

A STUDY ON DRUG UTILIZATION AND EVALUATION OF CEPHALOSPORIN'S IN A SECONDARY CARE HOSPITAL

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ABSTRACT

Introduction: The aim of the study is to explore possible regional variations and investigate determinants of cephalosporins consumption in a secondary care teaching hospital through DUE studies. The Drug Utilization Evaluation is a recognised quality assurance method used globally which is effective in identifying medicine use problems and as a method in improving pharmaceutical therapy. In this study DUE method was performed to evaluate the utilization pattern of Cephalosporins. **Methodology:** A prospective observational study on Drug Utilization of cephalosporins was conducted for 150 patients in a secondary care hospital over a 6 months period from August 2017 to January 2017. **Results:** In this study, we could observe females 97(66.66%) are predominantly prescribed with cephalosporins than males 53(33.33%). Out of 150 prescriptions enrolled, 137 were prescribed with brand name. Most prescribed route of administration for patients was parenteral 134(89.33%). Third generation cephalosporins are most commonly prescribed and Ceftriaxone 108(72%) was widely prescribed. Cephalosporins are generally prescribed for various conditions like pyrexia 68(45.3%), Acute gastritis (12%), Respiratory(4%), Urinary tract infections(9.33%), Uncontrolled Diabetes(2%) and many more. Metronidazole 16(13.18%) was highly co-prescribed antibiotic with cephalosporins. Periodic study on antibiotics enables the health care professionals to select appropriate antibiotic regimen and rationalise its use. **Conclusion:** The clinical pharmacist has a vital role in achieving rational antibiotic use by minimising their ADR's. From this, study it was observed that physicians are prescribing cephalosprins more rationally by avoiding banned and newer class of agents.

KEYWORDS: Drug Utilization, Cephalosporins, quality assurance.

INTRODUCTION

1.1 Background

Antimicrobials are the weapons against the several bacterial diseases improved just before the 20th century. In 1928, Fleming's major medical breakthrough came about as he serendipitously discovered penicillin, later to be claimed as the "miracle drug" during this period. Later on, antibacterials brought a revolutionary change in effectiveness against several infectious diseases. However, Just a few years after the golden age of antimicrobials, warning signs of developing resistance were observed. In the recent years, this was made even more complicated by the fact that the observed development of antimicrobial resistance has superseded the pace at which discoveries and development of better antibiotic treatments are made. More bacteria with multiple drug resistance are also being observed.^[1]

As, microorganisms are countering the impact of antimicrobial resistance worldwide at an often alarming

speed.^[24,25] Surveys have shown that 22–65% of antibiotic prescriptions are either inappropriate or incorrect.^[21] Drug Utilization Evaluation (DUE) studies are needed to improve rational use of antibiotics.

1.2 Aim of Study

Aim was to conduct a prospective observational study on Drug Utilization Evaluation of cephalosporins. Cephalosporins are the group of beta lactamases which show broad Spectrum of activity.

1.3 Introduction of Study

Cephalosporin is commonly used class of Anti-bacterials. They are preferred over other classes of antibiotics due to, lower hypersensitivity reactions, broad spectrum of action, cheaper cost and better outcomes. Third generation Cephalosporins are the most commonly prescribed empiric broad spectrum antibiotic. Having given its advantages, preserving the sensitivity of Cephalosporin is important. Though; Cephalosporin use

often provides lifesaving therapy to those who have a serious bacterial infection, resistance to antimicrobials is a global problem.^[18]

Over the past several decades, the increased prevalence of known resistant organisms and the emergence of newly resistant organisms such as penicillin-resistant pneumococci, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, extended-spectrum beta-lactamase-producing *Escherichia coli*, *Klebsiella pneumoniae*, and imipenem-resistant gram-negative bacilli.^[22]

1.4 Drug Use Evaluation (Due)

According to WHO, Drug utilization is defined as the “marketing, distribution, prescription, and use of drug in a society, with special emphasis on the resulting medical, social and economic consequences.”^[20,21]

Drug Utilization Evaluation (DUE) has been defined by the American system of health society Pharmacist (ASHSP) as “Drug use evaluation (DUE) is a system of ongoing, systematic, criteria-based evaluation of drug use that will help ensure that medicines are used appropriately (at the individual patient level).”^[20,21,26]

If therapy is deemed to be inappropriate, interventions with providers or patients will be necessary to optimize drug therapy. A DUE is drug or disease-specific and can be structured so that it will assess the actual process of prescribing, dispensing or administering a drug (indications, dose, drug interactions, etc.). DUE is the same as drug utilization review (DUR) and terms are used synonymously.^[19]

Medication Use Evaluation (Mue)

Medication use evaluation (MUE) is similar to DUE but emphasizes improving patient outcomes and individual quality of life; it is, therefore, highly dependent on a multidisciplinary approach involving all professionals dealing with drug therapy. An MUE will assess clinical outcomes (cured infections, decreased lipid levels, etc.).^[26]

Goals

The goal of a DUE or MUE is to promote optimal medication therapy and ensure that drug therapy meets current standards of care. Additional objectives may include:

1. creating guidelines (criteria) for appropriate drug utilization
2. evaluating the effectiveness of medication therapy
3. enhancing responsibility/accountability in the medicine use process
4. controlling medicine cost
5. preventing medication related problems, for example adverse drug reactions, treatment failures, over-use, under-use, incorrect doses and non-formulary medicine use

6. identifying areas in which further information and education may be needed by health-care providers.

Types of due

Quantitative DUE: The quantitative study of drug utilization figures from which patterns of drug acquisition, prescribing, dispensing, distribution and consumption may be determined.^[19]

Qualitative DUE: The qualitative evaluation of drug therapy and the drug therapy outcomes by comparison of practice with predetermined criteria and standards.

The DUE process is a continuous process and will be most valuable if the cycle is completed rather than different steps being performed in isolation.^[19]

Rational use of drugs is defined by the World Health Organization as “patients receive medicines appropriate to their clinical needs, in doses that meet their own requirements for an adequate period of time, and at the lowest cost to them and their community.”

Rational drug use implies an individual approach to patient’s treatment. Success of the treatment largely depends on the ability of a physician to diagnose the major health problem of a patient, select the correct drug, dosage form and route of administration, foresee probable adverse reactions and drug interactions, and prevent unnecessary or dangerous drug duplication therapy.

Further rational drug use depends on the performance of the pharmacy and nursing departments in preparing and administering drugs.

Programs that promote the rational prescribing of first-line antimicrobial agents are needed to address three major concerns.

1. Prevention of widespread bacterial resistance.
2. Prevention of adverse drug reactions, and
3. Control of health care costs.

Prescribing decisions are the result of a complex process that optimally considers a multiplicity of factors, including pharmacokinetics, antibacterial spectrum, patient tolerability, dosage regimen, recommended duration, palatability, and price.

The quality of prescriptions may be described as ‘appropriate’ or ‘inappropriate’. Appropriateness can be assessed on 3 levels.

Level 1- whether medication is warranted;

Level 2- which of several alternative drugs is the preferred choice; and

Level 3- appropriate prescription regimen, including dose, duration, type, and frequency of monitoring and drug interactions.

