Karim *et al.*
The Egyptian Journal of Internal Medicine (2022) 34:65
https://doi.org/10.1186/s43162-022-00154-4

The Egyptian Journal of Internal Medicine

RESEARCH Open Access

Use of cefepime, meropenem, or piperacillin/tazobactam as initial treatment for febrile neutropenia in patients with hematological malignancy — a real-life experience

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Abstract

Background: Antimicrobials like fourth-generation cephalosporins, carbapenems, or β-lactams are widely used in treatment of febrile neutropenia (FN). The present study aimed to compare the efficacy of cefepime, meropenem, and piperacillin/tazobactam as initial treatment for chemo-induced FN in patients with hematological malignancy.

Methods: This was an observational study conducted in the Department of Hematology of Dhaka Medical College Hospital from July 2020 to June 2021 including 99 adult FN patients with hematological malignancy who were randomized equally to three treatment arms to receive cefepime, meropenem, or piperacillin/tazobactam as an empirical antibiotic. Response to therapy was defined as improvement in symptoms (e.g., defervescence) or in laboratory values including neutrophil counts on day 3 and day 7 after the initiation of the therapy. Chi-square test and Fisher's exact test were used to compare the efficacy of the treatment regimens.

Results: Response rate to initial treatment with different antibiotic regimens was similar without any statistically significant difference (60.6%, 63.6%, and 51.5% on day 3 and 63.6%, 75.8%, and 66.7% on day 7 for cefepime, meropenem, and piperacillin/tazobactam, respectively, p-value > 0.05) irrespective of underlying diagnosis, the severity of neutropenia, and cause of fever.

Conclusion: Initial therapy with cefepime, meropenem, or piperacillin/tazobactam is safe and equally effective in chemo-induced FN in patients with hematological malignancy. This finding may be considered in clinical practice for optimum therapeutic outcomes.

Keywords: Febrile neutropenia, Hematological malignancy, Cefepime, Meropenem, Piperacillin/tazobactam

Introduction

Febrile neutropenia (FN) is a common and potentially life-threatening clinical consequence of myelosuppressive chemotherapy in patients with hematological malignancies. One out of six patients receiving chemotherapy due to hematological malignancy develops FN which may be as high as 50% in elderly and chemotherapy-naïve patients [1]. It is one of the major dose-limiting adverse events of chemotherapy that often lead to compromised treatment outcomes, frequent hospitalization, and the administration of empiric broad-spectrum antibiotics which has been associated with increased morbidity, mortality, and treatment cost [1, 2].

Etiology of fever in the majority of the FN patients remains unknown, while only around 20% of patients

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with profound neutropenia develop documented bacteremia [3]. Gram-negative bacteria (i.e., *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*) are the leading cause of infection in these patients [4]. Current guidelines recommend that parenteral empirical antibiotic monotherapy with an anti-pseudomonal β-lactam agent, such as cefepime, or a carbapenem such as meropenem or imipenem-cilastatin, or piperacillin/tazobactam, should be administered in high-risk patients [3]. Modification of the initial regimen might be considered based on patient's clinical condition as well as bacteriological report. Subsequent treatment may include aminoglycosides, fluoroquinolones, and/or vancomycin additional to the initial regimen [3]. However, resistance to these antimicrobial agents has become an emerging challenge in clinical management of FN [4]. Though broad spectrum antimicrobial agents like cefepime (broad spectrum cephalosporin), piperacillin/tazobactam (β-lactam antibiotic combined with β-lactamase inhibitor), or meropenem (β-lactam belonging to carbapenem family) has adequate coverage against gram-positive, gram-negative, and anaerobic pathogens and used widely in FN [5], emerging evidence of resistance against theses antimicrobials may compromise the treatment outcome. Moreover, choice of empirical antibiotic should be based on local epidemiology, resistance pattern, and patients' clinical condition [3].

Existing reports of experimental studies reported equal efficacy of piperacillin/tazobactam compared to cefepime [6] or meropenem [7] in adult as well as pediatric patients with chemotherapy-induced FN in hematological malignancies. A retrospective cohort study reported similar efficacy of carbapenem, cefepime, and piperacillin/tazobactam monotherapy for empiric treatment of bacteremia caused by extended spectrum β-lactamase producing *Escherichia coli* in patients with hematologic malignancy [8]. However, there is a lack of prospective randomized study comparing these three drugs together in the existing evidence especially in context of Asian population and developing countries vulnerable to high burden of antimicrobial resistance like Bangladesh. The objective of the present study was to compare the efficacy of cefepime, meropenem and piperacillin/tazobactam as initial treatment for febrile neutropenia in patients with hematological malignancy.

