Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Appropriate use of Cefoperazone-Sulbactam in clinical practice : The need of the hour: An observational drug use evaluation study from tertiary care hospital in South India

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ARTICLE HISTORY

Received: 07.10.2023

Accepted: 29.10.2023

Available online: 31.12.2023

DOI:

10.5530/ajphs.2023.13.55

Keywords:

Antibiotics, Appropriateness, Drug utilization, Cefoperazone-sulbactam, Antibiotic fixed dose combination.

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ABSTRACT

To study the utilization pattern and appropriateness of cefoperazone-sulbactam antibiotic FDC in general medicine, pulmonology and nephrology departments of the hospital along with finding out the most common department and indication for which cefoperazone-sulbactam is mostly prescribed. A prospective observational study was carried out for a period of one year among 156 inpatients of different departments in a tertiary care hospital in Kerala. Patients were enrolled based on inclusion and exclusion criteria. All patients were analyzed to study the utilization pattern and appropriateness of cefoperazone-sulbactam FDC. Data were analyzed using appropriate statistical tools. From the total of 156 cases, majority were males. Cefoperazone-sulbactam was prescribed more in general medicine, followed by nephrology. Urinary tract infection, followed by respiratory tract infection were the most common indications for which cefoperazone-sulbactam prescribed. Majority of prescription with cefoperazone-sulbactam was appropriate, among which general medicine department comprising highest proportion. Making the culture and sensitivity reports readily available and regular monitoring of its usage could improve the compliance. More studies need to be undertaken nationally to investigate the appropriateness of cefoperazone-sulbactam use.

INTRODUCTION

Antibiotics are the medications that can destroy or inhibit the bacterial growth by selectively killing or inhibiting the development of disease-causing bacteria.[1] Consumption of antibiotics in humans is increasing globally and in India as well.[2] Cephalosporins are most commonly used large group of related beta-lactam antimicrobial agents with broad spectrum of activity, low rates of toxicity and ease of administration, which are effective for treatment of many conditions.[2] Among them, third generation cephalosporins, including cefoperazone and ceftriaxone have widest spectrum of activity compared to other generations and are active against gram-negative organisms, including many of enterobacteriaceae and also very active against streptococci.[3] Cefoperazone, a semisynthetic broad-spectrum beta-lactam antibiotic, is known to have excellent antibacterial activity against a wide range of gram positive and gram-negative bacteria, whose antibacterial strength is markedly augmented by a combination with sulbactam which is an irreversible beta-lactamase inhibitor. The combination of cefoperazone and sulbactam is active against all organism sensitive to cefoperazone. So far, many studies have been done on DUE of ceftriaxone use. But there were not enough studies performed on appropriateness of cefoperazone-sulbactam. And, cefoperazone-sulbactam is the most commonly prescribed antibiotic FDC both for prophylaxis and therapeutic purpose in this hospital. All these factors led to the selection of cefoperazone-sulbactam for the study.

Even though the role of antibiotics in successful treatment of infectious diseases cannot be denied, the steady increase in the number of antimicrobial resistant microorganisms poses a serious threat to the control of infectious disease.[3] Antibiotic resistance is the ability of a bacteria to resist and survive the effects of an antibiotic that were previously thought effective against them.[4] It is a major factor contributing to increased morbidity and mortality of patients as well as cost of medical

care.[5] Currently, it is found that many microbes have become resistant to the most commonly available and effective first line agents mainly due to inappropriate prescribing practices.[1] Emergence of antimicrobial resistance is a result of the use, overuse and misuse of antibiotics. When considering this, the logical first step is to evaluate the suitability of antibiotic usage by conducting DUE/ DUR.[3] Drug Use Evaluation (DUE) is a system of ongoing, systematic, criteria-based evaluation of drug use to ensure that medicines are used appropriately at the individual patient level (World Health Organization, 2002).[6] It detects inappropriate drug therapy by comparing actual drug use with predetermined standards and ensures that drugs are used appropriately, safely, and effectively to improve patient health status.

There were lot of DUE studies conducted before in various antibiotics regarding their appropriateness in therapy. Drug utilization study by Yohana Haile Berhe *et al.* in 2017 and found that ceftriaxone therapy was inappropriate in either indication, dose, frequency or duration in 62.4% of the cases.[7] Result of a study conducted by Asnakew Achaw Ayele *et al.* showed that more than 2/3rd of ceftriaxone use were found to be inappropriate and majority of unjustified use emanated from inappropriate frequency of administration, absence of culture and sensitivity test, and then duration of therapy.[8] There were studies lacking on utilization evaluation of cefoperazone-sulbactam. So, present study is a drug utilization evaluation, designed to evaluate the appropriate use of cefoperazone-sulbactam antibiotic FDC in a tertiary care hospital, to provide an overview of its use in hospital in order to promote rationality in prescribing, dispensing, and administration of cefoperazone-sulbactam antibiotic FDC.

