SSR Institute of International Journal of Life Sciences
ISSN (O): 2581-8740 | ISSN (P): 2581-8732
Varaiya *et al*., 2024
DOI: 10.21276/SSR-IIJLS.2024.10.4.8

Research Article

open access

Antimicrobial Resistance and Susceptibility Patterns among Gram-negative Bacteria Isolated from ICU–An Indian Study

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Received: 12 Mar 2024/ Revised: 21 Apr 2024/ Accepted: 28 May 2024

ABSTRACT

Background: Antimicrobial Resistance is a major concern. The rising trend has created a nuisance affecting the global economy and sustainable development Goals. Data about antimicrobial resistance therefore might help in knowing the trends and acting. Critical care patients are prone to develop nosocomial infections. A brief knowledge about this would help in the judicious use of antibiotics. This multicentric study was undertaken to understand the trends in the prevalence of antimicrobial resistance pattern, Multidrug Resistance (MDR)/ Extensive Drug Resistance (XDR)/Pan-drug Resistance (PDR), among GNB isolates from respiratory, urinary, and bloodstream samples from Indian ICUs.

Methods: This is a retrospective study done in 16 Indian adult intensive care units (ICUs). The sensitivity pattern of defined GNB isolates against defined antibiotics was analyzed.

Results: A total of 20,874 isolates of *A. baumannii*, *P. aeruginosa, K. pneumoniae,* and *E. coli* from the included samples were obtained *A. baumannii*, *P. aeruginosa* species showed a higher prevalence of XDR than MDR whereas *K. pneumonia* detected MDR. Among all the GNBs in this study, *A. baumannii* was the most carbapenem-resistant organism (XDR) and *K. pneumoniae* demonstrated the highest percentage of PDR strains both being higher in the respiratory and bloodstream isolates than that in the urinary isolates.

Conclusion: This study shows high Prevalence of MDR/XDR GNB is high in Indian ICUs. Using the right antibiotic or introducing various strategies along with infection control measures can help in reducing antimicrobial resistance.

Key-words: Antimicrobial resistance, Multidrug-resistant GNB, Healthcare-associated infections, Susceptibility Patterns, Gram-negative Bacteria

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How to cite this article
Varaiya A, Gupta A, Siddiqui AH, Poojary A, Tarai B, et al. Antimicrobial Resistance and Susceptibility Patterns among Gram-negative Bacteria Isolated from ICU–An Indian Study. SSR Inst Int J Life Sci., 2024; 10(4): 5847-5855.

Access this article online
https://iijls.com/

INTRODUCTION

Antimicrobial Resistance is among the top ten global threats as per WHO.[1] It is responsible for killing millions globally. [2]. It is said that by 2050 it will be the leading cause of death.[3] Resistant superbugs are prevalent in the hospital environment and pose a threat to the treating consultant as well as patients and to the hospitals.

Therefore, in any hospital, one of the greatest hazards to patient safety is the occurrence of nosocomial infection. In the Indian scenario, nosocomial infection rates in ICU have ranged anywhere from 11–60% in different studies.[4] Device-associated Infections (DAIs) such as Ventilator-associated Pneumonia (VAP), Central Line-Associated Bloodstream Infections (CLABSIs), and Catheter-Associated Urinary Tract Infections (CAUTIs), along with Surgical Site Infections (SSIs) are the most frequently occurring Healthcare-associated Infections (HAIs) across the globe.[5] The HAIs are responsible for increased length of hospital stay for the infected patients and increased chance of mortality.[6]

About a quarter of patients suffering due to hospital infections are from ICUs.[7] It is more prevalent in this unit as the patients are exposed to high-end antibiotics. This location of the hospital may provide nidus for multidrug-resistant organisms and can become a source of infection if infection control measures are not taken properly. Cross-transmission of resistant bacteria is one of the reasons for the spread of infection (nosocomial infection) among patients. Moreover, a significantly higher prevalence of ICU-acquired infections is observed in developing countries than in industrialized nations, its frequency is 2–3 times higher in developing countries than in developed countries.[7,8]

WHO in 2017 listed the organisms based on their global threat and the urgency of action needed.[9] These pathogens are associated with high morbidity and mortality HAIs due to their acquired resistance toward a large number of antibiotics, including last-resort antibiotics such as carbapenems and colistin. [10]

