

Commentary on Cefepime versus Cefoperazone/Sulbactam in Combination with Amikacin as Empirical Antibiotic Therapy in Febrile Neutropenia

Introduction

Febrile neutropenia (FN) remains an oncologic emergency since the advent of chemotherapy. Its significance was recognized in 1970s which led to empirical antibiotic use and resulted in major reduction of mortality from 50% to 26% due to neutropenic fever and sepsis.^[1] Since then, several international guidelines have defined use of first line and subsequent lines of antibiotics in settings of high risk FN.^[2-5] For choice of first-line empirical antibiotic therapy (EAT), there is not one standard across all guidelines or institutes, many options exist directed by randomized controlled trails (RCTs) in different settings and guided by local antibiotic sensitivity data. We conducted a RCT comparing cefepime monotherapy versus cefoperazone/sulbactam with amikacin as EAT in FN at our center representative of a low resource setting with high prevalence of antibiotic resistance.^[6] Its been almost 2 years since the publication of results in May 2018, and we hereby review further developments in the same area and the current relevance of our study results.

Study Background and Context

The study was conducted from January 2015 to December 2016 at a Regional Cancer Centre in Southern India. Our previous practice was to use ceftazidime plus amikacin as initial EAT for FN. However, high incidence of resistance (80%) to ceftazidime in our audit of blood culture data, prompted us to switch over to cefoperazone/sulbactam, which had an overall lower resistance of around 40% (though limited published data were available on its use in FN setting). Aminoglycosides also had lower incidence of resistance (around 40%) but drug-induced nephrotoxicity is the major concern. Cefepime (one of the recommended first-line antibiotics in guidelines) had not been used in our center and sensitivity pattern was not available from older studies. We assumed that as cefepime had never been used in our setting, it would generally have a low resistance pattern and would provide the advantage of monotherapy.

Study Methodology and Results in Brief

Episodes of high risk FN (except for patients undergoing induction therapy for acute myeloid leukemia [AML] or undergoing hematopoietic stem cell transplant) were randomized into one of the study arms; patients in Group A (experimental arm) received cefepime (2 g every 8 h for adults and 50 mg/kg every 8 h for children) and in Group B (standard arm) received cefoperazone/sulbactam (2 g every 8 h for adults

and 50 mg/kg every 8 h for children) plus amikacin 15 mg/kg once daily. Clinical course of the FN episode was followed for response to treatment or occurrence of complications and treatment modifications. A total of 336 high-risk FN episodes in 175 patients were randomized equally into two arms (168 in each); and overall positive responses were similar in both the arms (53% in each group), although low as compared to other studies (60%–90%).^[7,8] We had a relatively high incidence of microbiologically documented infection (MDI) at 34%, compared to 10%–30% in other studies^[9,10] and a significantly high incidence of MDR GNB (multidrug-resistant Gram-negative bacillus) at 51% of total MDI. In patients with negative responses, 88% FN episodes were successfully salvaged with subsequent second- and third-line antibiotics and antifungals. Mortality in the entire cohort was 7.5% mostly infection related, a quarter of these deaths were due to progressive or refractory primary disease.

Current Status in 2020 (of First-Line Empirical Antibiotic in Febrile Neutropenia)

Several international guidelines that are periodically updated exists to guide the risk stratification and management of patients with FN in different settings.^[2-5] Last updated Infectious Disease Society of America^[2,5] and European Conference on Infections in Leukemia (ECIL)^[3] guidelines recommend monotherapy with cefepime, ceftazidime, carbapenem, piperacillin/tazobactam, or, cefoperazone/sulbactam as first-line EAT in high risk FN patients. Several hundreds of randomized controlled trials (RCTs), retrospective, and prospective studies have been conducted comparing one antibiotic with the other as monotherapy or in combination, in high risk and low risk FN, in adult and pediatric patients with FN, and in settings of hematological and solid malignancies. In general, all are comparable and a center can choose their first line based on their local antibiogram and experience.

