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Piperacillin/tazobactam vs. cefoperazone/sulbactam in adult low-risk febrile neutropenia cases

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SUMMARY

Aim: The aim of this study was to compare the efficacy of piperacillin/tazobactam (P/T) and cefoperazone/sulbactam (C/S) in the empirical treatment of adult neutropenic fever. **Methods:** Data and outcomes of low-risk adult cases with neutropenic fever and treated with P/T (4.5 g q6h) or C/S (2 g q8h) between 2005 and 2011 June were extracted from our database. Risk evaluation was made according to criteria of Multinational Association for Supportive Care in Cancer (MASCC) and a score of ≥ 21 was considered as low risk. Data were collected prospectively by daily visits and evaluated retrospectively. Primary outcome was – fever defervescence at 72 h in combination with success without modification (referring to episodes where the patient recovered from fever with disappearance of signs of infection without modification to initial empirical treatment). All-cause mortality referred to death resulting from a documented or presumed infection or unidentified reason during the treatment and 30-day follow-up period. **Results:** A total of 172 patients (113 cases P/T and 59 cases C/S) fulfilled the study inclusion criteria. Persistent response in P/T arm was 73.5%, whereas it was 64.5% in C/S arm ($p > 0.05$). Rates of any modification were also similar in both treatment arms. All-cause mortality during the treatment and 30-day follow-up period was not significantly different (P/T: 4/113 vs. C/S: 2/59, $p > 0.05$). There was no severe adverse effect requiring antibiotic cessation in both cohorts. **Conclusion:** In conclusion, our data suggest that C/S may be a safe alternative to P/T in the empirical treatment of adult low-risk febrile neutropenia cases.

What's known
Although recommended in some guidelines including those of Turkey, to our knowledge, there was no study evaluating efficacy of C/S in low-risk febrile neutropenia and comparing it with P/T in the same patient population.

What's new
These data suggest that there is no significant difference between the efficacy of C/S and P/T in the empirical treatment of adult low-risk febrile neutropenia cases.

Introduction

As bone marrow-oriented antineoplastic treatment modalities increase in the daily medical practice, neutropenic fever is encountered more commonly. Empirical antipseudomonal spectrum including antibiotherapy of febrile neutropenia has been considered obligatory for the last 50 years. At the beginning, carbenicillin–gentamicin combination, afterwards cephalothin, methicillin and gentamicin, thereafter third-generation cephalosporin and aminoglycoside combinations were the mainstays of the empirical antibiotic therapy. Finally, in the last decade, monotherapy with cefepime, carbapenems and beta-lactam/beta-lactamase inhibitors such as piperacillin/tazobactam (P/T) (1–3) or cefoperazone/sulbactam (C/S) (1) has been the main recommendations for the empirical antibiotherapy of neutropenic fever. Published data also suggest that C/S may be an effective option in the empirical therapy of febrile neutropenia (4–8). However, to our knowledge, there is no study comparing P/T and C/S in adult febrile neutropenia, as well as there are no data evaluating efficacy of C/S in low-risk febrile neutropenia. In this study, we compared the efficacy of P/T and C/S in the empirical treatment of adult low-risk neutropenic fever.

Methods

Setting

This retrospective cohort study was performed in a > 2000-bedded tertiary-care educational university hospital with a 31-bedded infectious diseases ward.

Patients

Neutropenic fever was defined as absolute neutrophil count < 500 mm^3 or a count < 1000 mm^3, but expected to fall < 500 mm^3 within 48 h, a single

measurement of temperature > 38.5 °C or 38.0 °C on two or more occasions within 12 h. Risk evaluation was made according to the criteria of Multinational Association for Supportive Care in Cancer (MASCC) and patients with ≥ 21 risk index were considered as low-risk cases (2,9–12).

Data related to patients who received P/T or C/S monotherapy between 2005 and July 2011 were extracted from our database. Patients were followed up prospectively by daily visits. However, data were analysed retrospectively.

Clinical and Laboratory Evaluation

Before the start of antibiotic therapy, a complete medical history and physical examination were performed. Complete blood cell and differential counts, routine biochemistry, at least two sets of blood cultures (from two different peripheral veins and all lumens of central venous catheter) and a chest X-ray were obtained before starting antibiotic treatment. In case of suspected pneumonia or urinary-tract infection, urine and sputum cultures were performed. Cultures of other sites of infection were performed as clinically indicated. Cultures were repeated during therapy, if fever persisted or to isolate the causative pathogen or to document the eradication of the isolated pathogen. In case of persistent fever, chest X-ray and computerised tomography or abdominal ultrasonography were obtained. Patients were monitored daily for clinical signs and symptoms and adverse events during antibiotic therapy. Complete blood cell counts, coagulation and biochemistry parameters, and urine analysis were performed at least once a week (4,12).

