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Research Article

Antibiotic Susceptibility Pattern of Bacterial Pathogens Isolated from Patients at A Tertiary Care Hospital in India

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Abstract

Objective

The continuous variations in the bacterial resistance patterns in different geographical niches necessitates updating of antimicrobial susceptibility profiles data regularly to guide clinicians in choosing the appropriate empiric therapies. This retrospective study assessed the characteristics of pathogens identified in clinical isolates from different clinical samples and their *in vitro* susceptibility to commonly used antibiotics for multi-drug resistant (MDR) pathogens in our hospital settings.

Methods

A total of 212 samples from 210 patients treated for various bacterial infections during October 2016 to November 2017 were included in the study. Three antimicrobial agents had been used and extended spectrum β-lactamases (ESBL) production was confirmed by double-disk synergy test.

Results

Of the 212 isolates from 210 patients, 196 (92.0%) were Gram negative and 16 (8.0%) were Gram positive organisms. Only 196 Gram negative isolates were included in the final analysis. 58.4% isolates were from urine, 12.3% from blood, 10.8% from pus and 18.5% from other sources. *Escherichia Coli* was detected in half (50%) of clinical samples, followed by *Klebsiella Pneumoniae* (25.8%) and *Pseudomonas Aeruginosa* (5.3%). The detection rate of the *ESBL*-producing isolates was 20.7%. Resistance to piperacillin-tazobactam was most common among all the isolates. CSE-1034(Ceftriaxone-sulbactam-EDTA-1034) had the greatest activity against both the *ESBL* and *non-ESBL E. coli* (98.1%; 96.8%) and *K. Pneumoniae* (90.9%; 75%) respectively whereas both CSE-1034 and meropenem exhibited similar level of activity against *P. Aeruginosa* (90.9%). All other isolates except one isolate of enterobacter showed 100% sensitivity to all the three drugs.

Conclusion

This retrospective data suggest that CSE-1034 can be considered an important therapeutic option for the treatment of both *ESBL* and *Non-ESBL* Gram-negative bacterial infections. A careful monitoring of antimicrobial usage and resistance patterns should be done at regular intervals in healthcare settings to combat the problem of antimicrobial resistance.

Introduction

The introduction of beta-lactam antibiotics heralded a new era in the fight against emerging bacterial resistance mechanisms and comprised more than half of the antibiotics most widely prescribed for Gram-negative infections [1]. However, the overuse and unrestricted consumption of these drugs for the long duration across hospital and community settings has led to a surge in anti-microbial resistance, threatening the use of the majority of large drug family [1]. Of particular concern are Asian countries that have witnessed a steady rise in ESBLs producing Enterobacteriaceae, Metallo β-lactamases (MBLs) producing *Enterobacteriaceae* and multidrug-resistant strains of *P. Aeruginosa* and *A. Baumannii* since last two decades [2]. The prevalence of ESBL producers in India range from 28%-84% and MBLs range from 7-71% [3]. ESBLs are β-lactamase enzymes capable of hydrolyzing various classes of antibiotics including penicillin's, monobactams and other several groups of β-lactam antibiotics, notably cephalosporins [4]. ESBL-producing organisms show cross-resistance to other groups of antibiotics also including fluoroquinolones, aminoglycosides, tetracyclines, and trimethoprim/sulfamethoxazole [4]. The majority of ESBL producing organisms produce more than one β-lactamase and strains producing multiple ESBLs are also reported.

Infections caused by multi drug-resistant *Enterobacteriaceae* are associated with increased morbidity and mortality compared to the ones caused by their susceptible counterparts [5,6]. This is mainly attributed to delayed active therapy supported by various studies demonstrating worse outcomes in patients with bacteremia due to *Enterobacteriaceae* with inactive empirical therapy [7,8].

The fact that antimicrobial resistance to first-line agents has been increasing makes the selection of empirical therapy more difficult [7,8]. Clinicians frequently face the dilemma between choosing one of those agents, which might not be active in some patients, or a drug with a very broad spectrum, knowing that this may further fuel the spread of resistance. For such decisions, various factors are considered in patients with infections potentially caused by *Enterobacteriaceae,* including individual risk factors, clinical severity and most importantly local epidemiology. The resistance patterns observed by a particular pathogenic species represent the sum of intrinsic and acquired mechanisms of resistance [9]. While the first are universally present, the latter ones are acquired and have heterogeneous prevalence and may be present only in some geographical areas. Thus, efficient reporting of the local epidemiology and the antibiotic susceptibility data of clinical isolates are helpful to clinicians for the appropriate management of patients. In the current study, the antibiotic susceptibility of Gram-negative clinical isolates, collected during the period of October 2016 to November 2017 against commonly used antibiotics was determined.

