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Comparative *in vitro* Activities of Different Antibiotics against Clinical Isolates of Gram-negative Bacilli

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Authors' contributions

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

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ABSTRACT

Objective: The local anti-microbial susceptibility profile plays a very critical role in guiding clinicians to choose the appropriate empiric therapies. This study was conducted to assess the pathogen characteristics and the in vitro susceptibility of different Gram negative isolates to commonly used antibiotics in our hospital settings.
Methods: A total of 110 Gram negative isolates were included in the study. A retrospective, observational analysis of antibiogram data was performed for four antimicrobial agents including CSE-1034 (ceftriaxone-sulbactam-EDTA), piperacillin-tazobactam (pip-taz), cefoperazone-sulbactam and meropenem.
Results: Of the 200 clinical specimens analysed, Gram negative isolates obtained from 110 samples were included in the final analysis. The most common Gram negative isolates were *Klebsiella species* (35.5%), *E. coli* (33.6%) and *P. aeruginosa* (21.8%). The overall susceptibility was highest to CSE-1034 (100%) followed by meropenem (66.4%), cefoperazone-sulbactam (56.4%) and pip-taz (45.5%). The MIC_{90} range of CSE-1034 for *Enterobacteriaceae* was ≤0.5-≤4µg/ml and ≤2µg/ml for susceptible *P. aeruginosa* isolates. The MIC_{90} of meropenem for 94.4% of meropenem-susceptible *Enterobacteriaceae* strains was <0.25µg/ml and 64.3% of *P. aeruginosa* were having MIC ≤0.25µg/ml. The MIC_{90} of pip-taz for 82.5% of the pip-taz susceptible

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Enterobacteriaceae strains was 4µg/ml and 63.6% of *P. aeruginosa* was ≤8.0µg/ml. The MIC_{90} of cefoperazone-sulbactam susceptible strains were between ≤8 to ≤16µg/ml and 45.8% isolates of susceptible *P. aeruginosa* were having MIC between ≤8 to ≤16µg/ml.

Conclusions: Overall, this *in vitro* surveillance study suggests that CSE-1034 can be considered an important therapeutic option for the treatment of various multi drug resistant Gram-negative bacterial infections and avert the threat of resistance to last resort antibiotics including carbapenems.

Keywords: Carbapenems; gram-negative; multi-drug resistance; Minumum inhibitory concentration.

1. INTRODUCTION

The ability to treat serious bacterial infections in clinical practice is often complicated by the new resistance mechanisms emerging and spreading globally [1]. Infections caused by drug-resistant bacteria are often associated with prolonged illness, disability, and death, compared to infections caused by their drug-susceptible counterparts, particularly if inappropriate empirical antibiotic therapy is prescribed [2]. Antimicrobial resistance also increase the socio-economic burden of healthcare costs and resource utilisation with lengthier stays in hospitals and requirement of more intensive care [2,3].

The topic of big concern today in healthcare is the rising anti-microbial resistance in gram-negative bacilli over the past decade. The situation is even more grave in Asian sub-continent where overuse and misuse of antibiotics has led to a higher level of anti-microbial resistance [4]. This problem is further complicated by the fact that many antibiotic resistance mechanisms in gram-negative bacilli render resistance to more than one class of antibiotics, and are placed on mobile genetic elements like plasmids and transposons that lead to horizontal gene transfer across different bacterial species with relative ease [3]. This problem is made even more acute by inadequate antibiotic options available for these resistant isolates currently and in the foreseeable future. Over the last three decades, beta-lactam antibiotics were being widely used for the treatment of various bacterial infections [5]. However, later these beta-lactams were replaced by carbapenems due to the emergence of extended-spectrum β-lactamases (ESBL) strains in clinical settings [3]. Although carbapenems are adequately effective for the treatment of bacterial infections caused by ESBL producing pathogens, the indiscriminate use of carbapenems has led to carbapenem resistance worldwide [6,7]. Various studies have suggested antibiotic adjuvant therapies as an alternate approach to curb multi-drug resistance [8,9,10]. Ceftriaxone in combination with sulbactam and antibiotic resistance breaker "EDTA" (CSE-1034) is a newly approved drug for the treatment of wide range of bacterial infections. The mechanisms through which CSE-1034 targets various resistance pathways in bacteria include increase in the membrane porosity, inhibition of curli formation and bacterial adhesion, chelation of ions required for the activity of relaxases for the conjugal spread of resistance gene, inhibition of metallo-beta-lactamases (MBLs) and down-regulation of MexAB-OprM and AcrAB-tolC efflux pumps [11,12,13]. In this study, we have compared the in vitro activity of CSE-1034 with meropenem and beta-lactam/beta-lactamase inhibitor combinations including pipericillin-tazabactam (Pip-Taz) and cefoperazone-sulbactam in Gram-negative clinical isolates collected over a period from Jan. 2016 to Dec. 2016.