Bacteriological isolates were identified by standard techniques and susceptibility tests were determined by disc diffusion method according to the recommendations of the Clinical Laboratory Standards Institute. C/S susceptibility was evaluated according to criteria for cefoperazone (13).

Classification of febrile episodes

Microbiologically documented infection (MDI) was defined as the isolation of microorganisms from any clinical sample including blood, urine, sputum, etc. Clinically documented infection (CDI) was considered, when there was a focus of infection on physical examination, without microbiological documentation. Fever of unknown origin (FUO) was considered when there was no clinical or microbiological evidence of infection in a febrile episode (12).

Treatment failure

Occurrence of one of the following events was considered as treatment failure: mortality caused by any reason, persistence of bacteraemia or documented breakthrough bacteraemia, fever still persisting after 72–96 h prompting modification in the initial therapy.

Antibiotic regimens

Patients who received P/T received the antibiotic as 4.5 g q6h and C/S as 2 g q8h. Each antimicrobial agent was infused intravenously over 30–60 min. Treatment was switched to amoxicillin/clavulanate 1 g q2h + ciprofloxacin 500 mg q12h, peroral in cases with at least 72 h fever defervescence and whose neutrophil counts recovered.

Evaluation of response

Primary outcomes were fever defervescence at 72 h in combination with clinical improvement/success without modification (referring to episodes where the patient recovered from fever with disappearance of signs of infection without all-cause mortality and/or modifications to initial empirical treatment). All-cause mortality referred to death resulting from a documented or presumed infection or a defined or unidentified reason during the treatment and 30-day follow-up period.

Treatment Modification

In case initial empirical therapy did not cover the susceptibility pattern of the MDI, it was modified according to susceptibility testing results. If the patient still had fever beyond the first 72–96 h of empirical therapy, the antibiotic used in the initial empirical regimen was substituted with a broad-spectrum agent including antipseudomonal activity (12). Antifungal therapy (conventional amphotericin-B at a dose of 0.5 mg/kg/day) was started to cases fulfilling possible, probable or definite fungal infection according to European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria (14). Antifungal treatment was also started empirically, if the patient was still febrile on the fourth to sixth day of antibiotic therapy despite treatment modification.

Statistical analysis

Objective of this study was to compare the clinical success rates of the study-drug regimens. All analyses were performed using SPSS version 13.0 (Chicago, IL). The significance of difference between groups was evaluated by χ^2-test and *t*-test as indicated. The significance level was accepted as $p < 0.05$.

Results

Characteristics of the study population

A total of 172 patients (113 cases P/T and 59 cases C/S) whose MASCC risk index was ≥ 21 fulfilled the study inclusion criteria. In case one patient had more than one episode, data of the first episode were considered in the study. Table 1 shows the clinical characteristics of the patients in the two treatment cohorts. Overall, 79.6% of the patients had solid tumours and 17.4% had hematologic malignancies in both groups ($p > 0.05$). Age, gender, the number of patients with chronic renal failure and/or chronic cardiac failure and/or chronic obstructive lung disease or diabetes mellitus or rheumatoid arthritis or severe neutropenia or central venous catheter were similar in both groups (Table 1, $p > 0.05$).

Type of infection and distribution of microorganisms

About 56.9% of the febrile neutropenia episodes were considered as FUO, whereas 19.1% were CDI and 24% were MDI episodes (Table 2). There was no statistically significant difference between the cohorts in terms of infection type ($p > 0.05$). Causative microorganisms were isolated from 42 episodes; 21 from blood, 17 from urine and 4 from sputum. The most common isolates were *Escherichia coli* and *Pseudomonas aeruginosa* (Table 2). There were two methicillin-resistant *Staphylococcus aureus* and three methicillin-resistant *S. epidermidis* in blood cultures. Gram-negative bacteria were isolated from 31 patients, whereas Gram-positive bacteria were isolated from 10 patients (Table 2). One case had probable fungal pneumonia (*Acremonium* spp.)

