Research Article

A Questionnaire-based Survey of Physician Perceptions of the Prevalence of Antimicrobial Resistance and Their Antibiotic Prescribing Patterns

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Abstract

Background: Antibiotic resistance is a serious problem being faced by physicians worldwide. This article was designed to study physician perceptions of antibiotic resistance and their prescribing patterns. **Materials and Methods:** A structured questionnaire was developed for reporting the prevalence of antibiotic resistance as perceived by physicians and recording their antibiotic preferences in specific contexts. A total of 539 intensivists across India participated in the study. **Results:** The prevalence of multidrug-resistant (MDR) Gram-negative pathogens was reported to be on the rise in Intensive Care Units. The prevalence rate of carbapenem-resistant *Enterobacteriaceae* was reported to be between 20% and 40% by 33% of the participants. Piperacillin-tazobactam was the preferred beta-lactam/beta-lactamase inhibitor antibiotic by the majority of intensivists (47%) in the treatment of infections caused by extended-spectrum beta-lactamase producers. Meropenem was recommended to be used at a higher dose (2 g t.i.d.) by 41% of intensivists for *Pseudomonas*/*Acinetobacter* infections with high minimum inhibitory concentration values for meropenem. De-escalation data revealed that 43% of intensivists "always" would like to de-escalate from carbapenems, based on the antibiotic susceptibility data. Minocycline was recommended by 33% for the treatment of ventilator-associated pneumonia (VAP) and by 21% for bloodstream infections caused by MDR *Acinetobacter*. Up to 83% of intensivists preferred the use of nebulized colistin for the management of VAP/hospital-acquired pneumonia. **Conclusion:** This study reveals that the prevalence of MDR Gram-negative pathogens is perceived to be on the rise. Prescription patterns indicate high levels of variability. Hence, antibiotic stewardship is essential to standardize antibiotic prescriptions not only for efficacy but also to reduce the burden of multiple drug resistance.

Keywords: Antibiotic resistance, multidrug-resistant, prevalence questionnaire

Introduction

Antibiotics encompass a great extent of important cornerstones in clinical medicine since the second half of the 20th century and have saved a great number of people from life-threatening bacterial infection.[1] However, nowadays, antibiotic resistance is a serious problem being faced by physicians worldwide. The increasing number of infections has mandated the use of different classes of antibiotics. The success of antibiotic treatment depends on the susceptibility, choice, dose, route, and duration of antimicrobial treatment, which needs to be individualized for each patient according to explicit patient characteristics, disease severity, possible infecting organisms, and local resistance patterns.[2]

Most of the physicians are aware of the drivers of antibiotic resistance, but appropriate antibiotic selection is, often, not reflected in their clinical practice.[3] Inappropriate selection of drugs, doses, and treatment duration is attentive to be the main reasons for increasing antibiotic resistance. Antibiotic resistance can be decreased by adopting evidence-based practices. Disparity in local antibiotic resistance and the prescription pattern is frequently observed in a developing country like India.[4] This called for a study designed to assess the physician knowledge and perceptions of the prevalence of antimicrobial resistance and their antibiotic prescribing patterns.

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Materials and Methods

Survey questionnaire

A structured self-reported questionnaire in English, with a total of 28 questions (Q), which was designed to admittance the perceptions of the physician across India about the prevalence of antimicrobial resistance, and their practice patterns were validated by the group of intensivists. It broadly comprised two types of questions, wherein the prevalence of pathogenic microorganisms in Intensive Care Unit (ICU) settings was captured by six questions (with options being given, ranging from "up to 20%," "21%–40%," "41%–60%," and ">60%" for the first three questions; from "up to 20%," "21%–40%," "41%–60%," "61%–80%" and ">80%" for the fourth question; and from "20%–40%," "41%–60%," "61%–80%" and ">80%" for the fifth and sixth questions), and preferences for the use of antibiotics alone or in combination for certain infectious conditions were captured by 22 questions. All these questions had options varying from "Yes"/"No" to "Always/Sometimes/Never." The option range was selected based on the opinions of the intensivists regarding the possible prevalence of pathogens and prescribing practices in Indian ICUs.

