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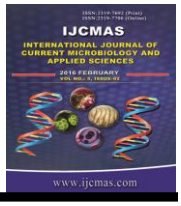

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Prevalence, Risk Factors and Antimicrobial Susceptibility of Beta Lactamase Producing Enterobacteriacea in a Tertiary Care Centre of Saudi Arabia

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A B S T R A C T

The main objective of this study was to determine the prevalence, risk factors and antimicrobial susceptibility of Beta lactamase (BL) producing Enterobacteriacea isolated from CAUTI and Non-CAUTI patients. This study was conducted at Dawadmi General Hospital, Saudi Arabia from March 2012 to March 2015. A total of 780 urine samples were collected from mid-stream, clean catch, suprapubic aspirate and Foley's catheter from both inpatient and outpatient departments for studying the presence of Beta lactamase enzymes producing Enterobacteriacea. The organisms were isolated by standard microbiological techniques and the isolates were tested for their species identification and antimicrobial susceptibility by modified Vitek 2 method. Out of the total 780 urine samples collected in this study, 388 (49.7%) came out to be positive for UTI isolates. Among them 231 (29.6%) isolates recovered were found to be Enterobacteriacea. Among Enterobacteriacea 150 (64.9%) isolates were producing beta lactamases and 81 (35.1%) isolates were non-beta lactamases. The risk factors in Beta lactamase isolates were found to be long term hospital stay 134(89.3%), urinary catheter 125(83.3%), ICU stay 109(72.7%), prior antibiotic use within 3 months 98(65.3%), obstructive uropathy 74(46.7%), renal disease/renal transplant 68(45.3%).The frequency of ESBL, CTX-M, AmpC, ESBL with Carbapenems, OXA and MBL were higher in catheterized patients as compared to non-catheterized patients. The β-lactamases producing isolates were resistant to most of the antibiotics tested but Tigecycline and Colistin showed promising efficacy against all the Beta lactamases in both CAUTI patients and Non-CAUTI patients Catheterized patients should be screened regularly for the prevalence beta lactamase producers. While handling catheterized patients the healthcare staff should follow proper guidelines and infection control measures to avoid the spread of nosocomial infections.

Introduction

Urinary tract infections (UTIs) along with pneumonia is considered as the second most

common type of healthcare-associated infection, secondly to Urinary system infections(USI) which accounts for more than 15% of infections as reported by acute care hospitals(Magill *et al.*, 2012). Among *Enterobacteriaceae* particularly *Escherichia coli and Klebsiella pneumoniae* are considered as the major causes of UTI in both inpatients and outpatients (Sharma *et al.*, 2012). Since the aetiology of UTI and the antibiotic susceptibility pattern of urinary pathogens have been changing over the past years, current knowledge on the burden and antimicrobial susceptibility pattern is essential for appropriate therapy. Gram negative bacteria has more than 1000 Beta lactamase(BL) producers which include Extended spectrum Beta lactamases (ESBLs), AmpC -lactamases (AmpC), *Klebsiella pneumoniae* carbapenemases (KPC), and the metallo - lactamases (MBLs) which are multidrug resistant bacteria. (Bush, 2011) They may also produce multiple Beta Lactamases such as combinations of ESBLs and carbapenemases, ESBLs and AmpC etc., The most common pathogens involved in producing beta lactamases are *Escherichia coli* and *Klebsiella pneumoniae* which produce the enzymes Extended Spectrum β-Lactamases (ESBLs). Catheter-associated urinary tract infections (CAUTI) accounts for 30% to 40% among all the nosocomial infections (Conway *et al.*, 2012). CAUTI occur in patients having urinary tract infections on the third day after insertion of catheter. In long term catheter use, the risk of antibiotic resistant pathogens further increases due to the formation of bio-film along the catheter. (Conway *et al.*, 2012). The risk of infection in patients catheterized for more than 7 days is 25% and increases to 100% after 30 days (Jaggi *et al*, 2012). The colonization of bacteria the drainage bags of catheterized patients is found to be main source of outbreaks of resistant bacteria in acute care facilities (Hooton *et al.*, 2009, Lo *et al.*, 2014). The main objective of this study was to study was to determine the prevalence and antimicrobial susceptibility of Beta lactamase (BL) producing Enterobacteriacea isolated from CAUTI and Non-CAUTI patients in Al-Dawadmi General Hospital, Saudi Arabia This study is important for clinicians in order to facilitate the effective treatment and management of patient with symptoms of urinary tract infections.

