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Comparison of Efficacy of Piperacillin/Tazobactam Vs Cefoperazone/Sulbactam as Empirical Therapy in Patients with Febrile Neutropenia.

V. R. Mujeeb[1], Prashant Jambunathan[2], Arun Tyagi[3]

[1]Senior Advisor (Medicine & Gastroenterology), Command Hospital (Southern Command), Wanorie, Pune- 411040.
[2]Resident Medicine, Command Hospital (Southern Command), Wanorie, Pune- 411040.
[3]Professor & HOD, Department Of Medicine, DVVPF'S Medical College, Vilad Ghat, Ahmednagar, Maharashtra, Pin-414111.

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ABSTRACT

Background: Febrile neutropenia is known to carry a mortality of 15%. Early empirical antibiotics are pivotal to the management. We compared the efficacy of Piperacillin/Tazobactam (PT group) and Cefoperazone/Sulbactam (CS group) for early empirical therapy in these patients over a 16-month period. **Methods:** We studied a total of 133 patients with febrile neutropenia over a 16-month period. These patients were assigned to either the PT group (n-67) or the CS group(n-66) and administered standard doses of these drugs (i.e. 4.5 gm, three times a day of PT and 2 gm twice a day of CS). The two groups were analyzed for various outcomes such as duration of neutropenia, duration of fever and mortality at 30 days. **Results:** The average number of patients with fever duration of more than 7 days in the PT group (n=67) was 18 (26.8 %) and 23 (34.8%) in the CS group (n=66) (p=0.159). 24 patients (35.8%) in the PT group and 21 (31.8%) (p=0.312) patients in CS group required additional agents such as antifungals or glycopeptides. 9 (13.4%) patients in the PT group and 10 (15.15%) (p=0.388) patients in the CS group died during the course of their illness. **Conclusion:** There is no statistical difference between the performance of the combinations of Piperacillin/Tazobactam and Cefoperazone/Sulbactam as empirical therapy in patients with febrile neutropenia. While the choice of antibiotic in these setting must be made with due cognizance to local usage, availability and resistance patterns, both these antibiotics form a solid first line of defense in neutropenia patients with fever.

Keywords: Febrile Neutropenia, Malignancy, Empiric Antibiotic Therapy, Iperacillin/Tazobactam, Efoperazone/Sulbactam.

INTRODUCTION

Infections in the setting of neutropenia is responsible for most of the deaths in cases of acute myeloid leukemia and more than half of the deaths in cases of lymphoma.[1] The signs and symptoms of inflammation and infection may be absent in these patients. Early empiric therapy[2-4] is imperative and may directly affect the clinical outcome during and after the illness. The time duration taken to start the patient on antibiotics has a correlation with the outcome.[5] There are several international guidelines recommending antibiotic strategies[3,6,7] in febrile neutropenia. Risk stratification and an evidence based algorithmic approach has been recommended and widely accepted.[8]

Name & Address of Corresponding Author
Gp Capt (Dr) V.R. Mujeeb,
Senior Advisor (Medicine & Gastroenterology),
Command Hospital (Southern Command),
Wanorie, Pune (Maharashtra)
Pin- 411040.

The choice of initial empirical therapy has remained a subject of much debate. The choice of agents should be made based on epidemiology and resistance patterns of organisms seen in the Indian subcontinent. Patients who have received antibiotics previously have a greater probability of harboring resistant organisms,[9] and therefore, must be initiated on a higher efficacy, wider spectrum antibiotics prima facie. The role of prophylaxis in low risk patients is well established and must consist of Amoxycillin/Clavulanic acid or a fluoroquinolone.[4,10] Finally, the choice of antibiotic must be made with due cognizance to cost effectiveness, since this is a major factor in a resource limited country like ours.

There are generally the three agents that may be chosen for first line empirical therapy in patients with prolonged (or with a likelihood of) febrile neutropenia. These include Ceftazidime, Cefepime or Cefoperazone/Sulbactam (CS), Piperacillin/Tazobactam (PT) and Imipenem/Cilastin (or meropenem).[1,11,12] Of these, the first two have been extensively used as initial therapy and multiple studies have compared them, both head to head and

in combination with an aminoglycoside[13,14] (Amikacin, being the most commonly used). Given the wide disparity between the cost of these antibiotics in our country with costs for PT and CS ranging from 900 INR and 350 INR respectively, coupled with different microbial epidemiology and resistance patterns, the need to assess the efficacy and outcome with these two drugs, in Indian scenario, is of paramount importance. Combinations with three anti-biotics upfront failed to show any additional benefit.[15]

Sequential addition of antibiotics is not recommended. One possible reason for this caveat was the unpredictable pharmacodynamic and kinetic properties of the two drugs added in tandem, with varying levels of two drugs, which is much more difficult to predict if the two drugs are added together.[16]

Aims and Objectives:

To compare the efficacy of Piperacillin/Tazobactam and Cefoperazone/Sulbactam in patients requiring these medications in the setting of Febrile neutropenia. The objective of the study was to assess the efficacy of these two antibiotics in an Indian setting, where the endemic microbiome, resistance patterns and cost, all play important roles in the outcome. These two antibiotics have been found to be equally efficacious in at least two head to head to comparison trials in the past two years.