Scoring and data analysis

The intensivists were asked to choose the most suitable option in their opinion. As the data were collected in percentage response, the options were scored for ranking. For the options given in the prevalence study (Q1–Q6), the scoring was done as follows: For the first three questions, the option "up to 20%" was scored as 2, "21%–40%" was scored as 4, "41%–60%" was scored as 6, and option ">60%" was scored as 8. For the fourth question, all the options were scored similar to the first three questions, except for option "61%–80%," which was scored as 8, and for ">80%," which was scored as 10. For the fifth and sixth questions, option "20%–40%" was scored as 2, "41%–60%" was scored as 4, "61%–80%" was scored as 6, and option ">80" was scored as 8. The score of each option was multiplied by the percentage of intensivists who selected that option and an average score of individual questions was calculated for comparison. A higher score indicates more prevalence. For the prescription pattern study (Q7–Q22), the percentage of intensivists choosing a particular option was calculated.

Study design and participants

A cross-sectional survey of intensivists practicing in government and private hospitals from tier I and tier II cities of India was conducted. For the survey, a total of 539 intensivists were contacted and were asked to respond to all the questions. The response rate from those invited to participate was 100%.

Content and face validity

Content validity was initiated in two steps. The first step was a concept elicitation step, where a group of intensivists ($n = 10$) identified the concept and framed the questions. In the second step, another group of intensivists ($n = 10$) was asked to complete the questionnaire and to comment on the relevance, clarity, and comprehensiveness of the questionnaire. For face validity, the intensivists were asked to make a note of any important content of the questionnaire, related to the objectives of the study, which was missed out. More emphasis was given to whether the questionnaire was relevant to the clinical practice and real-life experience of the intensivists.

The final list of questions relevant to the study objectives was then prepared and once again reviewed by the study groups. The final version of the survey questionnaire was then released for the study.

Internal consistency

Internal consistency was calculated for all the questions. The criteria for Cronbach's alpha for internal consistency reliability are as follows: excellent ($\alpha > 0.9$); good ($0.7 < \alpha < 0.9$); acceptable ($0.6 < \alpha < 0.7$); poor ($0.5 < \alpha < 0.6$); and unacceptable ($\alpha < 0.5$).[5] The mean $\alpha = 0.65$ for the study was deemed as acceptable.

Ethical clearance

Waiver of consent was obtained from the Independent Research Ethics Committee, Pune (CDSCO Reg No: ECR/232/Ind/MH/2015 OHRP Reg No. IORG 0008734), as this was only a questionnaire-based study and no patient data were involved.

Results

Prevalence study

In the general opinion of the survey respondents, the prevalence of extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* was highest with an average score of 109, followed by multidrug-resistant (MDR) *Pseudomonas* with a score of 100, MDR *Enterobacteriaceae* with 93.5, and MDR *Acinetobacter* with 86. The average score for the prevalence of carbapenem-resistant *Acinetobacter* (CRA) and carbapenem-resistant *Enterobacteriaceae* (CRE) was found to be 83.5 and 79.5, respectively [Figure 1].

Assessment of the prescription pattern of respondents

The results of the prescription pattern survey indicate that, for the treatment of infections due to ESBL producers, the preference was given to piperacillin-tazobactam followed by cefoperazone-sulbactam by 47% and 28% of intensivists, respectively. Least preference was given to ampicillin-sulbactam. Cefepime-tazobactam was the drug of choice of 30% and 26% of intensivists for Gram-negative bacteria such as *Enterobacteriaceae* and *Pseudomonas*, respectively. It was also preferred where local antibiograms showed resistance toward piperacillin-tazobactam and cefoperazone-sulbactam. Up to 75% of intensivists preferred cefepime-tazobactam over other beta-lactam/beta-lactamase inhibitor (BL-BLI) combinations as a carbapenem sparer. Up to 53% of intensivists "sometimes" recommended, while 44% of intensivists "always" recommended, and about 3% of intensivists "never" recommended using carbapenem in severe infection due to ESBL-producing *Enterobacteriaceae*. Meropenem was recommended by 53% of intensivists for

infections due to MDR *Enterobacteriaceae*, followed by imipenem [Figure 2 and Table 1].