Materials and Methods

This retrospective study was conducted at the Department of Medical Microbiology, Al-Dawadmi General Hospital, Al-Dawadmi Governorate, Kingdom of Saudi Arabia, KSA, a tertiary care 250 bed capacity hospital, with a CBAHI (Central Board for Accreditation of Health Institutes) accredited Lab, from March 2012 till March 2015. A total of 780 urine samples were collected from patient with symptoms suggestive UTI from both in and out patients using systematic random sampling technique. Socio-demographic characteristics such as gender and age were gathered from eligible patients. Clinical features such as history of hospitalization, ICU admission, prior antibiotic use within 3 months, long term hospital stay, presence of urinary catheter and chronic diseases were also collected. Urinary samples included mid-stream clean catch urine and urine obtained from Foley's catheter from both in and out patients. Urine samples were cultured using a 1µm calibrated loop onto CLED agar and blood agar (Media, Ministry of Health), incubated at 37°C for 18-24 hours and the number of colonies was counted. The specimen yielding more than or equal to 10^5 CFU/ml of urine was interpreted as significant, except for samples from elderly women and men. Colony count

of 10^4 and 10^3 CFU/ml of urine respectively was interpreted as significant. Plates with more than 3 different types of organisms were considered mixed insignificant growth, all the plates were inspected for growth and the isolates were identified by observing colony morphology, Gram-stain characteristics and relevant biochemical tests by Vitek 2 system for microbial identification and sensitivity Instrument. The isolates were tested for their antimicrobial susceptibility using AST N-291 and N-232. Reference strains included in the study were as follows: ESBL positive *Klebsiella pneumoniae* ATCC 700603, ESBL negative *Escherichia coli* ATCC 25922. The results were interpreted according to the guidelines of Clinical and Laboratory Standards Institute (CLSI, 2012).

Statistical Analysis

Statistical analyses were performed using the SPSS, Version 20. Chi-square test was used to compare categorical variables were ever applicable. A p-value less than 0.05 were considered significant.

Results and Discussion

Out of the total 780 urine samples collected in this study, 388 (49.7%) came out to be positive for UTI isolates. Among them 231 (29.6%) isolates recovered were found to be Enterobacteriacea. Among Enterobacteriaceae 150 (64.9%) isolates were producing beta lactamases and 81 (35.1%) isolates were non-beta lactamases. The overall prevalence of beta lactamases producing Enterobacteriacea in males was 36(24%) which are found to be less than the females 114(76%) which was statistically significant ($p<0.05$). Among inpatients the majority of beta lactamases producing Enterobacteriacea are from patients in Intensive care unit 30(30.3%) followed by Medical ward 26(26.3%) Surgical ward 23(23.2%), Paediatric ward 11(11.1%) and the least were from Obstetrics and gynaecology 9(9.1%) which was statistically significant ($p<0.05$). Most of beta lactamases producing Enterobacteriacea infected patients belonged to the 31-45 years age group 46(30.7%) followed by > 62years 39(26%) and 16 - 30 years 32(21.3%) respectively which was statistically significant ($p<0.05$). Similarly the percentage of beta lactamases producing Enterobacteriacea in outpatients was 51(34%) which are less than the inpatients 99(66%) which was statistically significant ($p<0.05$). The percentage of beta lactamases (BL) producers is more 90(60%) in catheter associated UTI patients (CAUTI) when compared to non-catheter associated UTI patients (Non-CAUTI) which was only 60(40%) which was statistically significant ($p<0.05$). The results were shown in Table 1.