MATERIALS AND METHODS

The study was conducted in inpatients of general medicine, pulmonology and nephrology departments of tertiary care Hospital situated in Perinthalmanna at Malappuram district of Kerala. A prospective observational design was used to evaluate the utilization pattern of cefoperazone - sulbactam antibiotic FDC. The study was carried out for a period of one year, commencing from November 2020 to October 2021. The study was conducted among 156 inpatients of age ≥ 18 years who has prescribed with cefoperazone-sulbactam FDC in selected departments. Both male and female patients and prescriptions collected during the study period were included in the study. The study excluded all the OP department patients, pregnant and lactating women. Prescriptions collected before and after the study period, patients with a known allergy to beta lactam antibiotics and those with a known history of epilepsy were also excluded from the study. Sample size of 156 was determined based on estimated population size in the same departments during last 1 year, using the Slovin's formula (1960). 258 were taken as the estimated population size for this study. Informed consent was not obtained from any subjects as no one received any intervention. The study was divided into 3 phases: Phase 1 includes approval of study protocol and obtained ethical committee clearance as well as official consent separately from physicians of each respective departments to collect data from patient record before the conduct of study. A well validated data collection form describing the patient's demographics, disease condition, past medical and medication history, abnormal diagnostic results, culture and sensitivity results, type of therapy and information regarding drug use including its indication, dose, frequency of administration, brand names, duration of therapy as well as information regarding co-prescribed medications was developed to collect the patient information. In phase 2, collected and recorded the patient data in data collection form during ward round participation and by means of medical record review of selected subjects. The datas were entered in Microsoft Excel spreadsheet for further analysis. Phase 3 involves evaluation of the collected data and the entire data were evaluated for appropriateness. The possible significant interactions of cefoperazone-sulbactam with other co-prescribed antibacterials were also analyzed using Medscape Interaction Checker and Drugs.com Interaction Checker. Appropriateness of cefoperazone-sulbactam use was determined using the criteria specified in 'National Treatment Guidelines for Antimicrobial Use in Infectious Diseases, version 1.0 (2016)'. Its use with respect to indication, dose and frequency of administration, duration of therapy, drug-drug interaction and culture sensitivity test was determined for each patient. Privacy and confidentiality of all the patients were strictly maintained throughout the study.

All statistical procedures were performed using Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 20.0). Descriptive statistics were used to summarize and describe the study variables as appropriate using mean and Standard Deviation (SD) for continuous variables while using frequency and percentage for categorical variables. The chi-

Table 1 : Age group of patients in relation with gender.

		Age groups of patients (years)							
		18-30	31-40	41-50	51-60	61-70	Above 70	**Total**	**%**
Gender	**Male**	3	3	6	20	15	38	85	54.5%
	Female	1	7	3	19	18	23	71	45.5%
	Total	4	10	9	39	33	61	156	
	%	2.6%	6.4%	5.8%	25%	21.2%	39.1%	100%	

