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Research Article

Meropenem *Versus* Ceftazidime-Avibactam *Versus* Ceftazidime-Avibactam with Aztreonam as Empiric, First-Line Treatment of High-Risk Febrile Neutropenia: First Report of the CAMerA Trial, an Open-Labelled, Randomized-Controlled Trial

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ABSTRACT

Introduction: Infections due to Extended Spectrum Beta-Lactam (ESBL) positive, Carbapenemase Producing Enterobacteriaceae (CPE) and NDM1 resistance Enterobacteriaceae have significantly increased internationally and may account for up to 70% of infections in some geographies. Parallelly, high colistin resistance rates have also been reported. We are reporting the initial results of the first randomized-controlled trial addressing this issue of antibiotic resistant Gram-Negative Bacteremia (GNB).

Objectives: The objective of the study was to assess the efficacy of first-line Ceftazidime–Avibactam with or without Aztreonam in high-risk FN, *versus* Meropenem.

Methodology: Adult patients with high-risk FN were randomized to Meropenem, Ceftazidime-Avibactum or Ceftazidime-Avibactum with Aztreonam as the first line antibiotic regimen.

Results: Compared to meropenem, there was a trend towards reduced antibiotic failure, as defined by breakthrough fever within 7 days, with ceftazidime-avibactam, with or without aztreonam, although this wasn't statistically significant, (p value=0.076). Besides this, antibiotic failure was significantly associated with blood culture positivity (p=0.015). Also, the presence of lung infiltrates was significantly associated with transfer to ICU (p=0.001).

Conclusion: In high-risk FN, there was a trend to a higher incidence of antibiotic failure with first-line therapy with meropenem, compared to ceftazidime-avibactam with or without aztreonam, (p=0.076).

Keywords: Febrile neutropenia; Hematological malignancies; Antibiotic resistant gram-negative bacterial infections

INTRODUCTION

Fever occurs in around 80% of neutropenic episodes and hence, Febrile Neutropenia (FN) is considered as the most common and serious complication in hematological malignancies with an average mortality of 3-20% [1-4]. Thus, while chemotherapy has improved the survival of patients with hematological malignancies, FN remains a major cause of morbidity and mortality at present [5,6]. Patients with FN have a twofold higher risk of transfer to the Intensive Care Unit (ICU) because of severe infection. Predictive modeling has reported ICU transfer in 19% of the patients with neutropenia. Infections in such patients are mainly bacterial, however, fungal, and viral infections are also possible [7,8].

The clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer by the Infectious Diseases Society of America (IDSA), 2010 update, suggests the use of beta-lactam agents, such as cefepime, a carbapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam as Intravenous (IV) empiric antibiotic therapy in high-risk patients who require hospitalization [4].

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However, over the years, infections due to Extended Spectrum Beta-Lactam (ESBL) positive and Carbapenemase Producing Enterobacteriaceae (CPE) have significantly increased worldwide and in some geographies, these may account for up to 70% of infections [4,9,10]. Additionally, high colistin resistance rates, of up to 40% in Carbapenem-Resistant (CR)-*K. pneumoniae* and 10% in CR-*E. coli*) have also been observed in GNB [11]. The most isolated carbapenemase gene products in this geography are NDM1-1 and OXA-48 [12]. A sharp increase in these drug resistant pathogens and their diverse mechanisms of antimicrobial resistance, has posed a challenge in choosing the optimal empirical combination therapy for FN in regions which have a high prevalence of such antibiotic resistant gram-negative bacteria [13,9].

Ceftazidime-avibactam is a combination of beta-lactam/beta-lactamase inhibitor. Avibactam restores the activity of ceftazidime and its spectrum is substantially expanded against Ambler class A (ESBLs and *Klebsiella pneumoniae* Carbapenemases), Class C (Amp C), and some class D β–lactamases (OXA-48 like) [12,14]. It is approved for use in various infections such as complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired pneumonia, and ventilator-associated pneumonia due to its increased clinical efficacy [15,16]. Ceftazidime-avibactam has also been reported to have higher cure rates with respect to other antibiotics within 14 days of treatment initiation in bacteremic patients with hematologic malignancies (85.7% *vs.* 34.8%, respectively, p=0.031) [17]. The main limitation of this combination is its ineffectiveness against metallo-β–lactamase producers (NDM1), the prevalence of which is increasing worldwide [17].