Tables 1 and 2 summarize some recent select RCTs comparing cefepime with other first line antibiotics and cefoperazone/sulbactam with other beta lactams or carbapenems, respectively. However, so far, ours has been the only study comparing these two antibiotics with each other. Majority of the studies conclude equal efficacy for the antibiotics compared. A recently published meta-analysis by Lan *et al.* in 2020, on efficacy and safety of cefoperazone-sulbactam in empiric therapy

Table 1: Summary of randomized controlled trials comparing cefepime with other antibiotics in empirical therapy of febrile neutropenia, published between 2015 and March 2020

Study, published year	Study design and site/setting	Study population	n (episodes)	Cefepime±combination	Comparator	Conclusion/remarks
Aamir <i>et al.</i> ^[11] 2015	Prospective, RCT; single centre, Northern India	Pediatric ≤18 years	40; 20 in each group	CEF 50 mg/kg/dose every 8h	PIPC/TAZ 100 mg/kg/dose every 8 h	Equally efficacious, RR 80% versus 75% Mortality 10% versus 20%
Nakane <i>et al.</i> ^[12] 2015	Open label, RCT; multi-centre, Japan	≥16 years, hematological or solid cancers	428, randomized into 4 arms	CEF (2 g, every 12h)	CZOP (2g, q12h), IPM/CS (1g, q12 h), MEPM (1g, q12 h)	Equally efficacious, RR - 66% versus 60-72% In subgroup with ANC ≤100 × 10 ⁶ /L for >7 days, there was significantly better efficacy in the carbapenem arm compared to 4 th generation beta-lactams (52% vs. 27% at days 3-5, P=0.006, and 76% vs. 48% at day 7, P=0.002)
Sano <i>et al.</i> ^[13] 2015	Prospective, RCT; single centre, Japan	Pediatric, hematological or solid cancers	213, randomized into 2 groups	CEF (100 mg/kg/day in four portions, 1-h drip intravenous infusion (maximum 4 g/day)	PIPC/TAZ (337.5 mg/kg/day in three portions, 1-h drip intravenous infusion (maximum 13.5 g/day)	Similar efficacy, RR - 59% versus 62% No difference in mortality
Fujita <i>et al.</i> ^[14] 2016	Randomized Phase II study, multi-centre, Japan	Adults, with lung cancer	45, randomized into 2 groups (21 and 24)	CEF (2 g, every 12 h)	MEPM (1 g, q8 h)	Similar efficacy and safety, RR - 94% versus 85%
Wrenn <i>et al.</i> ^[15] 2017	Prospective, randomized, pilot study, single centre, USA	>18 years, hematological malignancy or transplant	63, randomized into 2 groups (33 and 30)	CEF 2 g IV q8h, over 30 min (SI)	CEF 2 g IV q8 h, over 3h (EI)	Similar efficacy; clinical success rate - 88% versus 77%
Ponraj <i>et al.</i> ^[6] 2018	Prospective, open label RCT; single centre, Southern India	Both adults and pediatric, hematological (except AML induction) or solid tumors	336, randomized into 2 groups (168 each)	CEF (2 g q8 h for adults and 50 mg/kg q8 h for children)	CFP/SUL (2 g q8 h for adults and 50 mg/kg q8 h for children) plus Amikacin 15 mg/kg once daily	Similar efficacy, RR - 53% in both arms Mortality - 8% versus 7%

CEF – Cefepime; CFP/SUL – Cefoperazone-sulbactam; CZOP – Cefozopran; IPM/CS – Imipenem-cilastatin; MEPM – Meropenem; PIPC/TAZ – Piperacillin-tazobactam; RR – Response rate; RCT – Randomized controlled trials; SI – Standard infusion; EI – Extended infusion; AML – Acute myeloid leukemia

for FN, comprising of 10 RCTS including ours and one retrospective cohort study concluded that treatment success rate, risk of all-cause mortality, and common adverse events of cefoperazone-sulbactam are comparable to those of comparator drugs.^[20] Another meta-analysis by Andreatos *et al.* in 2017, with 32 trials reporting on 5724 patients, evaluating dose-dependent efficacy of cefepime in the empiric treatment of FN, however, demonstrated increased mortality with cefepime compared

to carbapenems, reduced efficacy in clinically documented infections and higher rates of toxicity-related treatment discontinuation.^[21] Authors concluded that although their findings required confirmation by future trials, the meta-analysis suggests that outcomes can be optimized by adjusting cefepime dosing recommendations and treatment indications, rather than discontinuing the use of this important antibiotic. In a meta-analysis by Kim *et al.* in 2010, evaluating a possible signal of increased mortality

