ISSN : 2350-0743

International Journal of Recent Advances in Multidisciplinary Research

Vol. 12, Issue 02 pp.10815-10820, February, 2025

RESEARCH ARTICLE

A PERFORMANCE EVALUATION AND ASSESSMENT STUDY ON DIFFERENTIAL IN VITRO SUSCEPTIBILITY OF RECENT CLINICAL ISOLATES IN INDIA TO CEFUROXIME-CLAVULANIC ACID

[1,*]Sonali Sanghavi, [2]Meenakshi Satpute, [3]Nilima Telang, [4]Prashant Agrawal, [5]Saher Khan and [6]Monjori Mitra

[1]Microbiology laboratory, King Edward Memorial Hospital and Research Centre, Pune
[2,3]Department of Microbiology, KEM Hospital, Pune, India
[4]Deputy General Manager, Medical Affairs, Mankind Pharma Ltd, New Delhi 110020, India
[5]Medical Advisor, Medical Affairs, Mankind Pharma Ltd., New Delhi 110020, India
[6]Department of Pediatrics, Institute of Child Health, 11, Dr. Biresh Guha Street, Kolkata 700017, India

ARTICLE INFO

Article History

Received 19th November, 2024
Received in revised form
17th December, 2024
Accepted 26th January, 2025
Published online 28th February, 2025

Keywords:

Cefuroxime; Clavulanic acid; Minimum Inhibitory Concentration (MIC); Susceptibility; E-test.

Corresponding author:
Sonali Sanghavi

ABSTRACT

Background: It is essential to investigate the effectiveness of antibiotics in the present-day scenario, especially because of the increasing threat of antimicrobial resistance. Cefuroxime, a second-generation cephalosporin, has a broad spectrum of antimicrobial activity. However, there is a dearth of data on the current susceptibility of pathogenic bacteria to cefuroxime or its combinations. ***Objective:*** This study aimed to evaluate the *in vitro* susceptibility of clinical isolates to cefuroxime in combination with β-lactamase inhibitor, clavulanic acid, as there are no clinical breakpoints for interpretation of antimicrobial susceptibility. ***Methods:*** Bacterial isolates were cultured from non-repetitive clinical samples from January to February 2024 at a single center in India. Minimum inhibitory concentration (MIC) of cefuroxime + clavulanic acid was evaluated using Epsilometer test (E-test). The MIC values thus obtained were used to assess susceptibility of isolates. ***Results:*** Among 100 clinical isolates tested, 78% were gram negative and 22% were gram positive. *Escherichia coli* was the most prevalent pathogen (38%), followed by *Klebsiella pneumoniae* (24%) and *Staphylococcus aureus* (16%). Since breakpoints for cefuroxime + clavulanic acid are not available, the corresponding values for cefuroxime provided in EUCAST and/or CLSI were used to deduce conclusions about susceptibility. Accordingly, susceptibility/intermediate susceptibility to cefuroxime + clavulanic acid was displayed by 68.42% of *E. coli*, 41.67% of *K. pneumoniae*, and 12.50% of *S. aureus* isolates. Other less-prevalent bacteria such as *Enterobacter cloacae, Serratia marcescens*, *Proteus mirabilis*, *Citrobacter koseri*, *Salmonella enterica*, *Proteus vulgaris*, and *Pantoea spp.* were also found to be susceptible/intermediately susceptible to cefuroxime + clavulanic acid. ***Conclusions:*** A fixed-dose combination (FDC) of cefuroxime and clavulanic acid was effective against pathogens like *E. coli, K. pneumoniae, S. aureus,* and others. Given these broad spectra of activity, this FDC appear well-suited for use in the treatment of a variety of healthcare-associated infections, such as pneumonia, surgical sepsis and/or bacteremia, UTIs, etc.

Citation: Sonali Sanghavi, Meenakshi Satpute, Nilima Telang, Prashant Agrawal et al. 2025. "A Performance Evaluation and Assessment Study on Differential In vitro Susceptibility of Recent Clinical Isolates in India to Cefuroxime-Clavulanic Acid", *International Journal of Recent Advances in Multidisciplinary Research,* 12, (02), 10815-10820.