This unmet need is met by Aztreonam, a monobactam that is effective against NDM1. However, it is hydrolyzed by ESBLs and Amp Cs that occur along with NDM1. Thus, when aztreonam is combined with Ceftazidime-avibactam, it potentially covers both NDM1 and OXA 48-like enzymes [15,16]. With the increasing burden of widespread antibiotic resistance worldwide, ceftazidime-avibactam in combination with aztreonam, appears to be a promising choice of antimicrobial therapy in FN. This could potentially reduce the ICU transfer and mortality rate in patients with hematological malignancies by abrogating the development of sepsis syndrome.

This study was conducted with an aim to analyze the efficacy of ceftazidime-avibactam, or ceftazidime-avibactam plus aztreonam, compared to the current standard of care, meropenem, for empiric therapy of high-risk FN, in our institution.

Trial objectives

The primary objective of the study was to assess the efficacy of first-line Ceftazidime–avibactam with or without Aztreonam in high-risk FN, *versus* that of meropenem.

The primary outcome measure was the failure of antibiotic therapy, as defined by the number of patients who need a change of antimicrobial drug or an addition of another antimicrobial within 7 days of starting the first antibiotic. Breakthrough fever within 7 days of the onset of neutropenia was defined as a recurrence of fever within 7 days, after an afebrile period of at least 48 hours. Breakthrough fever after 7 days of the first fever spike, was considered to be a second episode of FN.

The secondary outcome measures were hypoxia, hypotension, the need for transfer to ICU for critical care management and the mortality at the end of that episode of neutropenia.

MATERIALS AND METHODS

Methods

Trial design: The study was an open-labelled, randomized control trial conducted and analyzed by the hematology and stem cell transplant department of Health Care Global (HCG) Hospital, Bengaluru, India. After institutional ethics committee approval, the study was registered with Clinical Trials Registry India (CTRI), number CTRI/2021/10/037636. Patient enrolment was done in the two-year period between 22nd November 2020 and 30th November 2022.

Methodology: At the onset of fever, all the patients underwent two sets blood culture (5 ml of blood each was sent for aerobic and anaerobic culture). In patients with adequate financial coverage, blood was also sent for microbiologic analysis by multiplex PCR as reported previously [18,19]. Midstream urine culture was also done for all the patients. Computed Tomography (CT) scans of the chest were done to see if there were any respiratory signs or symptoms or if there was hypoxia on room air. If there were any findings on the Computed Tomography (CT) scan, then bronchoscopy and bronchoalveolar lavage was done and the fluid was sent for bacterial and fungal culture, Genexpert testing for mycobacterium tuberculosis and for microbiologic multiplex PCR analysis.

Patients were transferred to the ICU if they had at least one of the following: A requirement for airway management, hypoxia needing more than 2 liters of oxygen/minute, or hypotension greater than 20/10 mm Hg from baseline, which was not restored by two fluid boluses of 250 ml of normal saline, each given over 30 minutes. Patients were transferred back from the ICU to the hematology inpatient unit or the stem cell transplant unit after sufficient recovery from hemodynamic instability, as defined by, an oxygen requirement of 2 liters/minute and they had been off inotropes, both for more than 24 hours.

Antifungal prophylaxis was given with posaconazole for patients with acute myeloid leukemia (undergoing induction or consolidation chemotherapy), micafungin or anidulafungin for Hematopoietic Cell Therapy (HCT) patients and fluconazole for patients undergoing treatment for acute lymphoblastic leukemia. All the patients received antiviral prophylaxis with valacyclovir 500 mg once daily. Due to the high levels of cephalosporin/fluroquinolone resistance in our country, no patient received antibiotic prophylaxis.

