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Incidence of Beta Lactamases Mediated Resistance in Gram Negative Bacilli Isolated from Urinary Tract Infection in Patients with Type 2 Diabetes Mellitus

P. Ajay Kumar[1*] and C.S. VinodKumar[2]

[1]Research Scholar in Microbiology, Bharathiar University, Tamilnadu, India
[2]Department of Microbiology, S. S. Institute of Medical Sciences and Research Centre, Davangere-577005, Karnataka, India

**Corresponding author*

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A B S T R A C T

Diabetes mellitus is a chronic disorder and affects large segment of population and is a major public health problem. The infection leads to the early development of complication even after a trivial trauma, the disease progresses and becomes refractory to antibacterial therapy. Early diagnosis of microbial infections and screening for mechanism of drug resistance is aimed to institute the appropriate antibacterial therapy and to avoid further complications The aim of the present study is to find the prevalence of β-lactamases mediated resistance among Gram negative bacteria isolated from urinary tract infection from diabetic patients. A prospective study was carried out on 1560 diabetic patients with urinary tract infection during the period of July 2011 to June 2015. 277 Gram negative bacterial were isolated and identified by standard laboratory techniques and screened for the presence of extended spectrum beta lactamase, AmpC lactamase, Metallo beta lactamase and confirmed by the respective confirmatory tests. 44.4 % of Gram negative bacilli were ESβL producers. *E.coli* (34.1%) was the predominant ESβL producer followed by *Klebsiella pneumonia* (30.9%). 6.5% of Gram negative bacilli were Amp C producers and Amp C production was seen only in *Klebsiella pneumonia*, *Pseudomonas aeruginosa and Proteus mirabilis.* 17.7% of Gram negative bacilli were MβL producers, *E.coli* was the predominant MβL producer (36.4%) followed by *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Citrobacter freundii* β-lactamase producers are emerging threat and cause of concern for the clinicians, as it results in the resistance to penicillin, cephalosporins and limits therapeutic options. Screening techniques should be performed routinely to detect these β-lactamase producers so that suitable antimicrobial therapy can be instituted.

Introduction

Diabetes mellitus type 2 is a metabolic disorder that is characterized by hyperglycemia in the context of insulin resistance and relative lack of insulin (Joshi N, 1999). Patients with type 2 diabetes mellitus are at increased risk of infections,

with the urinary tract being the most repeated infection site (Patterson JE, 1997, Joshi N, 1999, Boyko EJ, 2005, Shah BR, 2004). Several impairments in the immune system (Delarnaire M, 1997, Valerius, 1982) in addition to poor metabolic control of diabetes, (Geerlings SE, Funfstuck R, 2012) and incomplete bladder emptying due to autonomic neuropathy (Truzzi JC, 2008, Hosking DJ, 1978) may all contribute in the pathogenesis of urinary tract infections (UTI) in diabetic patients.

Factors that were found to enhance the risk for UTI in diabetics include age, metabolic control, and long term complications, primarily diabetic nephropathy and cystopathy (Brown JS, 2008). In addition, these patients are more prone to have resistant pathogens as the cause of their UTI, including extended-spectrum β-lactamase-positive Enterobacteriaceae, fluoro-quinolone-resistant uropathogens (Wu YH, 2014), carbapenem-resistant Enterobacteri-aceae and vancomycin-resistant Enterococci (Papadimitrious, 2014).

The number of reports about incidence of ESBL producing strains among clinical isolates has been steadily increasing over the past few years resulting in limitation of therapeutic options. Initially restricted to hospital-acquired infections, now they have also been isolated from infections in community. Major outbreaks involving β-lactamase positive strains have been reported from all over the world, thus making them emerging pathogens. The routine susceptibility tests done by clinical laboratories fail to detect β-lactamases positive strains and can erroneously detect isolates sometimes to be sensitive to any of the broad-spectrum cephalosporin like cefotaxime, ceftazidime, ceftriaxone and for imipenem or meropenem (Jerestin BH, 1997, Mathur P, 2002, Chaudhary U, 2004).
It is necessary to know the prevalence of β-lactamase positive strains in a hospital so as to formulate a policy of empirical therapy in high risk units where infections due to resistant organisms are much higher. Equally, important is the information on an isolate from a patient to avoid misuse of extended spectrum cephalosporins, which still remain an important component of antimicrobial therapy in high risk wards (Abigali S, 1995, Cunha BA, 2000). There is not enough information from the Indian subcontinent regarding the prevalence of β-lactamases mediated resistance among Gram negative bacteria causing urinary tract infection in diabetic patients. The aim of the present study is to find the prevalence of β-lactamases mediated resistance among Gram negative bacteria isolated from urinary tract infection from diabetic patients.

