ORIGINAL ARTICLE

Enzyme Patterns and Factors Associated with Mortality among Patients with Carbapenem Resistant *Acinetobacter Baumannii* (CRAB) Bacteremia: Real World Evidence from a Tertiary Center in India

Parikshit Shirish Prayag[1], Sampada A Patwardhan[2], Rasika S Joshi[3], Shweta P Panchakshari[4], Tejashree Rane[5], Amrita P Prayag[6]

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Abstract

Introduction: In the Indian setting, antimicrobial resistance in *A. baumannii* is a considerable problem, especially in intensive care units (ICUs). Due to the limited data, clinicians are left with very few choices except polymyxins for treating serious infections caused by *A. baumannii*. There is sparse data regarding the local mechanisms of resistance. Given the current therapeutic challenges, it is critical to know the local enzymatic patterns and antibiograms.

Materials and methods: A retrospective analysis of 50 episodes of bacteremia caused by CRAB. We analyzed the enzyme patterns and the susceptibility rates to various antibiotics.

Results: The resistance rates for amikacin, tigecycline, minocycline, and fluoroquinolones were 88, 82, 50, and 88% respectively. OXA-23 was the most commonly isolated enzyme (86% of the isolates produced OXA-23) followed by OXA-51 and NDM. The overall mortality was high (58%). On univariate analysis, pneumonia, and higher Pitt's bacteremia score were significantly associated with mortality ($p = 0.04$ and $p = 0.001$ respectively). Of the total patients who received combination therapy, a majority (58%) received polymyxin plus meropenem. Combination therapy using polymyxins as a backbone was not associated with reduced mortality ($p = 0.1$).

Conclusion: *A. baumannii* is associated with significant morbidity and mortality, as shown in our study. The rates of resistance for aminoglycosides were very high, and minocycline showed better susceptibility rates in comparison with tigecycline. In our study, OXA-23 and NDM remained the most important enzymes. The routine use of the combination of polymyxin and meropenem may not offer a significant advantage over monotherapy.

Keywords: *Acinetobacter Baumannii*, *Acinetobacter baumannii* carbapenem, Bacteremia, Carbapenem resistant *Acinetobacter baumannii*, Polymyxin.

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Introduction

In the Indian setting, antimicrobial resistance in *Acinetobacter baumannii* is a considerable problem, especially in the ICUs. An article reviewing the epidemiology of CRAB stated that nearly 50% of the isolates in India may be carbapenem-resistant.[1] The annual report of the Antimicrobial Resistance Research and Surveillance Network (AMRSN) for the year 2021 stated that carbapenem resistance in *Acinetobacter baumannii* was 87.5%.[2] Susceptibility to minocycline was 50%.[2] These rates are alarming and often leave clinicians with very few therapeutic choices except polymyxins for *A. baumannii*. There is sparse literature with respect to the local enzymatic patterns of CRAB in India. A study of 75 isolates published in 2019 from India showed that oxacillinases such as OXA-51, OXA-23, and the New Delhi metallo beta-lactamase (NDM) were the predominant enzymes.[3] More data is needed on the local enzymatic patterns which would help us understand the enzyme epidemiology in India. The commonly used Cepheid Xpert® Carba-R assay (Cepheid, Sunnyvale, USA) for the detection of enzymes does not detect the common OXA enzymes of *A. baumannii* like the OXA-23, OXA-24/40, OXA-51, and OXA-58. The infrastructure for the detection of enzymes (beta-lactamases) is available at only a few centers across the country. Mortality rates for infections caused by CRAB can be high.

[1,3,4]Department of Infectious Diseases, Deenanath Mangeshkar Hospital & Research Center, Pune, India

[2]Department of Microbiology, Deenanath Mangeshkar Hospital & Research Center, Pune, India

[5]Department of Clinical Pharmacology, Deenanath Mangeshkar Hospital & Research Center, Pune, India

[6]Department of In house research, Deenanath Mangeshkar Hospital & Research Center, Pune, India

Corresponding Author: Parikshit S Prayag, Department of Infectious Diseases, Deenanath Mangeshkar Hospital, Pune, India, Phone: +91 7420079059, e-mail: pprayag100@gmail.com