In the Indian scenario, Gram-negative Bacteria (GNB) are the most common causative organisms of ICU-acquired infections.[11-13] According to a recent study conducted in an ICU of a tertiary care hospital in southern India, the most predominant among these were *E. coli* (20%), *K. pneumoniae* (14.3%), *Acinetobacter baumannii* (13.8%), and *P. aeruginosa* (9%).[11]

This study was undertaken to understand the trends in the prevalence of antimicrobial resistance pattern, Multidrug Resistance (MDR)/Extensive Drug Resistance (XDR)/Pan-drug Resistance (PDR), among GNB isolates from respiratory, urinary, and bloodstream samples from Indian ICUs, which will help in generating nationwide data. This study also includes *in vitro* susceptibility data of important antimicrobial agents against these common GNB. This study aids in guiding readers on the empirical therapy to be instituted till the culture reports are available.

MATERIALS AND METHODS

Study design- This was a retrospective study wherein the data from 16 tertiary care centers across India were collected to study the prevalence of resistance as well as the susceptibility pattern of pathogenic GNB. The clinical samples included in this study were respiratory, urine samples, and bloodstream samples of the ICU patients during the period from November 2016 to October 2017. The data obtained was further analyzed for this study. GNB isolates for the study included *A. baumannii*, *P. aeruginosa, K. pneumoniae,* and *E. coli.*

Antimicrobial resistance testing- Resistance pattern of GNB was assessed based on the following definitions: MDR (Multidrug Resistant) pathogens included bacteria resistant to at least 3 classes of drugs–beta-lactams including cephalosporins and beta-lactams/beta-lactamase inhibitor combinations, aminoglycosides, fluoroquinolones. XDR (Extensively Drug-resistant) pathogens were also resistant to carbapenems besides the above, and PDR (Pan Drug-resistant) pathogens were resistant to almost all classes of antimicrobials including polymyxins.[14]

Antimicrobial susceptibility testing- For most of the antimicrobials, antimicrobial susceptibility tests were performed using a standard drug susceptibility method such as an automated system (Vitek 2C)/e-strip/broth dilution/disk diffusion method; and sensitivity results were interpreted according to Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [15,16]

In most of the Indian ICUs, the antimicrobial susceptibility tests for polymyxins were not performed as per the newer recommendations of broth microdilution method from the CLSI/EUCAST, and disk diffusion or Vitek methods were used instead.[15,16] The antibiotics were included in the study to assess the susceptibility patterns of *A. baumannii*, *P. aeruginosa, K. pneumoniae,* and *E. coli*.

Inclusion- All the clinical samples received in the Microbiology laboratory were included in the study.

Exclusion- Duplicate isolates were excluded from the study.

Statistical analysis- In this study, all analyses were done on the SPSS software.

Ethical Approval- Approval for this study was obtained from the relevant ethical committee, ensuring that all research procedures adhered to ethical standards and guidelines for protecting participants' rights and confidentiality.

RESULTS

A total of 20,874 isolates of A. baumannii, P. aeruginosa, K. pneumoniae, and E. coli from the included samples were obtained. The total number of respiratory isolates was higher (n=9363) followed by urinary (n=8531) and bloodstream (n=2980) isolates. The details of isolates of included Gram-Negative Bacteria analyzed from clinical samples are shown in Table 1.

Table 1: Total number of GNB isolates analyzed from various samples

Isolates	Respiratory	Urinary	Bloodstream
Acinetobacter	2609	153	457
Pseudomonas	1772	577	267
Klebsiella	4129	2268	1119
E. coli	853	5533	1137
Total no. of isolates (N)	9363	8531	2980

Prevalence of MDR, XDR and PDR GNB

Respiratory isolates- Out of the total 2609 *Acinetobacter* isolated, a higher prevalence of XDR (89.65%) strains was observed than that of MDR (6.36%). However, the prevalence of PDR *Acinetobacter* strains was 1.49%. Out of the total 1772 *Pseudomonas* isolated, 26.47% and 22.97% strains were detected as XDR and MDR strains, respectively, and,1.86% strains of *Pseudomonas* were found to be PDR. Among the total 4129 *Klebsiella* isolated, 32.36% and 30.93% strains were observed to be MDR and XDR, respectively. However, 3.61% of PDR strains were observed in *Klebsiella* isolates. Out of the total 853 isolates of *E. coli,* a higher incidence of MDR (41.97%) strains was observed than that of the XDR (16.06%). However, the prevalence of PDR *E. coli* strains was 0.35% (Fig. 1).