1. Quality of life can be improved by enhancing standards of medical treatment at all levels of the health care delivery system.
2. Setting standards and assessing the quality of care through performance review should become part of everyday clinical practice. The study of prescribing patterns seeks to monitor, evaluate and suggest modifications in practitioner's prescribing habits so as to make medical care rational and cost effective.
3. Concern about increasing rates of multi-drug-resistant (MDR) organisms and spiraling expenditure on broad-spectrum antimicrobials has induced most hospitals to implement a range of measures.
4. These include supervision of their use by infectious disease consultants and/or clinical pharmacist's provision of continuing education regarding appropriate antimicrobial drug use, and implementation of automatic stop orders.
5. However, there is evidence that, in order to be effective, a multidisciplinary approach is warranted, with application of a range of measures, some of which should be individualized according to the hospital's circumstances and means. Managed care pharmacists review drug utilization to determine which patients and prescribers are using particular medications. This allows the pharmacist to determine whether some drugs are inappropriately prescribed or used. With this knowledge in hand, the pharmacist and other care providers can then actively intervene in the patient's care process to assure better outcome.

Pharmacist can aid in the reduction or avoidance of poly pharmacy in the following way:

1. Screening patient drug profiles.
2. Assessing the effect of comorbid conditions.
3. Reviewing potential drug-drug interactions.

The pharmacist, along with the prescriber has a duty to ensure that patients are aware of the risk of side effects with drug therapy and a suitable course of action should they occur. With their detailed knowledge of medicine, pharmacists have the ability to relate unexpected symptoms experienced by patients to possible adverse effects of their drug therapy. The practice in clinical pharmacy also ensures that adverse drug reactions (ADRs) are minimized by avoiding drugs with potential side effects in susceptible patients. Thus, pharmacist has a major role to play in relation to prevention, detection, and reporting of ADRs.

Steps of Due

The following eight steps outline the basic information necessary to start and maintain a DUE program.^[26]

Step 1: Establish Responsibility

Responsibility falls to the DTC or a subcommittee of the DTC that functions only to monitor DUEs in the hospital or clinic. The DTC should undertake this responsibility

with considerable interest, because this process can solve many medicine use problems, as has proven to be the case in many countries where this quality assurance function has been fully utilized.

The DTC or a subcommittee must establish procedures that will govern the committee in its activities concerning medicine use review and evaluation. As part of the responsibility of the DUE function, the DTC must establish a plan, outlining which medicines will be a part of the DUE process. This plan needs to be updated and evaluated each year.

Step 2: Develop Scope of Activities

The DTC should assess and identify medicine use problems and using this information to develop a scope of activity for the DUE program. The scope can be extensive or it can focus on a single aspect of pharmaceutical therapy. Methods to identify medicine use problems include and ABC or vital, essential, nonessential (VEN) analysis, defined daily dose analysis, ADR reports, medication error reports, antibiotic sensitivity results, procurement studies, hospital and primary care clinic indicator studies, patient complaints or feedback, and staff feedback. These screening mechanisms serve to provide the DTC with information concerning medicine use that would need further evaluation in a DUE.

Because of the large number of medicines available at a hospital or clinic, the DTC must concentrate on the most important medicines, those with the highest potential for problems, to get the most return on the work involved. These high priority areas would include.

1. High-volume medicine use.
2. Medicines with a low therapeutic index.
3. Medicines with a high incidence of ADRs.
4. Expensive medicines.
5. Medicines that are critically important, including those in the following categories.

Cardiovascular, emergency, toxicology, oncology, intravenous medicines, and narcotic analgesics.

1. Antimicrobial medicines, both prophylactic and therapeutic.
2. Injections.
3. Medicines undergoing evaluation for addition to the formulary.
4. Medicines used for off-label indications.
5. Medicines used for high-risk patients.

Steps 3 and 4, Establish Criteria, Define and Establish Thresholds.

Criteria are statements that define correct medicine use. Establishing criteria is the single most important procedure in a DUE. Criteria for the use of any medicine should be established by the DTC using relevant evidence-based literature sources and recognized international and local experts. The criteria for any DUE should reflect what is in the country's STGs (assuming

that they have been developed correctly) and any medicine-use protocols that exist. Credibility of the DUE relies on criteria that are based on evidence-based medicine. Criteria must be developed with and accepted by the medical staff for the process to be credible.

Criteria should be developed for three to five of the most important indicators for each aspect of medicine use. Reviewing larger numbers of indicators will make for a more difficult. After developing criteria, the DTC must establish a threshold or standard (benchmark) against which the criteria will be judged. A threshold refers to the percentage of charts or records that will meet or exceed the established criteria for the medicine. Ideally, this threshold will be 100 percent, but realistically, a smaller percentage will be more appropriate to account for exceptions to routine medicine prescribing. Therefore, a threshold of 90 to 95 percent is typically used for many criteria, but each instance must be carefully analyzed before reaching a conclusion.

Step 5: Collect Data and Organize Results

DUEs can be accomplished as prospective evaluations, or they can be performed retrospectively. A prospective analysis involves the collection of data as the medicine is being prepared or dispensed to the patient. Retrospective analysis is done using chart reviews or other data sources to review medicine use according to indicators and criteria prepared in advance. The advantage of a prospective review is that the pharmacist (or other reviewer) can intervene at the time the medicine is dispensed to prevent errors in, for example, dosage, indications, or interactions. Retrospective evaluation, which may involve more of the reviewer's time or require access to medical records, is best accomplished when the reviewer has time away from the patient care areas and distractions. Typically, medicine-related criteria that are reviewed in these types of evaluations are as follows.

- **Prospective studies** (obtained from prescription records), Indication, Dose, Duration of therapy, Dosage form and route of administration, Potential medicine interactions, Appropriate therapy and medicine selection (corresponds to STGs), Therapeutic duplication, Contraindications, Quantity dispensed
- **Retrospective studies** (obtained from prescription, medical records, laboratory records), Laboratory monitoring, Monitoring therapeutic use of high-cost medicines, ADRs to medications, Correct use of generic or therapeutic equivalents, Patient outcomes from pharmaceutical therapy.

Collection of the data is performed by reviewing a suitable sample of charts or prescription records from the health care facility, usually by selected pharmacy personnel.

Step 6: Analyze Data

Data are collected, tabulated, and analyzed to see if criteria and thresholds are met. The following important steps should be completed when analyzing data.

1. Tabulate results for each indicator.
2. Analyze results to see if the criteria are met and the thresholds are not exceeded.
3. Determine why thresholds are not met.
4. Analyze data quarterly or more frequently.

If a threshold is not met, it may indicate a medicine use problem that requires the attention of the DTC.

Step 7: Develop Recommendations and Action Plan

After completing the data analysis, information is presented to the DTC and a decision is made as to the appropriateness of the information in the DUE. The DTC also must decide on whether to continue, discontinue, or expand the functions of the DUE in question. All medicines that do not meet the thresholds must be evaluated carefully and plans must be made to improve the use of the medicine relative to the criteria.

Recommendations should be prepared for the DTC to address the following.

