A STUDY ON DRUG UTILIZATION EVALUATION OF FLUOROQUINOLONES IN MEDICINE UNITS OF RURAL TERTIARY CARE TEACHING HOSPITAL

By

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Mr. M. KUMARASWAMY
M. Pharm

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List of Abbreviations used

Abbreviations	Expansions
FQs	Fluoroquinolones
CAP	Community Acquired Pneumonia
UTI	Urinary Tract Infection
RT	Respiratory Tract
GIT	Gastrointestinal Tract
AECB	Acute exacerbations of chronic bronchitis
ATC	Anatomical Therapeutic Chemical
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
CNS	Central nervous system
PID	Pelvic Inflammatory Disease
OD	Once daily
BD	Twice daily
MIC	Minimum Inhibitory Concentration
AUC	Area Under the Curve
WHO	World Health Organization
FDA	Food and Drug Administration
DUE	Drug Utilization Evaluation/Drug Use Evaluation
MUE	Medication Utilization Evaluation
DUR	Drug Utilization Review
DDD	Defined Daily Dose
SD	Standard Deviation

List of Abbreviations used

ADR	Adverse Drug Reaction
DI/DDIs	Drug Interaction/Drug-Drug Interactions
AH&RC	Adichunchanagiri Hospital & Research Center

ABSTRACT

Background

Fluoroquinolones (FQs) are among the most commonly prescribed antimicrobials and are used inappropriately for unnecessary indication which may increase the risk of developing fluoroquinolone resistant in microorganisms.

Objective

This study was aimed to evaluate the drug utilization evaluation of fluoroquinolones among hospitalized patients in medicine units of rural tertiary care teaching hospital.

Methodology

A prospective and observational hospital based study was carried out in 108 inpatients of medicine units in Adichunchanagiri Hospital and Research Center, BG Nagara during the study period of 7 months. Ethical clearance was obtained from the ethical committee prior to the study. A well designed patient data collection form was developed and used for this study. Inpatients who met the study criteria were enrolled to the study for assessing drug utilization pattern of fluoroquinolones after obtaining their written consent from patients.

Results

Among 108 patients, 60 were males and females were 48. Mean ± SD number of drugs prescribed and duration of hospitalization were 10.10 ± 3.16 and 6.84 ± 3.77 days respectively. It was observed that 92.59% patients received fluoroquinolone for empirical treatment. An average of 1.06 fluoroquinolones per prescription was prescribed where oral route account more than the parenteral route. Ciprofloxacin was the most commonly prescribed FQs and it was mostly used BD. FQs were most commonly used for respiratory disorders followed by digestive disorders and urinary tract infections. During

the study period 2 cases of E. coli were found resistance to ofloxacin and another with ciprofloxacin. Total of 72 potential/major DDIs were identified in 54 patients and no any adverse drug reactions were found in the study population and for 45.83% of DDIs necessary action were taken for further management.

Conclusion

The present study concludes that specific use of fluoroquinolone based on culture and sensitivity test is less. Ciprofloxacin was the most commonly prescribed FQ and it was mostly used BD. FQs were most commonly used for respiratory disorders followed by digestive disorders and urinary tract infections.

Key words:

Drug Utilization Evaluation (DUE), Fluoroquinolones (FQs), Resistance

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Chapter-I

Introduction

Introduction

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".[1]

Drug Utilization Evaluation (DUE) has been defined by the American Society of Health System Pharmacists (ASHP) as a "Criteria-based, ongoing, 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".[2]

DUE is a method by which information is retrieved to identify problems of drug use and also serves as a means to rectify the problem, there by contributing to rational drug therapy. DUE examines the process of drug administration, dispensing, outcomes of treatment, thereby helping the health care system to realize, interpret and ameliorate the prescribing, administration and utilization of medication.[2]

Antibiotics deserve their place as one of the most powerful pillars of modern medical care, along with vaccines and oral rehydration salts represent potential agents in preventing mortality as well as morbidity. In India, the prevalence of antibiotics use varies from 24-67% and also contributes significantly to the cost of drugs. Antibiotics claimed worldwide to account for 15-30% of total health budget but in India cost is as high as 50% of the total health budget.[3]

Antibiotics are widely used medicines to treat both life threatening and trivial infections. Their indiscriminate use increases the risk of bacterial drug resistance. Hospitals are key places for antibiotic use and therefore also the settings for the selection and spread of resistant bacteria between patients, and finally in to the community.[4]

Introduction

The history of development of the synthetic broad-spectrum antibacterial agents with bactericidal activity is described from the first quinolone, nalidixic acid, discovered in 1962 by Lescher and colleagues, via the first 6-fluorinated quinolone norfloxacin, to the latest extended-spectrum fluoroquinolones. The first fluoroquinolones were widely used because they were the only orally administered agents available for the treatment of serious infections caused by gram-negative organisms, including Pseudomonas species. These compounds have been successfully used in the clinic for a decade and the size of the market has risen in recent years to only a little less than that for penicillins and macrolides.[5, 6]