MATERIALS AND METHODS

The study design is summarized in Table 1**.** 133 patients were followed over a 16-month period. Their baseline characteristics were comparable at baseline as shown in Table 2. They were randomly assigned to either the PT group or the CS group after adequate baseline comparability was ensured. They were administered these drugs in standard doses (4.5 gm three times a day for PT and 2 gm twice a day for CS) and closely monitored in an intensive care setting. The investigators and clinicians were allowed addition of a second agent, as dictated by the clinical scenario. The minimum duration after which the second agent (Vancomycin or a newer triazole in most cases) could be added, was 04 days. This duration is in concordance with existing guidelines and also allowed sufficient time for culture reports to become available. These reports directed therapy in all cases, making this an intention to treat analysis

Inclusion Criteria:

All adult patients who were diagnosed with febrile neutropenia, as per the standard definition discussed above were enrolled for the study. The patients baseline characteristics were comparable at baseline as shown in Table 2. The study participants were mostly receiving chemotherapy for Acute Leukemia or for Non-Hodgkin's Lymphoma.

Exclusion Criteria:

Patients who had received antibiotics in the previous 90 days were excluded from the study. This was because such patients were more likely to harbor resistant pathogens (or nosocomial pathogens).

Patients with renal impairment, overt sepsis or respiratory distress syndrome at presentation or significant co-morbidities such as cardiovascular disease (EF < 30 %) were excluded from the study as presence of these factors was thought to confound the analysis and ultimately, the outcome. These patients were, however, treated as per existing guidelines.

Patients with co-existing viral infections (HIV, HCV, HBV) on medication, were excluded from the study since these agents are likely to have significant drug interactions and effect the levels and availability of first line empiric therapy outlined herein.

Patients on high dose corticosteroids, Fludarabine therapy, Interleukin 2 (this subgroup benefitted from prophylactic Oxacillin for central venous line related infections as per a recent study) and monoclonal antibodies (Alemtuzumab for refractory CLL, Daclizumab for steroid refractory GVHD and Bevacizumab for colorectal carcinoma) were also excluded from the study since these subset of patients were likely to be on prophylaxis with antivirals and antifungals which could have significant interactions with the drugs in our original research question. Furthermore, these prophylactic measures also have direct impact of the clinical outcome, the confounding nature of which could not be adjusted statistically.

Statistical Analysis:

The Chi square test for association of attributes was used to delineate the differences between the two groups. As already mentioned, the baseline characteristics of the two groups was found comparable based on the aforementioned statistical tool.

RESULTS

The results of the study are tabulated in Table 3**.** Our study found no statistical difference between duration of neutropenia (mean 7.21, p=0.125) and outcomes (p=0.746) between the two groups. There was however, a significantly lower duration of fever in the PT group, when compared to the CS group. The duration of fever is influenced by several non-infective causes as discussed later. Since there is no significant difference between the outcomes and duration of neutropenia, the authors feel that these groups were equally efficacious. In the Indian context, this means that these drugs may be used interchangeably based on availability and cost-effectiveness.

Table 1: Study design

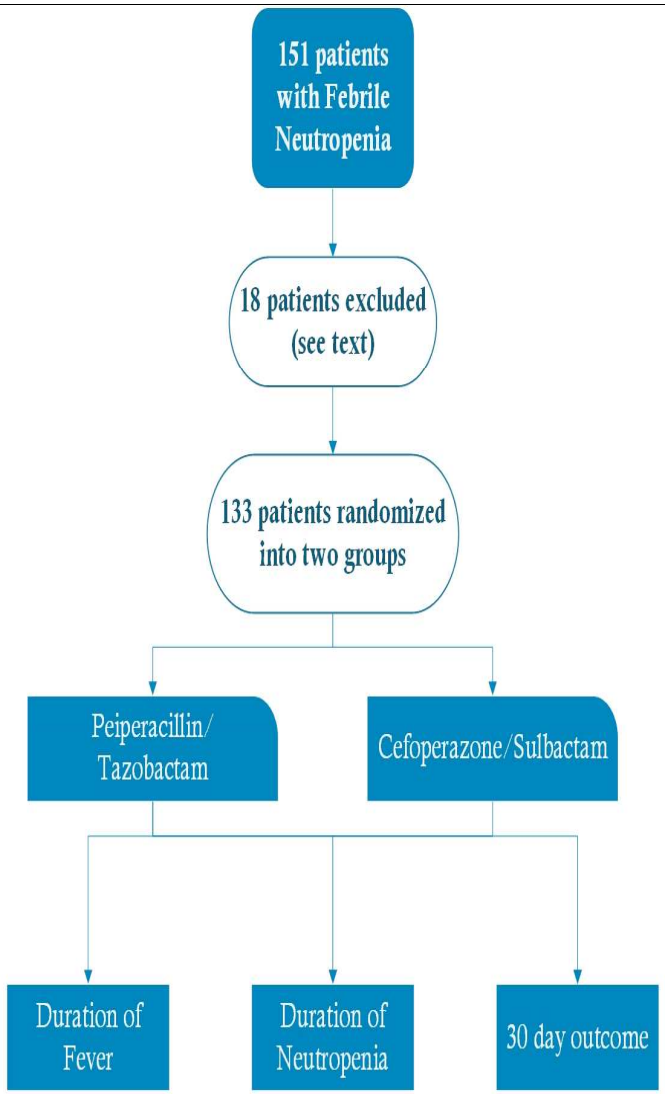

Table 2: Baseline Characteristics of patients in the two groups.