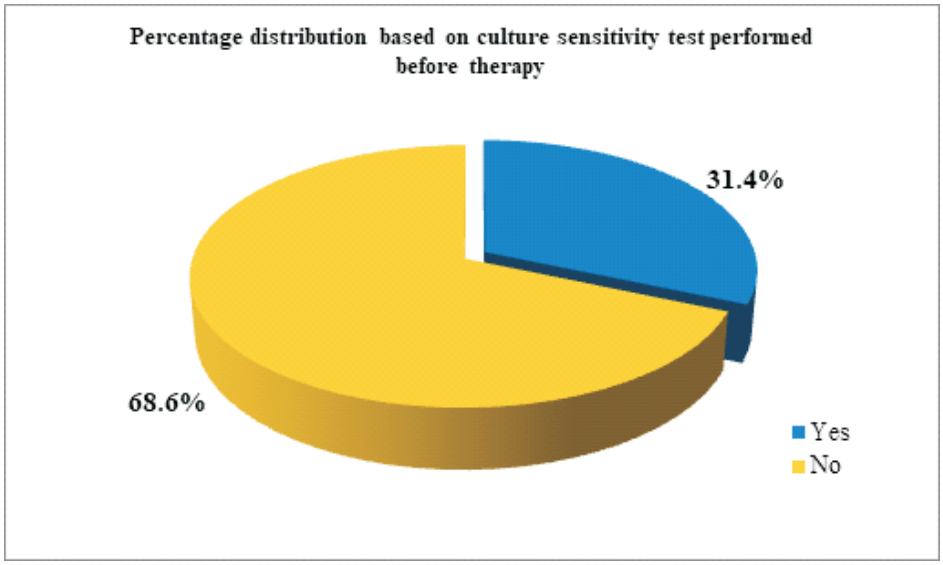

Figure 1 : Distribution based on culture sensitivity test before therapy.

square test was used to evaluate the association between variables. A *p*-value < 0.05 was considered statistically significant. The entire test was conducted at a confidence interval of 95%.

RESULTS

A total of 156 patients were included in the study, among which 54.5% (*n*=85) patients were males while remaining 45.5% (*n*=71) were females. The age of patients was categorized into six groups (18-30, 31-40, 41-50, 51-60, 61-70 and above 70). It was observed that maximum number of patients prescribed with cefoperazone-sulbactam were from the age group above 70yrs (*n*=61, 39.1%), followed by 51-60yrs (*n*=39, 25%) and 61-70yrs (*n*=33, 21.2%). When the patient's age was analyzed with gender, majority were males in both the highly prevalent age groups (Above 70 and 51-60 years). Amoung three departments included in the study, the use of cefoperazone-sulbactam was highest among patients admitted in general medicine (*n*=94, 60.3%), followed by nephrology (*n*=42, 26.9%) departments and lowest in patients admitted to pulmonology department (*n*=20, 12.8%).

Among 156 cases, culture sensitivity test was performed in 54.5% (*n*=85) cases. But, in only 31.4% cases (*n*=49) the tests were performed before starting the therapy. Remaining tests were performed after beginning therapy. Most of the therapy was empirical (*n*=105, 67.3%), followed by definite (*n*=46, 29.5%) and the least type was prophylactic (*n*=5, 3.2%). Out of samples of 54.5% (*n*=85) patients which were submitted to laboratory investigation, a bacterial etiology could be established in 44.7% (*n*=38) patients. The organisms which were isolated include *Escherichia coli (12), Klebsiella pneumoniae (7), Acinetobacter baumanii (3), Burkholderia cepacia (2), Pseudomonas putida (2),* and others (12).

The indication most commonly observed for prescribing cefoperazone-sulbactam was UTI (*n*=65, 35.9%) followed by respiratory infections other than pneumonia (*n*=32, 17.4%) and septicaemia (*n*=19, 10.3%). The most commonly prescribed dose of cefoperazone-sulbactam was 2gm (*n*=78, 50%), followed by 1.5gm (*n*=62, 39.7%) and the least prescribed dose was 1gm (*n*=7, 4.5%). Most used frequency of administration being twice-daily dosing (*n*=155, 99.4%). The mean duration of treatment was found to be 4.62 +/- 2.52 days (ranging from 2-16 days). It was observed that a possible moderate drug interaction was present in 9.6% (*n*=15) cases between cefoperazone-sulbactam and other antibiotics. Integrating the data for all the 3

Table 2 : Appropriateness in departments

Departments	Appropriate n (%)	Inappropriate n (%)	X^2 value	*p* value
General Medicine	74(60.2)	20(60.6)	0.29	0.86
Nephrology	34(27.6)	8(24.2)		
Pulmonology	15(12.2)	5(15.2)		
Total	123	33		