INTRODUCTION

Antimicrobials, such as antibiotics, are used to prevent and treat infection. Antimicrobial resistance (AMR) refers to situations wherein a pathogen no longer responds to antimicrobials making it difficult to treat infections caused by the pathogen. Development of drug-resistant pathogens increases the risk of disease spread, severe illness, and death (1). Duration of illness and of treatment also increases, thus increasing the global economic burden (2,3). An estimated 4.95 million deaths in 2019 were found to be associated with bacterial AMR, of which 1.27 million deaths were attributable to it (3,4). A report by Taneja and Sharma highlighted the situation of AMR in India and also emphasized that globally, around 700,000 people are victims of AMR each year and around 10 million people are projected to die from AMR by 2050 (5). Therefore, research on antibiotics and their effectiveness in the current day scenario is important so that there are multiple options in the armamentarium to combat a particular infection. The current study focussed on investigating the susceptibility/resistance of pathogenic bacteria to the combination of cefuroxime, a second-generation cephalosporin (β-lactam) antibiotic, and clavulanic

acid, a β-lactamase inhibitor. Cefuroxime has a broad spectrum of antimicrobial activity and is effective against both gram-negative and gram-positive bacteria. It exerts its bactericidal effect by inhibiting transpeptidase and carboxypeptidase enzymes required for cell wall biosynthesis (6). It features in the model list of essential medicines, published by WHO in 2019 (7). The combination of cefuroxime and clavulanic acid was found to be critical based on assessment of clinical practice for infection management in routine Indian healthcare settings (8). Evidence also exists on good *in vitro* activity of other oral cephalosporin-clavulanate combinations against ESBL-producers (9,10). Despite these evidences, there is a paucity of clinical data on the current susceptibility of pathogenic bacteria to the combination of cefuroxime and clavulanic acid, highlighting the safety profile, drug-drug interactions, and cross-indications for this fixed-dose combination (FDC). Thus, despite considerable research efforts, no clear picture has emerged on the clinical breakpoints for rational and empirical use of this FDC. Furthermore, discrepancies have been reported when the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodologies were used for interpreting susceptibility to other well-known clavulanate combinations of antibiotics (11). Taking cognizance of this prevailing scenario, the objective of the current study was to determine the minimum inhibitory concentration (MIC) of cefuroxime + clavulanic acid against gram-negative and gram-positive bacteria isolated from clinical samples using an easy-to-perform and rapid epsilometer test (E-test). The rationale for evaluating these procedures was to find a relatively accurate and scalable method of minimum complexity that can be routinely realized in clinical laboratories, as well as one that is cost-effective for use in resource-limited settings.

MATERIALS AND METHODS

This microbiological study was conducted during January-February 2024 at KEM Hospital Research Centre, Pune. Pathogenic bacterial isolates were cultured from a total of 100 non-repetitive clinical samples, including blood, pus, urine, swab, sputum, pleural fluid, etc. These were incubated in the presence of Ezy MIC™ strips (HiMedia Laboratories Pvt. Limited, Maharashtra, India) impregnated with a predefined concentration gradient of cefuroxime + clavulanic acid. MIC was evaluated according to manufacturer's instructions. The study was approved by the ethics committee of KEM Hospital Research Centre (Pune, India) and registered in the Clinical Trials Registry-India (CTRI) on January 08, 2024 (reference number: CTRI/2024/01/061197). This study was conducted in accordance with Indian GCP guidelines for clinical research, guidelines of the Indian Council for Medical Research (ICMR), and in compliance with the approved study protocol. Analysis of clinical samples was initiated only after obtaining approval in writing. All statistical methods were based on the International Council for Harmonization (ICH) E9 document 'Statistical Principles for Clinical Trials'. Since this was a pilot study, no formal sample size calculation was done. Since clinical breakpoints and susceptibility ranges are not available for cefuroxime + clavulanic acid at the CLSI and the EUCAST, the corresponding values available for cefuroxime were used as a proxy for determining susceptibility/resistance of isolates. Isolates were accordingly classified as susceptible, intermediately susceptible, or resistant, and reported as percentage of total number of isolates of each species.

