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Prevalence and Susceptibility Analysis of Carbapenem Resistant Gram-negative Pathogens in Super Specialty Tertiary Care Center, Mumbai, India

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Taking into account the rise in mortality rate due to multi-drug resistant Gram-negative bacteria, we purposed to retrospectively analyze the susceptibility behavior of 74 carbapenem-resistant clinical isolates towards common antibiotic classes [Sulphomide, β-lactams (BL), β-lactam/β-lactamase inhibitor combination (BL/BLI), aminoglycosides, cephalosporins, quinolone, peptide and glycylcycline] and a novel antibiotic-adjutant entity, CSE-1034 [Ceftriaxone/ Sulbactam/disodium edetate].
Materials and Methods: To characterize the anti-bacterial susceptibility pattern, a retrospective, observational analysis of antibiogram data obtained from different clinical samples in Super

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Speciality tertiary care center, Mumbai (India) between January 2015 to December 2015 was performed. 74 carbapenem-resistant clinical isolates with MIC>16 against imipenem and meropenem were analyzed in this study. *K. pneumoniae* (47.30%) was found to be the most common pathogen among all clinical isolates followed by *A. baumannii* (17.57%), *E. coli* (14.86%) and *P. aeruginosa* (10.81%).

Results: Antibiogram data suggested colistin as the most susceptible drug against all carbapenem-resistant isolates followed by tigecycline. CSE-1034 was determined as third most susceptible drug. The susceptibility rates of *K. pneumoniae, A. baumannii*, *E. coli* and *P. aeruginosa* to CSE-1034 were 81.8%, 57.1%, 69.2% and 75%. The susceptibility to aminoglycosides varied from zero for *A. baumanni* to 63.6% for *E. coli* in case of amikacin and 8.57% for *K. pneumoniae* and 37.5% for *P. aeruginosa* in case of gentamicin. The susceptibility to all other antibiotics tested was very poor.

Conclusion: From this study, it can be concluded that along with colistin and tigecycline, CSE-1034 and aminoglycosides can be considered for patients infected with carbapenem-resistant strains. Moreover, CSE-1034 or aminoglycosides can be good alternates in carbapenem resistant bloodstream, and urinary tract infections as tigelcycline is not preferred agent in these infections.

Keywords: Antibiotic; clinical isolates; CSE-1034; prevalence; susceptibility; resistance.

1. INTRODUCTION

Approximately, 71.8% infections in India are caused by Gram-negative bacteria, and the rising antimicrobial resistance has complicated the treatment of these bacterial infections. Carbapenems serve as therapies of last resort for MDR Gram-negative bacterial infections including those caused by extended-spectrum ß-lactamases (ESBL) strains. However, the emerging carbapenem resistance worldwide among clinical isolates of *Enterobacteriaceae* and non-fermentative Gram-negative bacilli facilitated by either clonal expansion of carbapenem-resistant isolates or horizontal spread of carbapenemase genes is of particular concern when treating patients infected with these pathogens [1,2,3,4]. The rising emergence of carbapenem-resistant infections is a menace to patients, particularly to those with debilitating conditions, serious infections, underlying diseases or medical interventions [1,2]. Various factors responsible for escalating carbapenem resistance rates include the increased dependence and selective pressure on penem family as e (ESBL)treatment option for the rapidly increasing number of infections by extended-spectrum β-lactamase (ESBL) strains worldwide [5,6]. Other factors include poor infection control practice and the lack of proper anti-microbial stewardship programs in many hospitals [5,6].

Carbapenem resistance is complex and can be mediated by several mechanisms, including the production of enzymes called carbapenemases. Though carbapenemase production is the main mechanism of carbapenem-resistance, AmpC β-lactamases, porin mutations/loss, expression of efflux pumps, and/or alterations in penicillin-binding proteins may also confer carbapenem resistance [5,6,7,8,9]. Since carbapenemases have the ability to hydrolyze penicillins, cephalosporins, besides carbapenems, Gram-negative bacteria carrying a carbapenemase-encoding gene frequently exhibit resistance to virtually all –lactams including cephalosporins, quinolones and aminoglycosides, leaving few or, in some cases, no optimal therapeutic options [7]. However, as carbapenem resistant strains are reported to exhibit other resistance mechanisms also, making them specifically resistant to carbapenems whereas sensitivity to other antibiotics is retained.