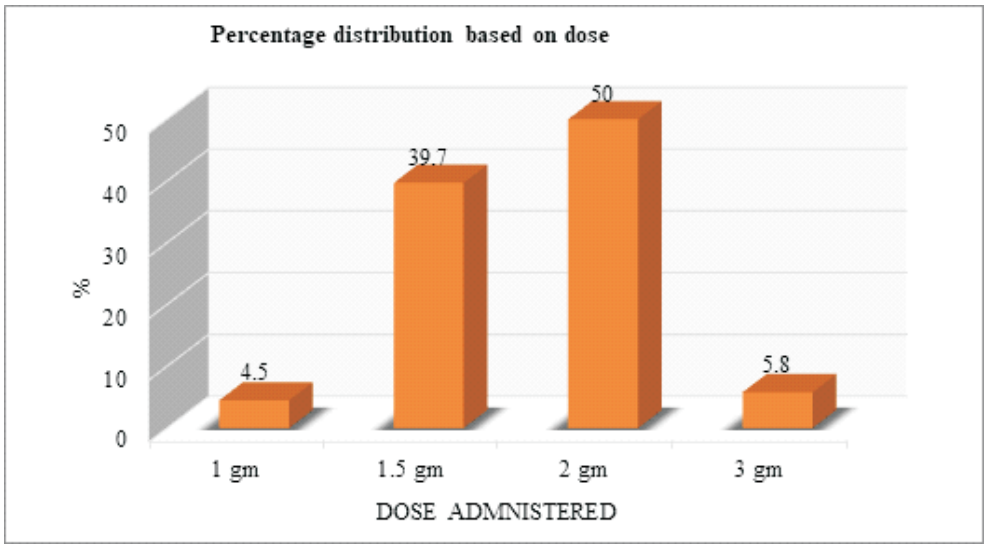

Figure 2 : Distribution based of dose and percentage.

departments, about 78.8% (*n*=123) prescriptions containing cefoperazone-sulbactam were according to the guidelines and were appropriate and in remaining 21.2% (*n*=33) cases, the prescriptions were not according to guidelines. Moderate drug interaction was present in 15 cases contributing to 41.7% of inappropriate use. Wrong indication was found in 11 cases (30.6%) while missed drug administration was identified in 3 cases (8.3%). And in 6 cases, the treatment was against the culture and sensitivity report contributing to 16.7% of inappropriate use. Antibiotics has been prescribed concomitantly with cefoperazone-sulbactam in 46.8% (*n*=73) cases. Among them carbapenem, followed by macrolides were the most frequently co administered antibiotic classes with a proportion of 21.6% (*n*=21) and 20.6% (*n*=20) respectively. Meropenem was the only carbapenem prescribed concomitantly in 21 cases. Among macrolides, azithromycin followed by clarithromycin were most common in 12 cases and 8 cases respectively. 74 cases out of 94, 34 out of 42, and 15 out of 20 cases were appropriate in departments of general medicine, nephrology and pulmonology, respectively. From the data it is clear that compared to total cases appeared in each department, nephrology is higher in appropriateness of cefoperazone-sulbactam (*n*=34/42, 81%) use and pulmonology has comparatively lower appropriateness (*n*=15/20, 75%) among the three departments. Among 33 inappropriate cases, majority of cases were from general medicine (*n*=20). P value < 0.05 is said to be statistically

Table 3 : Appropriateness of indication.

Indication	Appropriate n (%)	Inappropriate n (%)	X^2 value	*p* value
UTI	56(39.2)	9(22)	30.19	0.001**
Pneumonia	8(5.6)	4(9.8)		
Other respiratory Infections	26(18.2)	6(14.6)		
Gastrointestinal infections	12(8.4)	1(2.4)		
Sepsis/ Septicaemia	15(10.5)	4(9.8)		
Intra-Abdominal	16(11.2)	2(4.9)		
Skin infections	7(4.9)	6(14.6)		
Others	3(2.1)	9(22)		

Chi square test; *p value <0.05 is statistically significant; ** <0.001 is statistically highly significant.