All patients received pegylated Granulocyte Stimulating Factor (peg G-CSF) 6 mg once a week until the absolute neutrophil count was >1500 cell/mm for at least 2 days.

Study drug treatment

At the onset of fever, patients were randomly assigned to receive meropenem (1 g intravenously every 8 hours infused over 3 hours) or ceftazidime-avibactam (2.5 g intravenously every 8 hours infused over 2 hours) or ceftazidime-avibactam with aztreonam (2 g intravenously every 8 hours infused over 2 hours). Randomization was done with a simple randomization table with a 1:1:1 allocation.

Antibiotics were started within one hour of the onset of fever. Escalation of antimicrobials was done in accordance with IDSA guidelines as well as based on the results of microbiologic tests and the worsening of cardiorespiratory status and is detailed further

[10]. In the absence of informatory blood culture or molecular microbiologic reports, patients who were started on meropenem were escalated by the addition of polymyxin (loading dose 1,500,000 units followed by a maintenance dose 750,000 units Q12H) and those who had been on ceftazidime-avibactam were escalated by addition of aztreonam.

Crossover or de-escalation of antibiotics was based on microbiologic reports (culture-sensitivity or microbiologic multiplex PCR).

Antibiotics were continued for a minimum of 7-10 days, or until the patient was afebrile for at least 48 hours after recovery from neutropenia or until afebrile for at least 5 days, in the presence of ongoing neutropenia, whichever was longer.

Catheter-related bloodstream infections were managed as per the clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. [20,21].

Empiric gram positive cover with teicoplanin (400 mg Q12H for 3 doses followed by Q24H) was given if there was a cutaneous focus of infection, hemodynamic instability or for a suspected or proven pulmonary focus of infection. In the absence of positive microbiologic results, teicoplanin was stopped after 48-72 hours.

Sample size calculation: Based on the sensitivity patterns of meropenem (36%), ceftazidime-avibactam (43%) and ceftazidime-avibactam plus aztreonam (70%) [22,23] and a type 1 error of 5%, type 2 error of 20% and power of study 80%, planned accrual was for the initial study was of 33 patients in each group, i.e., a total of 99 patients, with 1:1:1 randomization. Interim data safety monitoring after the enrolment of 33 and 66 patients. This manuscript is the analysis of these first 99 patients and the trial will be continued further to understand time-based trends, in a larger set of patients, and study consort diagram represented in Figure 1.

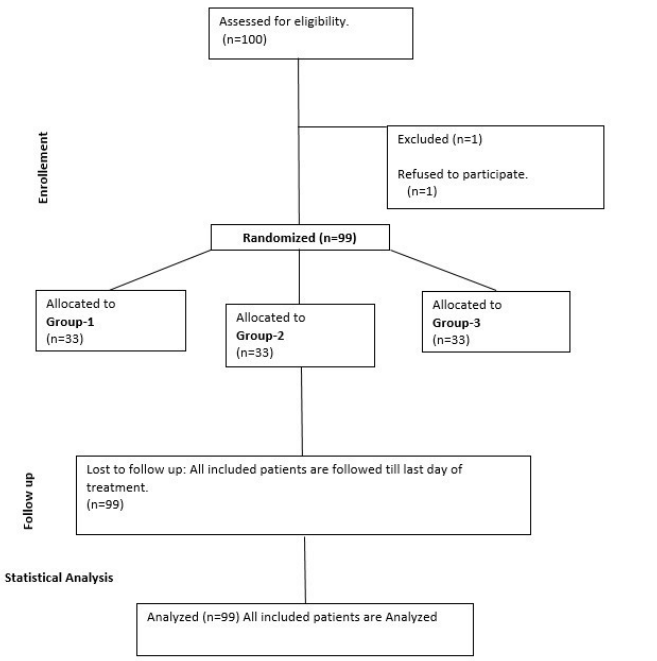

Figure 1: Consort diagram: Randomized controlled study.