1. Inappropriate medicine use.
2. Unacceptable patient outcomes.
3. Methods to resolve any medicine use problem.

Interventions to improve medicine use might include:

1. Education, including letters to practitioners, in-service education, workshops, newsletters, and face-to-face discussions.
2. Implementation of medicine order forms.
3. Prescribing restrictions.
4. Formulary manual changes.
5. Change (or better enforcement) of the STGs.

Step 8: Conduct DUE Follow-up

Follow-up in every DUE is critical to ensure resolution of any unresolved medicine use problems. The DUE may have identified new problems that need to be resolved within the health care system. If the problems are not resolved, then the DUE will have little usefulness to the health care system. As a part of a follow-up plan, the DTC must assess the need to continue, modify, or stop the DUE activity depending on the results of each specific medicine review.

All programs within the DTC should be evaluated yearly. This complete evaluation is necessary to look comprehensively at the entire program and analyze its merits and its utility in improving medicine use. Programs that do not have a significant impact on medicine use should be redesigned so that they can provide measurable improvements. Without improvements in medicine use and patient outcomes, the time spent on DUE will be of no value.

1.5 Introduction to antibiotics

Definition

Antibiotics may be informally defined as the subgroup of anti-infectives that are derived from bacterial sources and are used to treat bacterial infections.⁶ “Antibiotic” is a catch-all for any kind of molecule that is toxic to living microorganisms (including bacteria or fungi). This overarching term is often used interchangeably with “antibacterials” - or drugs that specifically kill bacteria or inhibit bacterial growth.^[5]

Antibiotics are the widely used drugs in modern medical care. These drugs are majorly used for both prophylaxis and treatment of infectious diseases.^[8] Antibiotics have been derived from natural products or synthesized chemically. There has been enormous development in the field of novel antibiotic discovery in the last seven decades. Based on their chemical structures, antibiotics have been classified as beta-lactam antibiotics, aminoglycosides, tetracyclines, macrolides, streptogramins, quinolones, glycopeptides, polyketides and oxazolidinones.^[9]

1.6 Resistance

Initially, antibacterials were seen as truly miraculous drugs and considered the “panacea” of Medicine, but nowadays the evolution of drug-resistant organisms has greatly impaired their therapeutic efficacy.^[10]

In 1928, Alexander Fleming made his mark on modern medicine when he isolated the first antibiotic from *Penicillium*, a common fungus. Unfortunately, this rapid emergence of penicillin-resistance has proven to be a trend. Since the 1940s, many new types of antibiotics have been discovered and approved in the clinic; however, resistant bacteria often emerge in as few as 5 years after an antibiotic's introduction.

As early as 1945, Sir Alexander Fleming raised the alarm regarding antibiotic overuse when he warned that the “public will demand [the drug and] then will begin an era of abuses.” The overuse of antibiotics clearly drives the evolution of resistance.^[11]

1.7 Beta Lactams

β -lactams are considered the most successful antimicrobial agents in the treatments of infections caused by gram-positive and -negative bacteria.^[13]

Mechanism of Action

The mode of action of beta-lactam antibiotics, and the non-enzymatic resistance mechanisms to their activity, are intimately linked to the structure and biosynthesis of the bacterial cell wall. The bacteriostatic effect of beta-lactam antibiotics is related to their various interactions and concomitant inhibition of essential enzymes (transpeptidases, carboxypeptidases) involved in the terminal stages of peptidoglycan biosynthesis. These cytoplasmic membrane-associated target enzymes bind the antibiotics covalently, and hence are known as

penicillin-binding proteins (PBPs). The bactericidal effect of these antibiotics is due to a second step following on from the inhibition of cell division and growth, in which the activation of an autolytic system causes cell death. Resistance to beta-lactam antibiotics in Gram-positive bacteria, in the absence of a beta-lactamase, is due to various modifications of the PBPs. Such mechanisms are often found in enterococci, pneumococcus, and staphylococci. With Gram-negative bacteria such modifications of PBPs are only a rare basis for resistance. The presence of an outer membrane brings another factor into the activity of beta-lactam antibiotics, which is the facility with which the antibiotics can diffuse through specialised proteins called porins.

1.8 Beta Lactamases

The most widespread cause of resistance to beta-lactam antibiotics like penicillins is the production of enzymes called beta-lactamases. Beta-lactamases are the enzymes produced by many Gram-negative and Gram-positive bacteria that inactivate beta-lactam antibiotics by opening the beta-lactam ring.^[14]

β -lactamases are enzymes that are responsible for many failures of antimicrobial therapy by hydrolysis of the beta-lactam ring. Most strains of *ENTEROBACTERIAE* and *PSEUDOMONAS AERUGINOSA* produce chromosomally determined class I beta-lactamases and these enzymes produce resistance to almost all β -lactams except imipenem and sometimes carbenicillin and tenocillin.^[14]

Types Of Beta Lactamases:^[14]

Major classification schemes exist for categorizing beta-lactamase enzymes.

Ambler classes A through D, based on amino acid sequence homology, is as follows:

Class A serine beta-lactamases

Class A ESBLs

Class A serine carbapenemases

Class B metallo- β -lactamases

Class C serine cephalosporinases: (AmpC)

Class D serine oxacillinases

1.9 Cephalosporins

These are the group of semisynthetic antibiotics derived from ‘cephalosporin-C’ obtained from a fungus cephalosporium.

Chemistry: Cephalosporins are β -lactam antibiotics that differ from the penicillins in that the B ring is a 6-membered dihydrothiazine ring. Variations among the cephalosporins are made on either the acyl side chain at the 7-position to change antibacterial activity or at the 3-position to alter the pharmacokinetic profile. The cephalosporins inhibit bacterial cell wall synthesis by blocking the transpeptidases.

Cephalosporins Mode of Action

Cephalosporins are a type of β -lactam antibiotic and have the same mechanism of action as penicillin. They are bactericidal, with the same MOA as other beta-lactams. Cephalosporins disrupt synthesis of the peptidoglycan layer of bacterial cell walls. Peptidoglycan is a strong structural molecule specific to the cells walls of bacteria. With the cell wall structure compromised, the bactericidal result is lysis and death of the cell.

Our cells do not have cells walls or peptidoglycan, therefore, B-lactam antibiotics are able to target bacterial cells without harming human cells.^[7]

Classification OF Cephalosporins

Cephalosporins are grouped into "generations" based on their spectrum of antimicrobial activity. Each newer generation of cephalosporins has significantly greater gram-negative antimicrobial spectrum than the preceding generation, and in most cases decreased activity against gram-positive organisms. Fourth generation cephalosporins, however, have true broad spectrum activity.^[16]

The newer agents have much longer half-lives resulting in the decrease of dosing frequency.

Cephalosporins are broad spectrum antibiotics classified into five generations. The list of chemical structures of different generations are shown below.

1.9.1 First-generation

These are most active against aerobic gram-positive cocci and include cefazolin, cephalixin, and cefadroxil and they are often used for skin infections caused by *S.aureus* and *Streptococcus*. They have activity against *E. coli* and some activity against *H.influenzae* and *Klebsiella* species, but because of the limited gram-negative coverage, they are not first-line agents for infections that are likely to be caused by gram-negative bacteria.