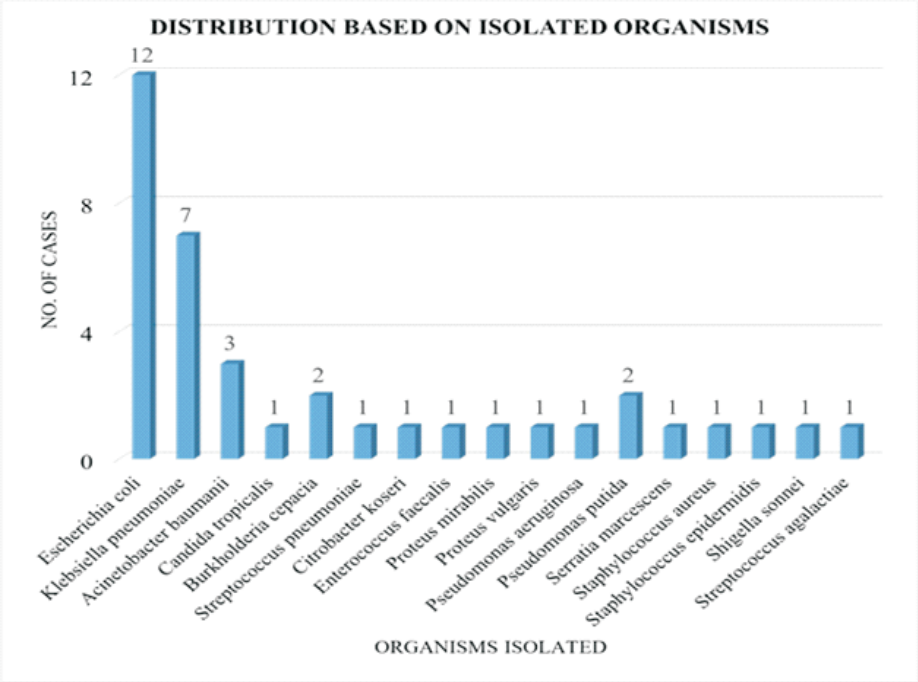

Figure 3 : Distribution based on isolated organism and no of cases

significant. Here, *p* value is > 0.05. Compared with appropriateness in the three departments, there is no difference in the inappropriateness in these three departments. So, the study was not statistically significant in the evaluation of appropriateness (X^2 = 0.29, P = 0.86). In the evaluation of appropriateness in indication, number of appropriate cases of UTI is higher than any other indications. *p* value of < 0.05 is considered statistically significant. The indications are statistically highly significant in the evaluation of appropriateness (X^2 = 30.19, P = 0.001). There is a difference in the appropriateness of indication.

DISCUSSION

A total of 156 cases were collected as per inclusion and exclusion criteria. All the collected cases contain prescription containing cefoperazone-sulbactam for at least 2 days. Among the total patients enrolled in the study, 54.5% (*n*=85) were males and 71 45.5% (*n*=71) were females. Predominance of male patients can be observed here. Similar results were obtained in studies conducted by Dilip Chandrasekhar *et al*.,[3] Jagadish Babu *et al*.[9] and Shankar *et al*.[10] that showed a male predominance compared to females. The probable reason that is noticed in the Indian scenario for this trend may be the reluctance of female populations to utilize health care facilities even if they are critically ill and especially by the lower socio economic strata.[11] This may be also due to the fact that female population usually get less exposed to environmental triggers compared to males, so they are less prone to get infectious diseases than males.When the