Up to 32% of intensivists preferred carbapenems, depending on the site of infection or on a hospital antibiogram, and 25% preferred them based on only a hospital antibiogram. For the treatment of severe MDR *Pseudomonas* infections, meropenem was preferred by 48% of intensivists, followed by imipenem and doripenem. Ertapenem was selected by only 3%. The carbapenem-colistin combination was preferred by 42% of intensivists for MDR *Acinetobacter baumannii* infections. Tigecycline with colistin was preferred by 23% of intensivists. Least preferred was the doxycycline-colistin combination (4% of intensivists). Only 1% preferred other combinations [Figure 3]. Up to 41% of intensivists used high-dose meropenem for the treatment of intermediately susceptible *Pseudomonas*/*Acinetobacter* infections. Up to 30% of intensivists prescribed a high dose of nosocomial meningitis.

De-escalation data revealed that 43% of intensivists "always" would like to de-escalate from carbapenem if the antibiotic sensitivity data revealed susceptibility to narrow-spectrum antibiotics. Only 6% of intensivists reported no de-escalation in their practice. Up to 51% of intensivists "sometimes" preferred to de-escalate [Figure 3].

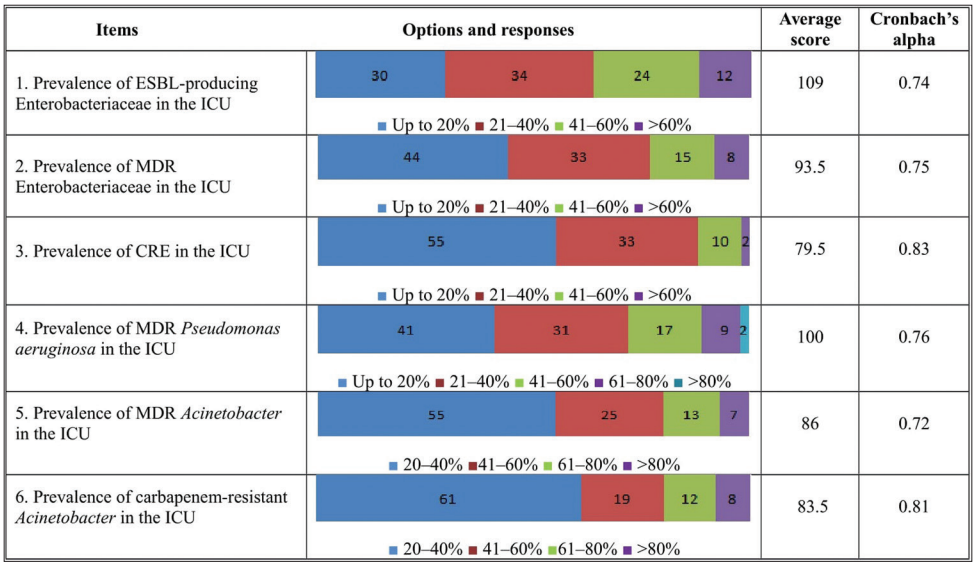

Figure 1: Values in the horizontal bar graph represent the percentage of intensivists who responded. Average Cronbach's alpha value for questions 1–6 was found to be 0.76. Average Cronbach's alpha value for questions 1–28 was found to be 0.65