Association between	Chi Square	P value	Significance	Conclusion
Age & Groups	3.70	0.5933	No	The distribution of Age is same across both the groups.
Sex & Groups	0.07	0.7872	No	The distribution of Sex is same across both the groups.
Diagnosis & Groups	0.73	0.6927	No	The distribution of Diagnosis is same across both the groups.
Remission & Groups	0.51	0.4759	No	The distribution of Remission is same across both the groups.
Co-morbidity & Groups	2.51	0.4731	No	The distribution of Co-morbidity is same across both the groups.
Absolute Neutrophil count & Groups	6.05	0.1091	No	The distribution of Absolute Neutrophil count is same across both the groups.

DISCUSSION

Numerous studies have compared variety of antibiotics in the empiric therapy in febrile neutropenia.[11,13,14,17,18] The Infectious Diseases Society of America, The National Comprehensive Cancer Network and ESMO have all published guidelines for management of fever in neutropenic patients. These have formed the validated basis of treatment of febrile neutropenia for decades. The initial empiric options and their modifications based on these recommendations. One major local modification that has crept into clinical practice is routine addition of Amikacin. However, routine addition of an aminoglycoside was associated with increased toxicity and was considered necessary only if the patients developed hypotension or there was evidence of prevalence of resistance in the

community.[9] Therefore, we began therapy in our patients with medications in accordance to the best available evidence. Many of our patients required modification after initial empirical therapy. These included glycopeptides (Vancomycin, for clinically apparent catheter infection, blood culture positivity, known colonizers of MRSA and hypotension with an unidentified pathogen), antifungals (Voriconazole (DeVita V, 2015 #1661), if invasive aspergillosis was either clinically suspected or objectively proven), antivirals (Acyclovir for oropharyngeal HSV, Foscarnet if Acyclovir resistance was suspected, Ganciclovir for CMV and Cidofovir if the patient was intolerant to Ganciclovir). Furthermore, the initial regimen was also modified when there were signs of breakthrough sepsis. For emphasis, the authors of this article would like to re-iterate that all patients in both groups were treated as per existing standard guidelines, and this study was only meant to delineate the differences between early empiric therapy, which is often made in routine clinical practice, in the absence of culture reports or other objective evidence. We compared our study with another,[19] which was similar insofar that it compared PT and CS, head to head, in a similar setting. However, there exist some key differences. These include a lower threshold in our study (and in the overall treatment protocol) to start antifungals and antivirals. This aggressive approach, the authors of this study feel, is justified in the Indian scenario, where endemicity for such pathogens is different. The financial strain on the average Indian haemato-oncology patient is severe and creation of a negative pressure day care center with mobile air asepticizer is a tall order and this is just the tip of the barrier nursing iceberg. Therefore, the outcomes are expected to be (at least marginally, if not statistically) different.

Table 3: Results of the study.

Association	Chi square	P value	Significance	Conclusion
Duration of neutropenia (days) & Groups	7.21	0.1250	No	The distribution of Duration of neutropenia (days) is same across both the groups.
Duration of fever (days) & Groups	13.78	0.0010	Yes	The distribution of Duration of fever (days) is different across both the groups. The duration of fever in Piperacillin/Tazobactam group is significantly lower than that in Cefoperazone/Sulbactam group.
Modification & Groups	0.00	0.9546	No	The distribution of Modification is same across both the groups.
Results & Groups	0.10	0.7486	No	The distribution of Modification is same across both the groups.

Limitations:

We realize that the duration of fever in these patients may have other (in addition to infectious causes, which are found in slightly more than half of these cases) contributing factors such as engraftment syndromes, drug fever and deep venous thrombosis.1,9 This important confounder may be responsible for the significant difference between the two groups. While every attempt was made to exclude these factors (a color Doppler flow imaging test was done in patients in whom the clinical suspicion arose) these could not be ruled out in all patients. The outcome in these patients is multifactorial and may include occult infections (whose clinical presentation is often enigmatic and their diagnosis, problematic), previously undiagnosed co-morbidities and idiosyncratic reactions to medications used.

CONCLUSION

The duration of fever was significantly lower in the Piperacillin/Tazobactam group. However, the authors find this to be insufficient stand-alone evidence to recommend it over and above CS group. There was no significant difference in all cause 30-day mortality or duration of neutropenia between PT and CS groups.

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