Escherichia coli was the most predominant one having 66(44%) isolates of beta lactamases producing Enterobacteriacea followed by *Klebsiella spp* 46(30.7%), *Enterobacter species* 15(10%), *Proteus mirabilis* 10(6.7%), Acinetobacter *species* 7(4.7%), *Serratia species* 4(2.7%) and *Citrobacter species* 2(1.3%). Among 90 BL isolates from CAUTI patients, 56(62.2%) were ESBL, 5(5.6%) were CTX-M, 11(12.2%) were AmpC, 11(12.2%) were ESBL with Carbapenems, 3(3.3%) were OXA and 4(4.4%) were MBL producing isolates as shown in Figure.1. Among 60 BL isolates from Non - CAUTI patients, 29(48%) were ESBL, 4(2.7%) were CTX-M, 9(6%) were AmpC, 13(8.7%) were ESBL with Carbapenems, 2(1.3%) were OXA, 3(2%) were MBL producing isolates as shown in Figure.2. The results showed that the BL isolates in catheter associated UTI patients (CAUTI) were more 90(60%) when compared to non-catheter associated

UTI patients (Non-CAUTI) which was only 60(40%) as shown in Table 2. Risk factors associated with BL UTI were analyzed by comparing patients with non-BL UTIs. The risk factors in Beta lactamase isolates were found to be long term hospital stay 134(89.3%), urinary catheter 125(83.3%), ICU stay 109(72.7%), prior antibiotic use within 3 months 98(65.3%), obstructive uropathy 74(46.7%), renal disease/renal transplant 68(45.3%).The risk factors in non-BL UTI is less when comparing to BL UTI as shown in the Table 3.

Rates of antibiotic resistance for beta lactamases producing Enterobacteriacea in CAUTI patients and Non-CAUTI patients are summarized in Table 4. Antibiotic resistance rates for CAUTI patients were greater than Non-CAUTI patients. ESBL isolates showed high rate of resistance to Ampicillin, Ceftazidime, Cifotaxime and Trimethoprim sulfamethoxazole in both CAUTI patients and Non-CAUTI patients. ESBL and CTX-M isolates showed high rate of resistance to Cefipime in addition to Ampicillin, Ceftazidime, Cifotaxime and Trimethoprim sulfamethoxazole in both CAUTI patients and Non-CAUTI patients. AmpC isolates showed high rate of resistance to even amoxicillin clavunalic acid, Cefoxitin in addition to Ampicillin, Ceftazidime, Cifotaxime and Trimethoprim sulfamethoxazole in both CAUTI patients and Non-CAUTI patients. ESBL and Carbapenem isolates showed high rate of resistance to Imipenem and Meropenem in addition to Ampicillin, Ceftazidime, Cifotaxime and Trimethoprim sulfamethoxazole in both CAUTI patients and Non-CAUTI patients. OXA isolates showed high rate of resistance to amoxicillin clavunalic acid, Imipenem and Meropenem, Amikacin, Gentamicin addition to Ampicillin, Ceftazidime, Cifotaxime and Trimethoprim sulfamethoxazole in both CAUTI patients and Non-CAUTI patients. MBL isolates showed high rate of resistance to amoxicillin clavunalic acid, Imipenem and Meropenem Norfloxacin in addition to Ampicillin, Ceftazidime, Cifotaxime and Trimethoprim sulfamethoxazole in both CAUTI patients and Non-CAUTI patients.

The current study aimed to study prevalence of antibiotic resistance enzymes among Enterobacteriacea isolated from different cases of urinary tract infections in Al-Dawadmi General Hospital, Saudi Arabia and also to analyze the antimicrobial sensitivity pattern of those isolates against various types of antimicrobial agents used for treating urinary tract infections. Previous studies conducted on Beta Lactamase resistance of urinary tract infections in hospital and community patients not focused on CAUTI and non-CAUTI patients (Zilberberg *et al.*, 2013; Azap *et al.*, 2010; Calbo *et al.*, 2006). Since CAUTI patients have different antibiotic resistance patterns those of non-CAUTI patients study of prevalence rate, antimicrobial resistance pattern and risk factors for beta lactamase producers unique to this population is important for the development of effective preventive measures (Yamamichi *et al.*, 2012). In our study various β lactamases were found both in CAUTI and non-CAUTI patients but the number is more in CAUTI than the non-CAUTI patients. Previous studies showed that patients having chronic indwelling catheters acting as the most common site of isolation of resistant gram negative organisms (Arnaldo *et al.*, 2013, Mody *et al.*, 2007). Among the β lactamases ESBL production was found to be high (56.7%) in both CAUTI and Non-CAUTI which is higher than reports on ESBL production by Enterobacteriaceae from Saudi Arabia which reported (35.16%, 39.8%, 35%, 27.5%) by Loveena *et al* (2013); Bandekar *et al* (2011); Babay