Knowledge of these specific phenotypes can open the route for re-exploring abandoned treatment options for these carbapenem-resistant infections which are often restricted to only polymyxins and mainly include colistin. Hence, we aimed to evaluate the susceptibility profiles of different drug classes towards different carbapenem resistant Gram-negative isolates from various clinical samples.

2. MATERIALS AND METHODS

2.1 Sample Collection

This retrospective study was carried on carbapenem resistant bacterial isolates obtained from clinical samples of patients suspected of bacterial infections during a period of one year (January to December 2015), from Super

Specialty tertiary care center, Mumbai (India). Different clinical samples used for pathogen isolation were urine, blood, wound, sputum, tracheal secretion and pus. The collection and processing of the samples were done as per a common standard operating procedure of hospital. In this 1 year study period, a total of 181 different clinical samples were collected from the patients and processed for pathogen isolation. The different clinical samples processed were urine (37.84%), sputum and tracheal secretions (13.51% each), wound and pus (12.16% each) and blood (10.81%).

2.2 Isolation and Identification of Microbes

All the clinical specimens were collected aseptically in sterile containers and inoculated on different selective and non-selective culture media as per the standard microbiological techniques. Enterobacteriaceae-N280 and Pseudomonas group-N281 cards (bioMérieux, France) were used for the detection of *Enterobacteriaceae* and *Pseudomonas species* (spp.) while *A. baumannii* was screened by using leeds acinetobacter agar base medium as a selective media.

2.3 Antibiotic Susceptibility Testing

Antimicrobial susceptibility testing was done using Vitek 2 (MIC method) as recommended by the CLSI guidelines [10]. The disc diffusion method was used to determine the susceptibility of clinical isolates towards CSE-1034. The discs of CSE-1034 (45µg) were obtained from third party.

3. RESULTS

Of the total 181 samples analyzed, carbapenem resistant Gram-negative isolates were obtained from 74 (40.8%) samples and used further in this study (Table 1). Eight different carbapenem resistant gram-negative species with MIC>16 against imipenem and meropenem as per CLSI guidelines were *E. coli* (n=11), *K. pneumoniae* (n=35), *A. baumannii* (n=13), *P. aeruginosa* (n=8), *C. freundii* (n=3), *E. aerogenes* (n=1), *E. cloacae* (n=2) and *P. luteola* (n=1). For details, refer to Table 2.

The distribution pattern of carbapenem resistant strains varied in different clinical samples processed. Carbapenem-resistant E. coli were

Table 1. A profile of clinical samples used as a source for the isolation of carbapenem resistant isolates

Sr. no.	Name of clinical samples	No. of clinical samples	Number of carbapenem resistant pathogens isolated (%)
1	Urine	62	28 (45.2%)
2	Blood	19	8 (42.1%)
3	Wound	24	9 (37.5%)
4	Sputum	25	10 (40%)
5	Tracheal secretion	26	10 (38.5%)
6	Pus	25	9 (36)
	Total	181	**74**

Table 2. Prevalence of different carbapenem resistant clinical isolates in different samples

Clinical samples	*E. coli* (%) N=11	*K. pneumoniae* (%) N=35	*A. baumannii* (%) N=13	*P. aeruginosa* & *P. luteola* (%) N=9	**Others* (%) N=6
Urine	5 (45.45)	19 (54.28)	3 (23.07)	3 (33.3)	4 (66.66)
Blood	1 (9.09)	3 (8.57)	1 (7.69)	0	1 (16.7)
Wound	1 (9.09)	3 (8.57)	2 (15.38)	0	1 (16.7)
Sputum	2 (18.18)	5 (14.28)	1 (7.69)	0	0
Tracheal secretion	1 (9.09)	3 (8.57)	5 (34.48)	1 (11.1)	0
Pus	1 (9.09)	2 (5.71)	1 (7.69)	5 (45.5)	0
Total	**11 (14.86)**	**35 (47.30)**	**13 (17.57)**	**9 (10.81)**	**6 (4.05)**