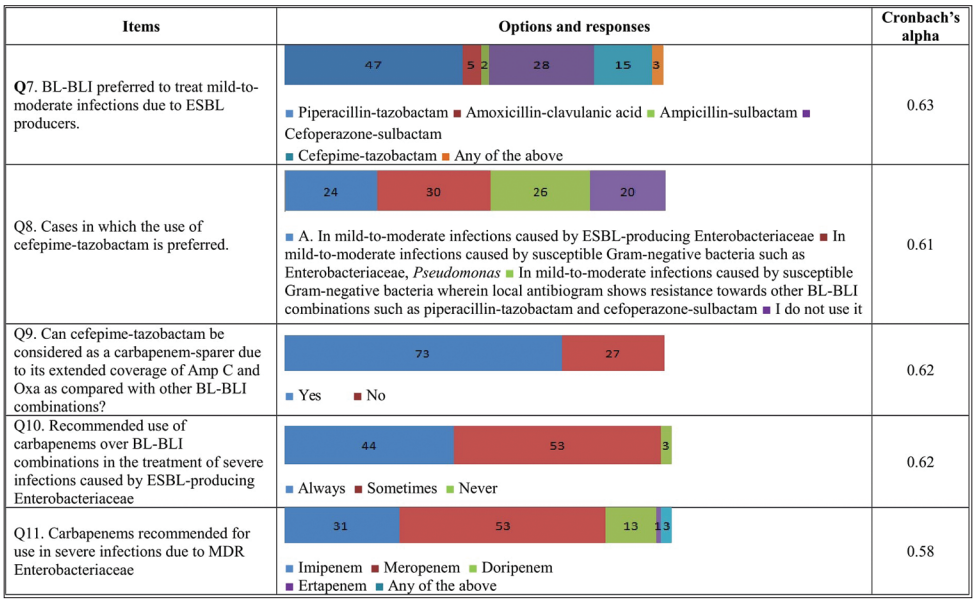

Figure 2: Values in the horizontal bar graph represent the percentage of intensivists who responded. Average Cronbach's alpha value for questions 7–11 was found to be 0.61. Average Cronbach's alpha value for questions 1–28 was found to be 0.65

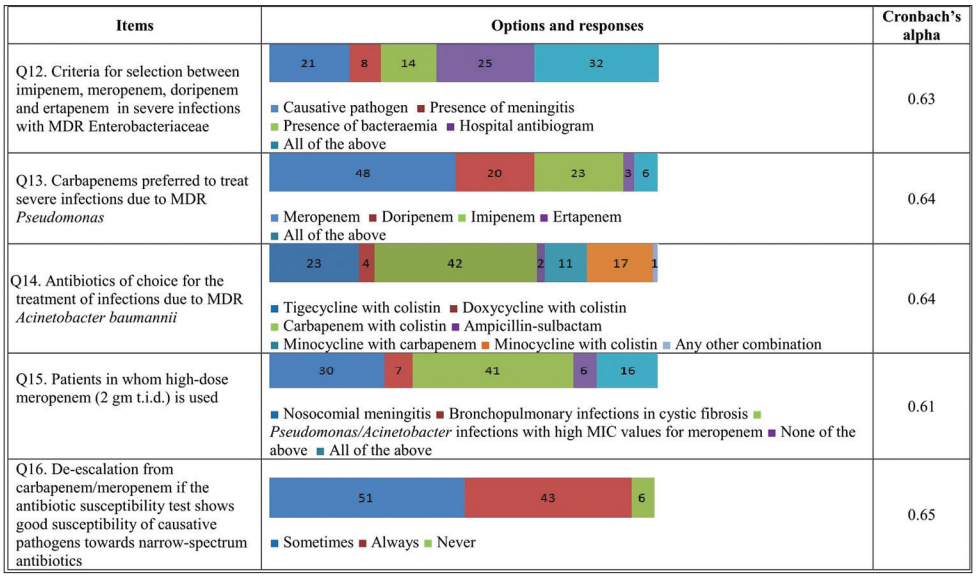

Figure 3: Values in the horizontal bar graph represent the percentage of intensivists who responded. Average Cronbach's alpha value for questions 12–16 was found to be 0.63. Average Cronbach's alpha value for questions 1–28 was found to be 0.65

Up to 41% preferred continuation of the initial treatment of carbapenem, no matter the susceptibility report in patients showing clinical improvement. However, 40% of intensivists preferred de-escalation based on susceptibility and cost of therapy.