Inclusion criteria

Unselected, consecutive, adult patients, who were being treated for benign and malignant hematologic disorders or were undergoing hematopoietic stem cell transplantation, and had presented with high-risk FN, were randomly assigned, to one of the three treatment arms of meropenem or ceftazidime-avibactam or ceftazidime-avibactam plus aztreonam, after obtaining their informed consent.

High-risk FN was defined as per the clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer by the Infectious Diseases Society of America (IDSA), 2010 update [4]. In short, this included patients who had fever with a single oral temperature of 38.3ºC (101 ° F) on one occasion or 38 ºC (100.4 ° F) on at least 2 occasions (1 hour apart), with/without significant comorbidities and had neutropenia with Absolute Neutrophil Count (ANC) <500/mm^3 or the ANC was expected to fall below 500/mm^3 in 48 hours and the neutropenia was expected to last for >7 days. An additional inclusion of prior inpatient admission in a healthcare facility for 5 days was mandated, since this increases the chances of the patient having a multidrug resistant infection [18].

Exclusion criteria

Patients age less than 18 years, pregnant and lactating women and those were being treated with a palliative intent were excluded from the study. Patient data was censored at death or discharge from the hospital.

Descriptive statistics were calculated for all variables. A comparison between the quantitative parameters was performed using Mann-Whitney U test or a t-test as appropriate, whereas difference in the qualitative parameters were evaluated using the chi-square statistics or the Fisher's exact test. The prognostic significance of clinical variables was tested using univariate logistic regression analysis and then a subsequent multivariate analysis as required. Clinically relevant variables with P<0.10 in the univariate analysis were included in the multivariate analysis. The overall survival probabilities were estimated using the Kaplan Meier method. A log rank comparison was used to assess any statistically significant difference. For all the tests, a 2-sided p-value ≤ 0.05 was considered to be statistically significant. The analysis was done using IBM SPSS statistics version 23.0.

RESULTS

A total of 99 patients with high-risk FN, who were undergoing treatment for hematologic disorders or undergoing stem cell transplantation, were enrolled, 33 in each treatment arm. The patient characteristics are given in Table 1. There was no significant difference in the underlying hematologic disorders as well as the initial suspected focus of infection between the groups at randomization. However, based on the radiologic tests in the first 7 days of treatment, lung infiltrates were seen in a greater number of patients in the meropenem group than in the other two groups, (p=0.028). Nevertheless, based on the results of the microbiologic evaluation of the blood, urine and the bronchoalveolar lavage, the confirmed focus of infection was identical in all 3 groups (p=0.392). The median duration of neutropenia was also similar among the 3 groups, p=0.636 which was shown in Table 1 patient characteristics.

Table 2 details the clinical outcomes. The majority of patients who had initially received meropenem, 24 (72.7%) required a change or addition of another antibiotic in the first 72 hours, compared to those in the ceftazidime-avibactam group (19 (57.6%)) and the ceftazidime-avibactam plus aztreonam group (9 (27.3%)), p=0.001. Similarly, the number of patients who had to be transferred to the

ICU was also higher in the meropenem group (p=0.023). And they also had to stay longer in the ICU for recovery from sepsis. The mean 2SD of days spent in the ICU was 9.00 (± 2.881) days for the meropenem group, 2.00 (± 1.001) days for the ceftazidime-avibactam group, and 3.00 (± 1.826) days for the ceftazidime-avibactam plus aztreonam group., p=0.031.

The details of the reason and the type of antimicrobial change are given in Table 3. Majority of the patients who had been first started with meropenem, required an additional antimicrobial or a complete change of antibiotic due to non-improvement or worsening of the clinical condition, p=0.014. 24 (72.7%) of the patients which received the combination of ceftazidime-avibactam plus aztreonam, were significantly more likely to complete their treatment without having to change to or add another antimicrobial, p=0.000133. A higher number of patients in the meropenem and ceftazidime-avibactam group did not achieve defervescence within 7 days, however, this was not statistically significant (p=0.184).