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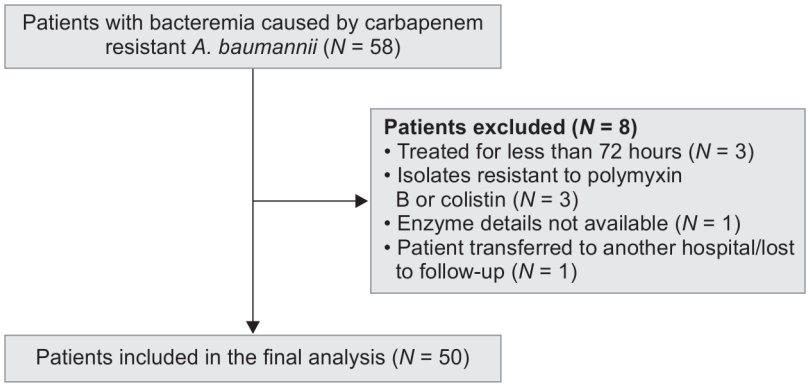

Fig. 1: Criteria for including patients in the final analysis

A retrospective analysis of 118 episodes of *A. baumannii* bacteremia published in 2013 demonstrated that resistance to carbapenems was associated with significant rates of mortality.[4] The role of combination therapy in treating patients with CRAB bacteremia has not been established. The OVERCOME trial, published in 2022, showed that combination therapy did not offer any advantage over colistin monotherapy for carbapenem-resistant organisms.[5] *A. baumannii* was the predominant organism in the study population.[5] There are concerns that sulbactam may not be an optimal choice for isolates producing the OXA-23 enzyme.[6] Given the current therapeutic challenges, it is critical to know the local enzymatic patterns and antibiograms. We conducted a retrospective analysis of 50 episodes of bacteremia caused by CRAB. We analyzed the enzyme patterns and the susceptibility rates to various antibiotics. We also investigated various factors associated with mortality in these patients.

Materials and Methods

Patient Selection

This was a retrospective analysis of patients with bacteremia due to carbapenem-resistant *A. baumannii*. Figure 1 shows the selection of patients for this retrospective analysis. Those patients who had bacteremia with CRAB and were treated with appropriate antimicrobial therapy for at least 72 hours were included in the final analysis. Patients with isolates resistant to polymyxins (MIC >2 μg/mL), or those isolates for whom the enzyme details were not available were excluded from the study. Ethics committee approval was procured prior to the commencement of the study.

Microbiological Methods

Blood Cultures

Blood cultures were performed using the BD BACTEC Fx system (Becton Dickinson and Company, New Jersey, USA). Broth from positive blood culture vials was used to perform gram stain identification of gram-negative bacteria and subcultured on blood agar (BA) and MacConkey (MA) agar for further identification.

Bacterial Identification

Genus and species-level bacterial identification was done by using the MALDI-TOF-MS (Matrix-assisted Laser Desorption and Ionization-Time of Flight Mass Spectrometry) technology on the MALDI Biotyper Sirius (Bruker Daltonics, Bremen, Germany).

Antibiotic Susceptibility Testing

Susceptibility to various antibiotics was determined by BD Phoenix™ M50 using antimicrobial susceptibility testing (AST) panels. Currently, tigecycline has no CLSI or EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints for *A. baumannii*. Sensitivity or resistance to this species was extrapolated from the recent 2023 EUCAST breakpoints of tigecycline for *Enterobacteriaceae*. Polymyxin MICs were determined with commercial panels (BD Phoenix broth microdilution CPO panels).

Table 1: Relative susceptibility rates for various antimicrobials tested against carbapenem resistant *A. baumannii* (excluding polymyxins and beta lactam antibiotics)

Antibiotic/class of antibiotics tested	*Sensitive n (%)*	*Intermediate n (%)*	*Resistant n (%)*
Amikacin	6/50 (12)	0 (0)	44/50 (88)
Minocycline	19/50 (38)	6/50 (12)	25/50 (50)
Tigecycline	9/50 (18)	NA	41/50 (82)
Fluoroquinolones	6/50 (12)	0 (0)	44/50 (88)

Enzyme Detection

Characterization of carbapenemases was performed by using the technique of multiplex PCR (polymerase chain reaction), followed by reverse dot blot hybridization [Sepsis Flow Chip Assay (Master Diagnostica, Granada, Spain)].