RESULTS

Among the 100 clinical isolates, 78/100 (78.00%) were gram-negative and 22/100 (22.00%) were gram-positive bacteria. The proportion of samples obtained from in-patients was 52/100 (52.00%) while that from out-patients was 48/100 (48.00%). Of the clinical isolates, 46.00% were sourced from urine samples, 32.00% from pus, 10.00% from blood, 3.00% from sputum, 2.00% each from bile, colonostomy swab, tissue, and trap secretion, while 1.00% was obtained from pleural fluid. The isolated gram-negative bacteria included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Citrobacter koseri*, *Salmonella enterica*, *Salmonella typhi*, *Proteus vulgaris*, and *Pantoea* spp., of which *E. coli* and *K. pneumoniae* were the most prevalent ones. The isolated gram-positive bacteria included *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus lugdunensis*, *Streptococcus anginosus*, and *Streptococcus pneumoniae*, of which *S. aureus* was the most prevalent. The proportion of each of these is given in **Table 1**.

Each of these clinical isolates was used for the evaluation of MIC for cefuroxime + clavulanic acid. The values thus obtained were compared to the MIC values for susceptibility (S), intermediate susceptibility (I), and resistance (R) to cefuroxime, as provided by EUCAST and/or CLSI. As shown in Table 2, 68.42% of *E. coli*, 41.67% of *K. pneumoniae*, , and 83.33% of *E. cloacae* were susceptible/intermediately susceptible to cefuroxime + clavulanic acid. Although only 1 or 2 clinical isolates of *Serratia marcescens*, *Proteus mirabilis*, *Citrobacter koseri*, *Salmonella enterica*, *Salmonella typhi*, *Proteus vulgaris*, and *Pantoea* spp. were detected, all were found to be susceptible/intermediately susceptible to cefuroxime + clavulanic acid. As clinical breakpoints for cefuroxime against *S. typhi* and *P. vulgaris* are not available at EUCAST, the S, I, and R classification for these were done based on information available for other gram-negative bacteria. Similar approach was used in case of gram-positive bacteria apart from *S. pneumoniae*. Thus, among gram-positive bacteria, 12.50% of *S. aureus* and all of *S. pneumoniae* and *S. anginosus* isolates were found to be susceptible/intermediately susceptible to cefuroxime + clavulanic acid. The few isolates of *E. faecalis* and *E. faecium* detected were found to be resistant to cefuroxime + clavulanic acid.

DISCUSSION

To our knowledge, this is the first concerted effort on detailed prospective clinical evaluation assessing rapid (<24 h) paper strip-based method to determine the *in vitro* efficacy of the cefuroxime + clavulanic acid combination (with the specific purpose of evaluating the impact of MIC on outcome). In the past, it has been difficult to demonstrate the clinical data supportive of the establishment of clinical breakpoints as such tests are often performed by non-standardized methods and exhibit wider heterogeneity in methodology.

Table 1. Distribution of clinical isolates, their source specimen and corresponding clinical diagnosis