Uses

Uncomplicated skin and soft-tissue infections, uncomplicated urinary tract infections, streptococcal pharyngitis, surgical prophylaxis. Good alternatives to antistaphylococcal penicillins. NOT indicated for otitis media.

First generation cephalosporins do not penetrate well into the cerebral spinal fluid and are not good for CNS infections.

Cefazolin is the most commonly used 1st generation cephalosporin.^[16]

1.9.2 Second generation cephalosporins

These are more active against gram-negative organisms, such as *Moraxella*, *Neisseria*, *Salmonella*, and *Shigella*. Cefoxitin and cefotetan, also have more coverage against

anaerobic bacteria. The true cephalosporins that are also part of this class are cefprozil, cefuroxime, cefaclor, cefoxitin, and cefotetan. These drugs are used primarily for respiratory tract infections because they are better against some strains of beta-lactamase producing *H. Influenza*.

Uses

Upper and lower respiratory tract infections, acute sinusitis, otitis media, uncomplicated urinary tract infections. Cephamycins are useful for mixed aerobic/anaerobic infections of the skin and soft tissues, intra-abdominal, and gynecologic infections, and surgical prophylaxis.

Second generation cephalosporins don't cross the blood-brain barrier and are NOT used for CNS infections.

Cefoxitin

1.9.3 Third generation cephalosporins:

These have the most activity against gram-negative organisms, including *Neisseria* species, *M. catarrhalis*, and *Klebsiella*, while ceftazidime is active against *P. aeruginosa*. These agents have less coverage of the gram-positive cocci, notably methicillin-sensitive *S. aureus*. In addition to the agent with antipseudomonas coverage, this class includes cefdinir, cefditoren, cefixime, cefotaxime, cefpodoxime, ceftibuten, and ceftriaxone. These drugs are useful for more severe community-acquired respiratory tract infections, resistant infections, and nosocomial infections (because of the high incidence of resistant organisms).

Uses

Gram-negative bacillary meningitis, serious infections of Enterobacteriaceae, upper respiratory tract infections, otitis media, pyelonephritis, skin and soft tissue infections. Ceftriaxone is indicated for Lyme disease and gonorrhoea. Cefotaxime, ceftazidime, ceftriaxone, ceftizoxime, and moxalactam have excellent penetration into the cerebrospinal fluid. Enterobacter species have a tendency to become resistant during cephalosporin therapy, and thus cephalosporins are not the drugs of choice for Enterobacter infections.^[16]

1.9.4 Fourth-generation

Cefepime is involved in this class because it has good activity against both gram-positive and negative bacteria, including *P. aeruginosa* and many Enterobacteriaceae. The gram-negative and anaerobic coverage makes cefepime useful for intra-abdominal infections, respiratory tract infections, and skin infections.

Uses

Cefepime and ceftiprome are highly active against nosocomial pathogens and are primary used for nosocomial infections.

Cefepime penetrates the CNS and can be used in the treatment of meningitis.^[16]

1.9.5 Fifth-generation cephalosporins

Ceftaroline fosamil is the only advanced generation cephalosporin; it has enhanced activity against many both gram negative and positive bacteria. It is active against community-acquired pneumonia infections caused by *E. coli*, *H. influenzae*, *Klebsiella*, *S. aureus* (methicillin-susceptible isolates only), and *S. pneumoniae* and safe for treating skin infections caused by multidrug-resistant *S. aureus*.

Adverse Drug Reactions

1. Cephalosporins are generally well tolerated, but are more toxic than penicillin.
2. Pain after I.M injection occurs with many. Thrombophlebitis of injected vein can occur.
3. Diarrhoea is more common with oral cephradine and parenteral cefoperazone.
4. Hypersensitivity reactions caused by cephalosporins are similar to penicillins but incidence is lower. About 10% patients allergic to penicillin show cross reactivity with cephalosporin.
5. Nephrotoxicity is highest with cephaloridine, cephalothin.
6. Bleeding with cefoperazone, ceftriaxone.
7. Neutropenia and thrombocytopenia are rare ADRS reported with ceftazidime Etc.
8. A disulfuram like interaction with alcohol has been reported with cefoperazone.

2. LITERATURE REVIEW

1). Dr. Bandari Kiran et al 2015: A prospective observational study was carried out for in-patients in various clinical departments. This study provides the data on the nature and extent of utilization of cephalosporins in patients admitted to different clinical departments in a tertiary care hospital, Hyderabad. A total of 121 cephalosporin's prescribed patients are identified in the different department ward are included in this study focused on the pattern of generation of cephalosporin prescribed. 115 patients analyzed from various in-patient departments in duration of six months periods of the study, it was observed that the hospital physicians prescribed cephalosporin's more rationally with no banned drugs and newer drugs. From over view of the study, cephalosporin's especially third generation drugs were widely used compare to second generation of drugs.

Because of their activity includes the aerobic gram negative bacteria covered by aminoglycosides, the clinical situations requiring use of third generation cephalosporins are likely to be encountered in patients who are hospitalized, have recently received antibiotics, or are immunocompromised.

2). Meher B. R.*et.al: A study on antibiotic utilization pattern in a general medicine ward of a tertiary care teaching hospital Meher B. R.*, Mukharjee D. and Udayshankar, Journal of Chemical and Pharmaceutical Research, 2014, 6(7):1847-1849.

Irrational use of antibiotics can cause increase adverse drug reaction, lead to antibiotic resistance and increase the treatment cost. Assessment of pattern of antibiotics utilization is significant in the context of its increase use and its overall impact on the health care system. The present study was a prospective study done in general medicine ward of a tertiary care teaching hospital to analyze the utilization pattern of antibiotics. 200 patients were included in the study. Most common cause of antibiotics intake was respiratory tract infection. Most common antibiotic used was ceftriaxone. Antibiotics were mostly prescribed by brand name. As antibiotics are most commonly prescribed drugs and report of misuse is not uncommon so proper strategy like educational intervention and antibiotic policy are necessary to control this. ceftriaxone(30.03%), coamoxiclav(22.6%), amikacin(16.33%), ciprofloxacin(13.41%), metronidazole(12.34%), levofloxacin(5.09%). Out of 373 antibiotics prescribed 332 (89%) were written in trade name and 41(11%) in generic name.

Our study concluded that most common disease for which antibiotics prescribed was respiratory tract infection. Most common antibiotic used was ceftriaxone, more than one antibiotic was prescribed and only 11% antibiotics were prescribed in generic name. A strict protocol for prescribers is required to promote rational use of antibiotics which would not only prevent antibiotic resistance but also reduce the treatment expenditure.

5). Vandana A Badar*: Study of Prescribing Pattern of Antimicrobial Agents in Medicine Intensive Care Unit of a Teaching Hospital in Central India Vandana A Badar*, Sanjaykumar B Navale**

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Objectives: Intensive care unit (ICU) is a setting where large numbers of drugs are administered to patients and where the cost of hospitalization and drug treatment are high. The primary objective was to evaluate the current usage of anti-microbial agents in the Medical Intensive Care Unit (MICU) of a teaching hospital in central India.