Statistical Methods

The inter-group statistical comparison was done using the Chi-square test or Fisher's exact probability test. Multivariate logistic regression analysis was used to obtain the statistically significant and independent determinants of incidence of the mortality. Data analysis was carried out with the Statistical Package for Social Sciences (SPSS version 24.0).

Definitions

Clinical Cure: Discontinuation of all anti-infective agents and survival for at least 72 hours without the need to restart antibiotics.

Microbiological Cure: Follow-up blood cultures reporting no growth (drawn after a minimum of 72 hours of appropriate therapy).

Results

Table 1 shows the percentage susceptibilities for various antimicrobial agents for the isolates that were a part of our study. As depicted, a large majority of the isolates were also resistant

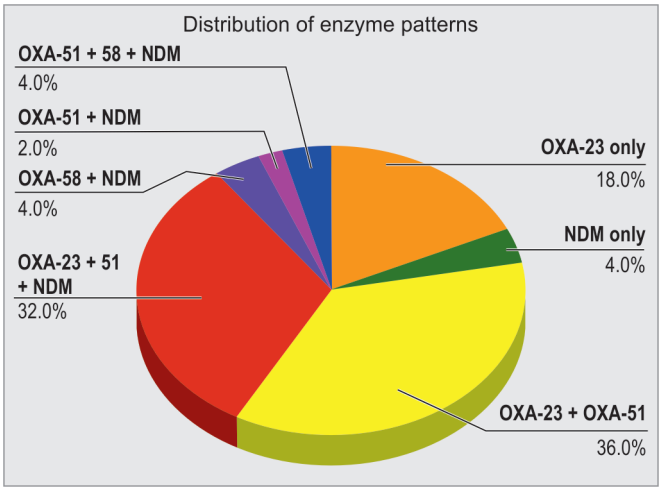

Fig. 2: Various enzymatic patterns observed in the isolates studied

Table 2: Incidence of day 28 mortality among the cases with *A. baumannii* bacteremia

Mortality	*No. of cases*	*% of cases*
Survivors	21	42.0
Non-survivors	29	58.0
Total	50	100.0

to other antimicrobials tested. Minocycline resistance rates were relatively less than tigecycline. Since we selected patients who harbored isolates that were resistant to carbapenems and had intermediate susceptibility to polymyxins, these classes have been excluded from this table.

Figure 2 shows the distribution of enzymes produced by the *A. baumannii* isolates that were a part of the study. As demonstrated, OXA-23 was the most commonly isolated enzyme (86% of the isolates produced OXA-23) followed by OXA-51 and NDM. More than two-thirds of the isolates (72%) produced more than 1 enzyme.

Table 2 shows the day 28 mortality in patients with *A. baumannii* bacteremia. It shows that 29 (58%) patients out of the 50 cases did not survive till day 28 and the overall survival rate was low.

Table 3 shows the distribution of baseline characteristics, comorbidities, and clinical factors across the survivors and the non-survivors. On univariate analysis, pneumonia as a source of bacteremia was demonstrated to be associated significantly with mortality (p = 0.04). Patients with higher Pitt's bacteremia score were found to have higher mortality rates with a significant association between the two (p = 0.001).

Table 4 depicts the details of the combination therapy used. The majority of the patients received meropenem in addition to polymyxins; the choice of the second agent was left to the discretion of the treating physicians.

Table 5 shows the multivariate analysis of the above factors to assess the independent factors that were associated with high

Table 3: Comparison of demographic, clinical characteristics and risk factors, severity indices and treatment type (Polymyxin B/E based monotherapy or combination therapy) according to mortality status at day 28 among the cases with Acinetobacter bacteremia studied (univariate analysis)