Clinical response and following antibiotic modification

The clinical outcomes of P/T and C/S cohorts are shown in Table 3. Mean duration of treatment was 8.3 ± 4.0 days in the PT group and 7.9 ± 3.6 days in the C group ($p > 0.05$). When we evaluated the persistent response in the FUO cases as a separate group in both P/T and C/S cohorts, there was also no significant difference (54/66 in P/T group vs. 22/32 in C/S group, $p > 0.05$). Persistent response was similar in the CDI and/or MDI cases, too (31/47 in the P/T group vs. 17/27 cases in the C/S group, $p > 0.05$). Need for change in the antibacterial treatment or glycopeptide or antifungal or antibacterial + glycopeptide modification was similar in both treatment groups (Table 3). All cases but two (one in P/T and one in C/S cohorts), who had resolution of fever at the end of 72-h treatment, had successful

Table 1 General characteristics of the piperacillin/tazobactam and cefoperazone/sulbactam groups

	P/T Total = 113 n (%)	C/S Total = 59 n (%)	p
Male	65 (57.5)	23 (61.7)	> 0.05
Female	48 (42.5)	36 (38.3)	> 0.05
Age	54.1 ± 15.0	50.6 ± 14.8	> 0.05
Underlying disease			
Solid organ tumour	90 (79.6)	47 (78.3)	> 0.05
Multiple myeloma	3	0	
Acute leukaemia	6	2	
Chronic leukaemia	3	0	
Lymphoma	5	7	
Myelodysplastic syndrome	2	2	
Other reasons	4	1	> 0.05
Prophylaxis (Levofloxacin)	46 (40.7)	16 (28.3)	> 0.05
Central catheter	9 (8)	9 (15)	> 0.05
Neutrophils < 100	68 (60.2)	30 (50)	> 0.05
Treatment duration (days)	8.3 ± 4.0	7.9 ± 3.7	> 0.05
Coexisting disease			
None	97	50	> 0.05
Diabetes mellitus	9	2	> 0.05
Rheumatoid arthritis	0	1	> 0.05
Congestive heart failure	0	1	> 0.05
Chronic liver disease	4	3	> 0.05
Chronic obstructive lung disease	2	2	> 0.05
Hypertension	1	0	> 0.05

Table 2 Fever of unknown origin, clinically diagnosed and microbiologically diagnosed infections

Infection type	Piperacillin/tazobactam	Cefoperazone/sulbactam	Total
Fever of unknown origin	66	32	98
Clinically diagnosed pneumonia	17	11	28
Clinically diagnosed soft tissue infection	5	0	5
Bacteremia			
Escherichia coli	4	2	6
Staphylococcus epidermidis	2	2	4
Pseudomonas aeruginosa	4	0	4
Staphylococcus aureus	1	2	3
Enterococcus faecium	1	0	1
Acinetobacter baumannii	0	1	1
Klebsiella pneumoniae	1	0	1
Aeromonas spp.	1	0	1
Total	14	7	21
Microbiologically confirmed pneumonia			
A. baumannii	1	0	1
MSSA	0	1	1
Haemophilus influenzae	0	1	1
Acremonium spp.	0	1	1
Total	1	3	4
Microbiologically confirmed urinary-tract infection			
E. coli	9	5	14
K. pneumoniae	0	1	1
P. aeruginosa	0	1	1
S. agalactiae	1	0	1
Total	10	7	17
Overall	113	59	172

outcome without any modification and had 30-day posttreatment survival. Of seven antifungal modifications, four were empirical, whereas one was probable *Aspergillus* sinusitis, one probable *Aspergillus* pneumonia and one possible *Acremonium* spp. pneumonia (14).

Mortality

All-cause mortality during the treatment and 30-day follow-up period was not different between P/T and C/S cohorts (4/113 vs. 2/59, $p > 0.05$). Two cases died as a result of septic shock (one with no aetiology, the other with a pansensitive *E. coli* in the urinary culture) and three died as a result of pneumonia and respiratory failure (one *Acinetobacter baumannii* in bronchoalveolar lavage and other MRSA in blood culture and one *E. coli* sensitive to third-generation cephalosporins in blood culture and the last case died as a result of vena cava superior syndrome). The mean age of the patients who died within the first month of therapy was 68.3 ± 10.3, whereas it was 52.3 ± 14.8 ($p = 0.01$) in the survivors. Mortality rate did not change significantly between male and female patients, cases with severe neutropenia and others and in cases receiving levofloxacin prophylaxis and others.

Adverse effects

There was no severe adverse effect requiring antibiotic cessation in both arms in both cohorts.

Discussion

Comparison of these two low-risk febrile neutropenia cohorts suggests that both C/S and P/T are similarly effective monotherapy options.

The main antibiotic recommendation in low-risk febrile neutropenia is amoxicillin/clavulanate and ciprofloxacin combination; however, intravenous antibiotics may be used as alternative monotherapy options. Although initial oral antibiotherapy could be an option in these cases, socioeconomical, educational status and geographical locations [or their clinical presentation as pneumonia in the period before 2011 (2)] were not proper to send them home during the initial evaluation. Hence, they were hospitalised and started intravenous antibiotics (2).