**Others incude C. freundii, E. aerogenes and E. cloacae*

Table 3. Susceptibility pattern of carbapenem resistant clinical isolates

Clinical isolates		***E. coli*** **(n=11)**	***K. pneumoniae*** **(n=35)**	***A. baumannii*** **(n=13)**	***P. aeruginosa & P. luteola*** **(n=9)**	**Others (n=6)**
Drug classes	**Drugs**					
AAE	CSE-1034	81.8	57.1	69.2	75	66.67
Sulphomides	Co-trimaxazole	54.5	14.29	7.69	-	33.33
BL	Ampicillin	0	-	-	-	-
BL-BLI	Amoxicillin/clavulanic acid	0	0	-	-	-
	Piperacillin-tazobactam	0	0	0	37.5	0
	Cefoperazone-sulbactam	0	0	61.5	12.5	0
Aminoglycoside	Gentamicin	36.36	8.57	30.76	37.5	16.6
	Amikacin	63.64	25.71	0	37.5	50
Cephalosporin	Ceftriaxone	0	0	0	-	0
	Cefuroxime	0	0	0	0	-
	Cefepime	0	0	0	25	0
Quinolone	Nalidixic acid	0	2.86	15.38	0	16.6
	Ciprofloxacin	0	2.86	15.38	25	16.6
	Levofloxacin	0	0	0	25	0
Peptide	Colistin	100	100	100	100	100
Glycylcycline	Tigecycline	90.91	60	84.62	-	100

Others include C. freundii, E. aerogenes and E. cloacae

- indicates intrinsic resistance and were not tested against these antibiotics

observed predominantly in urine (45.45%), *A. baumannii* exhibited prime occurrence in tracheal secretions (34.48%) and *P. aeruginosa* strains showed their high presence in pus (62.5%) samples. The least common pathogens including *C. freundii* was mainly isolated from urine (66.6%), *E. aerogenes* from wound (100%) whereas *E. cloacae* and *P. luteola* were isolated from urine (100%).

The susceptibility profile of these carbapenem resistance bacterial strains to various classes of antibiotics is shown in detail in Table 3. Overall, all the carbapenem-resistant clinical isolates were reported to be susceptible to colistin (100%) followed by tigecycline which possessed second highest activity against *K. pneumoniae* (90.91%), *A. baumannii* (60%), *E. coli* (84.62%), *C. freundii* (100%) and *E. cloacae* (100%) whereas none of the isolates of *E. aerogenes* were reported susceptible.

CSE-1034 has determined the third-highest effective drug after colistin and tigecycylcin. The susceptibility rates of *K. pneumoniae, A. baumannii*, *E. coli*, *P. aeruginosa, C. freundii* and *E. cloacae* to CSE-1034 were 81.8%, 57.1%, 69.2%, 75%, 66.6% and 100% respectively. Susceptibility to Co-trimoxazole (sulphomides) were 54.5%, 66.67%, 14.29% and 7.69% for *E. coli, C. fruendii, K. pneumoniae, A. baumannii* respectively. Among BL-BLI drugs, cefoperazone-sulbactam susceptibility observed was 61.5% for *A.baumanni;* 12.5% and 37.5% of *P. aeruginosa* showed susceptibility to cefoperazone-sulbactam and piperacillin-tazobactam respectively whereas all other pathogens showed zero susceptibility. Amoxicillin/clavulanic acid did not display any susceptibility against any tested isolates of *E. coli* and *K. pneumoniae*. Among aminoglycosides, gentamicin demonstrated average susceptibility against *E. coli* (36.36%), *A. baumannii* (30.76%), *P. aeruginosa* (37.5%) and *E. cloacae* (50%). Amikacin possessed 50% susceptibility against *E. coli* (63.64%), *C. freundii* (50%), *K. pneumoniae* (25.7%) and *P. aeruginosa* (37.5%). Cephalosporins including cefuroxime and ceftriaxone documented zero susceptibility against all clinical isolates except cefepime which displayed 25% susceptibility against *P. aeuroginosa.* Among quinolones, nalidixic acid and ciprofloxacin showed 50% susceptibility against *E. cloacae* whereas <16% susceptibility was observed against *A. baumannii* and *K. pneumoniae; P. aeuroginosa* exhibited 25% susceptibility towards Levofloxacin.