Total, N=100	n (%)	Clinical diagnosis	Nature of clinical specimen
Gram-negative bacteria			
Escherichia coli	38 (38.00%)	UTI: 10 (26.32%); Acute cholecystitis: 1 (2.63%); Amine poisoning- respiratory failure: 1 (2.63%); Appendicitis: 1 (2.63%); Chronic renal failure: 2 (5.26%); HIV positive-hypotension- electrolyte imbalance: 1 (2.63%); Post operation wound: 1 (2.63%); Pus from gall bladder: 1 (2.63%); Pus from groin- rectosigmoid carcinoma: 1 (2.63%); Ureteric calculus with hypertension: 1 (2.63%)	Urine, Sputum, Pus, Colostomy swab, Blood, Bile
Klebsiella pneumoniae	24 (24.00%)	UTI: 7 (29.17%), Chronic renal failure: 2 (8.33%); renal tubular acidosis: 1 (4.16%), Urinary retention: 1 (4.16%); Opium poisoning: 1 (4.16%); Perianal abscess/injury: 2 (8.33%); Rectosigmoid carcinoma: 1 (4.16%); Bed sore (sacrum), septic shock: 1 (4.16%) Tongue ulcer: 1 (4.16%); Burn injury: 1 (4.16%)	UTI: Urine; Opium poisoning: Trap secretion; Perianal abscess/injury: Pus; Rectosigmoid carcinoma: Colonostomy swab; Bed sore (Sacrum), septic shock: Pus; Tongue ulcer, burn injury: Pus
Enterobacter cloacae	6 (6.00%)	Acute cholecystitis: 1 (16.66%); Ulcer: 1 (16.66%); Postop wound: 1 (16.66%); Osteomyelitis: 1 (16.66%); Abscess: 1 (16.66%)	Acute cholecystitis: Bile; Ulcer; Postop wound: Pus; Osteomyelitis: Tissue; Abscess: Pus
Serratia marcescens	2 (2.00%)	Chronic renal failure	Blood and urine
Proteus mirabilis	2 (2.00%)	Bed sore pus and UTI	Pus and urine
Citrobacter koseri	2 (2.00%)	UTI	Urine
Salmonella enterica	1 (1.00%)	Fever	Blood
Salmonella typhi	1 (1.00%)	Fever	Blood
Proteus vulgaris	1 (1.00%)	Wound	Pus
Pantoea spp.	1 (1.00%)	UTI	Urine
Gram-positive bacteria			
Staphylococcus aureus	16 (16.00%)	Ear infection; Dermatitis medicamentosa; Wound abscess; Pleural effusion; Vaginitis; Post op infection; Pemphigus	Pus; Blood; Tissue; Pleural fluid
Enterococcus faecalis	2 (2.00%)	Septicemia	Blood
Enterococcus faecium	1 (1.00%)	Aneurysm post coiling	Urine
Staphylococcus lugdunensis	1 (1.00%)	Sebaceous cyst	Pus
Streptococcus anginosus	1 (1.00%)	Perianal abscess	Pus
Streptococcus pneumoniae	1 (1.00%)	Septicemia	Blood

Table 2. MIC values of cefuroxime + clavulanic acid compared to clinical breakpoints of cefuroxime

	MIC range for cefuroxime + clavulanic acid (min, max), as applicable	MIC of Cefuroxime[#]		MIC for cefuroxime + clavulanic acid: n (%)[¥]	Percentage of S and I isolates for cefuroxime + clavulanic acid[§]
Gram-negative bacteria					
Escherichia coli (n=38)	2, >256	S	≤4	14 (36.84%)	68.42%
		I	8-16	12 (31.58%)	
		R	≥32	6 (15.79%)	
Klebsiella pneumoniae (n=24)	6, >256	S	≤4	9 (37.50%)	41.67%
		I	8-16	1 (4.17%),	
		R	≥32	12 (50.00%)	
Enterobacter cloacae (n=6)	12, >256	S	≤4	1 (16.67%)	83.33%
		I	8-16	4 (66.66%)	
		R	≥32	1 (16.67%)	
Serratia marcescens (n=2)	8	S	≤4	2 (100.00%)	100.00%
		I	8-16	0	
		R	≥32	0	
Proteus mirabilis (n=2)	3, 1.5	S	≤4	2 (100.00%)	100.00%
		I	8-16	0	
		R	≥32	0	
Citrobacter koseri (n=2)	4, 8	S	≤4	2 (100.00%)	100.00%
		I	8-16	0	
		R	≥32	0	
Salmonella enterica (n=1)	3	S	≤4	1 (100.00%)	100.00%
		I	8-16	0	
		R	≥32	0	
Salmonella typhi (n=1)	8	NAV	NAV	≤4: 0, 8-16: 1 (100.00%), ≥32: 0	100.00%
Proteus vulgaris (n=1)	2	NAV	NAV	≤4: 1 (100.00%), 8-16: 0, ≥32: 0	100.00%
Pantoea spp. (n=1)	3	S	≤4	1 (100%)	100.00%
		I	8-16	0	
		R	≥32	0	
Gram-positive bacteria					
Staphylococcus aureus (n=16)	1.5, >256	NAV	NAV	≤1: 0, 2: 2 (12.50%), ≥4: 8 (50%)	12.50%
Enterococcus faecalis (n=2)	>256	NAV	NAV	≤1: 0, 2: 0, ≥4: 2 (100%)	0%
Enterococcus faecium (n=1)	>256	NAV	NAV	≤1: 0, 2: 0, ≥4: 1 (100%)	0%
Staphylococcus lugdunensis (n=1)	3	NAV	NAV	≤1: 0, 2: 0, ≥4: 0	NA
Streptococcus anginosus (n=1)	0.75	NAV	NAV	≤1: 1 (100.00%), 2: 0, ≥4: 0	100.00%
Streptococcus pneumoniae (n=1)	0.064	S	≤1	1 (100%)	100.00%
		I	2	0	
		R	≥4	0	