Since the incidence of lung infiltrates was significantly different and that of blood culture positivity was borderline different, among the treatment groups, we included these, along with the treatment groups, in the univariate analysis for the primary and secondary outcomes measures. The number of patients who were transferred to ICU was too small to be included in further analysis. The univariate analysis is detailed in Table 4.

The presence of lung infiltrates was significantly associated with the secondary outcome measures of transfer to ICU (p=0.000), hypotension (p=0.001) and hypoxia (p=0.002) but was not associated with the primary outcome measure of failure of antibiotic therapy, as defined by breakthrough fever within 7 days of starting antibiotics (p=0.507). Blood culture positivity was associated with a hazard ratio of 6 (95% CI of 1.927-18.796) for antibiotic failure. First line ceftazidime-avibactam was significantly better than meropenem for reducing the transfer to ICU (HR 0.083, 95% CI 0.010-0.703, p=0.022). While compared to meropenem, first line ceftazidime-avibactam plus aztreonam significantly reduced antibiotic failure by reducing breakthrough fever in <7 days by 79% (HR 0.212 (0.060-0.746), p=0.016) shows in Table 5.

There was no statistically significant difference in the mortality among the three groups. In the multivariate analysis, only the presence of lung infiltrates was significantly associated with transfer to ICU (p=0.001). Antibiotic failure, as determined by breakthrough fever within 7 days was significantly associated with blood culture positivity (p=0.015) and compared to meropenem, the risk of breakthrough fever was decreased by 30% by ceftazidime-avibactam and 70% by ceftazidime-avibactam plus aztreonam, although the p value of 0.076 was not significant.

Figure 1 represents the survival rate as per the first-line therapy of high-risk FN with ceftazidime-avibactam with or without aztreonam.

Table 1: Patient characteristics among three groups.

	Meropenem, n (%)	Ceftazidime-avibactam, n (%)	Ceftazidime-avibactam, n (%)	p value
Diagnosis				
ALL	6 (18.2%)	7 (21.2%)	6 (18.2%)	0.840
AML	10 (30.3%)	14 (42.4%)	14 (42.4%)	
MDS	1 (3.0%)	0 (0.0%)	1 (3.0%)	
HL	2 (6.1%)	1 (3.0%)	1 (3.0%)	
NHL	1 (3.0%)	0 (0.0%)	0 (0.0%)	
AA	0 (0.0%)	2 (6.1%)	1 (3.0%)	
Others	13 (39.4%)	9 (27.3%)	10 (30.3%)	
Clinically suspected focus of infection at the onset of FN				
Blood	14 (42.4%)	13 (39.4%)	12 (36.4%)	0.756
Urine	3 (9.1%)	3 (9.1%)	5 (15.2%)	
Blood and Urine	14 (42.4%)	16 (48.5%)	15 (45.5%)	
Lungs	2 (6.1%)	1 (3.0%)	0 (0.0%)	
Others	0 (0.0%)	0 (0.0%)	1 (3.0%)	
Lung infiltrates on CT chest scan	9 (27.3%)	2 (6.1%)	3 (9.1%)	0.028
Initial suspicion of CRBSI	5 (15.2%)	2 (6.1%)	1 (3.0%)	0.171