Materials and Methods

A prospective study was carried out on 1560 diabetic patients with urinary tract infection during the period of July 2011 to June 2015. 277 Gram negative bacteria were isolated and identified by standard laboratory techniques (CLSI, 2014). Antimicrobial sensitivity testing was performed on Mueller-Hinton agar plates with commercially available discs (Hi-Media, Mumbai) by the Kirby-Bauer disc diffusion method (Bauer AW, 1996). The results were recorded and interpreted as per CLSI recommendations (CLSI, 2014).

Tests for ESBL production

Double Disk Approximation Test for Screening

The test organisms were applied on to a Mueller Hinton agar plate by adjusting turbidity to McFarland no 0.5 tube. Antibiotic discs of Amoxicillin / Clavulanic acid (20/10 µg) and cefotaxime (30 µg) were placed at a distance of 15 mm apart

and incubated. Organisms that showed a clear extension of cefotaxime inhibition zone towards the disc containing Clavulanate were considered as ESBL producer (Brun-Buisson, 1987). The organisms which were screened and found positive for ESBL production were subjected to confirmatory test.

NCCLS Phenotypic Confirmatory Test

Ceftazidime (30 µg) and ceftazidime plus Clavulanic acid (30/10 µg) were placed on Mueller Hinton agar and incubated. Organism was considered as ESBL producer if there was a ≥ 5mm increase in diameter of Ceftazidime plus Clavulanic disc and that of ceftazidime disc alone (Coudron PE, 1997, Bhattacharya S, 2006).

Amp C Disk Test

A lawn culture of *E.coli* ATCC 25922 was prepared on MHA plate. Sterile disks (6mm) was moistened with sterile saline (20 µl) and inoculated with several colonies of test organisms. The inoculated disk was then placed 5mm beside a cefoxitin disc. Plates were incubated overnight at 35°C. A positive test was appeared as a flattening or indentation of the cefoxitin inhibition zone in the vicinity of the test disc (Singhal S, 2005, Black JA, 2005). A negative test had an undisturbed zone.

Metallo β-Lactamase (MBL) Production

Gram negative organisms that showed resistance to Imipenem were selected for MBL production.

Imipenem-EDTA Combined Disc Test

This test was performed according to Yong *et al*. test organisms were inoculated onto Mueller Hinton agar plates as per the CLSI recommendations. Two 10µg imipenem disks were placed on the plate and 10 µl of sterile 0.5 M EDTA solution was added to one of the imipenem disk. The inhibition zones of the imipenem and imipenem plus EDTA disks were compared after inoculation (Sinha M, 2007). If the increase in inhibition zone with the imipenem plus EDTA disc was ≥ 7mm than the imipenem disc alone, it was considered as MBL positive (Leek, 2003).

Results and Discussion

Percentage of resistance exhibited by 277 Gram negative bacilli isolated from urinary tract infection with type II diabetes mellitus to various antimicrobial agents is shown in table-1. All the strains were resistant to more than 2 or more drugs hence all the bacteria were designated as multidrug resistance Gram negative bacilli (MDRGNB).

Extended Spectrum Beta Lactamase Production among Gram Negative Bacilli Isolated from Urinary Tract Infection with Type II Diabetes Mellitus

All 277 Gram negative bacilli were screened for ESβL, MβL production and Amp C β lactamase production. 44.4 % of Gram negative bacilli were ESβL producers. *E.coli* (34.1%) was the predominant ESβL producer followed by *Klebsiella pneumonia* (30.9%), *Acinetobacter baumannii* (11.4%), *Proteus mirabilis* and *Citrobacter freundii* (9.8%) each, *Enterobacter cloacae* (2.4%) and *Aeromonas* (1.6%) (Table-2)

Amp C Production among Gram Negative Bacilli Isolated from Urinary Tract Infection with Type II Diabetes Mellitus

6.5% of Gram negative bacilli were Amp C producers and Amp C production was seen only in *Klebsiella pneumonia*, *E.coli and Proteus mirabilis.*

Klebsiella pneumonia (44.4%) was the

predominant Amp C producer followed by *E.coli* (33.3%) and *Proteus mirabilis* (22.2%) (Table-2)

MβL producers among Gram Negative Bacilli Isolated from Urinary Tract Infection with Type II Diabetes Mellitus

Not all Gram negative bacteria were tested for MβL production. Only those Gram negative bacilli resistant to imipenem were screened for MβL production. 16 out of 90 *E.coli* was resistant to imipenem. Similarly 10 out of 64 *Klebsiella pneumoniae* was resistant. Among 44 *Proteus mirabilis*, 12 were resistant. 10 out of 20 *Citrobacter freundii* was resistant to imipenem, 07 out of 29 *Acinetobacter baumanni* were resistant and 3 out of 13 *Enterobacter cloacae* were resistant to imipenem (Table-2) 17.7% of Gram negative bacilli were MβL producers, *E.coli* was the predominant MβL producer (36.4%) followed by *Acinetobacter baumannii* (18.2%), *Klebsiella pneumonia* (18.2%) and *Citrobacter freundii* (18.2%), *Proteus mirabilis* (6.0%) and *Enterobacter cloacae* (3.0%) MβL production was not observed in *Aeromonas* species

In our study we have isolated *E.coli* as the predominant organism causing urinary tract infection among type 2 diabetes mellitus. Even the aetiology prevalence is in concordance with the study of Habeeb et al, in which *E.coli* stains was the most prevalence (45%) followed by *Klebsiella* (18%).