Materials and Methods

Source of Isolates

This study was carried on patients between 0 months to 89 years old, suffering from various bacterial infections and treated in our hospital between October 2016 to November 2017. The clinical samples used for pathogen isolation were urine, blood and pus. The sample collection and processing were done as per standard microbiology laboratory operating procedures. Colony counts higher than or equal to 105 colony forming units (CFU)/mL were considered significant.

Pathogen Isolation and Identification

Clinical isolates were identified based on Gram-staining, colony morphology, motility and different biochemical reactions using standard techniques. The required clinical samples were collected in sufficient amount in sterile containers aseptically. The collected specimens were inoculated or streaked on different selective and non-selective culture media as per the standard microbiological procedures. Blood samples collected in brain heart infusion (BHI) broth were incubated aerobically overnight at 37°C followed by sub-culturing in the respective media.

Antibiotic Susceptibility Testing

In vitro susceptibility testing was done by Kirby-Bauer disk diffusion method for all the pathogen isolates as per Clinical Laboratory Standard Institute (CLSI) guidelines. Discs of Ceftriaxone-sulbactam-EDTA-1034 (45µg), Meropenem (10µg), piperacillin/tazobactam (110µg) were purchased from Microexpress, a division of Tulip Diagnostics private Limited, Goa, India. Inoculum suspension of 0.5 MacFarland standard turbidity was prepared in a Mueller-Hinton broth (MHB, Hi-media, Mumbai, India) from a single colony picked from 18-24 hours agar plates. A sterile cotton swab dipped into inoculum suspension and pressed against the wall of tube above fluid level was streaked on Mueller-hinton agar (MHA) plate.

The swab was streaked two or more times at 60°C over the agar surface to ensure even distribution. After 3-5 minutes, antibiotic discs were implanted on to inoculated agar plates ensuring complete contact with agar surface. The discs were distributed evenly and a minimum distance of 24mm from center to center was ensured. Within 15 minutes, the plates were then inverted and incubated for 16-18 hours aerobically at 37°C. Zones of inhibition were measured next day and were correlated with CLSI interpretive breakpoints to characterize them as sensitive, intermediate and resistant. CSE-1034, for which CLSI breakpoints are not available, interpretative breakpoints provided by the manufacturer were used. Criteria was >21mm-Sensitive, 14-20- Intermediate, ≤13- Resistance.

Results

Sample Collection and Pathogen Isolation

A total of 212 culture positive clinical samples from 210 patients were included in this retrospective analysis. The different clinical samples processed for pathogen isolation were urine, blood, pus, sputum, endo-tracheal secretions and abdominal fluids. Of the total 212 clinical samples processed, the majority were urine (58.4%) followed by blood (12.3%) and pus (10.8%). 59.5% isolates were from patients with UTI, 15% from wound infections, 10.5% from patients with respiratory tract infections and 9.5% from patients with blood infections. Further sub-group analysis on the basis of gender, had shown similar kind of pattern with urinary tract infections (UTIs) predominant in both the genders accounting for 70% in females and 48.4% among males. This was followed by wound infections (male; 22.1%: female; 10%) and respiratory tract infections (male; 12.6%: female; 8.2%). For other details, refer to Table no 1.

Table 1: *Demographic and baseline characteristics of all study subjects (n=210).*

Characteristics		Total	Male	Female	Infant (s)
Number	**n (%)**	210	97 (45.2)	113 (53.8)	
Age (year)	**Mean ± STDEV**	43.5±21.04	44±20.88	43.5±21.05	
Indication		**N=210**	**N=95**	**N=110**	**N=5**
	UTI/Urosepsis	124/1 (59.5)	46 (48.4)	76/1 (70)	2 (40)
	Blood infections	20 (9.5)	9 (9.5)	10 (9.1)	1 (20)
	LRTI/RTI	22 (10.5)	12 (12.6)	9 (8.2)	1 (20)
	Wound infections	32 (15.2)	21 (22.1)	11 (10)	0
	Others (Sepsis, conjunctivitis, etc)	11 (5.2)	7 (7.4)	3 (2.7)	1 (20)
Clinical sample (%)		**N=212**	**N=96**	**N=111**	**N=5**
	Urine	125 (58.9)	46 (47.9)	77 (69.3)	2 (40)
	Blood	26 (12.3)	13 (13.5)	11 (9.9)	2 (40)
	Pus	23 (10.8)	13 (13.5)	10 (9.0)	0
	Endo-tracheal secretions	12 (5.7)	10 (10.4)	2 (1.8)	0
	Wound	8 (3.8)	6 (6.3)	2 (1.8)	0
	Sputum	10 (4.7)	3 (3.1)	7 (6.3)	0
	Fluid Collections	1 (0.5)	0	1 (0.9)	0
	Tissue	4 (1.9)	4 (4.2)	0	0
	Stool	1 (0.5)	1 (1.0)	0	0
	Eye Swabs	2 (0.9)	0	1 (0.9)	1 (20)

