

## A PROSPECTIVE STUDY ON DRUG USE EVALUATION OF THIRD GENERATION CEPHALOSPORINS IN A TERTIARY CARE TEACHING HOSPITAL

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### ABSTRACT

Drug utilization research is an essential part of pharmacoepidemiology as it describes the extent, nature and determinants of drug exposure. The principal aim of drug utilization research is to facilitate the rational use of drugs in populations. Several studies revealed that antibiotics are very often inappropriately used. Appropriate use of antibiotics is central to limiting the development and the spread of resistant bacteria in hospitals and communities. Prospective evaluation of appropriateness of third generation cephalosporins was carried out in 300 in-patients in medicine, surgery, paediatric and orthopaedics wards of Navodaya Medical College Hospital and Research Center, Raichur from November 2015 to April 2016. Drug Utilization evaluation (DUE) was based on standards set forth by the American Society of Hospital Pharmacists. The DUE criteria used in this study were modified to be more suitable in our hospital setting. Relevant information was recorded in a structured proforma & data was evaluated. Ceftriaxone was most frequently prescribed (57.66%) third generation cephalosporins in parenteral form, followed by cefoperazone (16%). Among the 300 patients, 145(48.33%) were female and 155(51.66%) male. With regard to age, 14.66% of males were in 0-10 year's age group while 7.33% of females were in above 60 years age group. Out of 173 cases of ceftriaxone, the use was appropriate in 115 cases and inappropriate in 58 cases. Out of 48 cases of cefoperazone, the use was appropriate in 39 cases and inappropriate in 9 cases. Our study concludes that the involvement of clinical pharmacists in clinical practice helps to increase proper usage of cephalosporins and optimum outcome.

**Keywords:** ASHP criteria for DUE, antibiotics, drug utilization evaluation, prescribing pattern.

### INTRODUCTION

Drug Utilization Evaluation (DUE) has been defined by the American Society of Health System Pharmacists (ASHP) as a "Criteria-based, on-going, planning and systemic process for monitoring and evaluating the prophylactic, therapeutic and empiric use of drugs to help, assure that they were provided appropriately, safely and effectively."<sup>1</sup>

The goal of a DUE is to promote optimal medication therapy on right indication, with correct information at an affordable price. It will also help to evaluate the effectiveness of therapy as well as prevent medication related problems such as adverse drug reactions, treatment failures, over-use, under-use, incorrect doses.<sup>2,3</sup>

*Cephalosporium acremonium*, the first source of the cephalosporins, was isolated in 1948 by Brotz from Sea near a sewer outlet off the Sardinian coast. Crude filtrates from cultures of this fungus were found to inhibit the *in vitro* growth of *S. aureus* and to cure staphylococcal infections and typhoid fever in human beings.<sup>4</sup>

Cephalosporins are the most widely used antibiotics for treating common infections. These are large group of related beta-lactam antimicrobial agents with broad spectrum of activity, low rates of toxicity and ease of administration. Various cephalosporins are effective for treatment of many conditions, including pneumonia, skin and soft tissue infections, bacteremia and meningitis.<sup>5</sup>

Cephalosporins are bactericidal agents (which means that they kill bacteria). Cephalosporins disrupt the synthesis of the peptidoglycan layer of bacterial cell wall, which causes walls to break down and eventually the bacteria die.

They are classified by generation; first, second, third and fourth. In general lower generation cephalosporins have more gram positive activity and higher generation have more gram negative activity. Due to their activity against most gram negative organisms and their availability, third generation cephalosporins are most commonly used. Among 3rd generation cephalosporins, ceftriaxone is the most prescribed drug.<sup>6</sup>

The third generation cephalosporins have a marked activity against gram negative bacteria due to enhanced the beta lactamase stability and ability to penetrate the gram negative cell wall. They have more favourable pharmacologic properties than previous generations.