The ability to produce β-lactamases enzymes is the major cause of resistance of bacteria to β-lactam antibiotics. Numerous β-lactamases are encoded either by chromosomal genes or transferable genes located on plasmids or transposons (Mary VJ, 2005). Based on amino acid and nucleotide sequence studies, four distinct classes of β-lactamases have been defined. Class A (Extended spectrum β-lactamases) class B (Metallo β-lactamases), class C (AmpC β-lactamases) and Class D (Cloxacillin hydrolysing β-lactamases) (Mary VJ, 2005, Bush K, 1995, Jacoby GA, 1997).

Extended spectrum β-lactamases are plasmid mediated TEM and SHV derived enzymes isolated for first time in Western Europe in mid 1980s (Livermore DM, 1996) Initially theses enzymes were commonly found in *Klebsiella* species and *E.coli*, (Mathur P, 2002) but now these enzymes are produced by all the members of Enterobacteriaceae and few other gram negative bacilli (Albertini MT, 2002, Kumar MS, 2006). These enzymes are capable of hydrolysing broad spectrum cephalosporins and monobactams and inactive against cephamycins and imipenem. In the present study 44.4% of Gram negative bacteria were ESβL producers. Few studies in India have reported the prevalence of ESBL in the range of 58% to 68.1% (Chaudhary U, 2004, Habeeb K, 2009). Our prevalence rate is lesser than other reports from India and abroad, since the isolates were obtained from urinary tract infection patients with type 2 diabetes mellitus they might be wide disparity in the prevalence rate of ESβL producing Gram-negative bacteria when compared to other reports. *E.coli* was the predominant ESβL producer followed by *Klebsiella pneumoniae* and *Acinetobacter baumannii.* In addition to the intrinsic resistance to cephalosporins and aztreonam, ESBL producing organism's exhibit co-resistance to many other classes of antibiotics like quinolones and aminoglycosides resulting in limitation of therapeutic options. In the present study we found such associated resistance with Ciprofloxacin (62.7%).

Table.1 Antimicrobial Susceptibility Pattern of Gram Negative Bacilli Isolated from Urinary Tract Infection among type 2 Diabetes Mellitus

Antibiotics	E.coli				Klebsiella pneumoniae				Proteus mirabilis				Citrobacterfreundii				Acinetobacter baumannii				Enterobacter cloacae			
	S	%	R	%	S	%	R	%	S	%	R	%	S	%	R	%	S	%	R	%	S	%	R	%
Amikacin	64	71.1	26	28.9	44	68.8	20	31.3	32	72.7	12	27.3	22	73.3	8	26.7	11	37.9	18	62.1	7	53.8	6	46.2
Ampicillin	2	2.22	88	97.8	3	4.7	61	95.3	42	95.5	2	4.5	2	6.7	28	93.3	0	0	29	100.0	0	0.0	13	100.0
Cotrimaxozole	54	60	36	40.0	41	64.1	23	35.9	21	47.7	23	52.3	8	26.7	22	73.3	7	24.1	22	75.9	4	30.8	9	69.2
Ciprofloxacin	12	13.3	78	86.7	22	34.4	42	65.6	18	40.9	26	59.1	12	40.0	18	60.0	5	17.2	24	82.8	5	38.5	8	61.5
Cetriaxone	14	15.6	76	84.4	18	28.1	46	71.9	22	50.0	22	50.0	10	33.3	20	66.7	3	10.3	26	89.7	2	15.4	11	84.6
Gentamicin	11	12.2	79	87.8	7	10.9	57	89.1	10	22.7	34	77.3	8	26.7	22	73.3	0	0	29	100.0	0	0.0	13	100.0
Imipenem	74	82.2	16	17.8	54	84.4	10	15.6	32	72.7	12	27.3	20	66.7	10	33.3	22	75.9	7	24.1	10	76.9	3	23.1
Norfloxacin	42	46.7	48	53.3	38	59.4	26	40.6	20	45.5	24	54.5	14	46.7	16	53.3	8	27.6	21	72.4	4	30.8	9	69.2
Nitrofurantoin	54	60	36	40.0	28	43.8	36	56.3	16	36.4	28	63.6	16	53.3	14	46.7	7	24.1	22	75.9	7	53.8	6	46.2
Sparfloxacin	33	36.7	57	63.3	22	34.4	42	65.6	25	56.8	19	43.2	15	50.0	15	50.0	5	17.2	24	82.8	6	46.2	7	53.8
Moxifloxacin	39	43.3	51	56.7	44	68.8	20	31.3	28	63.6	16	36.4	21	70.0	9	30.0	4	13.8	25	86.2	7	53.8	6	46.2