[#]Reference: European Committee on Antimicrobial Susceptibility Testing Breakpoint tables for interpretation of MICs and zone diameters, Version 13.0, valid from 2023-01-01 Abbreviations: MIC = Minimum Inhibitory Concentration; NAV = Not available; S = MIC value for susceptibility; I = MIC value for intermediate susceptibility; R = MIC value for resistance [¥]Proportion of samples with the MIC value specified [§]In the absence of known breakpoints for cefuroxime + clavulanic acid, interpretations presented here are based on comparing the observed MICs for cefuroxime + clavulanic acid to the corresponding values for cefuroxime provided in EUCAST and/or CLSI.

However, our results indicate that a combination of cefuroxime and clavulanic acid is supportive of the establishment of clinical breakpoints as such tests are often performed by non-standardized methods and exhibit wider heterogeneity in methodology. However, our results indicate that a combination of cefuroxime and clavulanic acid is effective against a number of gram-negative and gram-positive pathogenic bacteria, notably the prevalent ones such as *E. coli*, *K. pneumoniae*, and *S. aureus*. These are also among the six leading pathogens for deaths associated with AMR (4). A high activity of cefuroxime against *E. coli* has been reported earlier (12–14). Cefuroxime is also known to inhibit *Klebsiella* spp., *S. aureus*, and *P. mirabilis* (9,11). These data are from studies that were conducted two to four decades ago. The current study showed that cefuroxime + clavulanic acid is effective against these pathogens even today in the face of widespread AMR. Species such as *S. faecalis* and *S. faecium* (also known as *E. faecalis* and *E. faecium*, respectively) were reported to be resistant to cefuroxime (13,14); data from the current study showed that these are resistant to cefuroxime + clavulanic acid as well. Our data were also found to be comparable to other landmark studies wherein well-established FDCs were reported; the modal MIC for a 2:1 amoxycillin-clavulanate FDC was reported as 24 (16+8) mg/L, equivalent to 'intermediate' as per the EUCAST/ CLSI/ BSAC recommendations (15,16). In a previous study, it was also found that biofilm producers isolated from skin and soft tissue infections were susceptible to the combination of cefuroxime and clavulanic acid (17).