Table 2: Summary of randomized controlled trials comparing cefoperazone/sulbactam with other antibiotics in empirical therapy of febrile neutropenia, published between 2010 and March 2020

Study, published year	Study design and site/setting	Study population	n (episodes)	CFP/SUL based regimen	Comparator	Conclusion/remarks
Demir <i>et al.</i> ^[16] 2011	Prospective, open label RCT; single centre, Turkey	≥16 years, lymphoma or solid cancers	208, randomized into 2 arms (108 each)	CFP/SUL (180 mg/kg/day, q8h)	Carbapenem group (IPM, 60 mg/kg/day, q8 h, max 4 g; MEPM 60 mg/kg/day, q8h).	Similar efficacy, RR - 79% versus 81%
Karaman <i>et al.</i> ^[17] 2011	Prospective, open label RCT; single centre, Turkey	1-18 years, acute leukemia, lymphoma, or solid tumors	102, randomized into 2 arms (50 and 52)	CFP/SUL 100 mg/kg/day, q8 h	PIPC/TAZ 360 mg/kg/day q8h	Equally safe and effective, RR - 56% versus 62%
Demirkaya <i>et al.</i> ^[18] 2013	Prospective, open label RCT; single centre, Turkey	0-18 years, lymphoma or solid cancers	116, randomized into 2 arms (57 and 59)	CFP/SUL 100 mg/kg/day, q8 h plus amikacin 15 mg/kg/day q8 h	PIPC/TAZ 360 mg/kg/day q6 h plus amikacin 15 mg/kg/day q8h	Equally safe and effective, RR - 52.6% versus 47.5%
Karaman <i>et al.</i> ^[7] 2013	Retrospective cohort study; single centre, Turkey	Adult, low risk FN	172, two arms (59 and 113)	CFP/SUL 2 g q8 h	PIPC/TAZ (4.5 g q6 h)	No difference in efficacy, RR- 64.5% versus 73.5%
Aynioglu <i>et al.</i> ^[19] 2016	Randomized study; single centre, Turkey	Adult, hematological malignancies	200, randomized into 2 arms (82 and 118)	CFP/SUL 2 g q8 h	PIPC/TAZ (4.5 g q6 h)	Equally effective and safe, RR- 61% versus 49%
Ponraj <i>et al.</i> ^[6] 2018	Prospective, open label RCT; single centre, Southern India	Both adults and pediatric, hematological (except AML induction) or solid tumors	336, randomized into 2 groups (168 each)	CFP/SUL (2 g q8 h for adults and 50 mg/kg q8 h for children) plus Amikacin 15 mg/kg once daily	CEF (2 g q8 h for adults and 50 mg/kg q8 h for children)	Similar efficacy, RR - 53% in both arms Mortality - 8% versus 7%

CEF – Cefepime; CFP/SUL – Cefoperazone-sulbactam; IPM – Imipenem; MEPM – Meropenem; PIPC/TAZ – Piperacillin-tazobactam; RR– Response rate; AML – Acute myeloid leukemia; RCT – Randomized controlled trials

associated with cefepime use, authors concluded that in both trial-level and patient-level meta-analyses they did not identify a statistically significant increase in mortality among cefepime treated patients compared with those treated with other antibacterials.^[22]

Our current practice is to use cefepime as first-line EAT in both adults and pediatric high risk FN requiring intravenous therapy with an average positive response of 60%–65%. We recommend that institutes follow their local antibiotic sensitivity pattern in choosing their first-line therapy and cefepime is a valid option that can provide benefit of monotherapy.

Status of Early Discontinuation of Empirical Antibiotics in Fever of Unknown Origin (FUO)

The traditional approach since advent of EAT for FN had been to continue antibiotics till resolution of fever and till recovery of counts. However, recent reports especially in pediatric FN found that discontinuation of antibiotics before marrow recovery did not increase fatality due to bacterial infections.^[23,24] ECIL recommends that in select

patients with FUO who have been hemodynamically stable since presentation and have been afebrile for ≥48 h, EAT can be discontinued within 72 h irrespective of neutrophil recovery, however, these patients should be kept under close observation.^[3] Evidence for this discontinuation approach comes from limited studies, recent ones are summarized in Table 3.

