Expert opinion on the prescription practice of carbapenem antibiotics for the treatment of drug-resistant bacterial infections in Indian settings

ABSTRACT

Objective: The current survey-based study aims to gather expert opinions on the prescription practice of carbapenem antibiotics for the treatment of drug-resistant bacterial infections in Indian clinical settings.

Methods: The cross-sectional, multiple-response questionnaire-based survey involving professionals with expertise in treating pathogenic illnesses was carried out between 2022 and 2023. The questionnaire comprised 25 questions, the majority of which dealt with the use of antibiotics as monotherapy and in various combinations to treat pathogenic illnesses.

Results: Out of 302 survey participants, 83% of them preferred meropenem medications more frequently than imipenem, biapenem, doripenem, and other antibiotics to treat pathogenic infections. For the management of multidrug-resistant (MDR), extensively drug-resistant (XDR), or pan-drug-resistant (PDR) infections, approximately 54% of the respondents preferred the administration of 1 gm of IV meropenem in 2 to 3 divided doses. About 61% of the responders suggested using IV meropenem together with colistin to treat infections. The combination of IV meropenem with β-lactams, aminoglycosides, tigecycline, colistin, and others was preferred by 91% of the respondents for the treatment of MDR, XDR, and PDR infections. For treating difficult intra-abdominal infections, meningitis, and urinary tract infections (UTIs), almost 43% of the respondents preferred meropenem in combination with sulbactam.

Conclusion: The survey findings emphasize the prominent role of meropenem, either as a standalone treatment or in combination with other antibiotics in the management of challenging infections caused by MDR, XDR, or PDR pathogens. In specific scenarios involving difficult intra-abdominal infections, meningitis, and UTIs, clinicians recommended meropenem in combination with sulbactam antibiotics.

Keywords: Multi-drug resistance, Antibiotics, Carbapenems, Meropenem, Sepsis

1. INTRODUCTION

With the emergence of multidrug-resistant Gram-negative bacteria (MDR-GNBs), intensivists, infectious diseases consultants, and other specialists have been facing numerous unique challenges for the last 15 years in managing critically ill patients in intensive care units [1,2]. According to a 2021 study, at least 700,000 subjects succumb to death every year globally due to antimicrobial resistance. According to the World Health Organization (WHO), this number is projected to increase by 10 million by 2050 without new

or effective treatments [3].For the treatment of serious bacterial infections, antibiotics are the drug of choice, significantly reducing the morbidity and mortality among critically ill patients since their adoption in the 1950s. The global overuse of these drugs has resulted in disease resistance and reduced effectiveness, making it difficult to choose appropriate antibiotic therapy for treating pathogenic infections [4,5].

In critically ill patients with severe infections and risk factors for MDR, it is essential to experimentally ensure adequate coverage for MDR to avoid delaying active treatment [6,7]. With numerous factors at play, treating MDR-GNB infections in critically ill patients has become a highly challenging task. It requires specialized knowledge, continuous updating of the patient's medical history, and an understanding of the local microbiology epidemiology to promptly identify the risk of MDR-GNB and the most likely resistance mechanisms involved. Carbapenems are members of the β-lactam class and are stable to almost all β-lactamases. These drugs exhibit bactericidal action against a wide variety of Gram-positive and Gram-negative aerobic as well as anaerobic bacteria. Meropenem, one of the most well-known members of the carbapenem class, along with imipenem/cilastatin, is typically used to treat moderately to critically ill patients with polymicrobial or nosocomial infections [8].

The application of meropenem for treating severe bacterial infections in various contexts has been investigated by various studies [9,10].In India and the majority of other nations, meropenem is authorized for use in a wide range of conditions, including severe community-acquired pneumonia, bacterial meningitis, febrile neutropenia, complicated skin and skin structure infection, obstetric and gynaecological infections, nosocomial pneumonia, and complicated intra-abdominal infections [11]. A 2019 tertiary care centre-based study by Patnaik et al. emphasized the increasing prevalence of MDR and extensively drug-resistant (XDR) strains. The study underscored the importance of rigorous surveillance, effective implementation of hospital infection control measures, and the practice of antimicrobial stewardship [12].Therefore, the present study aims to gather expert opinions on the prescription practice of carbapenem antibiotics for the treatment of drug-resistant infections in Indian clinical settings.