Ceftriaxone is one of the most commonly used antibiotics due to its high antibacterial potency, wide spectrum of activity and low potential for toxicity. It is used to treat different types of bacterial infections, including bronchitis, pneumonia, bone infections, abdominal and skin infections, and urinary tract infections etc.<sup>7</sup>

Cefoperazone is more active than cefotaxime against *Pseudomonas* (but less active than ceftazidime). It is good for *Salmonella typhi* and *B. fragilis* also. It is used for pseudomonal UTIs, bacteraemia and infections in immunocompromised patients. Other uses like meningitis, gonorrhoea and septicaemia are common to other drugs of this series.<sup>8</sup>

DUE studies are required for all drugs in general and particularly for antibiotics because use of antibiotics in hospitals account for 20% to 50% of drug expenditures.<sup>9</sup>

## **MATERIALS AND METHODS**

The prospective observational study was carried out in In-patient departments (IPD) which include General Medicine, Orthopaedics, Paediatrics and Surgery of Navodaya Medical College, Hospital & Research Centre, Raichur, which is a 1000 bedded Multi-specialty tertiary care teaching hospital. Patients from OBG, pregnant and lactating women were excluded from our study. 300 patients were randomly enrolled in to the study based on study criteria. A self-designed patient data collection form was developed and used for this study. Patient records from the inpatient wards of the selected departments of the hospital were obtained. A total of 300 prescriptions prescribed with third generation cephalosporins written by qualified medical doctors were collected from wards and analysed. Latest edition of CIMS drug manual (mims.com) was used to decode brand name of drugs to generic names for the purpose of analysis. The data collected were evaluated using Micromedex software, several guidelines and information regarding the number of drug-drug interactions in a prescription, their severity and management are summarized with help of Stockleys Drug interaction book and Drugs.Com. Data was analyzed using descriptive statistics namely total numbers, mean, standard deviation and percentage wherever applicable. Microsoft word and Excel

have been used to generate graphs, tables etc. The study was approved by Institutional Ethics Committee of Navodaya Medical College Hospital & Research Centre on 18<sup>th</sup> November 2015.

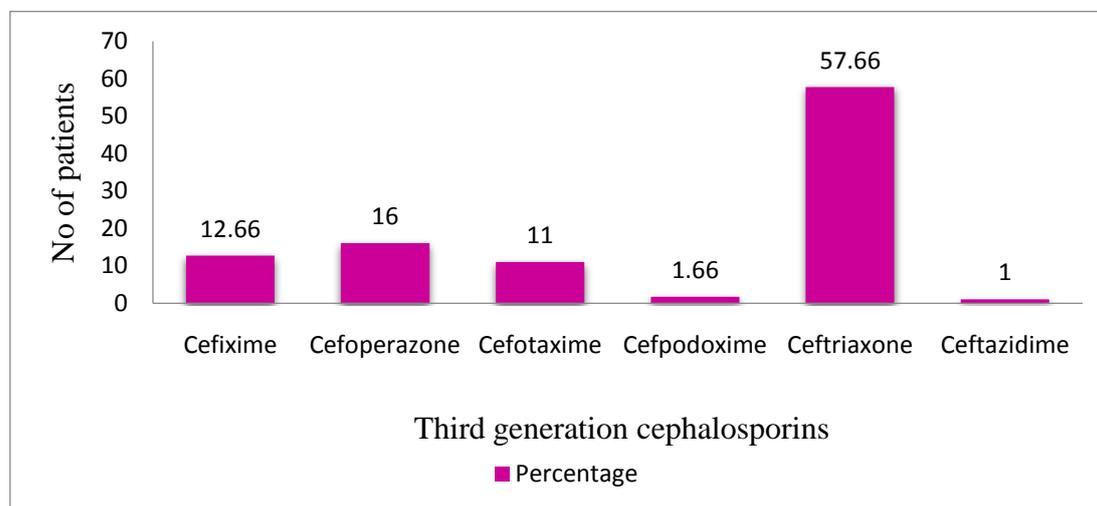
## RESULTS

In the study population 300 patients were enrolled. Table 1 shows demographic characteristics of patients which include gender distribution and age distribution. Ceftriaxone was commonly prescribed third generation cephalosporin with 57.66%, the results are presented in Fig; 1. Injection was mostly prescribed as dosage form with 86.33% [Table 2]. Ceftriaxone and sulbactam combination was prescribed more with 28% (Fig: 2). The prescriptions with interactions and without interactions are presented in Fig: 3. The appropriateness of the DUE was analysed based on “Criteria For Drug Use Evaluation” of the American Society of Hospital Pharmacist (ASHP). Indications for which ceftriaxone and cefoperazone was deemed either acceptable or unacceptable are enlisted in table 3 and 4 respectively. Fig 4 and Fig 5 represents the appropriateness and inappropriateness of ceftriaxone and cefoperazone with complications respectively.