2. METHODOLOGY

2.1 Bacterial Strains

A total of 110 clinical samples obtained from different infection sources in our hospital over a period from Jan. 2016 to Dec. 2016 were included in this study. Clinical isolates were obtained from urine, respiratory, wound, blood, skin and other sources. The sample collection and processing were done using the standard procedures mentioned in the manual for laboratory identification and anti-microbial susceptibility testing of bacterial pathogens of public health importance (WHO, 2015). All the isolates were identified by standard microbiological tests.

2.2 Pathogen Isolation and Identification

Pathogen isolates were identified based on motility, colony morphology, Gram-staining and different biochemical reactions using standard

techniques (Claus,1992). The desired clinical samples were collected in sufficient quantity in an aseptic manner in sterile containers. The specimens were inoculated or streaked on different selective and non-selective culture media as per the standard microbiological procedures (Baldauf et al., 2007). Blood samples that were collected in brain heart infusion broth were incubated aerobically overnight at 37˚C followed by sub-culturing in the respective media.

2.3 Antimicrobial Agents

All the isolates were tested for the susceptibility to CSE-1034 (ceftriaxone-sulbactam-EDTA), pip-taz 4.5g, cefoperazone-sulbactam 1g and meropenem 1g.

The antimicrobial susceptibility testing of the isolates was determined by Kirby Bauer disc diffusion method according to CLSI guidelines. MICs of all agents except CSE-1034 were interpreted as per CLSI break-points. CSE-1034 MICs were interpreted using the MIC breakpoints provided by the manufacturing company, Venus Remedies.

3. RESULTS

A total of 200 clinical samples from different infection sources were sent for microbiological analysis. The different clinical samples used for pathogen isolation were urine, blood, pus, semen, sputum, endo-tracheal secretions, stool, ischio-rectal abscess, throat secretions, throat swab, TT secretions, ear discharge, oral secretions and stents. Of the total 200 samples processed, Gram- negative pathogens were isolated from 55% (*n*=110), Gram- positive from 20% (n=40) whereas no growth was found in 25% (n=50) of the clinical samples. Only 110 identified Gram-negative isolates were further analysed and processed for in vitro anti-microbial susceptibility testing. The contribution of most prevalent Gram negative bacterial isolates is given in Table 1. The most common Gram negative isolates identified were *Klebsiella spp.* (35.5%), *E. coli* (33.6%) and *P. aeruginosa* (21.8%). The Gram-negative pathogens were majorly isolated from urine (28.2%), pus and wound swabs (25.5%), blood (9.1%) and endotracheal/tracheal secretions (12.7%). For other details, refer to Table 1.

Anti-microbial susceptibility testing results of 110 Gram-negative clinical isolates for CSE-1034 and comparator antibiotics are summarised in Table 2. Overall, the susceptibility of all isolates was greater to CSE-1034 (100%) compared to meropenem (66.4%), pip-taz (45.5%) and cefoperazone-sulbactam (56.4%). The MIC range of CSE-1034 for 86 isolates of *Enterobacteriaceae* was ≤0.5-≤4 µg/ml with 43.6% isolates having MIC of ≤2µg/ml. All the isolates with MIC of 4µg/ml were *Klebsiella spp.* and *E. coli*. The MIC of all *P. aeruginosa* isolates was ≤2µg/ml.