Methods

Study design and setting

The present one was an observational study conducted in the Department of Hematology of Dhaka, Medical College Hospital, Dhaka, Bangladesh, from July 2020 to June 2021.

Patients

Adult FN patients (aged 16 years or older) with hematological malignancy who had not undergone allogeneic stem cell transplantation were included in the present study. FN was defined as an axillary temperature $\geq$ 37.5 °C or oral temperature $\geq$ 38 °C and an absolute neutrophil count (ANC) $< 1000 \times 10^6$/L with no other infectious signs. Exclusion criteria were patients with (1) previous identified bacteria considered to be resistant to the initial drug before study entry; (2) severe cardiac, hepatic, or renal dysfunction; (3) history of hypersensitivity to β-lactam or drugs; (4) positive intradermal reaction to the antimicrobials tested; (6) inappropriateness for efficacy evaluation because of old age; (7) pregnancy, possible pregnancy, or lactation; or (8) judgment by the investigator of ineligibility for the study.

Based on a reported efficacy rate of 57% for cefepime therapy in FN, the calculated sample size was 30 per arm to detect any significant difference with an α of 0.05 and 80% power on the assumption that the expected efficacy rates of meropenem and piperacillin/tazobactam would be 80%. Assuming 10% dropout rate, we considered a total of 99 patients (33 patients per arm).

Before enrollment in the study, all patients who met the inclusion criteria and gave informed written consent underwent following laboratory tests: hematology, biochemistry, chest X-ray, and specimen culture (blood, urine, or nasopharyngeal aspirate as required). Eligibility was assessed based on the results of these tests, and all eligible patients were registered in the central registry of the Dhaka Medical College Hospital and randomly assigned to three treatment arms.

Initial therapy

The study method is illustrated in Fig. 1. Cefepime, meropenem, or piperacillin/tazobactam was administered 8 hourly by intravenous infusion at a dose of 2 g, 1 g, and 4.5 g 8 hourly (if body weight < 40 kg) or 50 mg/kg, 20 mg/kg, and 112.5/kg 8 hourly (if body weight is 40 kg or above) respectively along with other supportive care measures. A patient who showed improvement in symptoms (e.g., defervescence) or in laboratory values including neutrophil counts on day 3 after the initiation of the therapy was considered as "very responsive," and the therapy was continued for another 4 days and then followed up. A patient whose fever tended to defervesce and whose symptoms or laboratory values improved without full recovery on day 3 after the initiation of therapy was treated with the same antibiotic for another 4 days. If defervescence with further improvement in symptoms or laboratory values occurred on day 7 after the initiation