**Table 1: Demographic characteristics of enrolled patients**

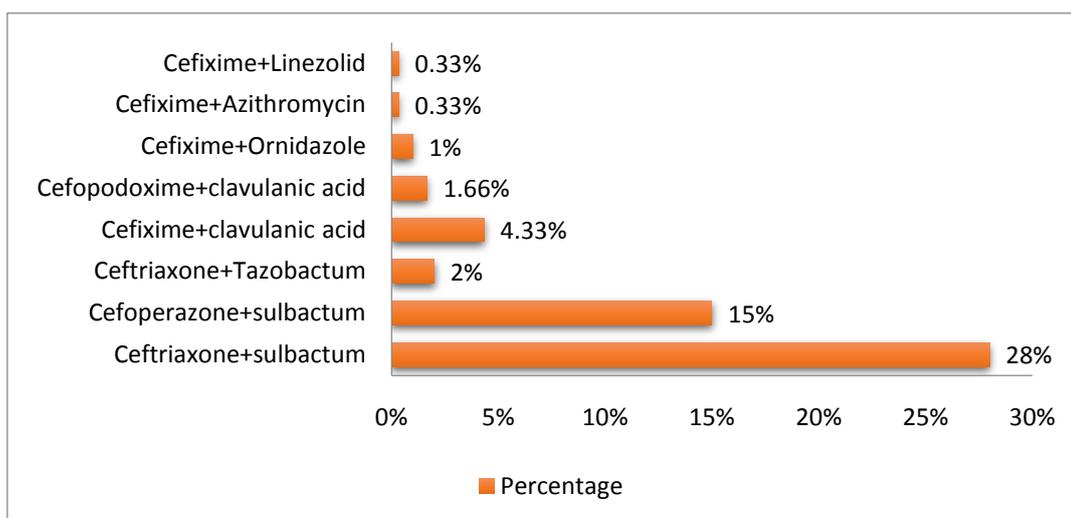
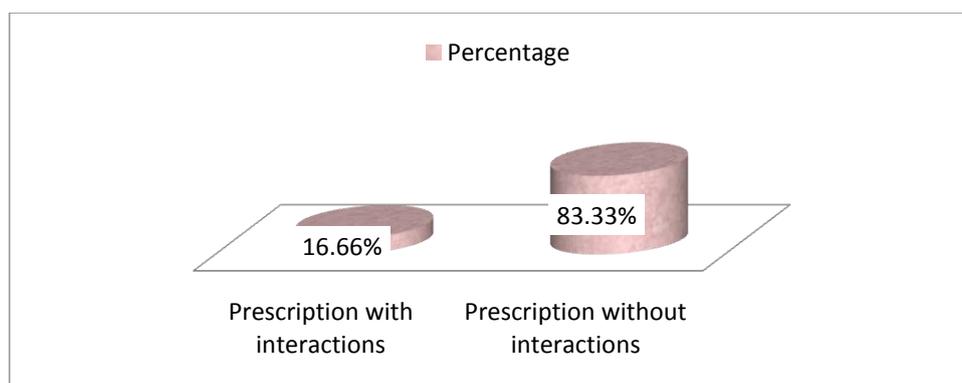
Characteristic		Data
<b>No of patients enrolled in study(n=100)</b>		
<b>Male</b>		155(51.66%)
<b>Female</b>		145(48.33%)
<b>Age wise distribution</b>		
Age	Male	Female
0-10	44 (14.66%)	24(8%)
11-20	25 (8.33%)	15(5%)
21-30	22(7.33%)	15(5%)
31-40	14(4.66%)	19(6.33%)
41-50	22(7.33%)	14(4.66%)
51-60	18(6%)	13(4.33%)
>60	33(11%)	22(7.33%)