In an open-label, randomized, controlled phase 4-trial on optimization of EAT in patients with hematological malignancies including transplant recipients with FN without etiological diagnosis, it was found safe to discontinue antibiotics after 72 h of apyrexia and clinical recovery irrespective of neutrophil count, without increasing the frequency of recurrent fever (recurrence rate 14%), secondary infections, or mortality.^[26] In the prospective observational ANTIBIOSTOP study (2018), feasibility and safety of short-term antibiotic treatment in patients exhibiting FUO irrespective of their neutrophil count was evaluated and found to be safe with a response rate of 57%–59% in the two groups studied.^[27] In a meta-analysis by Stern *et al.*, on early discontinuation

Table 3: Summary of studies evaluating early discontinuation of empirical antibiotic therapy in febrile neutropenia of unknown origin, published between 2015 and March 2020

Study, published year	Study design and site	Study population	n	Criteria for discontinuation/early withdrawal of EAT	Results	Conclusion/remarks
Santolaya <i>et al.</i> ^[25] 2017	Prospective randomized study, multi-centre, Chile	Pediatric ≤18 years, transplant recipients excluded	176, randomized to continue antibiotic (n=92) Or, to withdraw (n=84)	Positive for a respiratory virus, negative for a bacterial Pathogen and with a favourable evolution after 48 h of antimicrobial therapy	Similar frequency of uneventful resolution (89/92 (97%) and 80/84 (95%), respectively, not significant; OR 1.48; 95% CI 0.32–6.83, P=0.61),	Reduction of antimicrobials in children with FN and respiratory viral infections, based on clinical and microbiological/molecular diagnostic criteria, should favour the adoption of evidence based management strategies in this population
Aguilar-Guisado <i>et al.</i> ^[26] 2017	Open-label, randomised, controlled phase 4 clinical trial, multi-centre, Spain	Adults with haematological malignancies or transplantation recipients, with high-risk FN without aetiological diagnosis	157 episodes, randomly assigned to experimental group (early discontinuation, n=78) and control group (n=79)	After 72 h or more of apyrexia plus clinical recovery	Mean number of EAT-free days was significantly higher in the experimental group than in the control group (16.1 [SD 6.3] vs. 13.6 [7.2], P=0.0026) Recurrent fever (14% vs. 18%)	Safe to discontinue EAT after 72 h of apyrexia and clinical recovery irrespective of neutrophil count This clinical approach reduces unnecessary exposure to antimicrobials
Le Clech <i>et al.</i> ^[7] 2018	Prospective observational study, single centre, France	>18 years, presence of a malignant haematological disease	In the first phase of the study, EAT in FUO patients was stopped after 48 h of apyrexia, in accordance with ECIL (n=45). In the second phase of the study, antibiotics were stopped no later than day 5 for all FUO patients, regardless of body temperature or leukocyte count (n=37).		26 (57.3%) and 22 (59.5%) FUO episodes did not relapse during hospital-stay (P=1), and 9 (20%) and 5 (13.5%) presented another FUO, respectively.	Early discontinuation of empirical antibiotics in FUO is safe for afebrile neutropenic patients

EAT – Empirical antibiotic therapy; FN – Febrile neutropenia; FUO – Fever of unknown origin; ECIL – European Conference on Infections in Leukemia; SD – Standard deviation

of antibiotics for FN, 8 RCTs comprising a total of 662 distinct FUO episodes in both adults and children were included.^[28] Studies had variable designs and criteria for discontinuation of antibiotics. No significant difference was seen between the short-antibiotic therapy arm and the long-antibiotic therapy arm for all-cause mortality, clinical failure rates, and other secondary outcomes. However, the author's concluded that the existing evidence have low certainty to make strong recommendation on the safety of antibiotic discontinuation before neutropenia resolution and well-designed, adequately powered RCTs are required to address this issue in the era of rising antibiotic resistance.

In our study, discontinuation of antibiotics was successful in 60% FUO episodes, and we continue to practice this approach in select cases of FUO to minimize antibiotic use and its associated collateral damage of augmenting antibiotic resistance.