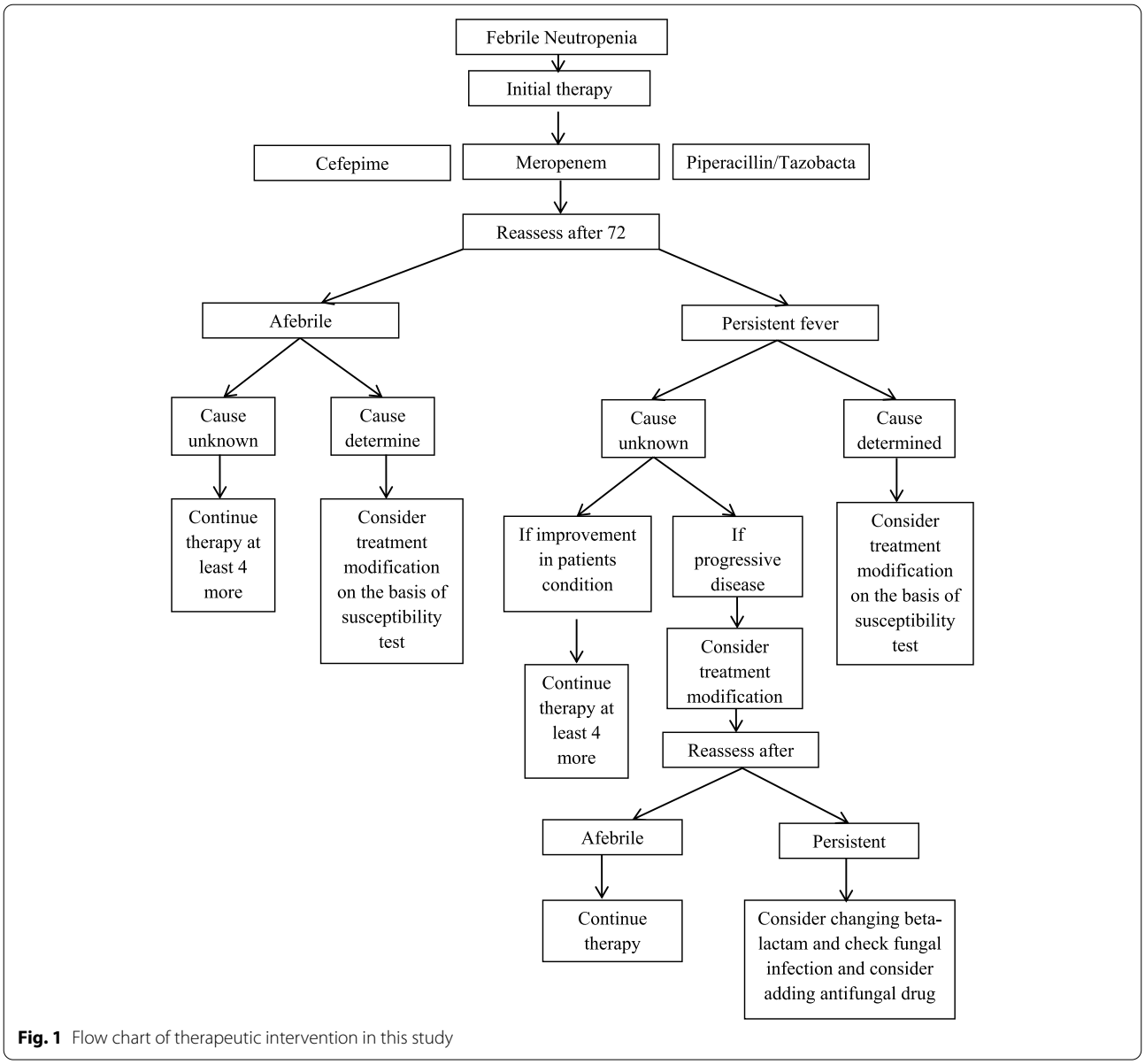

Fig. 1 Flow chart of therapeutic intervention in this study

of therapy, the patient was considered as "responsive." If a tendency toward improvement was observed without full recovery on day 7, the patient was characterized as "somewhat responsive." If no improvement with progressive disease was observed on day 3 after the initiation of therapy, the patient was considered as "unresponsive," and switching to another antimicrobial regimen was considered.

Defervescence, in this study, was defined as normal body temperature (< 37° C) for at least 3 consecutive days. The definition of tendency to defervesce is additionally stated as normal body temperature (< 37° C) for 2 consecutive days. The antibiotic sensitivity of any pathogen isolated from blood, urine, or other samples was tested, and the choice of antimicrobials was based on the test results. When no defervescence occurred on day 7, blood culture, fungal serological tests (β-D-glucan, etc.), chest X-ray, and C-reactive protein (CRP) assay were performed.

The percentage efficacy on days 3 and 7 after the initiation of therapy was calculated from the number of "very responsive" cases and the summative number of "very responsive" and "responsive" cases relative to the number of evaluable cases respectively.

Subsequent therapy

Patients unresponsive to initial therapy with no pathogen isolated were treated with the same antimicrobial agent plus aminoglycosides (amikacin) or quinolone (ciprofloxacin, moxifloxacin) additionally administered twice daily for another 2 days. The respective physician determined the antibiotic to be used. Reassessment of body temperature, symptoms, and laboratory values, including neutrophil counts, was performed 48 h after the addition of subsequent therapy. If defervescence with further improvement in symptoms or laboratory values occurred, the same therapy is continued for subsequent 2 days. If no improvement was observed, changing beta-lactam drug and test for fungal infection and addition of antifungal drug were considered. On the other hand, patients unresponsive to initial therapy with isolated causative organism, treatment modification on the basis of susceptibility test was considered.

During the study, patients were closely monitored for any concomitant symptoms or abnormal changes in laboratory values. For each such symptom or abnormal change, the date of onset, severity, treatment, treatment course (outcome), and causal relationship with the study drug were recorded in detail. Blood, hepatic function, renal function, and fungus testing were carried out routinely.