Microbiological Characteristics

Among 212 bacterial isolates, 196 (92.0%) were Gram negative and 16 (8.0%) were Gram positive organisms. The detailed profile of various organisms isolated is shown in Table no 2. Only the gram-negative isolates were included in the final analysis. Around half of the isolates were of *E. coli* (50%) followed by *K. Pneumoniae* (25.8%), *P. Aeruginosa* (5.2%) and *S. Typhii* (4.2%). *E. coli* was predominant in both the genders followed by *K. Pneumoniae* (Table 2).

Table 2: *Pathogen distribution in patients according to gender.*

Pathogen Type	Total	Male	Female	Infant
	N=210	**N=95**	**N=110**	**N=5**
E. coli	106	44	59	3
K. Pneumoniae	52	24	27	1
P. Aeruginosa	11	6	5	0
A. Baumannii	2	2	0	0
S. Typhii	9	6	3	0
B. Cepacia	1	0	1	0
C. Koseri	2	1	1	0
P. Mirabilis	3	3	0	0
Enterobacter Species	2	1	0	1
Enterococcus	2	1	1	0
Mixed Infections ***(K. Pneumoniae+S. marcescens)***	2	0	2	0
Mixed Infections ***(K. Pneumoniae+E.coli)***	1	1	0	0
Gram-positive cultures	17	6	11	0

Susceptibility Results for *E. Coli*

Antibiogram profile for all the pathogen isolates is shown in Table 3 and ESBL isolates in Table 4. Of the 107 *E. coli* isolates, 98.1% were susceptible to CSE-1034, 90.7% to meropenem and 60.7% to piperacillin-tazobactam. 31 (28.9%) *E. coli* isolates were ESBL producers. The sensitivity pattern observed for ESBL producers was although in line with all pathogen isolates but the number varied significantly in different antibiotic groups. 96.8% of ESBL *E. coli* isolates were sensitive to CSE-1034 compared to 83.9% to meropenem and significantly low (45.2%) to piperacillin-tazobactam.

Table 3: *Culture sensitivity profile of different pathogens*

Pathogen	Sensitivity	Number (%) (CSE-1034)	Number (%) (Meropenem)	Number (%) (Pip-taz)
E. coli **N=107**	Sensitive	105 (98.1)	97 (90.7)	65 (60.7)
	Resistant/Intermediate	2 (1.9)	10 (9.3)	36/6 (39.3)
K. Pneumoniae **N=55**	Sensitive	50 (90.9)	37 (67.3)	33 (60)
	Resistant	5 (9.1)	18 (32.7)	22 (40)
P.Aeruginosa **N=11**	Sensitive	10 (90.9)	10 (90.9)	8 (72.7)
	Resistant	1 (9.1)	1 (9.1)	3 (27.3)
A.Baumannii ***N=2***	Sensitive	2 (100)	1 (50)	1 (50)
	Resistant	-	1 (50)	1 (50)
S. Typhii **N=9**	Sensitive	9 (100)	9 (100)	9 (100)
	Resistant	-	-	-
C. koseri **N=2**	Sensitive	2 (100)	2 (100)	2 (100)
	Resistant	-	-	-
S. Marsecens **N=2**	Sensitive	2 (100)	2 (100)	2 (100)
	Resistant	-	-	-
Burkholderia Cepacia **N=1**	Sensitive	1 (100)	1 (100)	1 (100)
	Resistant	-	-	-
Proteus **N=3**	Sensitive	3 (100)	3 (100)	3 (100)
	Resistant	-	-	-
Enterobacter species **N=2**	Sensitive	2 (100)	2 (100)	1 (50)
	Resistant	-	-	1 (50)
Enterococcus **N=2**	Sensitive	1 (50)	2 (100)	1 (50)

Table 4: *Culture sensitivity profile of ESBL producing pathogens*

Pathogen No (%)	Sensitivity	ESBL (CSE-1034)	ESBL (Meropenem)	ESBL (Piperacillin - tazobactam)
E. coli **31/107 (28.9%)**	Sensitive	30 (96.8)	26 (83.9)	14 (45.2)
	Resistant	1 (3.2)	5 (16.1)	17 (54.8)
K. Pneumoniae **12/55 (21.8%)**	Sensitive	9 (75)	6 (50)	4 (33.3)
	Resistant	3 (25)	6 (50)	8 (66.7)
Enterobacter **1/2 (50%)**	Sensitive	1 (100)	1 (100)	0
	Resistant	0	0	1 (100)

The percentage of isolates positive for different pathogens by infection type, and the proportion of ESBL producing isolates are presented in Table 5.