Methods: The study was a prospective study for a period of six months from May 2010 – December 2010. Prescription and patient records are reviewed and analyzed. rationality of drug usage was also evaluated by analyzing the drug prescriptions.

Results: In intensive care unit cefotaxime was the most commonly used AMA by 32 % patients, followed by metronidazole 24% patients and ampicillin by 17.29% patients. 77% patients were given 1- 3 AMAs, 23 %

patients were given 4 – 8 AMAs. Most common indication for the antimicrobial therapy was infection. According to evaluation use of antimicrobial therapy was rational in only 30% patients. Average numbers of drugs per patients were 7.5 drugs.

Other antibiotics used were injection meropenem, amoxicillin + clavulanic acid levofloxacin, ceftriaxone(32%), vancomycin, ciprofloxacin, linezolid and amikacin.

Conclusion: interventional programme should focus on infection control with rational antibiotic prescription aimed at minimizing unnecessary cost, adverse drug reaction and emergence of bacterial resistance.

6). Harish Govind Naik: International Journal of Recent Trends in Science And Technology, ISSN 2277-2812 E-ISSN 2249-8109, Volume 10, Issue 2, 2014 pp 299-302

Drug Utilization Study on Antibiotics Use in the Upper Respiratory Tract Infection Harish Govind Naik¹, Chitra C. Khanwelkar², Ashwini Kolar^{3*}, Rohit Desai⁴, Sunil Gidamudi⁵

This drug utilization study was conducted to evaluate the pattern of antibiotics use in Medicine Department of a Krishna Hospital, Karad, and Maharashtra, India. 200 case records were examined, of which 56.5% were URTI (nonspecific URTI), 28% were sinusitis, pharyngitis and CSOM accounted for 24% and 7% respectively. Female accounted for 64% and male for 36% of total cases

The most frequently prescribed antibiotic was Azithromycin, followed by ceftriaxone.

Prescribing by generic names has to be encouraged.

7). Nalamaru Surendra Reddy 2015: The study concludes that the prescribing frequency of third generation cephalosporin's were more frequently in paediatric patients. The treatment regimen application in majority of the cases is done without doing any culture sensitivity test which may lead to wide spread of irrational prescription. So physician must be more specific in their diagnosis despite the financial burden of culture test. ADR recording habit in health care facilities will promote the rational therapy in future. Rational drug usage education programs and antibiotics order form application in the hospitals will inappropriate therapy. The involvement of the clinical pharmacist may also improve the rational prescribing of cephalosporins.

17). Reddy et al 2015: Cephalosporin was mostly used for specific therapy in general medicine department where as it is used as pre-surgical prophylaxis in the department of general surgery. In the department of General medicine, the most common indication for use of Cephalosporin was Respiratory tract infections, whereas in the department of General Surgery, wound

debridement was the most common indication. About 72.8% of patients received 3rd generation Cephalosporins only. Ceftriaxone was the most commonly prescribed cephalosporin in general medicine department, while Ceftriaxone- Tazobactam was the most prescribed cephalosporin in general surgery. Defined Daily Doses evaluation was conducted for all the Cephalosporins prescribed for the study patients. The hospital was largely compliant to WHO DDDs. The average duration of use of Cephalosporins in general medicine department was 5 days; while it was 8.5 days in general surgery department.

18). Kiran Nagaraju et al 2014: The frequently prescribed antibiotics were cephalosporins followed by quinolones and macrolides. In cephalosporin class, ceftriaxone usage was more common and also in combination with salbactam. Periodic study on the usage of antibiotics and sensitivity pattern in the study hospital set up should be conducted to enables the health care professionals to select the appropriate antibiotic regimen to promote rational usage of antibiotics.

19). Babu et al 2012: Cephalosporins especially third generation were widely used in medicine departments to treat various disease conditions. Urinary tract Infections is the major disease condition followed by Respiratory tract Infections and Digestive system infections were seen in the admitted patients. Antibiotics usage cost is accounted for 70% of the total Hospital stay.

20). Prakash Goudanavar 2016: Prescriptions of 100 patients containing third generation cephalosporins were collected and the utilization pattern were analyzed by using WHO drug core indicators. The average number of drugs per prescription was found to be 8.62. Only 2.43% of drugs were prescribed by generic name. The percentage of total prescriptions for antibiotics was 13.92%, for injections were 12.06% and drugs prescribed from EDL was 53.82%. Ceftriaxone was most frequently prescribed (64%) third generation cephalosporins in parenteral form, followed by cefoperazone(15%). Gender analysis revealed that male (56%) patients prescribed with third generation cephalosporins were more compared to female (44%). With regard to age, 73.33% of males were in above 60 years age group while 66.66% of females were in 11-20 years age group.

22). Hyuck Lee1 2009: The average patient age was 64.4 years. The utilization of ceftriaxone was appropriate in 262 cases (65.5%) for the justification of use, while inappropriate use was observed in 138 cases (34.5%). Common reasons for inappropriate use of ceftriaxone included continued empiric use for presumed infections, prophylactic perioperative injection, and empiric therapy for fever. Most of the critical indications showed a high rate of suitability (66.5-98.5%). Complications occurred in 37 cases (9.3%). With respect to outcome measures, clinical responses were observed in 60.7% of cases,

while only 15.7% of cases showed evidence of infection eradication via negative cultures.

23). Swarnalatha et al 2016: We collected 105 ceftriaxone contained prescriptions. Of these, males (63.8%) and patients with the age group of 1-5 (33%) years were more exposed. We found (71%) of cases were given the drug for correct indication. We also found that (24%) of diagnosis were central nervous system related. We have seen that the maximum dose given per day was highest in case of children of age group 5-14 years. We also identified that the duration of therapy (79%) was found to be high in the range of 2-7 days. We noticed that (50.5%) received the drug based on clinical symptoms.

Ceftriaxone was found to be mostly prescribed according to indication. It was found to be highly used in central nervous system diseases followed by gastrointestinal and respiratory diseases.

28). Deepak Prashar* et al 2014: From the present study it could be concluded that drug utilization of IIIrd generation cephalosporin in Solan is quite high. Cefixime (TIME) (30%) and ceftriazone (MONOCEF) (20%) are used in Solan. Since these agents are expensive hence it clearly indicates the economical standard of people of Solan. Also these agents are quite often used for neonatal infection which is matter of further consideration.

METHODOLOGY

3.1 Objectives

1. To determine the prescription pattern of antibiotics.
2. To obtain information about the most suitable routes of administration of cephalosporin's and inappropriate duration of drug treatment in patients.
3. To determine the average number of antibiotics per prescription (encounter).
4. Percentage of drugs prescribed by generic and brand name of cephalosporins.
5. Percentage of encounters resulting in prescription of cephalosporins and injection form.
6. Identify the rational/irrational usage, therapeutic treatment, co-morbidity conditions to the patients.
7. To monitor and reporting of adverse drug reaction, if any.
8. To monitor and report drug interactions, if any.

An Institutional Ethical committee clearance is obtained to conduct the study. This study was conducted in vijay marie hospital, tertiary care teaching centre, providing specialized health care services to all strata of people in and around Hyderabad. We conducted a hospital based prospective study, to study the drug utilization pattern of cephalosporin's, antibiotics for over a period of six months.