Table 1. Demographic and baseline characteristics of all study subjects (n=110)

Characteristics		**(n=110)**
Gender	Male, n (%)	57 (52)
	Female, n (%)	53 (48)
Age (year)	Mean±SD	51.5±20.24
Clinical sample (%)	**Urine**	31 (28.2)
	Pus and wound swabs	28 (25.5)
	Endo-tracheal/tracheal secretions	14 (12.7)
	Sputum, throat secretions, Pleural tissue, BAL	11 (10)
	Blood	10 (9.1)
	Fluids	6 (5.5)
	Tissue/Bile	5 (4.5)
	Vaginal swabs	2 (1.8)
	Ear discharge	2 (1.8)
	Stool	1 (0.9)
Causative pathogen		
	K. pneumoniae & K. oxytoca	39 (35.5)
	E. coli	37 (33.6)
	P. aeruginosa	24 (21.8)
	Salmonella spp.	7 (2.4)
	E. cloacacaea	2 (2.6)
	E. aerogenes	1 (2.2)

Table 2. *In vitro* activity of CSE-1034 and comparative agents against various Gram-negative isolates

	MIC range									
	<0.25	**0.25**	**0.5**	**2**	**4**	**8**	**16**	**32**	**64**	**128**
***E. coli* (37)**										
Meropenem	24	1	2	1	11	2	6	0	0	0
Pip-taz	0	0	0	0	14	2	1	0	5	15
Cefoperazone-sulbactam	0	0	0	0	0	20	7	0	1	9
CSE-1034	0	0	0	8	29	0	0	0	0	0
***Klebsiella. spp.* (39)**										
Meropenem	18	0	0	1	2	2	16		0	0
Pip-taz	0	0	0	0	12	1	3	1	0	22
Cefoperazone-sulbactam	0	0	0	0	0	15	2	7	15	0
CSE-1034	0	0	0	7	32	0	0		0	0
***P. aeruginosa* (24)**										
Meropenem	8	0	1	5	0	1	9	0	0	0
Pip-taz	0	0	0	0	3	4	4	2	0	1
Cefoperazone-sulbactam	0	0	0	0	0	9	2	7	6	0
CSE-1034	0	0	3	21	0	0	0	0	0	0
***S.enterica* (2)**										
Meropenem	2	0	0	0	0	0	0	0	0	0
Pip-taz	0	0	0	0	1	1	0	0	0	0
Cefoperazone-sulbactam	0	0	0	0	0	1	0	1	0	0
CSE-1034	0	0	1	1	0	0	0	0	0	0
***Salmonella spp.* (5)**										
Meropenem	4	0	0	1	0	0	0	0	0	0
Pip-taz	0	0	0	0	5	0	0	0	0	0
Cefoperazone-sulbactam	0	0	0	0	0	4	0	0	1	0
CSE-1034	0	0	1	5	0	0	0	0	0	0
***E. cloacacea* (2)**										
Meropenem	2	0	0	0	0	0	0	0	0	0
Pip-taz	0	0	0	0	0	0	0	0	0	1
Cefoperazone-sulbactam	0	0	0	0	0	1	0	1	0	0
CSE-1034	0	0	1	1	0	0	0	0	0	0
***E. aeruginosa* (1)**										
Meropenem	1	0	0	0	0	0	0	0	0	0
Pip-taz	0	0	0	0	1	0	0	0	0	0
Cefoperazone-sulbactam	0	0	0	0	0	1	0	0	0	0
CSE-1034	0	0	0	1	0	0	0	0	0	0