(2002); Bilal and Gedebou, (2002). However higher rates of ESBL production were reported by Agamy *et al* (2009) (55%) from Saudi Arabia, and by Mathur *et al* (2002)(68%) from India. and Pakistan Shah *et al* (2002)(45%).

The overall prevalence of beta lactamases producing Enterobacteriacea in males was 36(24%) which are found to be less than the females 114(76%). In a study conducted by Shafkat qamar (2015) in Saudi Arabia showed that among BL isolates from Enterobacteriacea 135 (39%) were male and 210 (61%) were female patients. In our study, 66% of the BL producing *Enterobacteriacea* isolates are from inpatients which is differs from other studies that reported high prevalence of BL in outpatients (Hernandez *et al.*, 2003; Mendonca *et al.*, 2007). Among inpatients the majority of beta lactamases producing Enterobacteriacea are from patients in Intensive care unit 109(72.7%).This coincides with the study conducted by AbdulRahman *et al* (2004) who found that the majority of ESBL isolates were from patients under long term care followed by ICU (80.9%). In our study, Most of beta lactamases producing Enterobacteriacea infected belonged to the 31-45 years age group 46(30.7%) followed by > 62 years 39(26%) and 16 - 30 years 32(21.3%) respectively.Our study showed that *Escherichia coli* was significantly the most predominant one representating 66(44%) of isolates of beta lactamases producing Enterobacteriacea followed by *Klebsiella spp* 46(30.7%). This result coincides with the previous studies conducted by Karou *et al* (2009) and Moyo *et al* (2010).

Multi type β-lactamases producing isolates were also reported in our study. Among beta lactamases producing Enterobacteriacea 85(56.7%) were ESBL, 9(6%) were CTX-M, 20(13.3%) were AmpC, 24(16%) were ESBL with Carbapenems, 5(3.3%) were OXA and 7(4.7%) were MBL producing isolates. In a similar study, Amreliwala *et al* (2015) reported that 52.5% of the isolates included in the study were ESBL producers, 25.25% were ESBL + AmpC co-producers and 22.25% were only AmpC producers. In a study conducted by Loveena *et al* (2013) of the 273 gram negative isolates, 96(35.16%) were ESBL producers, followed by 30(10.98%) metallo β-lactamase (MBL) producers and 15(5.4%) AmpC producers. In a study conducted by Khalid *et al* (2010) in Saudi Arabia indicate that 71% of ESBL isolates contain CTX-M genes. In our study antibiotic resistance rates for CAUTI patients were significantly greater than Non-CAUTI patients. Both BL and non-BL isolates were more resistant to antibiotics typically recommended for empirical initial therapy for UTI such as Ampicillin and Trimethoprim-sulphamethoxazole, whereas BL isolates were often resistant to antibiotics including Ceftazidime, Cifotaxime, Cefoxitin, Amoxicillin Clavunalic acid and Carbapenems in both CAUTI patients and Non-CAUTI patients.

In our study, ESBL isolates showed high rate of resistance to Ampicillin, Ceftazidime, Cifotaxime and Trimethoprim sulfamethoxazole in both CAUTI patients and Non-CAUTI patients. Susceptibility pattern of ESBL-producing isolates showed that these strains are not only resistant to beta-lactams but also to other classes of antibacterials including Gentamicin and Ciprofloxacin in both CAUTI patients and Non-CAUTI patients. The only beta-lactams which were active against the CTX-M, AmpC and the ESBL co-producers were the Carbapenems such as Imipenem and Meropenem in both CAUTI patients and Non-CAUTI patients.