Statistical analysis

Descriptive statistics was used to represent the findings. Patients' background characteristics of different treatment groups were compared by chi-square test. Chi-square test and Fisher's exact test were used to compare the efficacy of the treatment regimens on day 3 and 7 as well as efficacy according to the underlying disease, cause of fever, and neutrophil counts. STATA version 17.0 was used to perform the analyses.

Results

Baseline characteristics

The average age of the 99 included patients was 29.9 (*SD* 14.2) years, with male predominance (63.6%). Almost 43.4% of patients were suffering from acute myeloid leukemia (AML) followed by 38.4% patients from acute lymphoblastic leukemia (ALL) and 18.2% from other hematological malignancies such as chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), and Hodgkin lymphoma (HL). Almost half of the patients (47.5%) had a fever of unknown origin, 28.3% had clinically documented infection (CDI), and 31.3% had microbiologically documented infection (MDI). More than half of the patients had severe neutropenia (< 100 cells/μl) (Table 1).

Table 1 Background characteristics of the patients ($n = 99$)

Characteristics	Total	Cefepime	Meropenem	Piperacillin/tazobactam	*p*-value
Age	29.87 (14.21)	34.24 (13.68)	26.06 (12.82)	29.30 (15.22)	0.620
Sex					
Male	63 (63.64)	18 (54.55)	22 (66.67)	23 (69.70)	0.400
Female	36 (36.36)	15 (45.45)	11 (33.33)	10 (30.30)	
Diagnosis					
ALL	38 (38.38)	8 (24.24)	17 (51.52)	13 (39.39)	0.120
AML	43 (43.43)	18 (54.55)	9 (27.27)	16 (48.48)	
Others	18 (18.18)	7 (21.21)	7 (21.21)	4 (12.12)	
Comorbidity	8 (8.08)	3 (9.09)	1 (3.03)	4 (12.12)	0.386
Cause of fever					
CDI	28 (28.28)	9 (27.27)	7 (21.21)	12 (36.36)	0.388
MDI	31 (31.31)	12 (36.36)	10 (30.30)	9 (27.27)	0.720
PUO	47 (47.47)	16 (48.48)	16 (48.48)	15 (45.45)	0.960
Treatment duration	7 (1)	7 (1)	7 (1.5)	7 (2)	0.769
ANC (cells/μl), median (IQR)	80 (240)	125 (250)	90 (390)	50 (150)	0.362
ANC category (cells/μl)					
< 100	51 (51.52)	15 (45.45)	17 (51.52)	19 (57.58)	0.904
100–499	31 (31.31)	12 (36.36)	10 (30.30)	9 (27.27)	
≥ 500	17 (17.17)	6 (18.18)	6 (18.18)	5 (15.15)	

Bacteriological profile

Table 2 Isolates of microorganisms from patients' sample culture

Organism	Total	Cefepime	Meropenem	Piperacillin/tazobactam
Staphylococcus	8 (25.00)	6 (50.00)	0 (0.00)	2 (22.22)
E. coli	7 (21.88)	1 (8.33)	3 (27.27)	3 (33.33)
Klebsiella	5 (15.63)	0 (0.00)	3 (27.27)	2 (22.22)
Enterococci	3 (9.38)	3 (25.00)	0 (0.00)	0 (0.00)
Citrobacter	2 (6.25)	1 (8.33)	1 (9.09)	0 (0.00)
Enterobacter	2 (6.25)	0 (0.00)	1 (9.09)	1 (11.11)
Pseudomonas	2 (6.25)	1 (8.33)	1 (9.09)	0 (0.00)
Streptococcus	1 (3.13)	0 (0.00)	1 (9.09)	0 (0.00)
Candida	2 (6.25)	0 (0.00)	1 (9.09)	1 (11.11)

Treatment efficacy

Bacteriological profile

A total of 31 out of 99 samples yielded growth in culture. Among them, *Staphylococcus* was the most frequently isolated organism (25%), followed by *E.coli* (22%), *Klebsiella* (16%), and *Enterococci* (9%) (Table 2).

Treatment efficacy

Response rate to initial treatment with different antibiotic regimen was similar without any statistically significant difference (60.6%, 63.6%, and 51.5% on day 3 and 63.6%, 75.8%, and 66.7% on day 7 for cefepime, meropenem, and piperacillin/tazobactam, respectively, p-value > 0.05) (Table 3).