Of the 86 isolates of *Enterobacteriaceae* tested for meropenem, 54 isolates (62.8%) tested as meropenem-susceptible, 2 (2.3%) as meropenem-intermediate and 27 (31.4%) as meropenem-resistant. The MIC of 94.4% of *Enterobacteriaceae* strains was <0.25µg/ml whereas only 5.6% of the strains were having MIC between 0.25 to 1µg/ml. The MIC of all the meropenem-resistant strains belonging to *Enterobacteriaceae* were between 4 µg/ml to 16µg/ml. 14 (58.3%) of the *P. aeruginosa* isolates were meropenem-susceptible and 10 (41.7%) as meropenem-resistant. 64.3% of meropenem-susceptible strains of *P. aeruginosa* were having MIC ≤0.25µg/ml and 90% of the meropenem- resistant strains were having MIC of 16 µg/ml.

Pip-taz at the break point of ≤16µg/ml inhibited 47.6% (40/84) isolates of *Enterobacteriaceae*, 7.1% (6/84) showed intermediate susceptibility and 48.1% (38/84) were completely resistant. The MIC_{90} for 82.5% (33/40) of the susceptible strains was 4µg/ml, 8µg/ml for 7.5% (3/40), 16µg/ml for 10% (4/40) strains. The MIC_{90} for all the resistant strains was 128µg/ml. 78.6% (11/14) of *P. aeruginosa* were pip-taz susceptible, 14.3% (2/14) were having intermediate resistance and 7.1% (1/14) were reported to be resistant. No susceptibility data was available for 10 isolates of *P. aeruginosa.*

74.6% (62/83) strains of *Enterobacteriaceae* were susceptible to cefoperazone-sulbactam, 10.8% (9/83) showed intermediate susceptibility and 27.7% (23/83) were resistant. The MIC_{90} of all sensitive strains was between ≤8 to ≤16µg/ml and the resistant strains were between ≤64 to ≤128µg/ml. 45.8% (11/24) isolates of *P. aeruginosa* were susceptible to cefoperazone-sulbactam (MIC between ≤8 to ≤16µg/ml), 29.2% (7/24) isolates were intermediately susceptible (MIC of 32µg/ml) and 25% (6/24) were resistant with the MIC of 64µg/ml.

4. DISCUSSION

The wide spread of clinically relevant β-lactamase enzymes in a broad range of species continues to contribute to a growing global clinical challenge, where even drugs of last resort are no longer predictably reliable [3]. Carbapenems represent the first option for infections caused by ESBL producers , but the viability of this option is completely weakened in presence of MBL producing strains [14]. As MBLs are virtually capable of hydrolysing all class of beta-lactamases and given the paucity of development of newer MBL stable antibiotics, their continued spread may become a clinically big issue and thus pushing the need for alternate antibiotics. The results of this *in vitro* surveillance study indicate CSE-1034 a potent anti-microbial agent compared to meropenem, pip-taz and cefoperazone-sulbactam.