4. DISCUSSION

Of the 74 Carbapenem resistant strains identified, a marginally higher number of strains were isolated from urine samples (45.16%) closely followed by blood (42.1%) and sputum (40%). Nair et al. [11] reported that majority of the carbapenem isolates were detected in urine samples (46%) out of total 57 carbapenem-resistant isolates obtained from 465 Enterobacteriaceae isolates screened. The high prevalence of carbapenem resistance in uropathogens reported in this study could be simply because of higher number of urine clinical urine samples processed initially, thus creating a bias. The overall prevalence of carbapenem resistance in the screened strains was found to be 40.8%. This is similar to or little higher than the carbapenem resistance rates obtained in different studies from other parts of India. *Wattal* et al. [12] have reported a Carbapenem resistance rate ranging from 2% to 80% in various multi-drug resistant organisms including *E. coli, Klebsiella spp., Pseudomonas spp.* and *Acinetobacter spp.* in a tertiary care hospital in Delhi. Gupta et al. [10] reported a carbapenem resistance rate varying from 17 to 22% among Enterobacteriaceae while Datta et al. [13] reported carbapenem resistance of 7.87% among Enterobacteriaceae strains in a study conducted in a tertiary care hospital in North India. In consistent with the global distribution pattern, *K. pneumoniae* (47.30%) was the predominant carbapenem-resistant species reported followed by *A. baumannii* (17.57%) and *E. coli* (14.86%). *K. pneumoniae* isolates are the most common carbapenemase including metallo-beta-lactamase (MBL) producing *Enterobacteriaceae* reported worldwide, from United States, South and Central America, the Middle East, China Italy and Greece [14,3,7,15]. In a study based in India, Oberai et al. [16] have also reported MBL producing *K. pneumoniae* as the most common carbapenem resistant Gram-negative isolate. Moreover, our results have shown that the carbapenem resistant clinical pathogens showed highest susceptible to colistin (100%). However, polymyxins are always drug of last choice for the physicians and fall out of favor among many clinicians due to adverse nephrotoxic and neurotoxic effects. Moreover, in recent years increased use of polymyxins including colistin with rising rates of carbapenem resistant infections has lead to outbreaks of

colistin-resistant carbapenem-resistant infections through the world . To prevent further rise in colistin resistance, there is a high need to explore alternate options to reduce the excessive consumption of colistin. Although, the susceptibility reported to tigelcyclin is very good, tigecylcin cannot be considered as a drug of choice in urine and blood infections because of its inability to maintain the minimum MIC required for its anti-bacterial activity and the major mode of its excretion being through the biliary route. As CSE-1034 (AAE) was determined the third highest susceptible drug and is reported to effective in urinary and blood infections, it can be a drug of choice over tigecylcin in blood and urine infections which are the predominant source of isolated pathogens in this report. A good number of previous studies have reported the greater susceptibility of CSE-1034 (the novel antibiotic adjuvant entity) against different Gram negative pathogens. In an antimicrobial susceptibility pattern study, Sahu et al. [17] have reported that 100%, 64% and 63% of ESBL producing *A. baumannii*, *K. pneumoniae* and *E. coli* and 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.

Similarly, another study on 515 isolates of *P. aeruginos*a has reported 97.3% and 95.1% susceptibility to CSE-1034 of MBL and ESBL+MBL producing isolates resistant towards most of antibiotics including piperacillin+tazobactam, doripenem, imipenem, meropenem, ceftazidime and cefepime [18]. The susceptibility pattern observed to other antibiotics varied from average susceptibility rate of 30% for aminoglycosides, 19% to sulphonamides, 0% to BL/BLI except *P. aerugionosa* (12.5% to 37.5%) and *A. bauminni* (61.5% for Cefaperazone-Sulbactam). The susceptiblity rate to all generations of cepahlaopsorins was zero and for quinolones varied from 0-25% for different species. Almost similar to our pattern, Shanmugan et al. [19] have reported that the resistance of carbapenem resistant isolates to aminoglycoside antibiotics varied from 33% for amikacin to 94% to tobramycin. The same study has reported the resistance rate of 100% to ampicillin, cotrimoxazole, all 4 generations of cephalosporins and piperacillin-tazobactam [19].