In the current literature, it has mostly been reported that extended-spectrum beta-lactamase (ESBL)-positive members of the *Enterobacteriaceae* are resistant to nearly all oral antibiotics used to treat urinary tract infections, posing important challenges in the management of such patients (16,18–20). The potential inhibition of most class A β-lactamases by clavulanate, the only oral β-lactamase inhibitor available so far, makes the FDC of clavulanate with oral cephalosporin a potential oral regime against ESBL (+) *Enterobacteriaceae* species, for example, *E. coli* in outpatient settings (16,21). The capability of clavulanate to shield the potencies of the oral cephalosporins *in vitro* along with the drug pharmacokinetics in the urine advocated further assessment of such combinatorial strategies, particularly for the treatment of ESBL-*E. coli* and *K. pneumonia*-induced bacteremia or cystitis (16,22,23). This study has demonstrated that Ezy MIC™ strip testing can detect promising *in vitro* interactions and would offer a simple approach for testing by clinical laboratories.

Two FDCs (4:1 and 2:1) of cefuroxime and clavulanic acid have been approved and introduced in some countries for respiratory and urinary tract infections, as well as surgical prophylaxis, although this is not currently approved by the US FDA (9).While concerns were raised against the empirical usage of 3rd-generation cephalosporin-clavulanate FDCs due to antagonistic reports against some ESBL(-) *Enterobacter* and *Citrobacter* isolates and clavulanate-induced AmpC attack on the associated cephalosporin moiety (16,24), efforts to address these issue are also reported recently. Clavulanate was combined with a cephalosporin that is relatively more stable to AmpC, including cefepime and/or cefpirome (16,25). Through a pooled analysis, Stewart *et al.* showed good *in vitro* activity of novel cephalosporin/β-lactamase inhibitor combinations against ESBL-producing isolates (9). Pal *et al.* demonstrated that cefpodoxime/clavulanic acid FDC has more potent *in vitro* activity as compared with amoxicillin/clavulanic acid FDC against β-lactamase (+) gram-positive and gram-negative bacteria (26). The combination of clavulanic acid with cephalosporins as a strategy against ESBL-producers have also been substantiated in previous studies (16). The synergistic efficacy of clavulanate stems from its typical β-lactamase inhibitory action of the class A β-lactamase secreted by the *blaZ* gene (for example, in *S. aureus*) and its ability to bind to penicillin-binding proteins (17). These *in vitro* observations further require direct evidence from patient data for clinical outcomes to determine its microbiological and clinical merit for therapy.

Taken together, the current study is a worthy addition to the limited literature on MIC values for cefuroxime + clavulanic acid. Moreover, this particular FDC was active at a much lesser concentration (0.016-256 µg/ml vis-à-vis 1 mg/l as reported in the available literature), against 38/100 (38.00%) *E. coli* isolates and 24/100 (24.00%) *Klebsiella* spp. isolates. These findings align well or are at least as good as those for nitrofurantoin and fosfomycin as reported by others (15). It may be argued that a 1 mg/L breakpoint may be too moderate for UTIs; and contrary to nitrofurantoin and fosfomycin, cefuroxime-clavulanate would potentially be useful in progressive urinary infections. Cefuroxime + clavulanic acid was also found to be effective in orthopedic prophylaxis and treatment among 300 medical records of patients who underwent surgery (24). Such observations are expected to make physicians and microbiologists aware of the effectiveness of this antibiotic combination and encourage them to conduct further studies on the same and prescribe to patients, as appropriate. Cefuroxime + clavulanic acid can be considered a therapeutic option in infections with any of these as the causative organism. The combination may also be considered as an oral component in sequential treatment regimens or in patients with poor response to other antibiotics. However, further trials are required to establish the same. Most importantly, data from this study might prove instrumental in evaluation of clinical breakpoints for cefuroxime + clavulanic acid that are not available right now. Needless to mention, such information will be able to guide physicians towards better infection management in patients. Since the breakpoint of cefuroxime was used as a proxy for cefuroxime + clavulanic acid because of the absence of specific breakpoints, the interpretation of susceptibility data presented here might not be completely accurate. Apart from this, a limitation of this study is the small number of clinical isolates tested, especially for the less-prevalent bacteria. Therefore, future multi-center studies with a wider variety and a larger number of isolates (with diverse β-lactamases) as well as comparative evaluation with other MIC detection methods are warranted. This study is also limited by the lack of a comparator. Possible comparators could be cefuroxime alone or other combinations of β-lactam antibiotic and β-lactamase inhibitor. Further studies addressing these aspects are expected to complement the current data.