2. MATERIALS AND METHODS

We carried out a cross sectional, multiple-response questionnaire based survey among clinicians experienced in treating pathogenic infections in the major Indian cities from June 2022 to December 2022.

2.1 Questionnaire

The questionnaire booklet titled FAME (FActs on Meropenem- an Expert opinion study) study was sent to the physicians who were interested to participate. The FAME study questionnaire consisted of a total of 25 items, the majority of which pertained to the treatment of pathogenic infections using antibiotic therapy, both as monotherapy and in various combinations.

2.2 Participants

An invitation was sent to leading clinicians in managing pathogenic infections in the month of March 2022 for participation in this Indian survey. About 302 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provided necessary data. The participants were asked to complete the questionnaire without discussing with their peers.

2.3 Statistical Methods

Statistical analysis was conducted by using descriptive statistics. Percentages were used to represent categorical variables. The frequency and percentage distributions of each variable were presented. Pie charts and bar charts were created using Excel 2013 (16.0.13901.20400).

3. RESULTS

Out of the 302 survey participants, 35% of them reported that *Pseudomonas aeruginosa* is the most common bacterial strain found in patients presenting to clinical practice with infections. Whereas around 31% of the respondents identified *Klebsiella pneumoniae* as the most commonly encountered infectious bacterial strain (Table 1). About 60% of the participants indicated that individuals aged 50 years and above are frequently affected by MDR, XDR, and PDR pathogens.

Table 1: Response to the commonly found bacterial strains in clinical practice

Common MDR, XDR, or PDR pathogens noted in clinical practice	Response rate (n = 302)
Pseudomonas aeruginosa	107 (35.43%)
Klebsiella pneumoniae	94 (31.13%)
Acinetobacter baumannii	22 (7.28%)
Escherichia coli	20 (6.62%)
Staphylococcus aureus	15 (4.97%)
All the above	44 (14.57%)

Among the carbapenem antibiotics,the majority of the survey participants (83.44%) preferred meropenem antibiotics over imipenem, biapenem, doripenem, and other antibiotics to treat bacterial infections (Fig. 1).

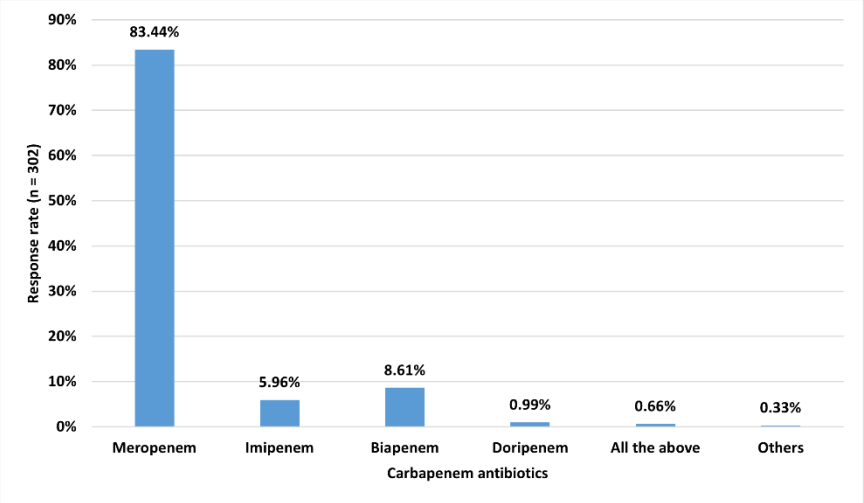

Fig. 1: Response to the prescription practice of carbapenem antibiotics

About 73% of the respondents indicated that they prefer the combination of IV meropenem with other antibiotics to treat MDR, XDR or PDR infections. A smaller percentage of clinicians (22.19%) reported that they use IV meropenem monotherapy for treating infections caused by various pathogens (Table 2). Nearly 54% of the respondents preferred administering 1 gm in 2 to 3 divided doses of IV meropenem to treat most MDR, XDR, or PDR infections. However, 37% of the respondents favoured using 2 gm in 2 to 3 divided doses of IV meropenem to treat most infections.

