial susceptibility of ESBL-producing organisms.

Discussion

The emergence of clinically significant antibiotic-resistant organisms, especially for those resistant to multiple classes of antibiotics, is increasing, making appropriate antimicrobial treatment and infection control challenging. Many pathogens resistant to first-line agents then require broader spectrum, more expensive agents with less favorable safety profiles. Hence local antimicrobial susceptibility profiles should be known in order to prescribe the most appropriate empiric antimicrobial agents with least cost.

Urinary Tract Infection (UTI) is one of the most common infections worldwide, and as many others, there is an increasing resistance among urinary tract pathogens to conventional drugs used to treat them [5].

The rate of ESBLs production in bacterial species differs greatly all over the world, and rapidly changing from time to time [14]. The prevalence of ESBL was reported to be over 10% in east Europe, 3.5% in Canada, 7.5%-41% in Persian Gulf region and 20-48.8% in Asia [15-19]. In the present study ESBL production rate (38.4%), was higher than a previous report by Odwan et al. (32.7%) [20].

Among the isolated ESBL producing-uropathogens, *E. coli* were the most prevalent (82.2%) followed by *K. pneumoniae* (17.2%). But the rate of ESBL-production was the highest in *K. pneumoniae* (54.9%), followed by *E. coli* (42.5%) and *P. mirabilis* (7.14%). This is in agreement with other studies in which *K. pneumonia* had the highest prevalence (54%) compared to that of *E. coli* (44%), as showed by Talat A EL-Kersh in Saudi Arabia [21]. RH Khoury also had the same conclusion, 24.4% for *K. pneumonia* and 5.1% for *E. coli* [22].

Many studies showed that the development of ESBL producing uropathogens is higher in patients with previous history of hospitalization, previous antimicrobial use, past history of catheterization, inpatient UTI, past history of urogenital operation and female gender [10,23,24]. In this present study, univariate analysis showed age, previous hospitalization, previous antibiotic use, past history of Foley catheterization, hemodialysis, diabetes mellitus, recurrent UTI, urolithiasis, chronic kidney disease and hydronephrosis to play a role in the emergence of ESBL producing uropathogens (Table 3).

Multivariate logistic regression analysis identified that recurrent UTI was the strongest risk of acquiring ESBL producing uropathogens followed by pervious antibiotic use, diabetes mellitus, chronic kidney disease and hemodialysis (Table 3). On the other hand, age (p-value=0.209), previous hospitalization (p-value=0.223), past history of Foley's catheterization (p-value=0.205), urolithiasis (p-value=0.275) and hydronephrosis (p-value=0.762) were not risk factors for developing ESBL producing uropathogens.

Several studies showed that the strongest risk factor for the emergence of ESBL- producing uropathogens was past history of hospitalization [10,24]. However, in our study, it had no association with the development of ESBL-producing uropathogens. On the other hand, the emergence of ESBL producing uropathogens was 5 times higher in those with recurrent UTI making it the strongest risk factor (OR,4.7:95% CI,2.68-8.27), and this is in agreement with many reports around the world [26-28]. Therefore, prevention and proper treatment of recurrent UTI through behavioral modification, non-antimicrobial measures and antimicrobial prophylaxis after counseling should be established to prevent the emergence of ESBL-producing uropathogens [29].

Maria Dolores Navarro reported that diabetes mellitus was a significant risk factor for acquiring ESBL-producing uropathogens (OR,5.5; 95% CI,1.6-18.7) [30]. Similarly, in the present study, the possibility of infection with ESBL-producing uropathogens was higher in patients with diabetes mellitus by approximately 2 times (OR, 1.87; 95% CI, 1.06-3.31).

Previous antibiotic use seemed to be associated with the emergence of ESBL producing uropathogens (OR,3.07; 95% CI,1.46-6.45), and this is consistent with many studies [30-32]. Actually, proper use of antibiotics reduces the emergence of multidrug-resistant bacteria [33]. Therefore, over the counter use of antibiotic and prescription of antibiotics for treatment of undocumented UTI should be restricted.