CONCLUSION

In summary, analysis of clinical samples in this study showed that growth of some isolates of the common gram-negative

pathogens, namely *E. coli* and *K. pneumoniae*, and some isolates of the common gram-positive pathogen, *S. aureus*, can be inhibited by a combination of cefuroxime and clavulanic acid. Cefuroxime + clavulanic acid was also found to be effective against *E. cloacae*, *S. marcescens*, *P. mirabilis*, *C. koseri*, *S. enterica*, *S. typhi*, *P. vulgaris*, and *Pantoea spp.* While the licensed and commercially available clavulanate combinations have inconsistent activity and are often imperfectly paired, cefuroxime-clavulanic acid might be better suited than the commercialized oral agents used to treat urinary tract infections due to ESBL producers in the community. Thus, cefuroxime-clavulanic acid combination is an efficient and convenient therapy for a wide range of infections and may be considered a therapeutic choice when empirical treatment of diverse infections caused by common gram-negative and gram-positive bacteria is needed. Moreover, given the promising results of this study, the combination may also be established as an oral component of sequential treatment regimens.

ACKNOWLEDGMENTS

The authors would like to acknowledge the support of Medclin Research Pvt. Ltd. in study conduct, data analysis, and manuscript preparation.

Authors' contributions: SS, MS, and NT were involved in protocol preparation, study supervision, evaluation of isolates, data collection and analysis, and manuscript preparation. PA and SK were involved in funding acquisition. MM was involved in manuscript preparation.

Glossary of abbreviations

AMR: Antimicrobial resistance
CLSI: Clinical and Laboratory Standards Institute
CTRI: Clinical Trials Registry-India
E-test: Epsilometer test
ESBL: Extended-Spectrum Beta-Lactamase
EUCAST: European Committee on Antimicrobial Susceptibility Testing
FDC: Fixed-Dose Combination
I: Intermediate susceptibility
MBC: Minimum Bactericidal Concentration
MIC: Minimum Inhibitory Concentration
R: Resistance
S: Susceptibility
WHO: World Health Organization