Table.1 Characteristics of UTI Patients Caused by BL Isolates at Al-Dawadmi General Hospital

Characteristics	Total Enterobacteriacea(N=231)	BL (N=150)	P-value
Male	82(35.5%)	36(24%)	<0.05
Female	149(64.5%)	114(76%)	
Age(Years) ≤15	21(9.1%)	9(6%)	<0.05
16-30	46(20%)	32(21.3%)	
31-45	68(29.4%)	46(30.7%)	
46-60	34(14.7%)	24(16%)	
≥61	62(26.8%)	39(26%)	
Outpatient	87(37.7%)	51(34%)	<0.05
Inpatient	144(62.3%)	99(66%)	
Medical ward	43(43.8%)	26(26.3%)	<0.05
Surgery ward	29(20.1%)	23(23.2%)	
Pediatric ward	23(16%)	11(11.1%)	
Intensive care unit	36(11.1%)	30(30.3%)	
Obstetrics and gynecology	13(9%)	9(9.1%)	
CAUTI	121(52.4%)	90(60%)	<0.05
NON-CAUTI	110(47.6%)	6040%)	

BL-Beta Lactamases producing isolates

Table.2 BL Isolates in CAUTI and Non-CAUTI Patients

Organism	Number and % of BL isolates (N = 150)											
	ESBL (N = 85)		ESBL + CTX - M (N = 09)		AmpC (N = 20)		Carbapenems + ESBL (N = 24)		OXA (N = 05)		MBL (N = 07)	
	CAUTI	Non-CAUTI	CAUTI	Non-CAUTI	CAUTI	Non-CAUTI	CAUTI	Non-CAUTI	CAUTI	Non-CAUTI	CAUTI	Non-CAUTI
***E. coli* (N =66)**	25	12	05	04	08	07	03	02	-	-	-	-
***Klebsiella pneumonia* (N = 46)**	22	13	-	-	-	-	05	06	-	-	-	-
***Enterobacter species* (N = 15)**	05	03	-	-	03	-	02	02	-	-	-	-
***Proteus mirabilis* (N = 10)**	04	01	-	-	-	-	01	03	-	-	-	01
***Acinetobacter species* (N = 7)**	-	-	-	-	-	-	-	-	03	02	01	01
***Citrobacter Species* (N = 02)**	-	-	-	-	-	02	-	-	-	-	-	-
***Serratia species* (N = 04)**	-	-	-	-	-	-	-	-	-	-	03	01
***Total* (N=231)**	56	29	05	04	11	09	11	13	03	02	04	03

CAUTI-Catheter Associated UTI; Non-CAUTI- Non-Catheter Associated UTI

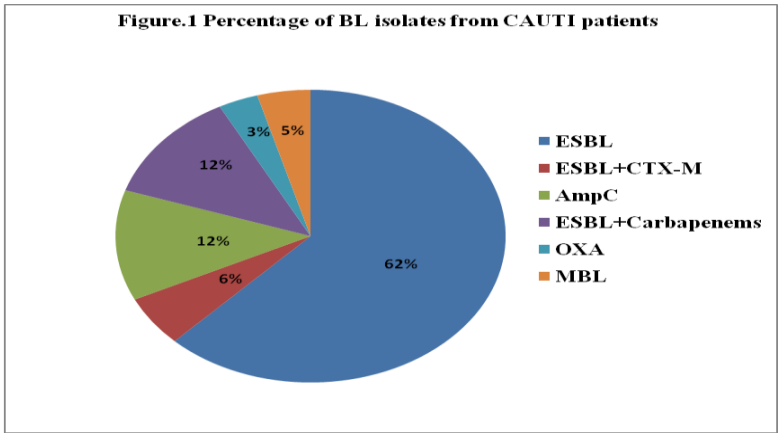
Table.3 Resistance Patterns of BL Isolates among CAUTI and Non-CAUTI Patients