**FIG 1: COMMONLY PRESCRIBED THIRD GENERATION CEPHALOSPORINS**



**Table 2: DOSAGE FORMS OF CEPHALOSPORINS PRESCRIBED IN STUDY POPULATION**

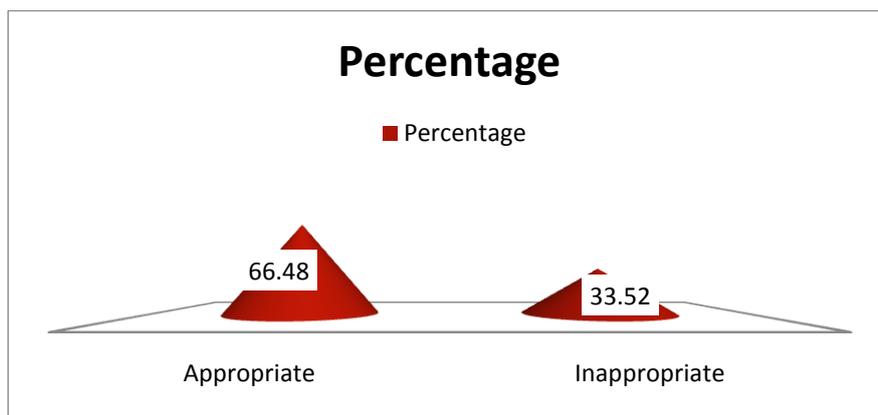
SL.NO	DOSAGE FORMS	NO OF PATIENTS	NO OF PATIENTS
1.	TABLET	38	12.66%
2.	INJECTION	259	86.33%
3.	SYRUP	3	1%

**FIG 2: DIFFERENT COMBINATIONS OF CEPHALOSPORINS PRESCRIBED IN STUDY POPULATION****FIG 3: DRUG INTERACTION****TABLE 3: CEFTRIAXONE DRUG UTILIZATION EVALUATION CRITICAL (PROCESS) INDICATORS**

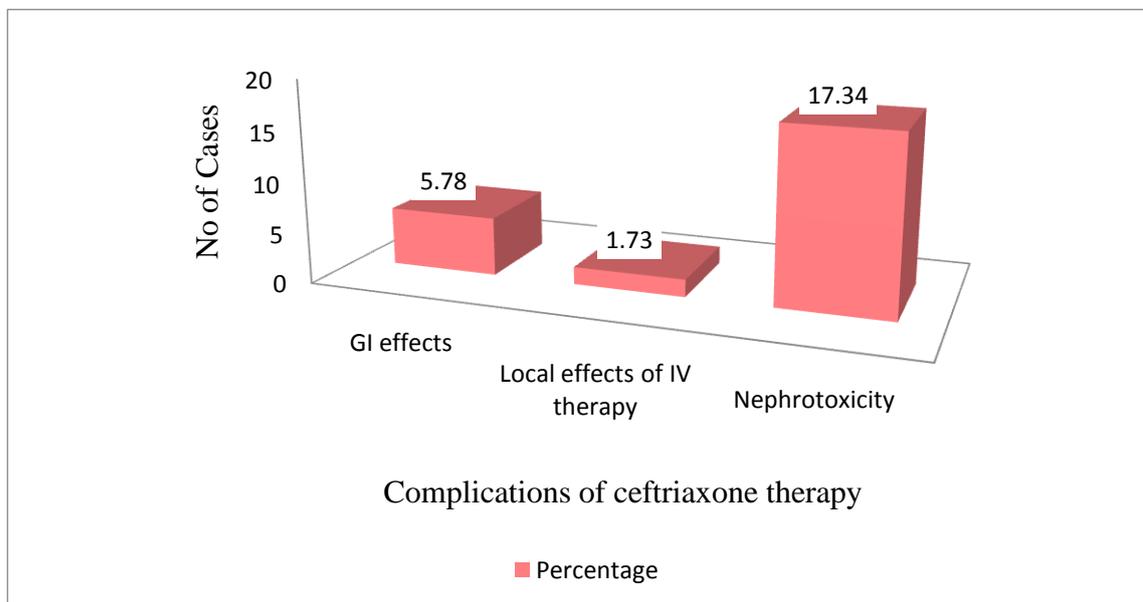
S.N	CRITERIA	ACCEPTED LEVEL	UNACCEPTED LEVEL
1.	Appropriate C & S obtained within 48 hrs before initial ceftriaxone dose	58(33.52%)	115(66.47%)
2.	CBC with differential obtained within 48 hr before initial ceftriaxone dose	131(75.72%)	42(24.27%)
3.	Appropriate ceftriaxone dosage	81(46.81%)	11(6.35%)

4.	Vital signs monitored atleast three times daily until patient becomes afebrile & atleast one daily during therapy	163(94.21%)	10(5.78%)
5.	Serum creatinine concentration obtained atleast once weekly during therapy	87(50.28%)	86(49.71%)
6.	WBC count obtained atleast once weekly during therapy	159(91.9%)	14(8.09%)
7.	Appropriate treatment duration 7 – 14 days	143(82.65%)	30(17.34%)