Urinary isolates- *Acinetobacter* strains showed a higher prevalence of XDR (39.22%) than MDR (5.23%) along with PDR (1.31%) among the total 153 isolates. Similarly, *Pseudomonas* strains showed a higher incidence of XDR (31.72%) than MDR (18.89%) along with PDR (2.25%) among the total 577 isolates. Out of the total 2268 isolates of *Klebsiella*, 29.45% and 28.75% were detected as XDR and MDR strains, respectively. Moreover, 2.43% of *Klebsiella* strains were observed to be PDR. Among the total 5533 *E. coli* isolates, a higher incidence of MDR (43.39%) strains was observed than that of XDR (9.63%) strains along with 0.29% of PDR strains (Fig. 2).

Bloodstream isolates- *Acinetobacter* strains showed higher incidence of XDR (76.15%) than MDR (6.35%) along with PDR (1.97%) among the total 457 isolates.

Similarly, *Pseudomonas* strains showed higher incidence of XDR (33.71%) than MDR (22.10%) along with PDR (1.87%) among the total 267 isolates. Out of the total 1119 *Klebsiella* isolates, higher incidence of XDR (46.20%) strains than MDR (16.35%) strains was observed. However, 5% of these *Klebsiella* strains were PDR. In contrast, out of the total 1137 *E. coli* isolates, higher incidence of MDR (28.32%) strains was observed than that of XDR (13.02%) strains along with 0.09% of PDR (Fig. 3).

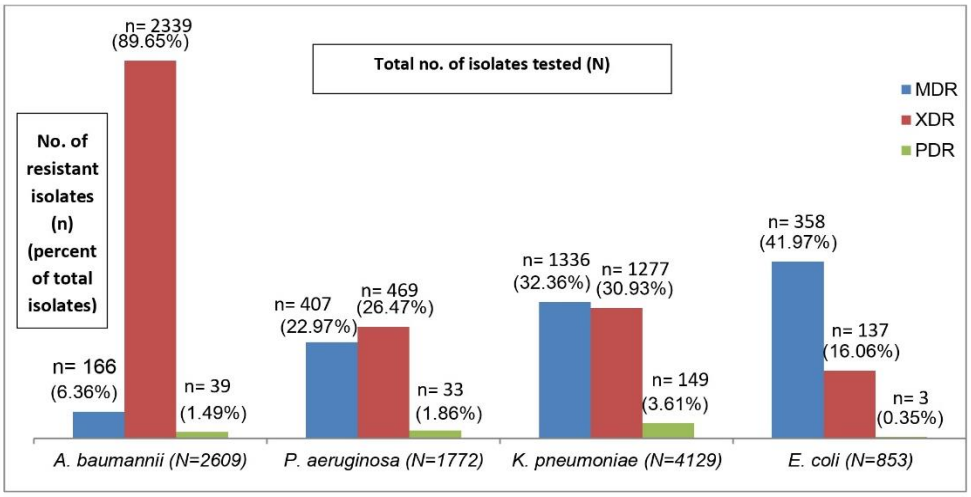

Fig. 1: Incidence of MDR, XDR and PDR strains of each species of GNB isolated from respiratory samples

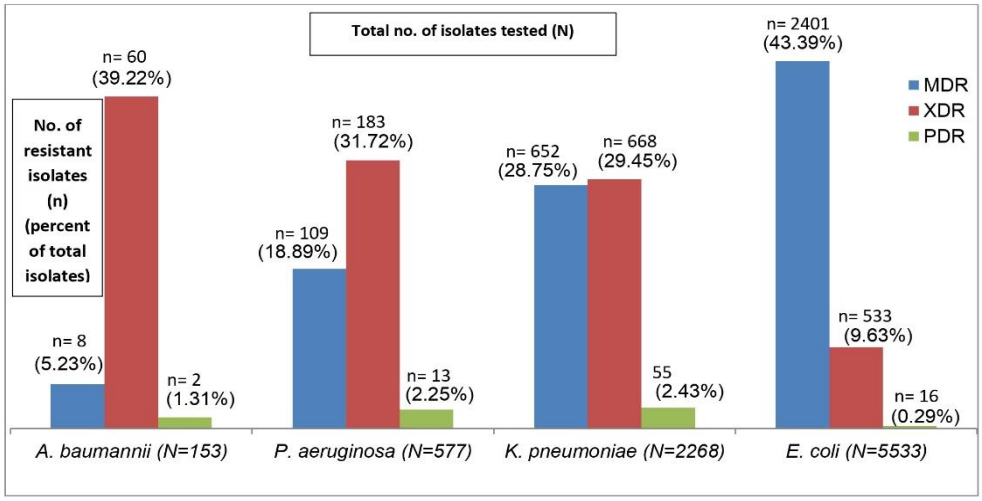

Fig. 2: Incidence of MDR, XDR and PDR strains of each species of GNB isolated from urinary samples