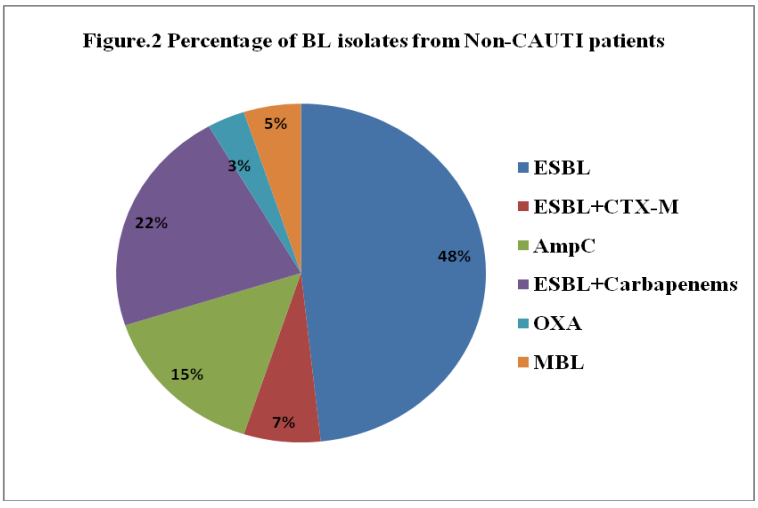
Antibacterial agent	Percentage of Resistance of BL isolates (N = 150)											
	ESBL (N = 85)		ESBL + CTX - M		AmpC (N = 20)		Carbapenems + ESBL (N = 24)		OXA (N = 05)		MBL (N = 07)	
	CAUTI	Non-CAUTI	CAUTI	Non-CAUTI	CAUTI	Non-CAUTI	CAUTI	Non-CAUTI	CAUTI	Non-CAUTI	CAUTI	Non-CAUTI
Ampicillin	56 (100)	27 (93.1)	5 (100)	4 (100)	11 (100)	9 (100)	11 (100)	12 (92.3)	3 (100)	2 (100)	4 (100)	3 (100)
Amoxycillin-Clavunalic acid	40 (71.4)	16 (55.2)	2 (40)	1 (25)	11 (100)	7 (77.8)	11 (100)	11 (84.6)	3 (100)	2 (100)	4 (100)	3 (100)
Ceftazidime	51 (91.1)	23 (79.3)	5 (100)	4 (100)	11 (100)	9 (100)	11 (100)	10 (76.9)	3 (100)	2 (100)	4 (100)	3 (100)
Cifotaxime	56 (100)	24 (82.8)	5 (100)	4 (100)	11 (100)	8 (88.9)	10 (90.9)	11 (84.6)	3 (100)	2 (100)	4 (100)	3 (100)
Cefoxitin	16 (28.6)	2 (6.9)	5 (100)	4 (100)	10 (90.9)	7 (77.8)	6 (54.5)	4 (30.8)	2 (66.7)	0	4 (100)	2 (66.7)
Cefipime	10 (17.9)	4 (13.8)	5 (100)	4 (100)	5 (45.5)	3 (33.3)	3 (27.3)	3 (23.1)	1 (33.3)	1 (50)	2 (50)	2 (66.7)
Imipenem	4 (7.1)	0 (0)	0 (0)	0 (0)	2 (18.2)	0 (0)	11 (100)	9 (69.2)	3 (100)	2 (100)	4 (100)	3 (100)
Meropenem	3 (5.4)	0 (0)	0 (0)	0 (0)	2 (18.2)	1 (11.1)	10 (90.9)	11 (84.6)	3 (100)	2 (100)	4 (100)	3 (100)
Amikacin	23 (41.1)	10 (34.5)	3 (60)	2 (50)	4 (36.4)	2 (22.2)	7 (63.6)	5 (38.5)	3 (100)	2 (100)	3 (75)	2 (66.7)
Gentamicin	29 (51.8)	15 (51.7)	3 (60)	3 (75)	4 (36.4)	3 (33.3)	3 (27.3)	4 (30.8)	3 (100)	2 (100)	1 (25)	1 (33.3)
Ciprofloxacin	30 (53.6)	19 (65.5)	3 (60)	2 (50)	6 (54.5)	4 (44.4)	4 (36.4)	5 (38.5)	1 (33.3)	1 (50)	2 (50)	1 (33.3)
Norfloxacin	17 (30.4)	10 (34.5)	2 (40)	2 (50)	5 (45.5)	4 (44.4)	8 (72.7)	6 (46.2)	2 (66.7)	1 (50)	3 (75)	2 (66.7)
Tigecycline	5 (8.9)	0 (0)	1 (20)	0 (0)	02 (18.2)	01 (11.1)	1 (9.1)	2 (15.4)	0 (0)	1 (50)	1 (25)	0 (0)
Colistin	3 (5.4)	0 (0)	0 (0)	0 (0)	01 (9.1)	0 (0)	1 (9.1)	0 (0)	1 (33.3)	0 (0)	1 (25)	1 (33.3)
Trimethoprim sulfamethoxazole	50 (89.3)	21 (72.4)	5 (100)	4 (100)	11 (100)	9 (100)	11 (100)	10 (76.9)	3 (100)	2 (100)	4 (100)	3 (100)
Total(%)	56 (100)	29 (100)	05 (100)	04 (100)	11 (100)	09 (100)	11 (100)	13 (100)	3 (100)	2 (100)	4 (100)	3 (100)