**FIG 4: a) CRITICAL (PROCESS) INDICATORS**

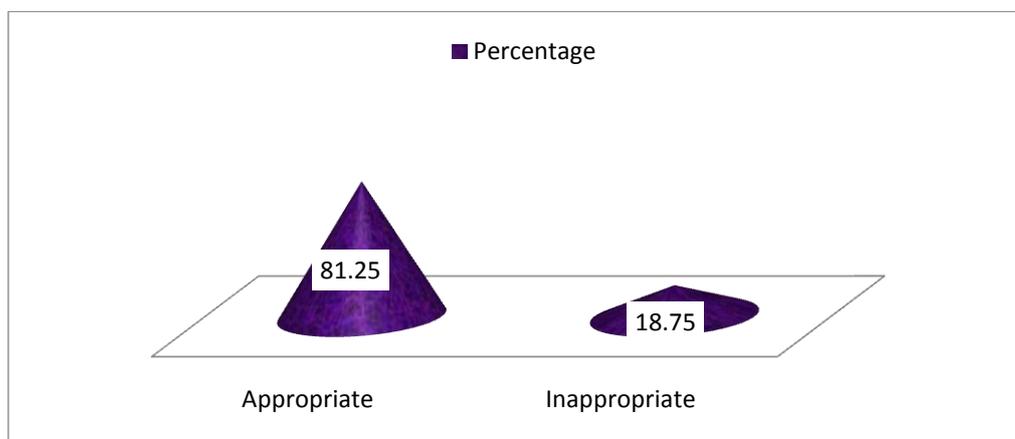
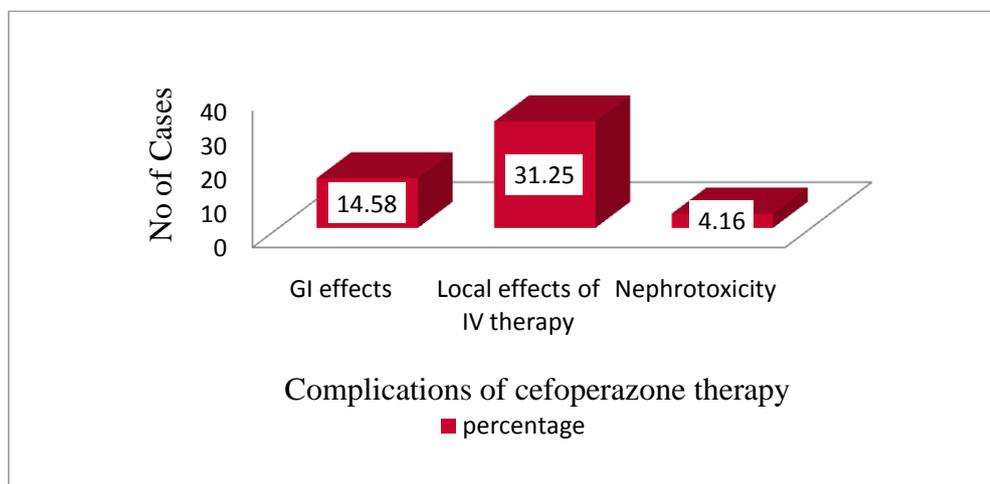


**b) COMPLICATIONS OF CEFTRIAXONE THERAPY**



**TABLE 4: CEFOPERAZONE DRUG UTILIZATION EVALUATION  
CRITICAL (PROCESS) INDICATORS**

S.N	CRITERIA	ACCEPTED LEVEL	UNACCEPTED LEVEL
1.	Appropriate C & S obtained within 48 hrs before initial ceftriaxone dose	9(18.75%)	39(81.25%)
2.	CBC with differential obtained within 48 hr before initial ceftriaxone dose	38(79.16%)	10(20.83%)
3.	Appropriate ceftriaxone dosage	8(16.66%)	None
4.	Vital signs monitored atleast three times daily until patient becomes afebrile & atleast one daily during therapy	43(89.58%)	5(10.41%)
5.	Serum creatinine concentration obtained atleast once weekly during therapy	27(56.25%)	21(43.75%)
6.	WBC count obtained at least once weekly during therapy	41(85.41%)	7(14.58%)
7.	Appropriate treatment duration 7 – 14 days	31(64.58%)	17(35.41%)