Foley's catheterization is considered one of the widely known risk factors for urinary tract infection [10]. Unskilled sterilization techniques during Foley's catheter insertion were responsible for about 20% of UTI [34]. Some reports pronounced that Foley's catheterization may play a major role in the emergence of ESBL-producing uropathogens [35]. However, in our study, it was not a risk factor, and that is similar to what is reported by OK Azap [27].

Males and females have similar chances for having ESBL-producing UTI (P-value=0.209), although some studies showed slightly higher risk in males and others in females [10,27,31,33], and this is similar to what was reported by Michael Osthoff [36]. In addition, ESBL positivity also was not significantly associated with age (P-value=0.056) as opposed to a report by Jesus Rodriguez-Bano who found that older age in male patients (OR,1.03; 95% CI, 1.03- 1.05) was a risk factor [25]. While OK Azap and Kandeel A did not find age as a risk factor (P-value=0.952 [27,14].

There are few reports describing the association between hemodialysis (HD) and ESBL infection. Similar to our findings, Chih-Chao Yang reported in a retrospective study that hemodialysis (HD) patients are at higher risk of acquiring ESBL-producing bacterial infections [37]. The longer the duration of catheter-dependent hemodialysis the higher the likelihood of developing ESBL infection [35]. So shortening the duration of catheter-dependent HD, proper sterile insertion technique, education and the commitment of both staff and institutions should be applied to decrease the risk of these infections. In addition, in our study, CKD appeared to play a role in the development of ESBL-producing uropathogens. M Sogaard observed in a case-control study that patients with renal disease had 2 times risk of developing ESBL infection (OR,2.2; 95% CI,1.4-3.4) [38]. On the other hand, urolithiases was not associated with ESBL infection, a similar finding was observed by OK Azap [27].

Past history of urogenital operation had no association with ESBL production. Similar to what was observed by Kandeel. A in a study conducted in Saudi Arabia and Dong Sup Lee in Korea [10,14]. Going to malignancy, in the current study, it was not significantly associated with UTI-ESBL. However several studies showed that patients with solid or hematologic malignancy are at higher risk for colonization and infection with ESBL-producing *Enterobacteriaceae* [39].

Dong Sup Lee observed that I-UTI associated with higher risk of developing ESBL infection (OR1.71; 95% CI,1.3-202) [10], which was not a significant risk factor in ours (OR 1.11; 95% CI,0.68-1.83).

ESBL-producing uropathogens showed high resistance rate to most of the currently used antimicrobial agents such as co-trimoxazole (≈70%), quinolones specifically ciprofloxacin and norfloxacin (>50%), but less resistant to other antibiotics such as gentamicin (38%) and

much less resistantto carbapenems such as ertapenem (0.6%) and meropenem (0%), *amikacin (4.3%), nitrofurantoin (4.9%), piperacillin/tazobactam (0%) and fosfomycin (0%).*

The carbapenems (imipenem, ertapenem and meropenem) are still the first line agents in treatment of serious infection with ESBL-producing organisms as >98% of ESBL-producing organisms still susceptible to these drugs [40]. The same findings were observed in our study that 98.8%susceptibility was observed for meropenem, 98.2% for ertapenem, however, a higher level of resistance was observed for imipenem (68.1%) compared to regional studies [41,42].

The role of aminoglycosides in the treatment of ESBL infection shouldn't be forgotten. In a Spanish study published in 2014, aminoglycosides were used in the treatment of carbapenems-resistant *Klebsiella* infection showing a statistically significant reduction in mortality [40,43]. In a study conducted by Sung-Yeon Cho, he observed that amikacin Outpatient Parenteral Antibiotic Therapy (OPAT) considers a reasonable therapeutic option for non-bacteremic ESBL-producing *Escherichia coli*-related lower urinary tract infection in settings with limited resources, and all patients in the study were able to tolerate amikacin OPAT without any significant nephrotoxicity or ototoxicity [44]. In our study, we found that about 94% of ESBL-producing uropathogens were susceptible to amikacin, however, a poor susceptibility for gentamicin (59.5%) was observed. In the present study, 93.9% of ESBL-producing uropathogens were sensitive to nitrofurantoin. Tasbakan MI evaluated the effectiveness of nitrofurantoin in the treatment lower UTI caused by ESBL-producing E. coli and found that clinical and microbiological success rates were 69% and 68%, respectively [45]. Hence, nitrofurantoin may be used in the treatment of lower urinary tract infection due to ESBL producing uropathogens.