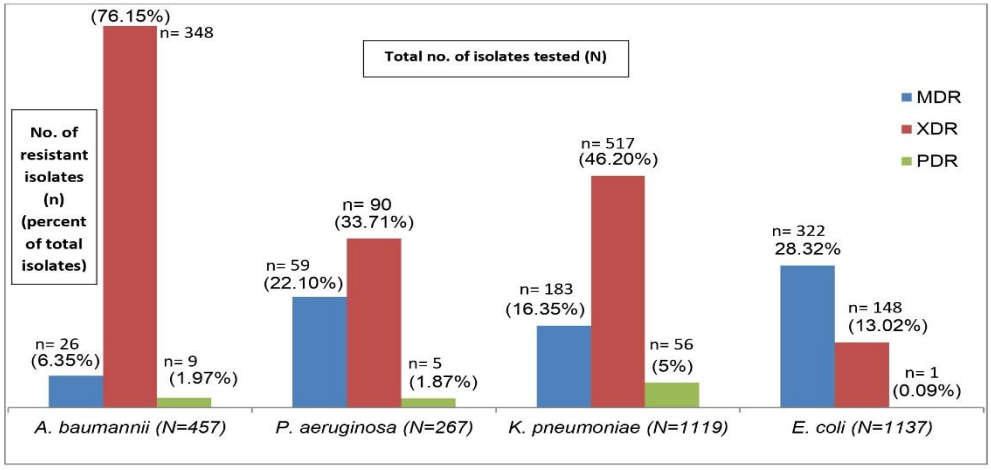

Fig.3. Incidence of MDR, XDR and PDR strains of each species of GNB isolated from bloodstream samples

Antimicrobial susceptibilities of GNB

Antimicrobial susceptibility pattern of respiratory isolates- The antimicrobial susceptibility pattern of the gram-negative respiratory isolates to different antimicrobials is described in Table 2. *A. baumannii*, P. *aeruginosa, K. pneumoniae*, and *E. coli* were mostly susceptible to polymyxins (colistin and polymyxin B).

Table 2: Antimicrobial susceptibility of GNB isolated from respiratory samples

Antimicrobial agents	% of susceptibility (No. of isolates susceptible/Total no. of isolates tested)			
	A. baumannii	***P. aeruginosa***	***K. pneumoniae***	***E. coli***
Carbapenems	8.85% (231/2609)	71.67% (1270/1772)	65.46% (2703/4129)	83.24% (710/853)
Colistin	98.46% (2561/2601)	98.08% (1734/1768)	96.33% (3967/4118)	99.77% (851/853)
Polymyxin B	99% (693/700)	98.38% (547/556)	96.34% (1107/1149)	99.05% (209/211)
Minocycline	59.84% 1389/2321	Not tested	63.15% (1738/2752)	69.34% (407/587)
Fosfomycin	Not tested	63.64% (84/132)	50.27% (458/911)	69.87% (109/156)

Antimicrobial susceptibility pattern of urinary isolates- The antimicrobial susceptibility pattern of the gram-negative urinary isolates to different antimicrobials is shown in Table 3.

Table 3: Antimicrobial susceptibility of GNB isolated from urinary samples

Antimicrobial agents	% of susceptibility (No. of isolates susceptible/Total no. of isolates tested)			
	A. baumannii	***P. aeruginosa***	***K. pneumoniae***	***E. coli***
Carbapenems	59.48% (91/153)	66.03% (381/577)	66.35% (1505/2268)	90.07% (4984/5533)
Colistin	98.69% (151/153)	97.74% (564/ 577)	97.52% (2208/ 2264)	99.71% (5516/5532)
Polymyxin B	100% (24/24)	99.17% (120/121)	98.12% (469/478)	99.78% (892/894)
Minocycline	93.33% (14/15)	Not tested	61.28% (592/966)	74.39% (607/816)
Fosfomycin	Not tested	53.85% (14/26)	71.95% (313/435)	89.23% (920/1031)

Antimicrobial susceptibility pattern of bloodstream isolates- The antimicrobial susceptibility pattern of the gram-negative bloodstream isolates to different antimicrobials is shown in Table 4.