**FIG 5: (a) CRITICAL (PROCESS) INDICATORS****b) COMPLICATIONS OF CEFOPERAZONE THERAPY**

## DISCUSSION

A study of prescribing pattern of antibiotics is an effective way of reflecting appropriateness of antibiotic use. The data was collected prospectively from 300 in-patients and drug utilization pattern were analysed. In this study demographics characteristics shows males (51.66%) are commonly prescribed with third generation cephalosporin as compared to females (48.33%). This findings is similar to study conducted by **Jyothi K *et al.***<sup>9</sup>

In age wise distribution, 14.66% of males and 8% of females in 0-10 years age-group were prescribed more with third generation cephalosporins followed by patients who were in the age group above 60 years (11% male & 7.33% female). This can be attributed to the fact that neonatal sepsis & bacterial meningitis were common condition for use of cephalosporins in infants while in the age group above 60 years they were mainly used for post-operative prophylaxis as the geriatric patients are more likely to be sick & to have more serious illness. This was similar to that of a study conducted by **Shankar PR *et al*** in **Pokhara, Nepal.**<sup>10</sup>

In our study, it was observed that ceftriaxone (57.66%) and cefoperazone (16%) were commonly prescribed drug among all other third generation cephalosporins in injection forms. This is due to low incidence of ADR, excellent penetration to the body tissues & parenteral third generation cephalosporins have excellent activity against most bacterial infections. Similar results were reported in **Jyothi K *et al.***<sup>9</sup>

Among various dosage forms of third generation cephalosporins use in in-patients, injection was most frequently used (86.33%), followed by tablet (12.66%) and syrup (1%). This may be due to the reasons that parenteral formulation results in a faster onset of action. Moreover, oral formulation is not a preferred route in post-operative patient presenting with nausea and vomiting. Also third generation cephalosporins like ceftriaxone and cefoperazone are more frequently used in our hospital setting and are available only as injection form. The most commonly prescribed combination of third generation cephalosporins were ceftriaxone & sulbactam (28%) for greater potency and efficacy in treatment of RTI followed by cefoperazone & sulbactam (15%) for surgical prophylaxis. Similar results were obtained in the study of **Abebe *et al.***<sup>11</sup>

The appropriateness of the DUE was analysed based on “Criteria For Drug Use Evaluation” of the American Society of Hospital Pharmacist(ASHP).The criteria for DUE used in this study were modified based on their suitability in our hospital setting: justification of drug use, critical (process) indication and complication.

Out of 173 cases of ceftriaxone, the use was appropriate in 115 cases and inappropriate in 58 cases. Most of the critical process indications showed high rates of appropriateness (66.48%) excluding inappropriate C & S test prior to initial ceftriaxone dose (33.52%).The causes of inappropriate ceftriaxone use included routine perioperative prophylaxis and systemic prophylaxis for infection. Complications of ceftriaxone therapy include GI effects (5.78%), local effects of IV therapy (1.73%) and nephrotoxicity (17.34%).Each case was managed appropriately.

Out of 48 cases of cefoperazone, the use was appropriate in 39 cases and inappropriate in 9 cases. Most of the critical process indications showed high rates of appropriateness (81.25%) excluding inappropriate C & S test prior to initial cefoperazone dose (18.75%). Complications of cefoperazone therapy includes GI effects (14.58%), local effects of IV therapy (4.16%) and nephrotoxicity (31.25%). Each case was managed appropriately. As ceftriaxone & cefoperazone

were more prescribed in the study population, these two can be considered as a representative of the third generation cephalosporin under study in our hospital setting. Hence the appropriateness of third generation cephalosporin usage was higher than inappropriateness. Similar results were obtained in the study by **Hyuck Lee *et al.***<sup>12</sup>

## CONCLUSION

The appropriateness of cephalosporins was found to be higher than inappropriateness. A combination of physician education programs and feedback control system directed towards rational cephalosporins use is suggested for proper medical treatment. Our study concludes that, awareness about drug-drug interactions among health care professionals, computerized systems for prescription and drug information, as well as collaborative drug selection and pharmaceutical care are some of the possible solutions to the drug usage related problems. Hence the involvement of clinical pharmacists in clinical practice helps to increase proper usage of cephalosporins and optimum outcome.

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