CAUTI-Catheter Associated UTI; Non-CAUTI- Non-Catheter Associated UTI

Table.4 Risk Factors Associated with BL and Non-BL Patients

Risk factors	BL (N=150)	Non-BL (N=81)
Pregnancy	45(30%)	13(16%)
Diabetes mellitus	56(37.3%)	6(7.4%)
Renal disease/renal transplant	68(45.3%)	23(28.4%)
Obstructive uropathy	74(46.7%)	16(19.8%)
Obesity	45(30%)	8(9.8%)
Prior antibiotic use within 3 months	98(65.3%)	32(39.5%)
Long term hospital stay	134(89.3%)	41(50.6%)
CAUTI	125(83.3%)	38(46.9%)
ICU stay	109(72.7%)	29(35.8%)





However, OXA and MBL are resistance to Imipenem and Meropenem. CTX-M, AmpC, OXA and MBL isolates are also resistance to Cefoxitin in both CAUTI patients and Non-CAUTI patients. But AmpC beta-lactamases were sensitive to 4th generation cephalosporin, cefepime in both CAUTI patients and Non-CAUTI patients similar to the previous study conducted by Bush *et al* (2010). CTX-M and MBL showed resistance to both Cefoxitin and forth generation cephalosporin Cefipime in both CAUTI patients and Non-CAUTI patients. OXA and MBL are often resistance to Amikacin and Norfloxacin in both CAUTI patients and Non-CAUTI patients. OXA isolates showed even resistance to Gentamicin in both CAUTI patients and Non-CAUTI patients which was similar to what has been reported by other studies in developing countries (Hima-Lerible *et al*, 2003; Ndugulile *et al*, 2005; Ahmed *et al*, 2000). In this study, we found that the β-lactamases producing isolates were resistant to most of the antibiotics tested but Tigecycline and Colistin showed promising efficacy against all the Beta lactamases in both CAUTI patients and Non-CAUTI patients.

In conclusion, according to the present study the empirical use of antibiotics like Ampicillin and trimethoprim-sulphamethoxazole, for UTI has not been proven efficient. The data regarding the prevalence of Beta Lactamase strains in CAUTI patients in Saudi Arabia is limited. Further studies regarding the BL producers in catheterized patients should be conducted in local hospitals in Saudi Arabia.

Catheterized patients should be screened regularly for the prevalence beta lactamase producers. While handling catheterized patients the healthcare staff should follow proper guidelines and infection control measures to avoid the spread of nosocomial infections. The Clinicians should follow local antibiotic policy for recommendations of alternative antibiotics to these patients.

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