Similarly, response to initial treatment in relation to underlying diagnosis, severity of neutropenia, and cause of fever was similar in cefepime, meropenem, and piperacillin/tazobactam group (Table 4).

Adverse events

A total of 10 patients out of 99 experienced different adverse events, most commonly skin rash and gastrointestinal discomfort. However, all of them had mild symptoms, and none of them discontinued the treatment regimen due to adverse events (Table 5).

Discussion

In the present study, we attempted to compare the efficacy of cefepime, meropenem, and piperacillin/tazobactam as initial treatment for FN in patients with hematological malignancy.

In the present study, the efficacy rate of cefepime was 60.6 and 63.6% on days 3 and 7 after the initiation of treatment. This efficacy rate was identical to a randomized trial from Japan (66%) [9], though some other studies reported comparatively lower efficacy of the drug (around 50%) [10, 11]. Meropenem, on the other hand, showed slightly better efficacy (63.6 and 75.7% on days 3 and 7, respectively), though statistically nonsignificant,

Table 3 Treatment response on days 3 and 7

Response	Cefepime	Meropenem	Piperacillin/tazobactum	p-value[a]	p-value[b]	p-value[c]
Day 3	20/33 (60.61)	21/33 (63.64)	17/33 (51.52)	0.800	0.319	0.457
Day 7	21/33 (63.64)	25/33 (75.76)	22/33 (66.67)	0.284	0.415	0.796

[a] Cefepime vs meropenem, [b]meropenem vs piperacillin/tazobactam, [c]cefepime vs piperacillin/tazobactam

Table 4 Clinical response according to underlying disease, baseline neutrophil counts, and cause of fever (day 7)

	Cefepime	Meropenem	Piperacillin/tazobactam	p-value[a]	p-value[b]	p-value[c]
Diagnosis						
ALL	5/8 (62.50)	15/17 (88.24)	10/13 (76.92)	0.133	0.410	0.477
AML	11/18 (61.11)	4/9 (44.44)	9/16 (56.25)	0.411	0.571	0.774
Others	5/7 (71.43)	6/7 (85.71)	3/4 (75.00)	0.515	0.658	0.898
ANC (cells/μl)						
< 100	9/15 (60.00)	10/17 (58.82)	13/19 (68.42)	0.946	0.549	0.610
100–499	9/12 (75.00)	9/10 (90.00)	6/9 (66.67)	0.364	0.213	0.676
≥ 500	3/6 (50.00)	6/6 (100.00)	3/5 (60.00)	0.046	0.087	0.740
Cause of fever						
CDI	3/9 (33.33)	5/7 (71.43)	8/12 (66.67)	0.131	0.829	0.130
MDI	6/12 (50.00)	5/10 (50.00)	4/9 (44.44)	0.990	0.809	0.801
PUO	13/16 (81.25)	15/16 (93.75)	11/15 (73.33)	0.285	0.122	0.598

[a] Cefepime vs meropenem, [b]meropenem vs piperacillin/tazobactam, [c]cefepime vs piperacillin/tazobactam

Table 5 Summary of drug-related adverse events ($n = 99$)

Adverse events	Cefepime	Meropenem	Piperacillin/tazobactam	Total
Skin rash	1	0	2	3
Nausea and vomiting	1	1	2	4
Diarrhea	1	0	0	1
Liver dysfunction	0	1	0	1
Renal dysfunction	0	0	0	0
Thrombocytopenia	0	0	1	1
Total	3/99 (3.03%)	2/99 (2.02%)	5/99 (5.05%)	10/99 (10.10%)

compared to cefepime in the present study which is comparatively better than some previous studies (efficacy rate ranging from 63 to 65%) [9, 10]. However, imipenem, another drug from carbapenem group, showed similar efficacy in the treatment of FN [9]. In bloodstream infections in the hospital settings of Bangladesh, meropenem had comparatively lower resistance rate than other commonly used antibiotic which might influence the efficacy of the drug in treatment of FN [12]. Piperacillin/tazobactam also showed similar efficacy as initial therapy for FN in our study (51.5 and 66.7% on days 3 and 7, respectively) comparable to some previous studies (response rate 62 to 73%) [6, 13, 14].