On the other hand, ESBL-producing uropathogens were totally (100%) susceptible to fosfomycin. In a study conducted by Pullukcu H to assess the effectiveness of fosfomycin in the treatment of lower UTI due to ESBL-producing uropathogens *reported that* overall clinical and microbiological success rate was 94.3% and 78.5% respectively [46]. Based on these findings fosfomycin may be a suitable, effective and cheap alternative in the treatment of ESBL-producing uropathogens.

Piperacillin/tazobactam (TZP) as an alternative treatment to carbapenems for infections involving ESBL-producing organisms remains debated [47]. In our study, a high rate of susceptibility (94.5%) was observed for TZP. In a Randomized controlled trial conducted by Yu Bin Seo, reported that TZP is effective in the treatment of UTI caused by ESBL-*E. coli* when the *in vitro* test indicates susceptibility [48]. So this antibiotic may be used as an alternative treatment to carbapenems for pyelonephritis caused by ESBL-producing uropathogens.

Although carbapenems are highly effective against ESBL-producing uropathogens, and this is consistent with what we found, our data suggested that EBL-producing uropathogens were also highly susceptible to aminoglycosides *(amikacin), nitrofurantoin, fosfomycin and piperacillin/tazobactam*. With the increase in multi-drug and carbapenem-resistant microorganisms, there is a need to minimize carbapenem use and they should be only used in the treatment of serious life-threatening infections. Hence, these drugs, other than carbapenems, could also be used cautiously as antimicrobial empiric therapy for urinary tract infection.

Limitations of the Study

1) The inclusion of bacterial isolates from both hospitalized and ambulatory patients 2) The small sample size might have prevented the identification of additional risk factors for ESBL-UTI.

Conclusion

In conclusion, the incidence of UTIs caused by ESBL-producing uropathogens seems to be Increasing, and this emerging issue complicates the use of antibiotics in the management of UTI. The overall prevalence of ESBL-producing microorganisms in urinary tract infection was 38.4%. The risk appeared to be increased in cases with recurrent UTI, previous antibiotic use, chronic kidney disease, hemodialysis and diabetes mellitus.

In this study, ESBL-producing uropathogens were highly susceptible, in addition to carbapenems, to aminoglycosides (amikacin), Nitrofurantoin and much more to fosfomycin and piperacillin/tazobactam. Hence these drugs should be a part of the empirical therapy for UTI. As resistance to carbapenems is growing, its use as a part of empirical therapy should be restricted, and a proper antibiotic policy for every health care institution should be made available to guide the clinicians in order to prevent the development of resistance to these antibiotics, reduce the burden of medical expenses and enhancing the clinical outcome among patients.

Declaration

Ethical consideration

The study was approved by the Institutional Review Board (IRB) and the scientific research committee at An-Najah National University (Faculty of Medicine and Health Sciences). Permission was obtained from General Administration of Primary Health Care of the Palestinian MoH prior to collecting any data. Participants' privacy and confidentiality have been assured (no names have been used, only file numbers were used) and all data and results have been handled and treated confidently.

Consent for Publication

Not applicable.

Availability of Data and Materials

All data generated or analyzed during this study are included in this article. The raw data are available from the corresponding author on reasonable request.

Competing Interest

The authors declare that they have no financial and/or non-financial competing interests.

Authors' Contributions

AAT and AJ designed the study and its protocol.

YD and AS collected the data, conducted the microbiological tests and performed the data analysis. AAT, AJ, YD and AS drafted the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgment

The authors would like to thank all Specialist medical laboratories in governmental hospitals of North West Bank study for their cooperation and understanding.

Funding

The study was funded by An-Najah National University.

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