	Mortality at day 28			
Parameters	*Survivors (n = 21)*	*Non-survivors (n = 29)*	*All (n = 50)*	*p-value*
Demographics				
Age (≥50 years)	13 (61.9%)	19 (65.5%)	32 (64.0%)	0.999^{NS}
Age, median (range)[§], years	56.0 (18–83)	62.0 (23–84)	57.5 (18–84)	0.088^{NS}
Male sex	14 (66.7%)	19 (65.5%)	33 (66.0%)	0.933^{NS}
Weight, median (range)[§], kgs	67.0 (50–88)	62.0 (50–97)	65.0 (50–97)	0.574^{NS}
Comorbidities				
Diabetes mellitus	8 (38.1%)	9 (31.0%)	17 (34.0%)	0.603^{NS}
Hypertension	8 (38.1%)	14 (48.3%)	22 (44.0%)	0.474^{NS}
Ischemic heart disease	2 (9.5%)	5 (17.2%)	7 (14.0%)	0.684^{NS}
Hematological malignancy	4 (19.0%)	5 (17.2%)	9 (18.0%)	0.870^{NS}
Autoimmune conditions	2 (9.5%)	7 (24.1%)	9 (18.0%)	0.271^{NS}
Chronic liver disease	0	4 (13.8%)	4 (8.0%)	0.129^{NS}
Chronic kidney disease	2 (9.5%)	3 (10.5%)	5 (10.0%)	0.999^{NS}
Recent COVID infection (within the preceding 28 days)	5 (23.8%)	9 (31.0%)	14 (28.0%)	0.574^{NS}
Source of bacteremia				
Pneumonia	4 (19.0%)	14 (48.3%)	18 (36.0%)	0.042***
CRBSI	6 (28.6%)	10 (34.5%)	16 (32.0%)	0.658^{NS}
Surgical site infection	6 (28.5 %)	3 (10.3 %)	9 (18 %)	0.097^{NS}
Others	3 (14.2%)	4 (13.7%)	7 (14%)	0.960^{NS}
Respiratory status				
Requiring mechanical ventilation	13 (61.9%)	24 (82.8%)	37 (74.0%)	0.116^{NS}
Tracheostomy	7 (33.3%)	14 (48.3%)	37 (74.0%)	0.291^{NS}

(Contd...)

Table 3: *(Contd...)*

Parameters	*Mortality at day 28*			
	Survivors (n = 21)	*Non-survivors (n = 29)*	*All (n = 50)*	*p-value*
Enzyme patterns				
OXA-23 only	2 (9.5%)	7 (24.1%)	9 (18.0%)	0.271^{NS}
NDM only	1 (4.8%)	1 (3.4%)	2 (4.0%)	0.999^{NS}
OXA-23 + OXA-51	8 (38.0%)	10 (34.4%)	18 (36.0%)	0.602^{NS}
OXA-23 + OXA-51 + NDM	8 (38.0%)	8 (27.5%)	16 (32.0%)	0.431^{NS}
OXA-58 + NDM	0	2 (6.9%)	2 (4.0%)	0.503^{NS}
OXA-51 + NDM	0	1 (3.4%)	1 (2.0%)	0.999^{NS}
OXA-51 + OXA-58 + NDM	0	2 (6.9%)	2 (4.0%)	0.503^{NS}
Severity indices				
CCI score:				
1–2 (Mild)	8 (38.1%)	4 (13.8%)	12 (24.0%)	0.083^{NS}
3–4 (Moderate)	6 (28.6%)	16 (55.2%)	22 (44.0%)	0.393^{NS}
>/= 5 (Severe)	7 (33.3%)	9 (31.0%)	16 (32.0%)	0.001***
Median (Range)	3.0 (1–10)	4.0 (1–10)	4.0 (1–10)	0.001***
Pitt's bacteremia score:	11 (52.4%)	2 (6.9%)	13 (26.0%)	
0–4 (no infection)	10 (47.6%)	27 (93.1%)	37 (74.0%)	
>4 (more likely infection)	3.0 (1–9)	10.0 (2–14)	9.0 (1–14)	
Median (Range)[§]				
Treatment				
Polymyxin monotherapy	7 (33.3%)	7 (24.1%)	14 (28.0%)	0.475^{NS}
Polymyxin based combination therapy	14 (66.7%)	22 (75.9%)	36 (72.0%)	

[§]*p*-value by Mann-Whitney *U* test; the rest of the *p*-values by Chi-square test or Fisher's exact probability test; *p*-value < 0.05 is considered to be statistically significant; **p*-value < 0.05; ***p*-value < 0.01; NS, statistically non-significant

Table 4: Details of the combination therapy used

Antibiotics used in addition to polymyxin	*Number of patients (%) (Total N = 36, who received combination therapy)*
Meropenem	21/36 (58%)
Minocycline	5/36 (14%)
Sulbactam	3/36 (8.3%)
Minocycline + Sulbactam	5/36 (14%)
Amikacin	1/36 (2.8%)
Ciprofloxacin	1/36 (2.8%)

mortality in those with *A. baumannii* bacteremia. On multivariate analysis, pneumonia was not found to be significantly associated with mortality ($p = 0.4$). Combination therapy using polymyxin as a backbone was not associated with reduced mortality ($p = 0.1$).