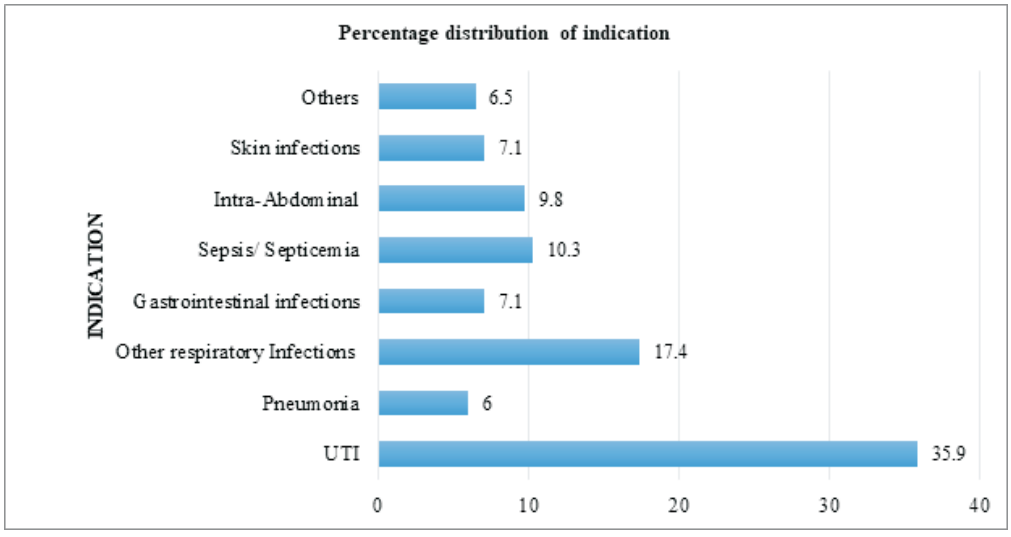

Figure 4 : Distribution based on indication

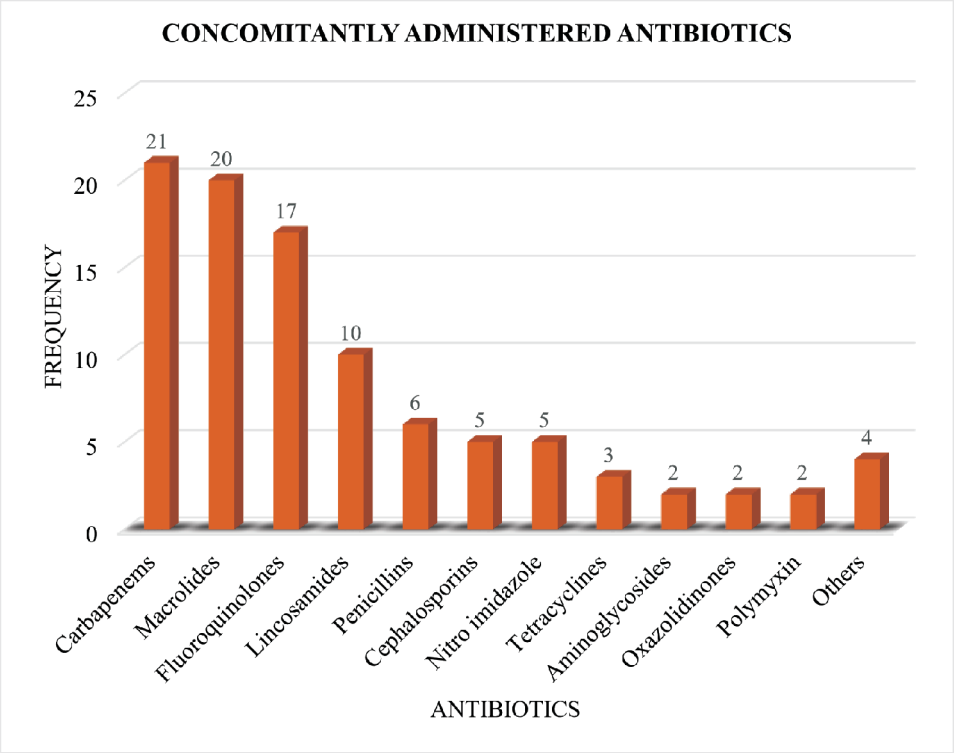

Figure 5 : Concomitant Administered antibiotics

prevalence of comorbidities and risk of infection was observed on the basis of age group, it was found that this core antibiotic preferably cefoperazone-sulbactam was most commonly prescribed in patients within the age group of > 70 years (61, 39.1%) with a predominance of males (n=38) population. The mean age of all the patients was 64.1 +/- 15.1 years. The current result is matching with that of study conducted by *Chia-Hung Chen et al.*[12] This trend may be due to the age-related physiologic changes that may affect several organ systems and contribute to increased vulnerability to infections. The reason for this may also be the occurrence of immunosenescence with progressing age, affecting both innate as well as adaptive immune systems and contributing to an increased risk of infection. Minimum number of patients were reported from the age group 18-30.From the total 156 cases, the patients were categorized based on department to which patients admitted. Three departments namely, general medicine, nephrology and pulmonology departments were included in this study. Among these, 60.3% (n=94) cases were from general medicine department implicating the highest use of cefoperazone-sulbactam, followed by nephrology (n=42, 26.9%). Reason for such an increased number of cases in general medicine department is that irrespective of specialties varying types of patients may first consult and get admitted in the general medicine department, and then depending upon the severity, they may get shifted to other departments or continued within the same department. Compared to other two departments, general medicine has a gross opportunity to accommodate many of the cases as it is a general department. The first two departments are specific for certain systems, while general medicine may receive many types of cases including those relevant to other two departments, making an increased number of cases in that department. When evaluating the appropriateness in departments p value < 0.05 is said to be statistically significant. Here, p value is > 0.05. Compared with appropriateness in the three departments, there is no difference in the inappropriateness in these three departments. So, the study was not statistically significant in the evaluation of appropriateness ($X^2 = 0.29, p = 0.86$).

Culture and sensitivity results play an important role in selection of appropriate antibiotics. Based on this, a therapy is being called as definite, empirical or prophylactic. A therapy initiated after performing culture sensitivity test is called a definite therapy, while empirical therapy is those in which culture sensitivity test not performed before starting the therapy. The present study revealed that 67.3% (n=105) patients received cefoperazone-sulbactam as empirical therapy. On evaluation, the cases of empirical type of therapy is higher than definite and prophylactic therapy, which is contradictory to the result of Dilip Chandrasekhar *et al.*,[3] with most of therapy was definite. This is similar to the study conducted by Shinu Mary John *et al.*,[13] where 64.9% was of empiric therapy. This is because the microbiological results cannot be obtained within 24-72 hr. The initial therapy is started according to the clinical judgment of physician, clinical condition of patient, and laboratory results. On the other hand, result in *Shankar et al.*[10] showed that the culture sensitivity test was carried out in 69.4% cases.During this study, cefoperazone-sulbactam was most extensively prescribed for treatment of urinary tract infections (n=65, 35.3%) followed by respiratory tract infections (n=32, 17.4%), septicaemia (n=19, 10.3%), intra-abdominal infections (n=18, 9.8%), gastro-intestinal and skin infections with 7.1% (n=13) and pneumonia (n=12, 6.5%). This findings was similar to the results of studies conducted by Jagadish Babu *et al.*[9] and Arul B *et al.*[14] while study conducted by Shankar *et al.*[10] showed that UTI was second to respiratory tract infection as most common indication. UTI is usually more prevalent in females. Even so, as the majority of our