In our study, 62% isolates were meropenem-susceptible, 1.8% as meropenem-intermediate and 33.6% as meropenem-resistant. The meropenem resistance was highest in *P. aeruginosa* (37.5%) followed by *K. pneumoniae* and then *E. coli*. The MICs of 64.3% of meropenem-susceptible strains was ≤0.25µg/ml and 90% of the meropenem-resistant strains were having MIC between 4µg/ml to 16µg/ml. The MICs of all meropenem-resistant *P. aeruginosa* isolates was 16µg/ml. Carbapenem resistance has been reported worldwide in clinical isolates of *Enterobacteriaceae* [15]. Similar to our results, Porwal et al. [16] have reported *K. pneumoniae* (44%) as the most common carbapenem resistant Gram-negative isolate followed by *E. coli* (26%). A retrospective study conducted on the patient blood cultures collected over a 7-year period from 2008–2014 has shown that carbapenem resistance increased among *E. coli* from 7.8% to 11.5% and from 41.5% to 56.6% among *K. pneumoniae* [17]. The average carbapenem resistance among *P. aeruginosa* was 49% for all years, with no significant change in the trend observed. Similar to our results, Chauhan K et al. [18] have reported a carbapenem resistance of 14.6% in *E. coli* and 29.6% in *Klebsiella spp.* in hospital isolates from various in and outpatient areas [19]. Wattal et al. [19] have also reported a carbapenem resistance rate of 31-51% in *Klebsiella spp*. and 2-13% in *E. coli.* In contrast, Arora et al. [20] have reported a very high meropenem resistance of 73.1% in *Klebsiella spp.* and comparatively less in *E. coli* (23.8%). 47.6% of the isolates of *Enterobacteriaceae* were sensitive whereas 35.5% of the isolates were resistant to pip-taz. Among *P. aeruginosa* strains, 78.6% of *P. aeruginosa* were pip-taz susceptible, 14.3% were having intermediate resistance and 7.1% were reported resistant. 74.6% (62/83) strains of *Enterobacteriaceae* were susceptible to cefoperazone-sulbactam, 10.8% (9/83) showed intermediate susceptibility and 27.7% (23/83) were resistant. 45.8% (11/24) isolates of *P. aeruginosa* were susceptible to cefoperazone-sulbactam (MIC between ≤8 to ≤16µg/ml), 29.2% (7/24) isolates were intermediately susceptible (MIC of 32µg/ml) and 25% (6/24) were resistant with the MIC of 64µg/ml. Surprisingly, the susceptibility pattern observed towards these beta-lactam/beta-lactam inhibitors particularly cefoperazone-sulbactam were almost similar to meropenem which is actually worrisome. The various reasons for this high resistance towards carbapenems include the increased dependence on carbapenems for the treatment of burgeoning number of infections worldwide caused by ESBL-positive pathogens, poor infection control practice and the lack of anti-microbial stewardship programs in many hospitals [21,22].

The susceptibility reported to CSE-1034 was 100%. Various studies have reported a high efficacy of CSE-1034 against vast number of bacterial infections [23,24,25]. CSE-1034 is a novel antibiotic adjuvant entity having ceftriaxone, sulbactam and disodium EDTA with synergistic action. Use of adjuvant along with antibiotic is a novel approach to counter antibiotic resistance. EDTA used as adjuvant along with ceftriaxone and sulbactam in CSE-1034 enhances the penetration of antibiotic into cell membrane, decreases over-expression of efflux pump, bio-film eradication, chelation of divalent ions required for activity of MBLs, etc [11,26]. In an antimicrobial susceptibility pattern study, ESBL producing *K. pneumoniae* clinical isolates were reported to be highly susceptible (67–81%) to CSE-1034 [27]. A susceptibility study on 515

isolates of *P. aeruginosa* has shown MBL and ESBL+MBL producing isolates were resistant towards most of antibiotics including pip-taz, carbapenems and cephalosporins. Bhatia [28] has also reported overall success rate of >75% of CSE-1034 against ~61% in meropenem for the treatment of various Gram-negative bacterial infections. In a recent study on antibiotic susceptibility pattern of Gram-negative pathogens from ICU patients in India, CSE-1034 was reported to have higher efficacy compared to carbapenem family [29]. The enhanced activity of this novel combination against *A. baumannii* could likely be associated with synergistic effect of ceftriaxone plus sulbactam plus disodium edetate. Synergism of ceftriaxone and sulbactam against *A. baumannii*, *E. coli, K. pneumoniae* and *P. aeruginosa* has also been proved by a cup-plate agar diffusion method.