Discussion

Acinetobacter remains a significant cause of concern in hospitals in India. Increasing rates of carbapenem resistance have compounded this problem and have limited the therapeutic options available for treating these patients. It is important to generate data of high quality about the local enzyme patterns and susceptibility rates. We describe a single-center experience of bacteremia caused by CRAB.

The therapeutic options for treating infections caused by carbapenem-resistant acinetobacter isolates can be limited. A study from north-east India published in 2018 showed that 79.2% of the multidrug resistant isolates of *A. baumannii* who recovered from the ICU were found to exhibit high-level aminoglycoside resistance (HLAR).[7] In our study, 88% of the isolates were resistant to amikacin. Plazomicin, a newer semisynthetic aminoglycoside, is not readily

Table 5: Multivariate logistic regression analysis to obtain the independent determinants of incidence of mortality (day 28)

Risk factors (Variables entered in the model)	*Odds ratio (OR)*	*95% CI for Odds ratio*	*p-value*
Age group (years)			
<50 years	1.00	–	–
≥50 years	1.112	0.569 – 1.752	0.742^{NS}
Comorbidity			
Absent	1.00	–	–
Present	1.341	0.622 – 1.810	0.509^{NS}
Pneumonia status			
Absent	1.00	–	–
Present	1.325	0.595 – 1.845	0.400^{NS}
Pitt bacteremia score			
0–4 (no infection)	1.00	–	–
>4 (More likely infection)	2.489	1.239 – 4.983	0.003**
Treatment group			
Polymyxin monotherapy	1.00	–	–
Polymyxin combination	1.087	0.503 – 1.982	0.122^{NS}

Odds ratio = 1: Reference category; Dependent variable: Mortality at day 28 (inclusive of day 14 mortality); ***p*-value < 0.01; NS, statistically non-significant

available in India. Though it has demonstrated promising efficacy against *Enterobacteriaceae* resistant to amikacin, it may be similar to amikacin with respect to its efficacy against *A. baumannii*.[8] As shown in Table 1, minocycline resistance was seen in half of the isolates but was considerably lower than tigecycline resistance. These findings show that minocycline may be a viable option in some patients with infections caused by carbapenem-resistant *A. baumannii* in our settings. Also, susceptibility to minocycline should not be extrapolated based on tigecycline MICs and vice versa. Eravacycline is a newer tetracycline and can be a useful option in the treatment of carbapenem-resistant acinetobacter infections. In vitro studies have shown that it can be more potent than minocycline and tigecycline against Acinetobacter species.[9] However, it is currently not available in India. Cefiderocol and sulbactam-durlobactam are emerging options for such infections. Fosfomycin remains a poor option for *A. baumannii* infections.[10] Overall, our study throws light on the limited options for treating carbapenem-resistant *A. baumannii* infections currently in our settings. Hence, polymyxins, despite their limitations, still remain the backbone of therapy for most patients in India with carbapenem-resistant *A. baumannii* infections.

Figure 2 shows the various patterns of enzymes produced by the isolates included in our study. As shown in this figure, the commonest pattern observed was the production of OXA-23 and OXA-51, followed by the production of OXA-23, OXA-51, and NDM. Among the isolates studied, 86% of the isolates produced the OXA-23 enzyme. The enzyme pattern may have some clinical implications. There are no effective beta-lactamase inhibitors available currently in clinical practice in India which can inhibit the OXA-23 enzyme. Even the newer BLIs such as avibactam, relebactam, and vaborbactam do not have any activity against this enzyme. Durlobactam offers hope on the horizon, as it has activity against the OXA enzymes of *A. baumannii* such as OXA-23, OXA-24, and OXA-58.[11] Also, there are concerns about the utility of sulbactam in the presence of the OXA-23 enzyme.[6] A recent study by Chandran et al. showed that minocycline and sulbactam were an effective combination in vitro against those isolates which produced the OXA-23 and NDM enzymes.[12] Hence, more data is needed on the efficacy of sulbactam in our settings. Also, more data is needed on the local enzyme patterns, especially as newer therapeutic options emerge.