Intravenous (IV) fosfomycin was recommended by 28% of intensivists for the treatment of MDR/CRE infections and by 17% for the treatment of MDR/extensively drug-resistant (XDR) *Pseudomonas*. It was recommended by 16% of intensivists for ESBL-producing *Enterobacteriaceae* infections. Up to 48% used IV minocycline, whereas 52% had never used the drug. Up to 33% recommended minocycline for the treatment of ventilator-associated pneumonia (VAP), 21% for the treatment of any systemic/bloodstream infections, and 6% for the treatment of urinary tract infection (UTI) caused by *Acinetobacter*.

Up to 36% of intensivists preferred IV minocycline as an alternative to tigecycline for the treatment of VAP and 23% for the treatment of bacteremia. Up to 78% do not prefer to use IV doxycycline as an alternative to minocycline for the treatment of *Acinetobacter* [Figure 4].

Up to 24% of intensivists preferred to use IV minocycline for the treatment of VAP/hospital-acquired pneumonia (HAP) caused by Gram-negative bacteria other than *Acinetobacter* as well. It was preferred by 17% for the treatment of infections due to CRE, by 12% for the treatment of UTI caused by *Klebsiella*, and by 11% for ESBL-producing *Enterobacteriaceae*. Minocycline was not recommended for any of the above three indications by 19%.

Up to 85% of intensivists recommended the use of high-dose colistin for the treatment of infections caused by MDR/XDR Gram-negative bacteria.

Up to 63% of intensivists cautioned against the use of high-dose colistin in the presence of compromised renal function. Only 10% of intensivists did not prefer to use a high dose of colistin.

Up to 37% of intensivists preferred polymyxin B over colistin only in patients with renal impairment, and 15% preferred polymyxin B as an alternative to colistin in all infections.

Up to 83% of intensivists preferred the use of nebulized colistin in the management of VAP/HAP as an adjuvant to other IV antibiotic therapy (option for IV antibiotic therapy was not given). While 41% recommended the dose of 1–2 MIU b.i.d., 17% and 16% recommended the dose of 2 MIU t.i.d. and 2 MIU b.i.d., respectively. Up to 9% of intensivists preferred the dosage other than mentioned above, and 17% of intensivists did not recommend nebulized colistin in their clinical practice. Up to 62% of intensivists have not used intrathecal/intraventricular colistin in the management of meningitis caused by susceptible Gram-negative pathogens [Figure 5]. From the study, it was observed that the choice of antimicrobials depends on the type of organism and its susceptibility.

Discussion

Recent studies in India have reported the widespread occurrence of both primary and secondary infections with Gram-positive and Gram-negative bacteria. Antibiotic overuse, misuse, and under-dosing have all been associated with increased risk of inducing antimicrobial resistance.[6]

ICU settings present a higher risk of nosocomial infections such as pneumonia, UTI, catheter-associated bloodstream infection, and surgical site infection.[7] According to the Center for Disease Dynamics Economics and Policy (CDDEP) antibiotic resistance data for 2014, the prevalence of various pathogens in India was as follows: ESBL-producing *Enterobacteriaceae*, up to 66.5%; CRE, up to 40%; MDR *Pseudomonas*, up to 54.66%; MDR