Table 4: Antimicrobial susceptibility of GNB isolated from bloodstream samples

Antimicrobial agents	% of susceptibility (No. of isolates susceptible/Total no. of isolates tested)			
	A. baumannii	***P. aeruginosa***	***K. pneumoniae***	***E. coli***
Carbapenems	21.88% (100/457)	64.42% (172/267)	50.04% (560/1119)	86.89% (988/1137)
Colistin	97.81% (447/457)	95.09% (252/265)	95% (1063/1119)	99.91% (1136/1137)
Polymyxin B	96.67% (116/120)	88.17% (82/93)	95.74% (315/329)	99.41% (168/169)
Minocycline	57.72% (228/395)	Not tested	44.55% (184/413)	66.67% (180/270)
Fosfomycin	Not tested	65% (13/20)	73.82% (172/233)	96.97% (128/132)

DISCUSSION

Infections in ICU are due to intrinsic risk factors associated with the patient, use of invasive medical devices, overcrowding, and animate objects that act as reservoirs for bacterial isolates. Other associated factors are higher age, higher Acute Physiology and Chronic Health Evaluation (APACHE-2) score, and associated co-morbid conditions of critically ill patients in the ICU.[11] Management becomes difficult due to resistant strain acquired from ICU. [17] Particularly, GNB has been observed to be more resistant. [18] This is observed in a South Indian study, which reported that the prevalence of MDR GNB in the culture reports of the patients admitted to all the ICUs is 55.7%.[12] Another study of Indian origin conducted at a tertiary care center in Western India also reported the prevalence of XDR and PDR GNB to be 8.1% and 0.9%, respectively.[13] This has led to the revival of old antimicrobials such as polymyxins (colistin and polymyxin B), fosfomycin, and minocycline, whose spectrum of coverage frequently comprises the MDR GNB and the carbapenem-resistant GNB (XDR).[18]

Among the most prevalent Gram Negatives isolated, high resistance was noted to beta-lactams including cephalosporins and beta-lactam/beta-lactamase inhibitor combinations, aminoglycosides, fluoroquinolones, and carbapenems. In the present study, the commonest MDR strains were detected from *E. coli,* which is consistent with another Indian study (31.6%).[18]

An increasing trend in resistance to carbapenems by *Acinetobacter*, *Pseudomonas,* and *Klebsiella* spp. was identified in this study, which is similar to the pattern of change in resistance observed in previous Indian studies.[11]. The non-susceptibility of *A. baumannii* to most of the antimicrobials observed here is consistent with other Indian studies, such as the recent ICMR-Antimicrobial Resistance Surveillance & Research Network (AMRSN) data (2016–2018) which observed more than 70% of its isolates to be non-susceptible to most of the antimicrobials tested (except colistin) and its carbapenem resistance ranged from 78.3% to 82.2%.[18]

In consistency with the recent ICMR-AMRSN data (2016–2018) which states that the resistance situation for *K. pneumoniae* remains problematic, as 8.8% of strains were non-susceptible to the last resort antimicrobial colistin [19], this study also shows *K. pneumoniae* to be the commonest PDR. *P. aeruginosa* isolates from various samples showed resistance to carbapenems, i.e. XDR pattern in the range of 26.47% to 33.71%, which is lesser than *Acinetobacter* species and in line with the recent CDDEP and ICMR antimicrobial resistance surveillance data (29.6–31.3% carbapenem resistance). [18,20]

Maximum sensitivity was reported to the polymyxins, i.e. colistin and polymyxin B ranging from 88.17% to 100% which is similar to another recent study from an Indian ICU.[11]

Among the non-fermenting GNBs, *A. baumannii* was found to be more resistant than *P. aeruginosa,* which is similar to another Indian study wherein 83.5% of *Acinetobacter* spp. as compared to 56% of *Pseudomonas* isolates were found to be resistant to be meropenem.[12]

The isolates of *E. coli*, the commonest MDR species from all the samples, were found to be highly susceptible to the old antimicrobial fosfomycin similar to an Eastern Indian study wherein the isolates of *E. coli* derived from urinary and nonurinary (pus, blood, and endotracheal secretion/sputum) samples showed 99% and 62% susceptibility rates, respectively, to fosfomycin. [21]