Type of Infection	ESBL No. (%)	Pathogen (No.)	ESBL	Non-ESBL
UTI	**30/125 (24)**	***E. coli*** **(87)**	24 (27.6)	63 (72.4)
		K. Pneumoniae **(28)**	5 (17.9)	23 (82.1)
		Enterobacter **(1)**	1 (100)	0
Blood infections	**1/20 (5)**	***E. coli*** **(7)**	1 (14.3)	6 (85.7)
Respiratory tract Infections	**4/22 (18.2)**	***K. Pneumoniae*** **(14)**	4 (28.6)	10 (71.4)
Wound infections	**7/32 (21.9)**	***E. coli*** **(9)**	4 (44.4)	5 (55.6)
		K. Pneumoniae **(9)**	3 (33.3)	6 (66.7)
Others (7)	**2/11 (18.2)**	***E. coli*** **(2)**	2 (100)	0

Susceptibility Results for *K. Pneumoniae* and *P. Aeruginosa*

Overall, 55 (25.8%) isolates were identified as *K. Pneumoniae* and 11 (5.1%) as *P. Aeruginosa*. The meropenem susceptibility rate of *K. Pneumoniae* was 67.2% (37/55) and P. aeruginosa was 90.9% (10/11). The least sensitivity among all the isolates was shown towards piperacillin-tazobactam; *K. Pneumoniae* (60%; 33/55) and *P. Aeruginosa* (72.7%; 8/11).

CSE-1034 had a better activity than meropenem and piperacillin-tazobactam against both the pathogen isolates; 90.9% towards both *K. Pneumoniae* (50/55) and *P. Aeruginosa* (10/11). 12/55 (21.8%) of *K. Pneumoniae* isolates were ESBL producers whereas none of the *P. Aeruginosa* isolates was ESBL producer.

The sensitive percentage of ESBL producing *K. Pneumoniae* to CSE-1034 was 75% which is significantly high compared to meropenem (50%) and piperacillin-tazobactam (33.3%).

Susceptibility Results for *S. Typhii, A. Baumannii, C. Koseri* and *S. Marsecens*

Overall, 6% isolates of *S. Typhii*, 2.9% of *A. Baumannii* and *C. Koseri*, 1.4% of Proteus, 0.9% each of *S. Marsecens* and *Enterococcus* were isolated. All these isolates showed 100% sensitivity to piperacillin-tazobactam, meropenem and CSE-1034 and none was reported as ESBL. Out of two isolates of *Enterobacter,* one isolate reported as ESBL producer was resistant to piperacillin-tazobactam.

Discussion

Although, various guidelines are available for the management of bacterial infections, however adoption of these guidelines at the hospital level is challenged by difference in the predominant pathogens, their sensitivity pattern and health care-associated economic conditions that varies with different geographical locales [7,10]. Therefore, the audit and analysis of the microbiological isolates and their sensitivity pattern is indispensable to clinicians for right empiric therapy. In this study, it was found that UTI was the most prevalent infection in both the genders accounting for almost half of isolates. Based on gram staining, Gram-negative pathogens were predominately isolated (92%) in all clinical samples analyzed with urine being the most processed one followed by blood and pus. The results obtained in this study are in concordance with other studies conducted in other parts of India and Asian sub-continent. A recent retrospective anti-microbial susceptibility study conducted at a tertiary care center in Delhi, India has reported 76.4% isolates as gram negative [11]. Similarly, Karanwal *et al.* [12] have reported same pattern from Ahmedabad with Gram-negative isolates comprising 78% of the total isolates and Prabhash *et al.* [13] from Mumbai (Gram-negative organisms comprising 68.1% of blood cultures). Bacteriological profile in India differs from that in the west. Although, the gram-positive pathogens predominate in Europe, on the contrary more incidences of gram-negative pathogens are reported in Asia. Among the identified Gram-negative isolates, *E.coli* was the most frequent pathogen in both the genders accounting for 42% of total isolates. Other pathogens identified were *K. Pneumoniae* (27.3%) and *P. Aeruginosa* (9.3%). Although *E coli* was the leading cause of UTI in both the sexes, its proportion was significantly higher in women compared to men. In accordance to our results, various studies have reported Gram-negative bacilli as the most common pathogens causing UTIs in both men and women with a ratio of 1:2, and *E. coli* being the most prevalent type [14,15].