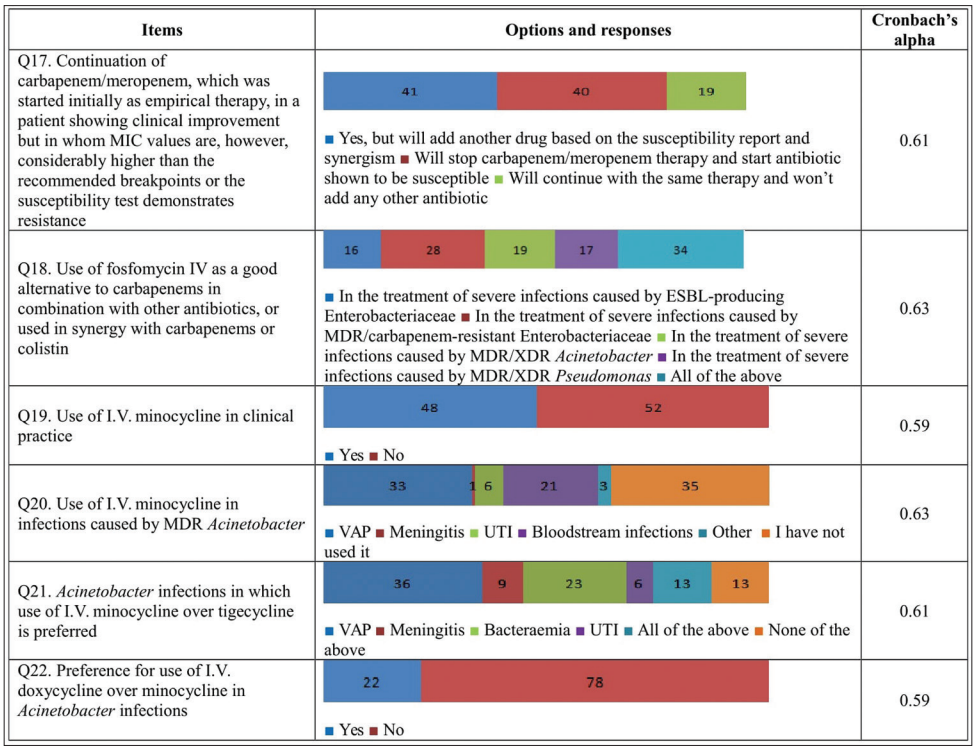

Figure 4: Values in the horizontal bar graph represent the percentage of intensivists who responded. Average Cronbach's alpha value for questions 17–22 was found to be 0.61. Average Cronbach's alpha value for questions 1–28 was found to be 0.65

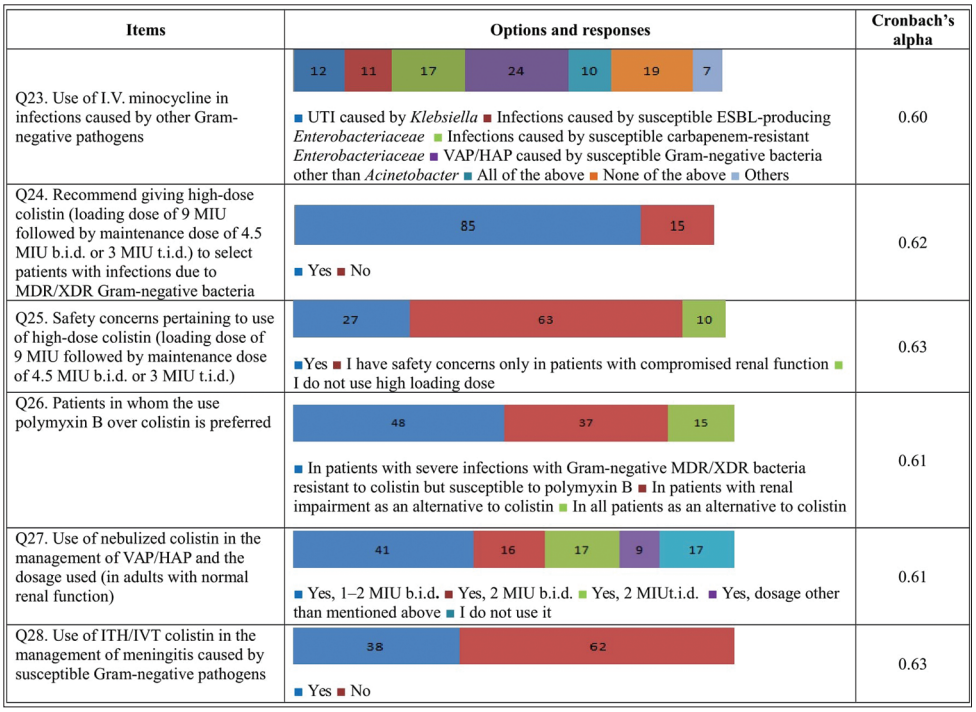

Figure 5: Values in the horizontal bar graph represent the percentage of intensivists who responded. Average Cronbach's alpha value for questions 23–28 was found to be 0.61. Average Cronbach's alpha value for questions 1–28 was found to be 0.65