3.2 Materials and Methods

The data was collected in a predesigned Performa from the medical case sheets, drug charts, and laboratory investigations of 150 in-patients. This was a prospective observational study carried out for in-patients in varies clinical departments. Prescribing data are usually extracted from inpatient prescription forms. Prescribing data were extracted from patient records. Information that may be obtained from prescriptions includes patient demography, drug name, dosage form, strength, dose frequency, route of administration and duration of treatment. Cephalosporins co-prescribed with other antibiotics, varies cephalosporins utilization in hospital stay, department wise cephalosporins utilization.

Study Site: Vijaya Marie Hospital, Khairatabad, Hyderabad.

Study Design: Study is designed to be a Prospective Observational Study.

Study Period: Study was conducted over period of 6 months.

Study Subjects: The participants enrolled in the study involved inpatients coming to the hospital, only after filling a properly written informed consent. Basic demographic information and details of the prescribed antibiotics and their prescribing patterns, diseases for which they were indicated, dosage form of antibiotics and whether mono- or multi-therapy is used, were documented in all patients. In view of collecting the after mentioned details, the data from patients was obtained every day from the clinical assessment records, including medical records and other relevant information sources as documented, including laboratory investigations. Descriptive analysis was carried out for the data obtained.

3.3 Selection Criteria

Inclusion Criteria: We have included the inpatients from various departments of medicine, surgery, orthopedics and paediatrics.

Inpatients

1. Department of Medicine
2. Department of Surgery
3. Department of Paediatrics

Exclusion Criteria: We have excluded the malignancy, HIV and pregnant patients.

1. Malignancy Patients
2. HIV associated patients
3. Pregnant patients.

3.4 Source of Data: Patient data relevant to our study was obtained from the following sources and recorded in the well-designed patient data collection form:

1. Treatment chart/case sheet, lab report.

3.5 Study Procedure

Patient enrolment

1. A hospital based prospective conducted in medicine units of vijay marie hospital hyderabad. The information was collected from case note of patient prescribed with Cephalosporin antibiotics or in combination during our six month study period. A total patient's case note were selected from inpatient medical record. The information obtained from each patient case note was entered into a well-designed data collection form.
2. Determination of prescribing pattern :Well-designed data collection form was prepared and required information was extracted from inpatient's information sheet which includes all the detail of patients like:
3. Patient Demographics: Name, age, gender, weight, blood pressure, personal history, medication history. Presenting complain, past medical history, any drug allergy, family history of patients.
4. Drug data which includes name of the drug, dosage regimen, dose and route of anti-microbial agent (AMA), AMAs per patient, duration of therapy.

3.6 Data Collection

A Performa were designed and pre tested to be used for entry of patient's specific information. The format provided the following information.

1. Patient's Name
2. IP Number
3. Bed number , ICU room name
4. Age, Sex
5. Date of admission (DOA) and Date of discharge (DOD)
6. Different specialties and consultant name
7. Previous drug allergy
8. Diagnosis
9. Past medical & medication history
10. Dose of the drug
11. Dosage form
12. Route of administration
13. Frequency of administration
14. Antibiotics prescribed at the time of discharge
15. Patient demographic details, medical and medication history will be collected and will be documented in a suitably designed data collection form.

3.7 Statistical Analysis: Descriptive analysis will be done by using MEAN and simple percentage method.

3.8 Items Monitoring in the Study

1. Sex and age distribution of patients using Cephalosporins.
2. Generations of Cephalosporins prescribed.
3. Duration, dosage form & route of administration of Cephalosporins.
4. Average number of Cephalosporins per prescription.
5. ADRs associated with prescribed Cephalosporins.
6. Drug-drug interactions associated with Cephalosporins.

7. Cephalosporins co-prescribed with other antibiotics.
8. Co-morbidity conditions in patients.
9. Department wise cephalosporins utilization.

3.9 Limitations

- a. It is a short duration of DUE study conducted for evaluation of prescribing pattern of drugs.
- b. There was no standard treatment guidelines prepared and implemented to check the utilization pattern of cephalosporins.
- c. The study population size was less for a drug utilization evaluation studies to conclude the rationality of prescribing, these cephalosporins.

RESULTS AND DISCUSSIONS

4.1 Total Number of Patients

Corresponding to Table (1) represents One hundred fifty (150) patients were treated with cephalosporins during the six months period of study from August 2016 to January 2017. Those patients utilized the different clinical departments in the hospital.

The study included total of 150 patients among which 97(66.66%) patients were female and 53(33.33%) patients were male.

Table 4.1: Number Of Patients: (N=150).

Gender	Number of patients	Percentage (%)
Male	53	33.33
Female	97	66.67
Total	150	100
Mean	75	50

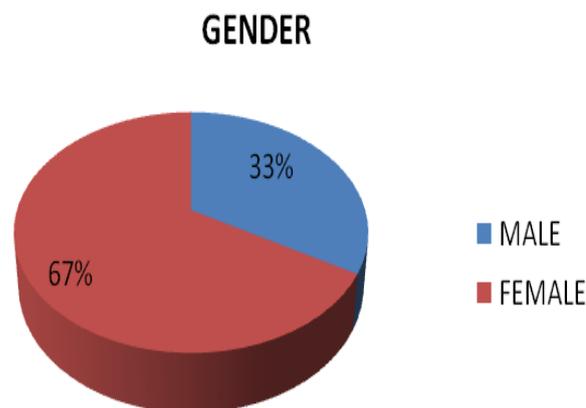


Figure 4.1: total number of patients.

4.2 Distibution of Patients Age

Corresponding to table (2) represents age with gender distribution of the study population. It was found that 33(22%) patients were between the age of 0 to 5 years out of which 17 patients were female and 16 were male. 28(18.67%) patients were between the age of 6 to 15 years, out of which 15 were female and 13 were male. 29(19.3%) patients were between the age of 16 to 25 years, out of which 18 of them were female and 11 were found to be male. 21 (14%) patients in the range of 26 to

35 years, out of which 15 were female and 6 were found to be male. 15(10%) patients were between the age of 36 to 45 out of which 13 were female and 2 were found to be male. 13(8.67%) patients were between the age of 46 to 55 years, out of which 10 were female and 3 were found to be male. 5(3.33%) patients were between the age of 56 to 65 years, out of which all 5 were found to be female. 6 (4%) patients were between the age of 66 to 75 ,out of which 4 were female and 2 were found to be male.

Amongst all the age groups, it was found to be highest number of population (22%) prescribed with cephalosporins were between 0-5yrs of age group.