5. CONCLUSION

Overall, this *in vitro* surveillance results reinforce and support existing clinical data regarding CSE-1034 activity against various pathogenic Gram-negative isolates. Moreover, the high carbapenem resistance reported among gram negative strains as a consequence of excessive consumption of carbapenems is a worrisome scene and needs to be controlled immediately by imposing proper anti-microbial stewardship programs and stopping the irrational consumption of carbapenems. Considering the value of carbapenems as one of the last option for various MDR bacterial infections, CSE-1034 should be a drug of choice for patients infected with MDR pathogenic strains to avert the threat of post-antibiotic era where virtually no antibiotics will be effective against these MDR infections.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard written ethical permission has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Zaman SB, Hussain MA, Nye R, Mehta V, Mamun KT, Hossain N. A review on antibiotic resistance: Alarm Bells are Ringing. Cureus [Internet]. [Cited 2018 Jul 2];9.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5573035/
2. Barriere SL. Clinical, economic and societal impact of antibiotic resistance. Expert Opin Pharmacother. 2015;16:151–3.
3. Shaikh S, Fatima J, Shakil S, Rizvi SMD, Kamal MA. Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment. Saudi J Biol Sci. 2015;22:90–101.
4. Zellweger RM, Carrique-Mas J, Limmathurotsakul D, Day NPJ, Thwaites GE, Baker S, et al. A current perspective on antimicrobial resistance in Southeast Asia. J Antimicrob Chemother. 2017;72: 2963–72.
5. Thakuria B, Lahon K. The Beta Lactam Antibiotics as an Empirical Therapy in a Developing Country: An Update on Their Current Status and Recommendations to Counter the Resistance against Them. J Clin Diagn Res JCDR. 2013;7:1207–14.
6. Liu Q, Li X, Li W, Du X, He J-Q, Tao C, et al. Influence of carbapenem resistance on mortality of patients with *Pseudomonas aeruginosa* infection: A meta-analysis. Sci Rep. 2015;5:srep11715.
7. Lee Y, Choi H, Yum JH, Kang G, Bae IK, Jeong SH, et al. Molecular Mechanisms of Carbapenem Resistance in Enterobacter cloacae Clinical Isolates from Korea and Clinical Outcome. Ann Clin Lab Sci. 2012;42:281–6.
8. Gill EE, Franco OL, Hancock REW. Antibiotic adjuvants: Diverse strategies for controlling drug-resistant pathogens. Chem Biol Drug Des. 2015;85:56–78.
9. Bernal P, Molina-Santiago C, Daddaoua A, Llamas MA. Antibiotic adjuvants: Identification and clinical use. Microb Biotechnol. 2013;6:445–9.
10. Verma S. A retrospective study to evaluate the efficacy of a new antibiotic adjuvant

entity (β-lactam/β-lactamase inhibitor/ adjuvant disodium edetate combination) for management of sepsis. Res J Infect Dis. 2015;3:3.