Acinetobacter, up to 68.8%; carbapenem-resistant *Klebsiella pneumoniae*, up to 55%; and CRA, up to 85%. In 55% of the ICU, CRE prevalence was up to 20% and was found to be lower as compared to above-mentioned data by the CDDEP.

Use of beta-lactam/beta-lactamase inhibitors

Prescription pattern of antimicrobials for mild-to-moderate infections by ESBL producers reveals that the preferred BL-BLI was piperacillin-tazobactam. Although piperacillin-tazobactam

was the most preferred drug, cefepime-tazobactam was the choice of a significant proportion of intensivists in the management of mild-to-moderate infections caused by *Enterobacteriaceae* and *Pseudomonas*. The use of this combination may help minimize the usage of carbapenems in the above-mentioned infections and thereby decrease the chances of development of carbapenem resistance.[8] Due to the extended spectrum of activity against Amp C and Oxa, cefepime-tazobactam was considered as a carbapenem sparer and similar results presented in a study conducted for Indian scenario.[9,10] The cefepime-tazobactam combination was also preferred in cases where the local antibiogram showed resistance to piperacillin-tazobactam and cefoperazone-sulbactam.

Use of carbapenems

Previous study data suggest superior efficacy of carbapenems against Gram-negative pathogens as compared with other BL-BLIs.[10] It was observed that the selection of carbapenems was based on the hospital antibiogram, causative pathogen, presence of nosocomial meningitis, and bacteremia.

In the treatment of acute bacterial meningitis, meropenem is the only approved carbapenem. High-dose meropenem should be reserved for a few specific indications such as *Pseudomonas*/*Acinetobacter* infections with high minimum inhibitory concentrations for carbapenems.[11]

The survey results suggest that most respondents use the carbapenem-colistin combination for the treatment of MDR *A. baumannii* which are in agreement with previously reported findings.[12]

The de-escalation approach is safer and more practical. Antimicrobial stewardship program-guided de-escalation of carbapenems leads to comparable clinical success, fewer adverse effects, and lower incidence of the development of resistance.[13] Surviving sepsis guidelines recommend (1B grade evidence) de-escalation to a narrower-spectrum antibiotic. In this study, it was observed that a significant number of intensivists (94%) report de-escalation of carbapenems if the antibiotic susceptibility is toward narrower-spectrum antibiotics.[13]

Use of fosfomycin

Fosfomycin, due its unique mechanism of action, has returned as an option against a range of MDR and XDR pathogens.[14]

Pharmacokinetic data suggest that therapeutic levels of fosfomycin are achieved in tissues and serum. Therefore, fosfomycin has been prescribed in combination with other antibiotics for the treatment of nosocomial infections due to MDR and XDR pathogens.

Fosfomycin IV in combinations with carbapenems or colistin was recommended by the present study respondents for the treatment of MDR/CRE and other MDR/XDR Gram-negative pathogens.

A study conducted by Michalopoulos *et al*. showed good bacteriological and clinical outcomes after treatment with IV fosfomycin in patients with ICU-acquired infections due to carbapenem-resistant *K. pneumoniae*. This study reveals the effective use of IV fosfomycin against New Delhi metallo-beta-lactamase 1-producing bacteria, which is a major concern in Indian ICUs.