Table 2: Response on the preference of meropenem monotherapy or combination antibiotic therapy to treat MDR, XDR or PDR infections

Preference for IV meropenem monotherapy or combination antibiotic therapy to treat MDR, XDR, or PDR infections	Response rate (n = 302)
Monotherapy with IV meropenem	67 (22.19%)
Combination of IV meropenem along with other antibiotics	219 (72.52%)
All the above	4 (1.32%)
Others	12 (3.97%)

About 61% of the participants recommended using colistin in combination with IV meropenem for treating infections (Table 3). The majority of the respondents (91.06%) preferred the synergistic effect of IV meropenem with β-lactams, aminoglycosides, tigecycline, colistin, and other antibiotics in the treatment of MDR, XDR, or PDR infections.

Table 3: Response to the antibiotic of choice for combination therapy with IV meropenem

Antibiotic of choice for combination therapy along with IV meropenem	Response rate (n = 302)
Fosfomycin	45 (14.9%)
Colistin	185 (61.26%)
Tigecycline	46 (15.23%)
All the above	7 (2.32%)
Others	19 (6.29%)

More than half of the respondents (50.33%) indicated that complicated urinary tract infections (UTIs) require IV meropenem antibiotic therapy. Approximately 26% of the participants preferred IV meropenem for nosocomial lower respiratory tract infections. About 43% of the respondents expressed a preference for meropenem + sulbactam antibiotics when treating complicated UTIs, meningitis, and complicated intra-abdominal infections (Fig. 2).

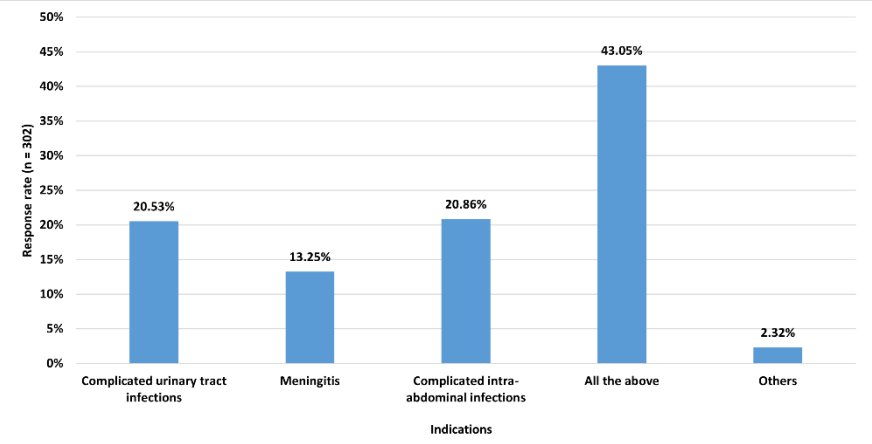

Fig. 2: Response on the preferred indications for the clinical use of meropenem + sulbactam antibiotics

As indicated by 63% of the respondents, meropenem is the preferred choice for treating sepsis patients. Piperacillin + tazobactam antibiotic therapy was favoured by 54% of the respondents for treating nosocomial pneumonia in the absence of meropenem. However, 31% of the participants opted for the ceftazidime + avibactam antibiotic combination for treating this pneumonia. Around 76% and 71% of the participants preferred meropenem for treating bacterial meningitis and Gram-negative MDR pathogens, respectively.

4. DISCUSSION

The survey results suggest that meropenem is a widely preferred antibiotic for the treatment of challenging infections caused by MDR, XDR, or PDR pathogens among experts. These study findings offer valuable guidance to clinicians in making decisions to effectively manage such infections in routine clinical settings.