		Confirmed site of infection		
Unknown	1 (3.0%)	0 (0.0%)	1 (0.0%)	0.392
Blood	4 (12.1%)	9 (27.3%)	19 (18.2%)	
Lungs	2 (6.1%)	2 (6.1%)	5 (3.0%)	
CRBSI	2 (6.1%)	2 (6.1%)	5 (3.0%)	
Urine	1 (3.0%)	3 (9.1%)	12 (24.2%)	
Others	18 (54.5%)	14 (42.4%)	46 (42.4%)	
Blood and lungs	3 (9.1%)	0 (0.0%)	4 (3.0%)	
Blood and CRBSI	1 (3.0%)	1 (3.0%)	2 (0.0%)	
Blood and urine	1 (3.0%)	2 (6.1%)	4 (3.0%)	
Lung and urine	0 (0.0%)	0 (0.0%)	1 (3.0%)	
Positive blood culture	7 (21.2%)	9 (27.3%)	0 (0.0%)	0.007
Polymicrobial infection	2 (6.1%)	4 (12.1%)	2 (6.1%)	0.580
Microbiologic PCR positive	7 (21.2%)	10 (30.3%)	12 (36.3%)	0.396
Duration of neutropenia mean	14.45 ± 9.4	15.81 ± 13.21	12.43 ± 6.75	0.636

Note: Abbreviations: ALL- Acute Lymphoblastic Leukemia, AML- Acute Myeloid Leukemia, MDS- Myelodysplastic Syndrome, HL- Hodgkin Lymphoma, NHL- Non-Hodgkin Lymphoma, AA- Aplastic Anemia. Others include (Thalassemia major, Hemophilia), CLABSI- Central Line Associated Blood Stream Infections, CRBSI- Catheter Related Blood Stream Infections.

Table 2: Clinical outcomes among three groups.

	Meropenem	Ceftazidime-avibactam	Ceftazidime-avibactam plus Aztreonam	P value
Antimicrobial changed in 72 hrs	24 (72.7%)	19 (57.6%)	9 (27.3%)	0.001
Days required for defervescence	7 (21.2%)	7 (21.2%)	7 (21.2%)	7 (21.2%)
Median (range)	8 (2-42)	7 (2-20)	5.5 (2-16)	0.285
Hypotension	3 (9.1%)	1 (3.0%)	3 (9.1%)	0.541
Hypoxia	4 (12.1%)	0 (0.0%)	2 (6.1%)	0.119
Transferred to ICU	9 (27.3%)	1 (3.0%)	5 (15.2%)	0.023
Days in ICU	7 (21.2%)	7 (21.2%)	7 (21.2%)	7 (21.2%)
mean 2SD	9.00 (± 2.881)	2.00 (± 1.001)	3.00 (± 1.826)	0.031
Death	3 (9.1%)	1 (3.0%)	2 (6.1%)	0.587

Table 3: Reason for and the type of change of antimicrobial.

	Meropenem, n (%)	Ceftazidime-avibactam, n (%)	Ceftazidime-avibactam plus aztreonam, n (%)	p value
Completed therapy with the initial drug	7 (21.2%)	10 (30.3%)	24 (72.7%)	0.000133
Type of change of antimicrobial				
Added another antibiotic or changed to another treatment group	23 (69.7%)	19 (57.58%)	6 (18.2%)	0.014
Completely changed antibiotics	3 (9.1%)	0 (0.0%)	3 (9.1%)	
Reason for antimicrobial change				
Culture sensitivity report	0 (0.0%)	0 (0.0%)	1 (3.03%)	0.184
Deterioration	2 (6.05%)	0 (0.0%)	0 (0.0%)	
New focus of infection during the inpatient stay	2 (6.05%)	2 (6.05%)	2 (6.05%)	
Lack of defervescence within 7 days	22 (66.7%)	17 (51.52%)	6 (18.18%)	

Table 4: Comparison of multivariate analysis.

	Breakthrough fever <7 days		Transferred to ICU	
	HR (95% CI)	p value	HR (95% CI)	p value
Lung infiltrates	1.1 (0.29-4.31)	0.877	14.5 (3.02-69.79)	0.001
Blood culture positivity	4.5 (1.34-14.88)	0.015	9.1 (1.26-65.78)	0.029
Meropenem	1.0	-	1.0	-
Ceftazidime-avibactam	0.7 (0.23-2.10)	0.513	0.1 (0.01-1.07)	0.057
Ceftazidime-avibactam plus Aztreonam	0.3 (0.08-1.13)	0.076	1.5 (0.29-7.64)	0.628

Table 5: Comparison of univariate analysis.