Our results suggest that all of the cefepime, meropenem, and piperacillin/tazobactam monotherapies are equally effective as initial treatment for FN in patients with hematological malignancy. Previous studies comparing meropenem to cefepime [9, 10, 15], piperacillin/tazobactam to cefepime [6, 16], and piperacillin/tazobactam to meropenem [7] reported no significant difference between these regimen in the efficacy of treatment of chemotherapy-induced FN in malignant patients. However, there is scarcity of literature on combined comparison of these three drugs in treatment of FN. A retrospective study reported equal efficacy of these antimicrobial agents for empiric treatment of bacteremia caused by extended spectrum β-lactamase producing *Escherichia coli* in patients with hematologic malignancy [8].

In this study, the efficacy of cefepime, meropenem, and piperacillin/tazobactam was not affected by the underlying disease or type of infection which supports the findings of previous research works [6, 9, 10, 16]. Though research works evidenced that efficacy of these drugs is similar irrespective of baseline neutrophil count [9, 10], some studies reported that the therapeutic efficacy of antimicrobials depended on recovery of neutrophil counts after the initiation of treatment [9, 10, 17]. Similar to the reports of previous studies, ours one suggests that the efficacies of the study drugs are not influenced by the baseline neutrophil count, probably because of their broad antimicrobial spectra though efficacy based on subsequent neutrophil count after initiation of therapy was not evaluated.

Though gram-negative organisms are considered as major causative agents of sepsis in FN patients, our study as well as previous epidemiological evidence suggests that gram-positive organisms also play a substantial role in this regard [18]. Hence, it may be rational to use fourth-generation cephalosporins like cefepime and carbapenems like meropenem with activity against both gram-negative and gram-positive bacteria, as the first-line therapy for FN. In patients unresponsive to initial therapy with β-lactam antibiotic, additional treatment with fluoroquinolone, aminoglycosides, or vancomycin (in case of resistant gram-positive bacteria like MRSA) may be considered [3]. In case of ineffective additional therapy, the possibility of infections by resistant bacteria or fungi must be taken into consideration and treated accordingly [3, 10].

In Bangladesh, still there is lack of a national level guideline for management of chemotherapy-induced FN in patients with hematological malignancy. Considering this limitation, our study suggests that the recommendations of using cefepime, meropenem, and piperacillin/tazobactam as the empirical treatment of chemotherapy-induced FN by the clinical practice guideline of the Infectious Diseases Society of America (IDSA) [3] can be implemented on patients of Bangladesh.

The major strength of this study was consideration of cefepime, meropenem, and piperacillin/tazobactam as alternative therapy, while most of the prior studies have compared only two of these three alternatives. However, the study has several limitations. First, the primary endpoint of this study was evaluated based on the response including modification of the initial therapy. Secondly, only a single set of blood cultures were collected; thus, there was a possibility of a lower rate of pathogen detection and a higher rate of false positives. Moreover, this one was a single-center study where the antimicrobial

susceptibility pattern might influence the efficacy of the study drugs which might limit the generalizability of the findings.

Conclusion

Our study suggests that cefepime, meropenem, and piperacillin/tazobactam are equally effective as initial treatment for chemotherapy-induced febrile neutropenia in patients with hematological malignancy irrespective of underlying disease, cause of infection, and baseline neutrophil count. This will act as baseline evidence to establish guideline at national level for management of FN. Further multicenter randomized control trials including large sample size are suggested to validate the findings.

Acknowledgements
The authors would like to express their sincere gratitude to the Pi Research Consultancy Center, Dhaka, Bangladesh (www.pircc.og), for their help in data analysis and manuscript revision and editing.

Authors' contributions
Conceptualization: AK, MNK, and MJH. Formal analysis: TT, MJH, MMI, and ARB. Investigation: MNI, ARB, MW, NC, MMA, and MMI. Methodology: MNK, AK, ARB, NC, MNI, TT, and MMI. Resources: MMA, MMI, ARB, NC, MNI, and MW. Supervision: MJH, AK, MNK, and NC. Writing — original draft: TT, AK, MNI, MW, and MMA. Writing — review and editing: MJH, TT, MNK, MW, and MMA. The authors read and approved the final manuscript.

Funding
The authors have no support or funding to report.

Availability of data and materials
Patient-level data will be available on request from the corresponding author.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Dhaka Medical College (memo no. ERC-DMC/ECC/2019/364, Date 11.12.2019), Dhaka. Informed signed consent was obtained from all eligible participants who agreed to participate. The authors declare that the procedures followed the regulations established by the Helsinki Declaration of the World Medical Association.

Consent for publication
All participants gave consent for publication.

Competing interests
The authors declare that they have no competing interests.

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Received: 11 June 2022 Accepted: 6 August 2022
Published online: 19 August 2022

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