As shown in Table 2, CRAB was associated with a high rate of crude mortality. This is congruent with previously published literature. In a study analyzing patients with Acinetobacter bacteremia, the attributable mortality rate was found to be 58.2%.[13] In this study, resistance to carbapenem was identified as a risk factor for mortality. In our study, we only analyzed patients with carbapenem-resistant bacteremia.[13] Pneumonia was found to be a factor associated with mortality, though this effect did not persist on multivariate analysis. However, patients with a higher Pitt bacteremia score were likely to have higher chances of mortality. Overall, our findings suggest that carbapenem-resistant Acinetobacter is truly a condition associated with high mortality and is a genuine therapeutic challenge in the Indian scenario.

As shown in our study, the use of combination therapy involving polymyxins was not shown to be associated with reduced mortality. A randomized controlled superiority trial published in 2018 showed that adding meropenem to colistin was not associated with better outcomes in infections caused by *A. baumannii*.[14] In our study majority of the patients received meropenem as the second drug. The use of combination therapy did not offer any advantage over polymyxin monotherapy and is consistent with previously published literature about using polymyxins plus meropenem combination regimens for Acinetobacter infections. However, further data is needed to extrapolate this conclusion to other combination regimens. A prospective study published in 2018 showed that the combination of colistin and ampicillin-sulbactam was associated with a superior clinical response in patients with CRAB ventilator-associated pneumonia when compared with colistin monotherapy.[15] A systematic review and meta-analysis published in 2018 found that the combination of colistin with sulbactam showed higher microbiological cure for multidrug-resistant Acinetobacter infections.[16] Accurate polymyxin MICs and the site of infection should be considered carefully before deciding to use polymyxin monotherapy. If there are concerns regarding MICs or infections at sites with limited polymyxin penetration, combination therapy needs to be carefully considered, and agents other than meropenem should be given preference. These decisions should be made carefully in conjunction with infectious physicians.

Limitations

This was a retrospective observational study. The sample size is relatively smaller. Though the majority of the resistance burden comes from enzymatic mechanisms, the non-enzymatic mechanisms of resistance have not been evaluated in this study. Also, the choice of the second drug as a part of combination therapy was left to the discretion of the treating physician. The majority of the patients in the combination therapy group received meropenem, and hence, these findings cannot be extrapolated to other combination regimens.

Conclusion

A. baumannii is associated with significant morbidity and mortality, as shown in our study. In our settings, the options for treating infections caused by Acinetobacter species are limited. As shown in our study, OXA-23 and NDM remain the most important enzymes, compromising the efficacy of the currently available therapeutic options. Polymyxins remain the backbone, and the routine use of polymyxin plus meropenem combination therapy may not offer a significant advantage over monotherapy. More data needs to be generated about the efficacy of other combination regimens in our settings. There is an urgent need for more therapeutic options, stringent stewardship programs, and generation of more local data to overcome this problem of considerable magnitude.

Orcid

Parikshit Shirish Prayag https://orcid.org/0000-0003-2102-7627
Sampada A Patwardhan https://orcid.org/0000-0003-0998-5742
Rasika S Joshi https://orcid.org/0009-0005-1551-0390
Shweta P Panchakshari https://orcid.org/0000-0002-5708-3287
Tejashree Rane https://orcid.org/0009-0007-3705-7691
Amrita P Prayag https://orcid.org/0000-0002-2498-9576