	Lung infiltrates (yes)		Blood culture positivity		Meropenem *vs.* Ceftazidime-avibactam		Meropenem *vs.* Ceftazidime-avibactam plus aztreonam	
	HR (95% CI)	P value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Breakthrough fever <7 days	1.498 (0.454–4.939)	0.507	6.019 (1.927-18.796)	0.002	0.769 (0.281-2.103)	0.609	0.212 (0.060-0.746)	0.016
Transferred to ICU	14.857 (4.005-55.113)	0.000	3.318 (0.954-11.544)	0.059	0.083 (0.010-0.703)	0.022	0.476 (0.140-1.616)	0.234
Hypotension	23.056 (3.895-136.476)	0.001	0.856 (0.096-7.630)	0.889	0.313 (0.031-3.171)	0.325	1.000 (0.187-5.357)	1.000
Hypoxia	16.600 (2.690-102.428)	0.002	1.040 (0.113-9.547)	0.972	0.000	0.998	0.468 (0.080-2.750)	0.400
Death	3.375 (0.557-20.467)	0.186	2.821 (0.471-16.899)	0.256	0.313 (0.031-3.171)	0.325	0.645 (0.101-4.137)	0.644

DISCUSSION

The growing prevalence of multidrug-resistant GNB necessitates a trial of antibiotics such as ceftazidime-avibactam with or without aztreonam, against established drugs such as meropenem. This is especially critical for the front-line treatment of high-risk FN, which has a high rate of mortality. To our knowledge, this is the first prospective, randomized, controlled, clinical trial of meropenem *versus* ceftazidime-avibactam *versus* ceftazidime-avibactam plus aztreonam in this clinical setting. Our data shows that in a region with high prevalence of carbapenem resistant GNB, front-line therapy of high-risk FN with ceftazidime-avibactam with or without aztreonam shows a strong trend towards reducing the chances of antibiotic failure (breakthrough fever in 7 days), although this was not statistically significant, probably due to the small sample size. In addition, in those patients who required ICU care, those who had initially received meropenem, spend a longer time recovering from the sepsis, in the ICU. These benefits were seen regardless of the site of infection.

Expectedly, as described previously, those patients who had lung infiltrates had a higher risk of transfer to ICU [22].

Clinical trial number

Clinical Trials Registry of India number CTRI/2021/10/037636 date on 27/10/2021.A Preprint has previously been published, Sachin Suresh Jadhav, et.al., 17 July 2023 [24].

CONCLUSION

However, in our analysis, they responded equally well to the antibiotics, compared to the patients without lung infiltrates. The limitations of the study include the small sample size and the single institution methodology. We intend to continue this study to a larger sample size to understand the time-based trends in a larger sample size.

In high-risk febrile neutropenia, patients presenting with lung infiltrates have a high risk of sepsis requiring ICU care. First-line therapy of high-risk FN with ceftazidime-avibactam with or without aztreonam had a trend to lesser antibiotic failure compared to meropenem along with a faster recovery from sepsis.

DECLARATIONS

Ethical approval and consent to participate

We confirm that all methods were carried out in accordance with relevant guidelines and regulations. We confirm that all experimental protocols were approved by a named institutional and/or licensing committee. [HCG central ethics committee] REG.NO: ECR/386/INST/KA/2013/RR-19

We confirm that informed consent was obtained from all subjects and/or their legal guardian(s).

Consent for publication

The authors do not have any conflict of interest in publishing this article.

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Competing interests

Funding has been issued for patient benefit only during trial, here by I declare that no authors were benefited for financial benefits. Financial support and sponsorship.

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Authors contribution

" All Authors have reviewed the manuscript".

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Sachin Suresh Jadhav and Jyothi Goutham Kumar designed the research study, performed the research, analysed the data and wrote the paper. Anjali Matani, Amey C Panchal, Nishit Ojha, Sonu Tony and Yesheswini N Naik performed the research.

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