REFERENCES

1. World health Organization. Antimicrobial Resistance. Accessed onApr 26, 2024. Available from:https://www.who.int/health-topics/antimicrobial-resistance#:~:text=AMR%20occurs%20when%20bacteria%2C%20viruses,spread%2C%20severe%20illness%20and%20death.
2. Kumar SG, Adithan C, Harish BN, et al. Antimicrobial resistance in India: A review. J Nat Sci Biol Med. 2013;4:286–91.
3. World health Organization. Antimicrobial Resistance-Key facts. 2023; Accessed onApr 26, 2024). Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
4. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399:629–55.
5. Taneja N, Sharma M. Antimicrobial resistance in the environment: The Indian scenario. *Indian J Med Res.* 2019;149:119–28.
6. Gold B, Rodriguez WJ. Cefuroxime: Mechanisms of Action, Antimicrobial Activity, Pharmacokinetics, Clinical Applications, Adverse Reactions and Therapeutic Indications. *Pharmacotherapy*. 1983;3:82–100.
7. World Health Organization (WHO). Model List of Essential Medicines (Internet). 2023 (cited 2024 Apr 29). Available from: https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists
8. Manjula S & Krishna Kumar M. Assessment of Cefuroxime and Cefuroxime Clavulanic Acid Prescription Practices for Infection Management in Routine Indian Healthcare Settings: Expert Insights. *Asian J. Res. Infect. Dis.* 2024;15(6), 12–19.
9. Stewart AG, Harris PNA, Henderson A, et al. Oral cephalosporin and β-lactamase inhibitor combinations for ESBL-producing Enterobacteriaceae urinary tract infections. *J Antimicrob Chemother.* 2020;75:2384–93.
10. Campbell JD, Lewis JS, McElmeel ML, et al. Detection of Favorable Oral Cephalosporin-Clavulanate Interactions by *In Vitro* Disk Approximation Susceptibility Testing of Extended-Spectrum-Beta-Lactamase-Producing Members of the Enterobacteriaceae. *J Clin Microbiol.* 2012;50:1023–6.
11. Delgado-Valverde M, Valiente-Mendez A, Torres E, et al. MIC of amoxicillin/clavulanate according to CLSI and EUCAST: discrepancies and clinical impact in patients with bloodstream infections due to Enterobacteriaceae. *J Antimicrob Chemother.* 2017; dkw562.
12. Perry CM, Brogden RN. Cefuroxime axetil. A review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs*. 1996;52:125–58.
13. O'Callaghan CH, Sykes RB, Griffiths A, et al. Cefuroxime, a new cephalosporin antibiotic: activity in vitro. *Antimicrob Agents Chemother.* 1976;9:511–9.
14. Neu HC, Fu KP. Cefuroxime, a beta-lactamase-resistant cephalosporin with a broad spectrum of gram-positive and -negative activity. *Antimicrob Agents Chemother.* 1978;13:657–64.
15. Potz NAC. Prevalence and mechanisms of cephalosporin resistance in Enterobacteriaceae in London and South-East England. *J Antimicrob Chemother.* 2006;58:320–6.
16. Livermore DM, Hope R, Mushtaq S, et al. Orthodox and unorthodox clavulanate combinations against extended-spectrum β-lactamase producers. *Clin Microbiol Infect.* 2008;14:189–93.
17. De A, Tayal R, Baveja S. Comparison of sensitivity of cefuroxime-clavulanic acid combination v/s cefuroxime alone in biofilm and/or beta-lactamase-producing bacteria. *Eur J Biomed Pharm Sci.* 2016;3:242–6.
18. Pajares-Chamorro N, Hammer ND, Chatzistavrou X. Materials for restoring lost Activity: Old drugs for new bugs. *Adv. Drug Deliv. Rev.* 2022;186:114302.

19. Filby BW, Weldrick PJ, Paunov VN. Overcoming Beta-Lactamase-Based Antimicrobial Resistance by Nanocarrier-Loaded Clavulanic Acid and Antibiotic Cotreatments. *ACS Appl Bio Mater.* 2022;5:3826–40.
20. Thelen H, Dilworth TJ, Mercier RC. Examining the Combination of Cefixime and Amoxicillin/Clavulanate against Extended-Spectrum Beta-Lactamase-Producing *Escherichia coli* Isolates. *Chemotherapy*. 2022;67:261–8.
21. Papp-Wallace KM. The latest advances in β-lactam/β-lactamase inhibitor combinations for the treatment of Gram-negative bacterial infections. *Expert Opin Pharmacother.* 2019;20:2169–84.
22. Bassetti M, Garau J. Current and future perspectives in the treatment of multidrug-resistant Gram-negative infections. *J. Antimicrob. Chemother.* 2021;76 Suppl:iv23–37.
23. Coppola N, Maraolo AE, Onorato L, et al. Epidemiology, Mechanisms of Resistance and Treatment Algorithm for Infections Due to Carbapenem-Resistant Gram-Negative Bacteria: An Expert Panel Opinion. *Antibiotics*. 2022; 11:1263.
24. Anand TVP, Sree SK, Pavani S, et al. Assessment of Rational use of Antibiotics in Orthopedic Surgery Procedures. *J Young Pharm.* 2020;12:s102–7.
25. Nikaido H, Liu W, Rosenberg EY. Outer membrane permeability and beta-lactamase stability of dipolar ionic cephalosporins containing methoxyimino substituents. *Antimicrob Agents Chemother.* 1990;34:337–42.
26. Pal RB, Pal P, Jain S, et al. In vitro study to compare sensitivity of amoxicillin+clavulanic acid and cefpodoxime+clavulanic acid among beta-lactamase positive clinical isolates of gram-positive and gram-negative pathogens. *J Indian Med Assoc.* 2008;106:545–8.

****