Table 1: Drugs preferred for the treatment of infections caused by resistant microorganisms

MDR microorganisms	Drugs preferred for the treatment of infection
ESBL-producing *Enterobacteriaceae*	Piperacillin-tazobactam
MDR *Pseudomonas*	Meropenem
MDR *Enterobacteriaceae*	Meropenem
MDR *Acinetobacter baumannii*	Carbapenems, colistin, tigecycline and minocycline

ESBL: Extended-spectrum beta-lactamase; MDR: Multidrug-resistant

Use of minocycline

Minocycline IV was preferred by most of the intensivists for the treatment of VAP and bacteremia caused by MDR *Acinetobacter*, and they preferred it over IV doxycycline for *Acinetobacter* infections. The intensivists also preferred it over tigecycline for bloodstream infections and VAP caused by *Acinetobacter*. Minocycline has better *in vitro* susceptibility against *Acinetobacter* as compared with doxycycline. Since minocycline achieves ideal blood and tissue levels and has notable central nervous system penetration, it could be an option in MDR *A. baumannii* infections, including bloodstream infections, VAP, and meningitis. Owing to the low mean peak serum concentrations of tigecycline achievable at recommended doses,[15] minocycline may be preferred in *Acinetobacter* bacteremia.[16]

Use of colistin

High dose of colistin (loading dose of 9 MIU followed by a maintenance dose of 4.5 MIU b.i.d. or 3 MIU t.i.d.) was recommended by the majority of intensivists for infections due to MDR/XDR Gram-negative bacteria. However, a few intensivists have not used the high dose; thus, varied clinical practice was observed. The European Medicines Agency has approved the use of high doses of colistin up to 12 MIU.

In the present study, the intensivists were found to have safety concerns with the use of high dose of colistin, especially in renal dysfunction. Previous studies have shown that the higher dose with extended-interval colistin can be given to critically ill patients without any increased risk of kidney damage.[17] The loading dose remains the same, irrespective of kidney function.

Nebulized colistin 1–2 MIU b.i.d. as adjuvant therapy was recommended as the most appropriate dose for the management of VAP/HAP in adults with normal renal function. In the patients with VAP due to Gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins (colistin or polymyxin B), the Infectious Diseases Society of America guidelines recommend both inhaled and systemic antibiotics, rather than systemic antibiotics alone.[18]

Use of polymyxin B

Polymyxin B was preferred over colistin in the treatment of severe infections due to MDR/XDR bacteria resistant to colistin and especially in patients with renal impairment.[19]

It is easy to administer polymyxin B compared to colistin. Polymyxin B treatment is associated with less nephrotoxicity. Unlike colistin, polymyxin B is an active drug and less inter-subject variability is observed. Due to nonrenal clearance, dose reduction is not required for polymyxin B in renal impairment.[20] Polymyxin B, thus, has added advantage over colistin, which may, thus, have encouraged its use by the intensivists.

Limitations and exclusivity of the study

This questionnaire was an attempt to study the prevailing clinical practices of intensivists in the management of microbial infections and drug resistance. The main limitation was that this was a study based on a self-reported questionnaire rather than on objective data. Thus, the data reflect perceptions and opinions and are not based on the actual hospital records or laboratory data of the isolates. Till date, many studies have been published on the prevalence and use of antimicrobials, but these have been conducted at a particular site and in a specific region. The present study was unique in that it was a survey comprising intensivists from diverse locations across India and had a 100% response rate.

Conclusion

In the Indian scenario, physicians perceived a high prevalence of ESBL-producing *Enterobacteriaceae* and a relatively lower prevalence of CRE in ICU settings. In this survey, prescription patterns of the antibiotics indicated high levels of variability. De-escalation, which plays a critical role in decreasing antimicrobial resistance, was not adopted by all the intensivists surveyed. There is an urgent need to encourage de-escalation by adopting antibiotic stewardship to overcome the challenge of increasing antimicrobial resistance. An antibiotic policy should be formed and followed in all ICU settings, and these policies should be regularly updated after considering the hospital antibiograms so as to ensure therapeutic success.

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Conflicts of interest

There are no conflicts of interest.

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