Table.2 Prevalence of Beta Lactamase Mediated Resistance among the Gram Negative Bacilli in Type 2 Diabetes Mellitus

Organisms	No. of Isolates	ESBL		MBL		Amp C	
		Number	Percent	Number	Percent	Number	Percent
E.coli	90	42	34.1	12	36.4	6	33.3
Klebsiella pneumoniae	64	38	30.9	6	18.2	8	44.4
Proteus mirabilis	44	12	9.8	2	6.0	4	22.2
Citrobacterfreundii	30	12	9.8	6	18.2	Nil	
Acinetobacter baumannii	29	14	11.4	6	18.2	Nil	
Enterobactercloaco	13	3	2.4	1	3.0	Nil	
Aeromonas species	7	2	1.6	Nil		Nil	
Total	277	123		49		18	

As quinolones are strong selectors of ESBL producers, their use should be restricted as far as possible. Major risk factors for colonization or infection with ESBL producing organisms are long term antibiotic exposure, prolonged hospital stay, high rates of the third generation cephalosporin use and invasive procedures. However in the present study we could not retrieve the previous hospitalization and treatment to reinforce the above arguments.

Treatment of ESBL producing strains of Enterobacteriaceae has emerged as a major challenge in hospitalized as well as community patients. There are many factors which determine the choice of antibiotics and the management of diabetic foot infections. Although β-lactamases inhibitors have significant activity against ESBL *in-vitro*, their clinical effectiveness against serious infections due to ESBL producing organisms is controversial. ESBL producing strains might show a false sensitive zone of inhibition in the Kirby Bauer's disc diffusion method. The antibiotics for the treatment include carbapenems, aminoglycoside and β-lactamases inhibitor combinations.

AmpC β-lactamases are clinically important cephalosporinases encoded on chromosomes of many of the Enterobacteriaceae and a few other organisms (Sinha M, 2007), where they mediate resistance to cephalothin cefazolin, cefoxitin, most of the penicillins and β-lactamase inhibitor (Singhal S, 2005, Black JA, 2005). In many bacteria Amp C enzymes are inducible and can be expressed at high levels by mutation (Black JA, 2005, Leek, 2003). Over expression confers resistance to broad spectrum cephalosporins. In the present study 6.5% were AmpC producers and *Klebsiella pneumoniae* was the predominant Amp C producer followed by *E.coli* and *Proteus mirabilis.*

Metallo β-lactamase (MBL) is a group of carbapenem hydrolysing β-lactamase (Chu Y, 2001). They have been reported from many countries, as well as from different parts of Indian subcontinent, particularly in multidrug resistance pathogens like *Pseudomonas aeruginosa* and *Acinetobacter* species. The MBLs are inhibited in-vitro by CuCl3, FeCl3, EDTA and thiol compounds like 2 mercaptopropionic acid, sodium mercaptoacetoic acid and 2 mercaptoethanal, but not by β-lactamase inhibitors like Clavulanic acid, sulbactum or tazobactam (Goossens H, 2000). Detection of MBL production in MDR organisms from urinary tract infection patients with type 2 diabetes mellitus has tremendous therapeutic consequences, as the treatment option for such isolates are aztreonam or potentially toxic polymyxin B and colistin. In the present study not all Gram negative bacteria were tested for MBL production. Only those Gram negative bacilli resistant to imipenem (58/277) were screened for MBL production and 84.5% (49/58) were metallo β-lactamase producers. *E.coli*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Proteus mirabilis* were the predominant MBL producers.

The present study could not elicit the reason for multidrug resistance in our isolates because we could not extract previous hospitalization details in study subjects. This information could have helped in explaining the reasons for the high prevalence of MDROs in our patients. But one of the reason could be the bacteria isolated may be nosocomial colonizers

In conclusion, the present study highlights the high prevalence of β-lactamases among the multi -drug resistant Gram negative isolates in diabetic foot infections. It also reflects grim future of the treatment options available for these notorious pathogens. The

high incidence of β-lactamases production due to multiple mechanisms in urinary tract infection in type 2 diabetes mellitus is alarming and urgent action needs to be taken from both the therapeutic and infection control perspective. Clinical microbiology laboratories should perform the screening techniques to detect these β-lactamases routinely so that the suitable antimicrobial therapy can be instituted and the dissemination of these isolates may be prevented by employing appropriate control measures.

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