In the present study, a notable number of experts have reported that *P. aeruginosa* and *K. pneumoniae* are the commonly found bacterial strains in infectious patients presenting to clinical practice. According to the reports of WHO in 2017*, Enterococcus faecium, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa,* and *Enterobacter spp*., are pathogens resistant to antimicrobial agents [13]. These pathogens, including *Acinetobacter, Pseudomonas,* and some *Enterobacteriaceae* such as *K. pneumoniae, E. coli,* and *Enterobacter spp.,* are given critical priority due to their resistance to multiple antibiotics and their ability to cause serious infections such as pneumonia and bloodstream infections [13,14].

Meropenem is the best choice of treatment for difficult-to-treat Gram-negative infections, such as nosocomial infections in ICU settings and neonatal care settings [15].The majority of the current participants preferred meropenem antibiotics to treat pathogenic infections over imipenem, biapenem, doripenem, and other carbapenem antibiotics in the present study. Meropenem exhibits a broad spectrum of *in vitro* activity against both Gram-positive and Gram-negative infections, including *Enterobacteriaceae.* Its effectiveness is comparable to that of other antibacterial agents, such as imipenem/cilastatin, in the treatment of complicated intra-abdominal infection (cIAI), complicated skin and skin structure infection, febrile neutropenia, complicated UTI, obstetric or gynaecological infections, and severe community-acquired pneumonia.

Meropenem is recommended as a monotherapy by the majority of the current survey respondents for the treatment of bacterial meningitis and infections caused by Gram-negative MDR pathogens. The effectiveness of meropenem extends beyond other antibiotic combinations. It is more effective than clindamycin plus tobramycin or gentamicin for cIAI or obstetric gynaecological infections, surpasses cefotaxime plus metronidazole for cIAI, and outperforms cefepime and ceftazidime plus amikacin in the treatment of febrile neutropenia or septicemia. Additionally, meropenem is superior to the combination of ceftazidime, clarithromycin, and ceftriaxone for the management of severe community-acquired pneumonia [16].A multicenter, randomized, controlled clinical trial has reported that both biapenem and meropenem antibiotics demonstrate similar clinical efficacy and are well-tolerated by patients affected by moderate and severe lower respiratory tract infections and UTIs [17].Additionally, for the effective treatment of complicated skin and soft tissue infections, it is recommended to administer meropenem at a higher dose of 1 gm every 8 hours, especially in high-risk patients with suspected *P. aeruginosa* infections [18].

In the current survey, the majority of the clinicians have recommended the use of IV meropenem 1 gm in 2 to 3 divided doses, in combination with other antibiotics for the treatment of most of the MDR, XDR, and PDR infections. A prospective multicenter study, which included 204 subjects, observed that imipenem/cilastatin achieved clinical success in 77% (67 out of 87) of cases, while IV meropenem, administered at 1 gm every 8 hours, achieved clinical success in 76% (68 out of 90) of cases [19].The survey has also highlighted a synergistic approach involving IV meropenem in combination with various other classes of antibiotics, including β-lactams, aminoglycosides, tigecycline, and colistin. A prospective, comparative clinical study has highlighted the superiority of meropenem with colistin combination therapy over colistin monotherapy for the treatment of MDR *K. pneumoniae*-induced hospital-acquired pneumonia or ventilator-associated pneumonia [20].

The current survey findings are beneficial for guiding treatment decisions and improving patient outcomes, especially in light of the increasing challenge posed by antimicrobial resistance. The study highlights the significance of medication adherence and customized treatment options for treating various antibiotic-resistant diseases. It is important to acknowledge certain limitations of the study. The sample size in this study may limit the generalizability of the results to a larger population. Additionally, the reliance on expert judgment in the study introduces the potential for bias, as different perspectives and preferences may have influenced the reported findings. It is essential to consider these limitations when interpreting the results and to conduct further research to validate and expand upon the findings.

4. CONCLUSION

The survey findings underscore the prominent role of meropenem and combination therapies in the management of challenging infections, providing valuable guidance to healthcare professionals in their efforts to combat antibiotic-resistant pathogens. In specific clinical scenarios involving difficult intra-abdominal infections, meningitis, and UTIs, clinicians favour the use of meropenem in combination with sulbactam antibiotics.

Consent:
A written informed consent was obtained from each practitioner’s prior initiation of the study.

Ethical Approval:

The study was conducted after receiving approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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