An important mechanism of antibiotic resistance in gram negative pathogens is through ESBL production. ESBLs are plasmid mediated and derived from class A b-lactamases, and their spectrum includes oxyimino-β-lactams including penicillin's, aztreonam, monobactams, cephalosporins (with the exception of cephamycin's) [4]. In addition, ESBL-producing organisms frequently show cross-resistance to other classes of non-β-lactam antibiotics including trimethoprim-sulfamethoxazole, aminoglycosides, and fluoroquinolones, thus making the treatment of these infections a therapeutic challenge. ESBLs are commonly found in Gram-negative bacterial isolates mainly in *Enterobacteriaceae* and have been reported worldwide [16-18]. Consistent with these results, all the ESBL-producing pathogens were from *Enterobacteriaceae* family and none was reported from non-*Enterobacteriaceae* family. Further, in *Enterobacteriaceae* family, *E.coli* and *K. Pneumoniae* leaped out as the significant ESBL producers and contributed 28.9% and 21.8%, respectively. In India, Sentry surveillance study has reported the prevalence of ESBLs from 62% to 100% in *E. coli* and *Klebsiella* spp. isolated from respiratory infections, blood stream infections, skin and soft tissue infections,[11] The proportion of ESBL isolates also varied with the infection type: the prevalence of EBSL-producing isolates was highest from UTI cases. The ESBL isolates from wound infections was 15.9% followed by respiratory infections (9.1%).

Susceptibility results showed that the resistance rate of ESBL-producing isolates against used antimicrobial drugs was higher than the rate observed in ESBL-negative isolates. A high rate of resistance of both ESBL and non-ESBL isolates was observed to piperacillin-tazobactam. The indiscriminate consumption of piperacillin-tazobactam could be one of the vital reasons for the high antimicrobial resistance reported towards the normally recommended second line of treatment in our hospital. Singh *et al.* have reported 22% of *E. coli* isolates, 50% of *Klebsiella* and 35% of *P. Aeruginosa* resistant to piperacillin-tazobactam in their study.

A 98.1% and 96.8% sensitivity of Ceftriaxone-sulbactam-EDTA-1034 (CSE-1034) was reported against ESBL-negative and ESBL-producing *E. coli* and 90.9% and 75% against *K. Pneumoniae* respectively in our study. The anti-bacterial effect of this compound on non-ESBL and ESBL-producing isolates was superior to meropenem; 90.7 & 83.9% for *E. coli* and 67.3% & 50% for *K. Pneumoniae*, respectively. Our study has shown that non-ESBL *P. Aeruginosa* showed 90.9% sensitivity rate. The emergence of carbapenem-resistant strains, which ranges from 9-32% in this study is a matter of big concern as carbapenems are considered as the last resort drugs for ESBL strains. A significantly higher incidence of carbapenem-resistant Gram-negative bacteria has also been reported by Ghosh *et al.* [19] from AIIMS, Delhi. Similarly, Singh *et al.* [11] have reported that 15-22% of the gram-negative isolates were metallo-beta lactamases (MBLs)in their study. Interestingly, a significant number of both ESBL and non-ESBL isolates were sensitive to CSE-1034. The high sensitivity of gram-negative pathogens to CSE-1034 has been reported by several other studies also [20] [21]. 100%, 64% and 63% of ESBL producing *A. Baumannii, K. Pneumoniae* and *E. coli* were reported susceptible to CSE-1034 in an antimicrobial susceptibility pattern study conducted by Sahu *et al.* [22]. In the same study, 89%, 60%, 42% and 41% of MBL producing isolates of *A. Baumannii, E. coli*, *P. Aeruginosa* and *K. Pneumoniae*, respectively were susceptible to CSE-1034.

Conclusion

Our analysis suggests that pathogen isolates from various clinical sources demonstrated a varied rate of resistance to different antimicrobials in our hospital. CSE-1034 and carbapenems remained the most effective drugs against gram-negative pathogens. This finding assumes significance in the backdrop of formulating empirical therapy for patients suspected of suffering from multi drug resistance (MDR) infections. As CSE-1034, a beta-lactam/beta-lactamase combination was equally effective against various infections, it can be a drug of choice for MDR bacterial infections to combat the overuse of carbapenems and reduce the selection pressure on carbapenem-resistant strains. Moreover, a high resistance pattern observed in this study warrants a careful monitoring of anti-microbial use in hospitals.

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