Table 4.2: Distribution Of Patients Age Table

Age	Male	Female	Total	Percentage (%)
0-5	16	17	33	22
6-15	13	15	28	18.67
16-25	11	18	29	19.3
26-35	6	15	21	14
36-45	2	13	15	10
46-55	3	10	13	8.67
56-65	-	05	05	3.33
66-75	2	4	06	4
Total	53	97	150	100
Mean			18.75	12.5

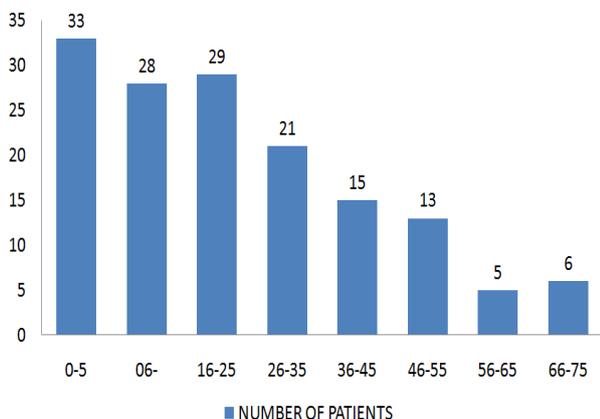


Figure 4.2: distribution of patients age.

4.3 Cephalosporins Utilization

Prescribed drugs during hospital stay

Corresponding to table (03) represents. The cephalosporins were prescribed to the patients (150), used generic (13) 8.66% and brand drugs (137) 91.3% with the mean percentage 50% were prescribed during hospital stay. The low rate of generic prescribing has been linked to pressure from patients and high marketing strategy of the pharmaceutical companies. Generic prescribing helps the hospital pharmacy to have a better inventory control. Confusion among the pharmacists while dispensing can also be reduced, when prescribed by generic names. Moreover, generic drugs are more cost effective than the branded ones.

Table 4.3: Cephalosporins Utilization Table.

Drugs	Number of patients	Percentage(%)
Brand	137	91.34
Generic	13	8.66
Total	150	100
Mean	75	50

CEPHALOSPORINS UTILIZATION

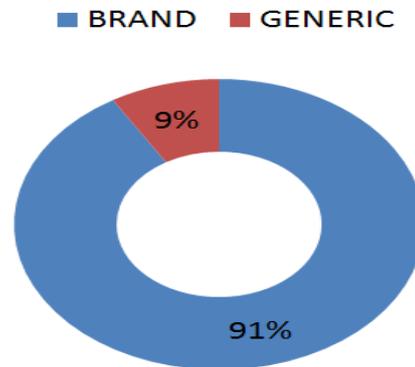


Figure 4.3: Cephalosporins Utilization.

4.4 Route of Administration

Corresponding to the table represents The route of administration of cephalosporin's were intravenous (134) 89.33%, oral (16) 10.66%, with the mean percentage was 50%.

Table 4.4: Route Of Administration Table.

S.no	Route of administration	Number of drugs	Percentage (%)
1	Intravenous(iv)	134	89.33
2	Oral	16	10.67
	Total	150	100
	Mean	75	50

IV vs ORAL

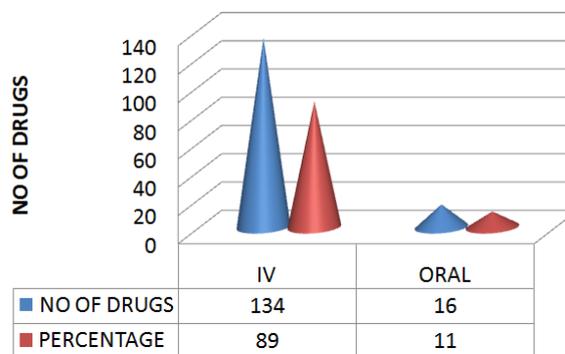


Figure 4.4: Route of Administration.

4.5 Generations of Cephalosporins Used in Hospital Stay

Corresponding to table represents It was observed that second (4%) and third generation (96%) cephalosporins were prescribed mostly among the five classes, with the mean 50.

Table 4.5: Generations Of Cephalosporins Used In Hospital Stay.

S.no	Generation	Number of patients	Percentage (%)
1	2 nd generation	6	4
2	3 rd generation	144	96
	Total	150	100
	Mean	75	50

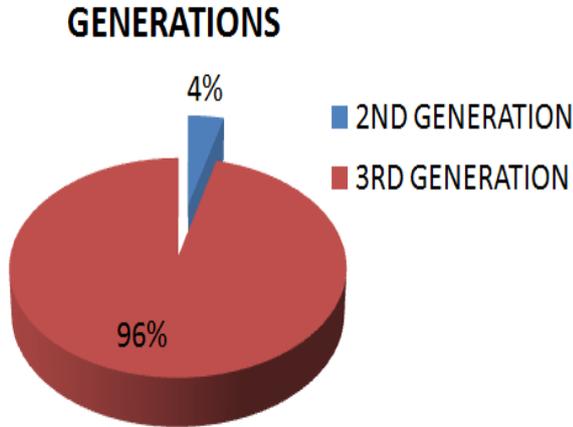


Figure 4.5: Generations of Cephalosporins Used in Hospital Stay.

4.6 Most prescribed cephalosporins during hospital stay

cephalosporins were used in the treatment of patients in various diseases, variety of drugs were prescribed mainly, Ceftriaxone (108) 72%, Cefotaxime (33)22%, Cefpodoxime (5)3.33 %, Cefixime (2)1.33%, ceferazone (1) 0.67%, Cefuroxime(1)0.67%, with the mean percentage of 16.66% . Ceftriaxone (72%) was the most prescribed third generation cephalosporin and used more frequently in injection form. This is because the parenteral third generation cephalosporins have excellent activity against most bacterial infections.

Table 4.6: Most Prescribed Cephalosporins During Hospital Stay.

S.No	Type of cephalosporins	Number of patients	Percentage (%)
1	Ceftriaxone	108	72
2	Cefotaxime	33	22
3	Cefixime	02	1.33
4	Cefpodoxime	05	3.33
5	Cefuroxime	01	0.67
6	Cefoperazone	01	0.67
	Total	150	100
	Mean	25	16.66

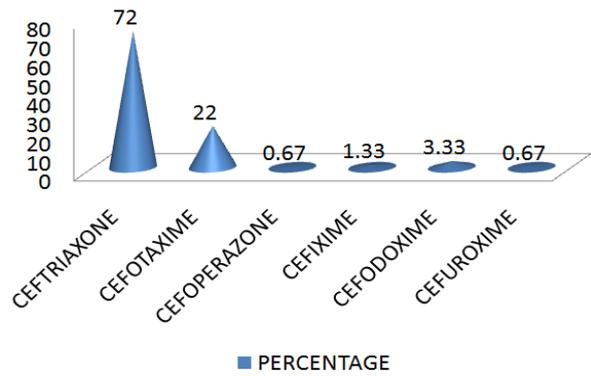


Figure 4.6: Most Prescribed Cephalosporins During Hospital Stay.

4.7 Disease Wise Distibution

Corresponding to table represents The study on the utilization pattern of cephalosporin antibiotics for various infections revealed that it was commonly used to treat 68(45.3%) patients with fever(viral,enteric,dengue) followed by 18(12%) patients for acute gastro enteritis, 14(9.33%) patients for urinary tract infections,11(7.33%) patients for gynaec related problems ,6(4%) patients for lower respiratory tract infections ,5(3.33%) patients for epilepsy ,4(2.66%) patients for having URTI and cystitis ,3(2%) patients for having uncontrolled DM,haemorrhoids,2(1.33%) patients for having cholelithiasis, hepatitis and miscellaneous. Other conditions like 1 (0.66%) patient for having pancreatitis, measles, cervicalspondylitis, appendicitis, VBI, cholecystitis, hypo glycaemia, and hypotension.