cases are from elderly above 60 years and because most among are male, the presence of severe comorbidities such as diabetes, kidney disease, or BPH, etc., in them may increase the prevalence of UTI in male patients in this study.

The interrelation of appropriateness with indication showed that the number of appropriate cases of UTI is higher than any other indications. p value of < 0.05 is considered statistically significant. The indications are statistically highly significant in the evaluation of cefoperazone-sulbactam appropriateness (X^2 = 30.19, p = 0.001). There is a difference in the appropriateness of indication.In this study, *Escherichia coli (n=12)* followed by *Klebsiella pneumoniae (n=7)* were the most frequently isolated organism that is susceptible to cefoperazone-sulbactam. A similar result was obtained in a study conducted by *Sohil P Makwana et al*.[15]The present study revealed that the mean length of therapy with cefoperazone-sulbactam was 4.62 days. Similar results were observed in studies by *Shankar et al.*[10] and *Shinu Mary John et al.*[13] In our study it was found that patients stayed for a duration ranging from 2-16 days in hospital which was determined by the severity of patient illness. And in this study the cases were of varying severity.

Even though the culture sensitivity test is an important parameter for assessing appropriateness, here it was not taken as a specific parameter. Because, cefoperazone-sulbactam was mostly prescribed empirically in our study setting. This was prescribed for many conditions without taking samples for culture test. Some of the tests were performed after initiating the treatment, which cannot be included under definite. So, instead, the presence of culture resistance was taken as a parameter for appropriateness assessment. Six parameters were utilized for evaluating the compliance of cefoperazone-sulbactam use towards the national treatment guidelines for antimicrobial use in infectious diseases. Indication, dose, administration, frequency and drug interaction were the other five parameters.Multiple antibiotic treatments are generally opted under conditions of lower therapeutic response or in cases of super-infection. Being a broad-spectrum antibiotic generally, often other antibiotics will be added to regimen in order to treat super-infection. With respect to the number of cases admitted in each department, concomitant antibiotic use was comparatively higher in pulmonology than other two departments. Among the antibiotics concomitantly administered, carbapenems (21.6%) followed by macrolides (20.6%) were the most frequent class. Azithromycin was the macrolide antibiotic that most commonly co-administered. In contrast, gentamycin was the most commonly co-prescribed antibiotic in a study carried out by *Yohana Haile Berhe et al.*[7] in Ethiopia. The observation of sub therapeutic response in the monotherapy with cefoperazone-sulbactam is the reason for this concomitant administration of these other antibiotics.The compliance of cefoperazone-sulbactam use according to the national antimicrobial guideline (version 2016) was evaluated for indication, dose, administration, frequency, culture resistance and drug interaction in a total of 156 patients.[16] Among these, 123 (78.8%) were compliant whereas 33 (21.2%) cases were noncompliant. This was different from the results produced by *Dilip Chandrasekhar et al.*[3] The 21.2% cases of noncompliance was distributed with different reasons. Wrong indication, administration errors, wrong frequency, resistant culture and drug interaction were the reasons for inappropriate use. One or more factors were present in some cases among which drug interaction (n=15) was the most frequent factor observed followed by wrong indication (n=11) or prescribing with no reason. In 6 cases the treatment was done against the culture sensitivity report in which, treatment was initiated or continued after obtaining a positive culture resistance report. Among them, 3 prescriptions of cefoperazone-sulbactam can be justified being the best possible choice with minimum resistance that could be prescribed to MDR patients.While evaluating the appropriateness of cefoperazone-sulbactam use in all departments, general medicine is first with a greater number of appropriate cases (n=74) than other two departments. Meanwhile, the comparison of percentage of appropriate cases across departments with respect to number of cases admitted revealed a clear-cut result that number of appropriate cases of cefoperazone-sulbactam use was comparatively higher in nephrology department (n=34/42, 81%) followed by general medicine department (n=74/94, 78.7%), and least rate of appropriateness was observed in pulmonology department (n=15/20, 75%). Even though the number of appropriate cases in total is more in general medicine, the number of inappropriate cases of general medicine (n=20) was also comparatively higher than inappropriate cases of nephrology (n=8). p-value < 0.05 is considered statistically significant. p-value is 0.86 which is showing that the current result is statistically not significant. There is statistically no difference between the appropriateness of these departments. This reveals that we cannot correlate the appropriateness of antibiotic cefoperazone-sulbactam with departments.Compared to 1st and 2nd generation, 3rd generation cephalosporins were used in more than 85% cases according to a study previously conducted on cephalosporins in this hospital setting by *Dilip Chandrasekhar et al.*[3] The use of cefoperazone-sulbactam is higher than any other antibiotics in the current departments of this setting. This is matching with the findings observed in a study conducted on drug use evaluation of cephalosporins in the same hospital setting where cefoperazone-sulbactam was the most frequently prescribed antibiotic.[3] But, it was quite different from the results of a study conducted by *Satapathy S S et al.*[16] where cefoperazone-sulbactam was ranked 4th following ceftriaxone. Study conducted by *Kousalya Kaliamoorthy et al.*[17] revealed that the use of cefoperazone was in 4th place following cefixime (32.69%), cefotaxime (31.32%) and ceftriaxone (19.51%). A similar higher utilization of cefoperazone-sulbactam can also be observed in another study carried out by *Lisha Jenny John et al.*[11] This extensive use may be due to its extended spectrum of activity, excellent penetration to the body tissues and wide coverage to all bacteria.[3] Drug interactions observed which were categorized into moderate interactions. No serious interactions were detected. A total of 15 (9.6%) moderate interactions and no major interactions were detected. In the present study diuretics, especially furosemide followed by heparin were the drugs that caused most reported interaction with cefoperazone-sulbactam. This finding is similar with the result of a study conducted by *Arul B et al.*[14]Most of the therapy with cefoperazone-sulbactam was found appropriate. But, in current study culture sensitivity test was not taken as a parameter for appropriate prescription as the drug is prescribed mostly as empirical compared to definitive therapy. The strict pursuing of bacteriological investigation will further improve the treatment. This necessitates the need of performing culture and sensitivity tests.