References

1. Hsu LY, Apisarnthanarak A, Khan E, Suwantarat N, Ghafur A, Tambyah PA. Carbapenem-resistant Acinetobacter baumannii and Enterobacteriaceae in South and SouthEast Asia. Clin Microbiol Rev 2017;30(1):1–22. DOI: 10.1128/CMR.masthead.30-1.
2. Annual report (January 2021 to December 2021) of the Antimicrobial Resistance Research & Surveillance Network (AMRSN), Division of

epidemiology and communicable diseases, Indian Council of Medical Research 2021;6.
3. Vijayakumar S, Mathur P, Kapil A, Das BK, Ray P, Gautam V, et al. Molecular characterization & epidemiology of carbapenem-resistant Acinetobacter Baumannii collected across India. Indian J Med Res 2019;149(2):240–246. DOI: 10.4103/ijmr.IJMR_2085_17.
4. Park SY, Choo JW, Kwon SH, Yu SN, Lee EJ, Kim TH, et al. Risk factors for mortality in patients with Acinetobacter baumannii bacteremia. Infect Che mother 2013;45(3):325–330. DOI: 10.3947/ic.2013.45.3.325.
5. Bosch X, Rovira M, Sitges M, Domènech A, Ortiz-Pérez JT, de Caralt TM, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). J Am Coll Cardiol 2013;61(23):2355–2362. DOI: 10.1016/j.jacc.2013.02.072.
6. Yang Y, Xu Q, Li T, Fu Y, Shi Y, Lan P, et al. OXA-23 is a prevalent mechanism contributing to sulbactam resistance in diverse Acinetobacter baumannii clinical strains. Antimicrob Agents Chemother 2019;63(1):e01676–e016718.
7. Upadhyay S, Khyriem AB, Bhattacharya P, Bhattacharjee A, Joshi SR. High-level aminoglycoside resistance in Acinetobacter baumannii recovered from intensive care unit patients in Northeastern India. Indian J Med Microbiol 2018;36(1):43–48. DOI: 10.4103/ijmm.IJMM_17_225.
8. Clark JA, Burgess DS. Plazomicin: A new aminoglycoside in the fight against antimicrobial resistance. Ther Adv Infect Dis 202;7:2049936120952604. DOI: 10.1177/2049936120952604.
9. Seifert H, Stefanik D, Sutcliffe JA, Higgins PG. In-vitro activity of the novel fluorocycline eravacycline against carbapenem non-susceptible Acinetobacter baumannii. Int J Antimicrob Agents 2018;51(1):62–64. DOI: 10.1016/j.ijantimicag.2017.06.022.
10. Behera B, Mohanty S, Sahu S, Praharaj AK. In vitro Activity of fosfomycin against Multidrug-resistant urinary and nonurinary Gram-negative isolates. Indian J Crit Care Med 2018;22(7):533–536. DOI: 10.4103/ijccm.IJCCM_67_18.
11. Durand-Réville TF, Guler S, Comita-Prevoir J, Chen B, Bifulco N, Huynh H, et al. ETX2514 is a broad-spectrum β-lactamase inhibitor for the treatment of drug-resistant Gram-negative bacteria including Acinetobacter baumannii. Nature microbiology 2017;2(9):1-0.
12. Chandran S, Manokaran Y, Vijayakumar S, Shankar BA, Baktha-vatchalam YD, Dwarakanathan HT, et al. Enhanced bacterial killing with a combination of sulbactam/minocycline against dual carbapenemase-producing Acinetobacter baumannii. Eur J Clin Microbiol Infect Dis 2023;42(5):645–651. DOI: 10.1007/s10096-023-04583-z.
13. Liu CP, Shih SC, Wang NY, Wu AY, Sun FJ, Chow SF, et al. Risk factors of mortality in patients with carbapenem-resistant Acinetobacter baumannii bacteremia. J Microbiol Immunol Infect 2016;49(6):934–940. DOI: 10.1016/j.jmii.2014.10.006.
14. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: An open-label, randomised controlled trial. Lancet Infect Dis 2018;18(4):391–400. DOI: 10.1016/S1473-3099(18)30099-9.
15. Makris D, Petinaki E, Tsolaki V, Manoulakas E, Mantzarlis K, Apostolopoulou O, et al. Colistin versus colistin combined with ampicillin-sulbactam for multiresistant Acinetobacter baumannii ventilator-associated pneumonia treatment: An open-label prospective study. Indian J Crit Care Med 2018;22(2):67–77. DOI: 10.4103/ijccm.IJCCM_302_17.
16. Kengkla K, Kongpakwattana K, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy and safety of treatment options for MDR and XDR Acinetobacter baumannii infections: A systematic review and network meta-analysis. J Antimicrob Chemother 2018;73(1):22–32. DOI: 10.1093/jac/dkx368.