Table 4.7: Disease Wise Distribution Table.

1	Fever	68	45.3
2	Acute gastro enteritis	18	12
3	Urinary tract infection	14	9.33
4	Gynaec	11	7.33
5	Lower respiratory tract infections	06	4
6	Epilepsy	05	3.33
7	Upper respiratory tract infections	04	2.66
8	Cystitis	4	2.66
9	Uncontrolled diabetes mellitus	3	2
10	Haemorrhoids	3	2
11	Cholelithiasis	2	1.33
12	Hepatitis	2	1.33
13	Miscellaneous	2	1.33
14	Pancreatitis	1	0.66
15	Measles	1	0.66
16	Cervical spondylitis	1	0.66
17	Appendicitis	1	0.66
18	VBI	1	0.66
19	Cholecystitis	1	0.66
20	Hypoglycemia	1	0.66
21	Hypotension	1	0.66
	Total	150	100

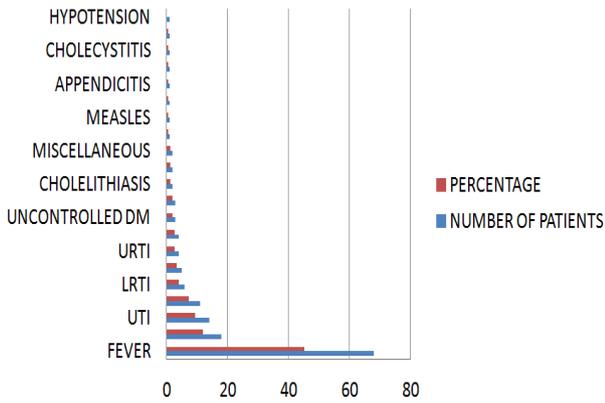


Figure 4.7: Disease Wise Distribution.

4.8 Co-prescribed antibiotics with cephalosporins

Corresponding to table represents Fifty three (53) patients were received cephalosporins along with other co-prescribed antibiotics in the treatment. The majority of other co-prescribed antibiotics were Metronidazole prescribed in sixteen (16) patients ,with the mean percentage of 30.18%,followed by amikacin and azithromycin prescribed in ten (10) patients each .ofloxacin prescribed in seven (7) patients and amoxicillin prescribed in six(6)patients .other antibiotics like ciprofloxacin and levofloxacin prescribed in two(2) patients each.

Table 4.8: Co-Prescribed Antibiotics With Cephalosporins Table.

S.no	Co-prescribed antibiotics	Ceftriaxone	Cefotaxime	Cefpodoxime	Total	Percentage(%)
1	Amikacin	7	3	-	10	18.86
2	Amoxicillin	5	-	1	06	11.32
3	Azithromycin	8	1	1	10	18.86
4	Ciprofloxacin	1	1	-	2	3.79
5	Levofloxacin	2	-	-	2	3.79
6	Ofloxacin	6	-	1	7	13.20
7	Metronidazole	12	4	-	16	30.18
	Total	41	9	3	53	100
	Mean				7.57	14.28

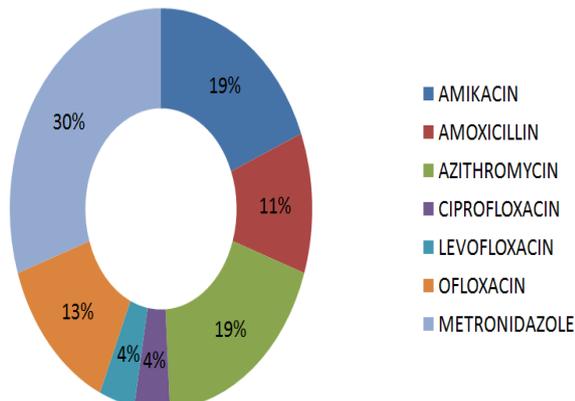


Figure 4.8: Co-Prescribed Antibiotics With Cephalosporins.

4.9 Co-Morbidity Conditions in Patients

Co-morbidity conditions were experienced in thirty two (32) patients with(21.3%) and one hundred eighteen (118) patients 78.67% patients were not experienced with co-morbidity conditions in out of 150 patients, with the mean percentage were 10%.

The majority of co-morbidity condition with diagnosis was HTN in seven(7) patients with 4.66%, and also other co-morbidity conditions were significantly followed DM(6) 4%, EPILEPSY(5) 3.33%, HYPOTHYROIDISM(3) 2%, ASTHMA (2) 1.33%, HYPERTHYROIDISM(1)0.66%, COPD(1)0.66%, HTN, DM (6) 4%.

Table 4.9: Co-Morbidity Conditions In Patients Table.

S. no	Co-morbidity	No.of patients	Percentage
1	None	118	78.6
2	Hypertension	07	4.66
3	Diabetes mellitus	06	4
4	Hypothyroidism	03	2
5	Hyper thyroidism	01	0.66
6	Epilepsy	5	3.33
7	Asthma	02	1.33
8	Hypotension	01	0.66
9	Copd	01	0.66
10	Dm,htn	06	4
	Total	150	100
	Mean	15	10%

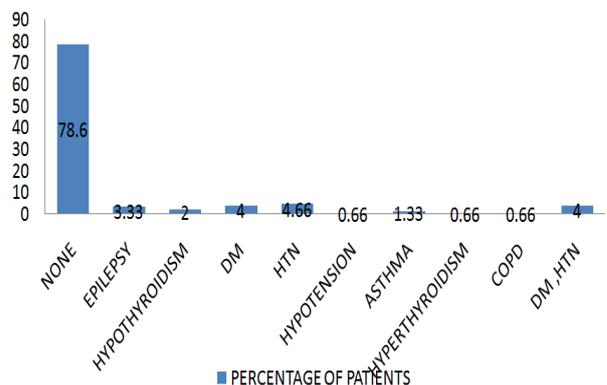


Figure 4.9: Comorbidity Conditions in Patients.

CONCLUSION

This is a prospective observational study provides data about utilisation pattern of cephalosporins conducted over a period of six months which includes 150 patients prescribed with cephalosporins. Amongst all, highest population prescribed with cephalosporins are between 0-5 years of age group. It was observed that, Third generation cephalosporins most importantly, Ceftriaxone was more frequently prescribed drug. Cephalosporins are generally prescribed for various diseases like fevers, Acute gastritis, Respiratory and Urinary tract infections and Uncontrolled Diabetes, of which major are given for fevers. The physician must rely more on laboratory data for definitive diagnosis to minimise empirical therapy. Wide range of use cephalosporins without relevant data may cause resistance. Alternatives such as Low class of antibiotics like aminoglycosides, tetracyclines etc. can be prescribed for less severe diseases. Metronidazole was the most commonly co-prescribed antibiotic along with cephalosporins. From this, study it was observed that physicians are prescribing cephalosporins more rationally by avoiding banned and newer class of agents. Periodic study on antibiotics enables the health care professionals to select appropriate antibiotic regimen.

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