Extended spectrum beta lactamase (ESBL)-producer bacteria are global problems. Addition of beta-lactamase inhibitors such as tazobactam or sulbactam to penicillins or cephalosporins adds resistance to some of the ESBL subtypes. Besides, sulbactam has antibiotic activity against *A. baumannii* (15,16).

Table 3 Clinical outcomes

	Piperacillin/tazobactam Total = 113 n (%)	Cefoperazone/sulbactam Total = 59 n (%)	p
Persistent response to therapy	85 (75.2)	39 (66.1)	> 0.05
Duration of therapy, mean days	8.3 ± 4.0	7.9 ± 3.6	> 0.05
Number of episodes with modification	28 (24.8)	20 (33.9)	> 0.05
Change in the empirical antipseudomonal treatment	16 (14.2)	8 (13.6)	> 0.05
Only glycopeptide	8 (7)	7 (11.9)	> 0.05
Only antifungal	1 (0.89)	2 (3.4)	> 0.05
Both glycopeptide and antifungal	2 (1.8)	2 (3.4)	> 0.05
Mortality	4* (3.5)	2* (3.4)	> 0.05

*One case died before any modification.

Continuous monotherapy with a single beta-lactam may be problematic that widespread use of only one agent may contribute to the emergence of resistance to it. Therefore, increasing the number of available empirical therapy options may also increase the effective consumption periods of the available antibiotics (17). During the study period, among non-carbapenems, P/T and C/S were the most commonly used antibiotic in low-risk febrile neutropenia cases, whereas cefepime was used in a very few cases. P/T was used more commonly because C/S was not consistently available in the hospital pharmacy.

Cefoperazone/sulbactam is not available in the USA and is not considered as a therapy option in the Infectious Diseases Society of America guidelines (2). However, there are several studies related to empirical C/S for febrile neutropenia reporting 60–88% success without modification with concomitant non-inferiority against imipenem or imipenem + amikacin or ceftazidime + amikacin (4–8). C/S is one of the main empirical therapy options according to Turkish neutropenic fever guidelines (1).

However, data related to either P/T or C/S in low-risk neutropenic fever are scarce. To our knowledge, there are no data related to C/S monotherapy in low-risk febrile neutropenia cases. In terms of P/T, Cornely et al. (9) compared P/T monotherapy with levofloxacin and reported 88.3% success without modification and no mortality in P/T arm consisting 34 cases. In another study published by Innes et al. (10), they compared P/T + gentamicin with amoxycillin/clavulanate + ciprofloxacin and reported 90% success without modification in P/T + gentamicin arm without any mortality.

In our series, persistent success without any modification was 75.2% in P/T arm and 66.1% in C/S arm. Clinical response without modification was about 9% lower in C/S receiving cases, but the difference was not statistically significant. Although it has to be mentioned that there is no study comparing C/S with any drug in low-risk neutropenic fever cases, this value of 66.1% is in concordance with previous trials' success rates of 60–88% with and without modification (4–8). Despite 75.2% success without modification with P/T is somewhat lower than 88.3% in 17 cases in the only study evaluating P/T monotherapy in low-risk cases, it is higher than findings of Freifeld et al. (18) reporting 67% success with ceftazidime monotherapy in the same patient group. We can speculate that the probably higher number of cases with severe neutropenia might have decreased the success rate in comparison with the study of Cornely et al. (9).

In this study, FUO rates in P/T and C/S cohorts were 58.4% and 54.2%, respectively. These rates are in concordance with 66–84% FUO rates in previous low-risk febrile neutropenia studies (9–11). Our MDI and CDI rates are also in concordance with the literature.

In our study, the mortality rate was 3.5% in the P/T cohort and 3.4% in the C/S cohort. These rates are also in concordance with three previous studies involving low-risk neutropenic fever cases reporting 0–2.9% mortality (9–11).

As this was a retrospective cohort study analysing patients who were diagnosed and treated according to national guidelines and agreements, ethical approval was not requested.

Our study has several limitations. This study represents a single-centre experience. Although data were collected prospectively by routine daily visits, this is a retrospective cohort study. Although baseline characteristics of the C/S and P/T cohorts were similar, this was not a randomised-controlled study; hence, we cannot exclude a selection bias. In addition, we could not analyse the infection-related

mortality, instead we used one-month survival as all-cause mortality data. However, despite these disadvantages, to our knowledge, this is the first study comparing P/T with C/S in adult febrile neutropenia and also the first study evaluating efficacy of C/S in adult low-risk febrile neutropenia. In addition, these data represent the largest cohort evaluating P/T in low-risk neutropenic fever. In conclusion, our data suggest that C/S may be a safe alternative to P/T in the empirical treatment of adult low-risk febrile neutropenia cases.

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