Challenges: Then and Now

One of the most important challenges at our center and in other resource limited settings from developing countries is the high prevalence of multidrug-resistant gram-negative infections both in the community and in hospital acquired settings. In our study, MDI was 34% of

total episodes of FN, with a significantly high incidence of MDR GNB at 51% of total MDI. Our latest antibiogram in 2019 shows that various Gram-negative bacilli have 43%–85% sensitivity to cefoperazone-sulbactam, 45% to 95% sensitivity to amikacin, 40%–80% to cefepime, and 30%–76% for piperacillin-tazobactam. Resistance to carbapenems was seen in 5%–15% of *Pseudomonas* and *Burkholderia* species, while resistance rate was up to 55% for *Klebsiella*, *Acinetobacter*, and *Escherichia coli*. As there is growing resistance worldwide, newer antimicrobial agents especially against MDR GNB are very limited and pipeline of drug development is also very slow and parched, rational use of available antibiotics becomes essential for short-term patient-related outcomes and for long-term outcomes of containment of resistance.

Sending blood cultures and timely initiation of EAT at the onset of fever is essential for optimal outcome, however, full and consistent compliance to FN protocol is variable in different settings. Delayed presentation to health-care facility after onset of fever which can lead to a complicated clinical course is an added challenge in resource limited settings.

Most of the guidelines define use of empirical first line antibiotic and outline pathways for antibiotic modification at 48–72 h depending on the microbiological results and clinical course of patients. They also describe indications for the use of antifungals and antivirals. Nevertheless, the management of complicated FN beyond empirical treatment requires more of clinical experience and expertise and intensive supportive care.

Another challenge faced mostly in resource limited settings is implementation of infection control practices for both health-care workers (HCW), patients and their care-givers because of lack of alertness and incentive among HCW and poor personal hygiene, lack of resources and awareness among patients and care-givers belonging to low socioeconomic background. Regular and systematic educational sessions for all cadres of HCW as well as for patients and care-givers and methods for the assessment of compliance are imperative to improve infection control.

Way Forward

The management of FN is a collective effort, requires collaboration with Departments of Microbiology, Pharmacology, Hospital Infection Control Committee, besides the treating clinical departments of Medical Oncology, Medicine, and Pediatrics. It needs continuous monitoring of infection control practices, institute's antibiotic sensitivity patterns over time, regular audits of clinical outcomes and revision of antibiotic policies if needed, and a robust antibiotic stewardship program. Finally, institutional policies for using appropriate antibiotics has to be tailored to (i) local sensitivity data, (ii) patient's risk factor for resistant infection, and (iii) patient's risk factors for a complicated clinical course.^[3] Early

discontinuation of EAT is a promising approach in select cases of FUO.

FN is generally stratified as low or high risk in majority of guidelines and the standard approach in stable presentation is escalation. However, the subset of patients with prolonged and profound neutropenia as in AML induction and during salvage induction for relapsed leukemia should be considered as very high risk and may benefit from a de-escalation approach, though this indication and approach is not very clearly and separately defined in the literature. Furthermore, as stated in the ECIL guidelines, escalation and de-escalation approach with relevant indications can be a more appropriate method in the setting of high prevalence of MDR GNB.^[3] This will help in reducing high infection related mortality by avoiding initial inadequate EAT and by timely initiation of appropriate antibiotic covering resistant pathogen. However, physicians frequently hesitate to de-escalate appropriately and change a regimen that has already achieved clinical improvement; this has to be overcome by a good stewardship program. Novel biomarkers for early identification of resistant pathogens like rapid molecular diagnostic tests for sepsis using nucleic acid amplification techniques or host targeted technologies may guide the way forward.^[29,30]

At our center, we have initiated a study evaluating role of sepsis bundle (with tailored antibiotic de-escalation approach based on clinical biomarkers) at the onset of very high risk FN during AML and relapsed leukemia induction. The application of sepsis bundle in FN has not been studied prospectively so far and we expect our results to be available by mid of 2021.

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Conflicts of interest

There are no conflicts of interest.

**Smita Kayal¹, Ponraj Madasamy¹,
Jogamaya Pattnaik²**

¹Department of Medical Oncology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, ²Department of Medical Oncology, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India

Address for correspondence: Dr. Smita Kayal, Department of Medical Oncology, Jawaharlal Institute of Postgraduate Medical Education and Research, Dhanvantari Nagar, Puducherry - 605 006, India. E-mail: kayalsmita@gmail.com

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