Generally, carbapenem-resistant strains are inherently considered resistant to broader classes of antibiotics because of carbapenemase production, but various other mechanisms including efflux pumps, membrane impermeability, expression of class D enzymes making them specifically resistant to carbapenems can't be ignored [20]. A study by Mosca A et al. [21] in Italy has shown that only 84% of the carbapenem resistant strains evaluated by MHT showed the production of carbapenemase clearly indicating that other mechanisms of resistance also co-exist. Establishing the contribution of different mechanisms of resistance to carbapenems among a collection of imipenem- and meropenem-non-susceptible *P. aeruginosa* isolates, Rodríguez-Martínez et al. [22] have reported that genes encoding metallo-β-lactamases or carbapenem-hydrolyzing oxacillinases were not identified in any of the isolates. The main mechanisms associated with carbapenem resistance reported were loss of outer membrane protein OprD, over-expression of extended-spectrum cephalosporinases (ESACs) and specific efflux pumps [20]. Similar to our observations, Campana et al. [23] have reported Carbapenem-resistant and cephalosporin-susceptible phenotype among *P. aeruginosa* clinical isolates in Brazil. A carbapenem resistant, beta-lactam susceptible phenotype is characteristic for diminished expression of OprD as carbapenems are known to enter the periplasmic space of bacteria through the OprD outer membrane porin. The OprD gene inactivation leading to porin loss probably by acquisition of mutations including insertions or deletions is known cause of imipenem resistance [24]. Moreover, strains with OprD downregulation have reduced susceptibility to meropenem while susceptibility to other beta-lactams are not affected [25]. OXA-23-like and OXA-48-like are also reported to be closely related to carbapenem resistant phenotype. OXA-23 and OXA-48 which belong to class D β-lactamase, are reported to have selective carbapenem-hydrolyzing activity in *A. baumannii and P. aeruginosa* [26,27,28]. Moreover, overexpression of MexAB-OprM, MexCD-OprJ and MexXY-OprM efflux systems are also involved in reduced susceptibility to meropenem, quinolones, antipseudomonal penicillins, cephalosporins, aminoglycosides whereas, ceftazidime and imipenem are not usually affected [29,30,31]. All these studies clearly indicate that some strains are specifically resistant to carbapenems and the choice of drug in these cases could be other than colistin and tigelcycin.

It becomes imperative to mention that although carbapenem-based combination therapy is suggested for carbapenem resistant infections, its efficacy appears to be MIC dependent. Various studies have concluded that this combination therapy helps to reduce mortality in patients with carbapenem MIC ≤8 µg/mL, and the mortality rate shoots up if the MIC is >8 µg/mL (Discussed in detail by Morril. et al. [32]). The carbapenem-based combination therapy can't be considered at all for MIC>16 µg/mL. Though amikacin also showed a good susceptibility pattern against many clinical isolates, only 7/32 of urinary and blood isolates were reports susceptible to amikacin compared to 21/32 reported for CSE-1034. Thus, CSE-1034 alone or in combination with other drugs can be preferred choice for all infections particularly urinary and blood infections caused by carbapenem resistant strains.

CSE-1034 has probably high susceptibility rates among multi-drug resistant Gram-negative bacteria due to the presence of antibiotic resistance breaker, i.e. EDTA which interferes with the stability of outer membrane of microbes via chelating the cations and increasing the permeability of the antibiotics [33,34]. Hence from the present study, it is evident that colistin, tigecycyclin, amikacin and CSE-1034 should be an empirical choice of treatment for bacterial infections where the carbapenem resistant strains are suspected.

5. CONCLUSION

Overall, it can be concluded that carbapenem resistance among Gnegative strains have become a common scenario in the hospitals as a consequence of excessive consumption of carbapenems. From the antibiotic susceptibility profile, it can be clearly inferred along with colistin and tigecycline, CSE-1034 and amikacin can be a drug of choice for patients infected with carbapenem resistant strains. Moreover, considering the value of carbapenems as one of the last option for various MDR bacterial infections, irrational consumption of carbapenems should be stopped.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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