The isolates of *A. baumannii* were sensitive to old antimicrobial minocycline (respiratory 59.84%, urinary 93.33%, bloodstream 57.72%), which is similar to a South Indian study. [22,23]

The isolates of *K. pneumoniae* were susceptible to the old antimicrobial fosfomycin (respiratory 50.27%, urinary 71.95%, bloodstream 73.82%). This finding is similar to susceptibility rates observed to fosfomycin among the isolates of *K. pneumoniae* isolated from nonurinary (pus, blood, and endotracheal secretion/sputum) samples (44.4%) and urinary samples (91.3%) in an Eastern Indian study.[19]

The isolates of *P. aeruginosa* showed 64.42% to 71.67% susceptibility rates to carbapenems among all samples which is similar to that observed overall in the Indian studies, range for imipenem being 43%–72.5% and for meropenem being 33%–69%.[23] These results indicated the utility of older antimicrobials like minocycline, fosfomycin, and polymyxins in managing the BSIs caused due to resistant pathogens. There is a lack of data on antimicrobial surveillance, especially from the Indian ICUs. The vast antimicrobial resistance and susceptibility data included in this study will assist in providing an overview of the Indian ICUs as it involves isolates of GNB from the most common infection site samples

(respiratory, urinary, and bloodstream) collected from 16 ICUs from various regions of India. The reliability of this data is also enhanced by the fact that this is a multicenter study, unlike most other Indian studies which are single-centered.

As we are running out of effective treatment options for infections caused by MDR bacteria and the development of new and effective drugs is a time-consuming and costly process, the role of older antimicrobials becomes crucial in the management of such infections in the ICUs.[23,24] The activity of older polymyxins is not carbapenemase selective and their spectrum of coverage comprises all carbapenemases and non-carbapenemase-producing carbapenem-resistant GNB such as the CRE, *Acinetobacter,* and *Pseudomonas* spp. A considerable percentage of carbapenem-resistant *A. baumannii* are susceptible to minocycline; its use could delay the emergence of polymyxin resistance as it can be used in combination with polymyxins.[25]

Minocycline has also demonstrated a higher rate of susceptibility against carbapenem-resistant members of *Enterobacteriaceae*, *E. coli,* and *K. pneumoniae;* where it can act as a carbapenem sparer.[23] Fosfomycin, when administered intravenously, as monotherapy, or as combination therapy, might be effective against systemic infections due to its activity against antimicrobial-resistant bacterial pathogens including MDR *Enterobacteriaceae* such as ESBL-producing, KPC-producing, carbapenemases (KPC, VIM, NDM, and OXA-48) producing species, and some isolates of MDR *Pseudomonas aeruginosa*. [24,26]

LIMITATIONS

There are several limitations of this study such as being a retrospective study, adequate data on clinical information is lacking, the study does not look for the outcome of the patients with hospital-acquired infections, the choice of treatment given to the patients with infections associated with MDR organisms is not analyzed, detailed genetic analysis to identify a mechanism of resistance is not done, and the susceptibility of old antimicrobials (minocycline and fosfomycin) has been assessed overall for a limited number of isolates and not for isolates which are carbapenem-resistant thus lacking subset analysis. Another drawback was that the susceptibility tests of polymyxins were not determined using the micro-broth dilution method recommended in the current EUCAST and CLSI guidelines.

CONCLUSIONS

The prevalence of MDR/XDR GNB is high in Indian ICUs. Significant resistance was observed among GNB isolates against beta-lactams including cephalosporins and beta-lactam/beta-lactamase inhibitor combinations, fluoroquinolones, aminoglycosides, and even carbapenems. However, they showed good susceptibility to colistin, polymyxin B, minocycline, and fosfomycin. There is a need to adapt appropriate methods for polymyxin drug susceptibility to obtain true susceptibility to these two important agents. Thus, the revival of these older antimicrobials may provide a useful treatment option for infections caused by the resistant GNB.

To further assist in the rational use of such old antimicrobials, we have included the susceptibility data of these commonly used older antimicrobials in this study, which can guide the clinicians in the selection of appropriate empirical antimicrobial therapy depending upon the site of infection as well as the commonly prevalent types of pathogens.

ACKNOWLEDGMENTS

We thank Cipla for funding article publication charges.

CONTRIBUTION OF AUTHORS

All authors are equally contributed in this article.

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