CONCLUSION

The rate of cefoperazone-sulbactam utilization was marginally high in general medicine department. Among varying types of diagnosis, urinary tract infection was dominating, followed by respiratory infections were the major indications for

prescription of this antibiotic combination. Mostly cefoperazone-sulbactam was given 2 g BID among seventy eight patients whereas 1.5 g BID among sixty two patients. There was an acceptable rate of compliance towards policy which reflects the success of antimicrobial stewardship program implemented in this hospital setting. The majority of appropriate number of prescriptions with cefoperazone-sulbactam was identified in general medicine and lowest number in pulmonology. The inappropriate use of cefoperazone-sulbactam was found to be low in this hospital. But, still the lower number of culture sensitivity tests are a risk for developing antibiotic resistance. Ensuring the strict order and follow up of culture sensitivity results may help in reducing such a risk. Cefoperazone-sulbactam prescriptions was inappropriate in one fifth of cases, some of the reasons of which includes drug interaction, wrong indication, culture resistance and administration errors. Regular monitoring of cefoperazone-sulbactam usage evaluation and strict adherence to the updated guidelines on its use should be initiated by health professionals. Finally, more studies to evaluate the appropriate use of cefoperazone-sulbactam need to be undertaken nationally to study the utilization pattern and their extent of inappropriate use.

ACKNOWLEDGEMENT

We extend our sincere appreciation to the staff and administration of KIMS AL-SHIFA Super Specialty Hospital for their invaluable support and unwavering cooperation throughout the data collection process, which served as the cornerstone of this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest in conducting this study, the design, data collection, analysis, interpretation, reporting its findings or publication of this research.

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Cite this article : Mohammed Imthiyas Peringodan, Dilip Chandrasekhar, Athira N.K., Mohammed Salman
Appropriate use of Cefoperazone-Sulbactam in clinical practice : The need of the hour: An observational drug use evaluation study from tertiary care hospital in South India
Asian J. Pharm. Hea. Sci.. 2023;13(4):2904-2912. DOI : 10.5530/ajphs.2023.13.55