11. Chaudhary M, Kumar S, Payasi A. A Novel Approach to Combat Acquired Multiple Resistance in Escherichia coli by using EDTA as Efflux Pump Inhibitor. J Microb Biochem Technol [Internet]. 2012 [cited 2017 Jun 13];4. Available: https://www.omicsonline.org/a-novel-approach-to-combat-acquired-multiple-resistance-in-escherichia-coli-by-using-edta-as-efflux-pump-inhibitor-1948-5948.php?aid=9411
12. Chaudhary M, Payasi A. Role of EDTA and CSE1034 in curli formation and biofilm eradication of *Klebsiella pneumoniae:* A comparison with other drugs. J Antibiot (Tokyo). 2012;65:631–3.
13. Chaudhary M, Payasi A. Comparative efficacy of antibiotics in biofilms eradication formed by ESBL and non ESBL producing micro-organisms. Int J Drug Dev Res [Internet]. 2015 [cited 2017 Jul 23];4. Available:http://www.ijddr.in/abstract/comparative-efficacy-of-antibiotics-in-biofilms-eradication-formed-by-esbl-andnon-esbl-producing-microorganisms-5018.html
14. Falagas ME, Lourida P, Poulikakos P, Rafailidis PI, Tansarli GS. Antibiotic treatment of infections due to carbapenem-resistant enterobacteriaceae: Systematic evaluation of the available evidence. Antimicrob Agents Chemother. 2014;58: 654–63.
15. Logan LK, Weinstein RA. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. J Infect Dis. 2017;215:S28–36.
16. Porwal R, Gopalakrishnan R, Rajesh NJ, Ramasubramanian V. Carbapenem resistant Gram-negative bacteremia in an Indian intensive care unit: A review of the clinical profile and treatment outcome of 50 patients. Indian J Crit Care Med Peer-Rev Off Publ Indian Soc Crit Care Med. 2014;18:750–3.
17. Gandra S, Mojica N, Klein EY, Ashok A, Nerurkar V, Kumari M, et al. Trends in antibiotic resistance among major bacterial pathogens isolated from blood cultures tested at a large private laboratory network in India, 2008–2014. Int J Infect Dis. 2016;50:75–82.
18. Chauhan K, Pandey A, Asthana AK, Madan M. Evaluation of phenotypic tests for detection of Klebsiella pneumoniae carbapenemase and metallo-beta-lactamase in clinical isolates of Escherichia coli and Klebsiella species. Indian J Pathol Microbiol. 2015;58:31.
19. Wattal C, Goel N, Oberoi JK, Raveendran R, Datta S, Prasad KJ. Surveillance of multidrug resistant organisms in tertiary care hospital in Delhi, India. J Assoc Physicians India. 2010;58 Suppl:32–6.
20. Arora S, Munshi N. Comparative Assessment of Antibiotic Susceptibility Pattern of Gram Negative Pathogens Isolated from Intensive Care Unit Patients in Pune. Br Microbiol Res J. 2015;10:1–9.
21. Nordmann P, Dortet L, Poirel L. Carbapenem resistance in enterobacteriaceae: Here is the storm! Trends Mol Med. 2012;18:263–72.
22. Bogan C, Marchaim D. The role of antimicrobial stewardship in curbing carbapenem resistance. Future Microbiol. 2013;8:979–91.
23. Chaudhary M, Mir MA, Ayub SG. Safety and efficacy of a novel drug elores (ceftriaxone + sulbactam + disodium edetate) in the management of multi-drug resistant bacterial infections in tertiary care centers: A post-marketing surveillance study. Braz J Infect Dis. 2017;21:408–17.
24. Chaudhary M, Ayub SG, Mir MA. Comparative efficacy and safety analysis of CSE-1034: An open labeled phase III study in community acquired pneumonia. J Infect Public Health [Internet]. 2018 [cited 2018 May 30]; 0. Available:https://www.jiph.org/article/S1876-0341(18)30042-X/fulltext
25. Chaudhary M, Payasi GA and A. Advancing in the Direction of Right Solutions: Treating Multidrug-Resistant Pneumonia. Contemp Top Pneumonia [Internet]. 2017 [cited 2018 Aug 31]; Available:https://www.intechopen.com/books/contemporary-topics-of-pneumonia/advancing-in-the-direction-of-right-solutions-treating-multidrug-resistant-pneumonia
26. Chaudhary M, Kumar S. Catering ESBL resistance challenge through strategic combination of Ceftriaxone, Sulbactam and Ethylenediaminetetraacetic Acid. Int J Drug Dev Res [Internet]. 2015 [cited 2017 Jul 23];4.

Available:http://www.ijddr.in/abstract/catering-esbl-resistance-challenge-through-strategic-combination-ofceftriaxone-sulbactam-and-ethylenediaminetetraacetic-acid-4954.html

27. Sahu M, Sanjith S, Bhalekar P, Keny D. Waging war against extended spectrum beta lactamase and metallobetalactamase producing pathogens- novel adjuvant antimicrobial agent Cse1034- An extended hope. J Clin Diagn Res JCDR. 2014;8: DC20–3.

28. Bhatia P. Alternative empiric therapy to carbapenems in management of drug resistant gram negative pathogens: A new way to spare carbapenems. Res J Infect Dis. 2015;3:2.

29. Sathe P, Maddani S, Kulkarni S, Munshi N. Management of ventilator associated pneumonia with a new antibiotic adjuvant entity (ceftriaxone + sulbactam + disodium edetate) - A novel approach to spare carbapenems. J Crit Care. 2017;41:145–9.

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