Gatifloxacin, moxifoxacin and trovafloxacin have all greatly improved the activity against gram-positive cocci, particularly pneumococci, and against anaerobes. Clinafloxacin, gemifloxacin and sitafloxacin have even better activity against gram-positive cocci and are as active as ciprofloxacin against most gram-negatives, though gemifloxacin is less active than the other new compounds against gram-negative anaerobes. These three compounds do retain some activity against a number of ciprofloxacin-resistant species (gram-positive and gram-negative), but whether this activity will be adequate for clinical use is at present unclear.[5]

Fluoroquinolones account for about 11% of antimicrobial prescriptions in human medicine worldwide and represent the drug of choice for the treatment of a wide range of human infectious diseases including UTI, respiratory tract infections, skin and soft tissue infections, bone and joint infections and infections in the ear and eyes. The fluoroquinolones are also uses in different diseases like exacerbation of pulmonary disease in patient with cystic fibrosis, typhoid and paratyphoid fevers, gastrointestinal

tract infection, chronic suppurative otitis media, gram negative neonatal sepsis/meningitis, mycobacterial, chronic or acute osteomyelitis or osteochondritis. Following their introduction, resistant strains of bacteria, including Salmonella, started to emerge. In one study conducted in Europe suggested that there was decrease in susceptibility to ciprofloxacin with Klebsiella pneumonia (7.2%) and Klebsiella oxytoca (3.4%) but fluoroquinolones are on the WHO list of drugs that should be reserved for human use.[7, 8, 9]

The mechanism of action of quinolones is through the inhibition of bacterial DNA gyrase and topoisomerase IV, an enzyme involved in DNA replication, recombination and repair. By interfering with gyrase, quinolones arrest bacterial cell growth. The affinity of quinolones to metal ions seems to be an important prerequisite of their antibacterial activity: probably, quinolones bind to the DNA-gyrase-complex via a magnesium ion. However, unexpected adverse reactions, such as the CNS reaction, arthropathy, dysglycemia, idiosyncratic toxicities, the drug-drug interaction, phototoxicity, hepatotoxicity and cardiotoxicity such as the QTc interval prolongation of ECG, have been reported in the clinical evaluations or the post-marketing surveillance of several new quinolones. [6, 10, 11]

The classes of drugs showing the various potential of drug-drug interaction with fluoroquinolone are like di and trivalent metallic agents, gastric acid reducing agents, anti-TB drug, antiprotozoic drugs, analgesic, cardiaca, antigout, bronchodilator, anesthetics, muscle relaxant, antidiabetics, anticoagulant, opioids.[12]

Introduction

Several fluoroquinolones have had to be withdrawn or strictly limited in their use post-marketing and in some cases no obvious relationship can be seen between the adverse effects and structural features, making this an area for urgent research.[7]

Drug utilization evaluation (DUE) is an effective tool for monitoring the appropriateness of the usage of various medications and essential component of pharmacy service provision, and clinical pharmacy practice. DUE is a structured process to analyze the pattern of drug administration in various practice settings, including hospitals in relation to guidelines or predetermined standards. DUE programs will maintain the interventions that will improve patient outcomes.[13]

Study of drug utilization pattern in a particular setting give an idea about the prescribing practices and characterizes the early signals of irrational drug use and evaluate whether the drugs are properly utilized in terms of efficacy, safety, convenience and economic aspects at all levels in the chain of drug use.[14]

DUE study are required for all drugs in general and particularly for antibiotics because use of antibiotics in hospital account for 50% of the total health budget.[2, 5]

Adichunchanagiri Hospital and Research Center (AH&RC). AH&RC is a 1050 beded tertiary care teaching hospital situated in a rural area of B.G.Nagara, Mandya District, Karnataka-571448. The present study is designed to identify the utilization of fluoroquinolones and give a review of the prescribing practice of physicians in rural hospital which can be modified if necessary and facilate better health care delivery and also helps to promote the rationality and minimising the errors in the drug therapy.

Chapter -II

Objectives

"If you aim at nothing, you will hit it every time"

Author Unkown

Objectives

Objectives:

Primary objective:

- To study the drug utilization evaluation of fluoroquinolones in medicine units of rural tertiary care teaching hospital.

Secondary objective:

- To determine the incidence of use of fluoroquinolones.
- Assess the nature and extent of use of fluoroquinolones.
- To identify the potential drug-drug interaction/s between prescribed drugs.
- To assess the Adverse Drug Reactions (ADRs) of prescribed drug.

Chapter -III

Review of Literature

Drug Utilization Review (DUR) / Drug Use Evaluation (DUE)

DUE is an authorized, structured, ongoing, systematic review of physician prescribing, pharmacist dispensing, and patient use of medication. It involves a comprehensive review of patients prescription and medication data before, during and after dispensing to ensure appropriate medication decision making and positive patient outcomes.[15] DUE is the same as **drug utilization review** (DUR) and terms are used synonymously.

Drug utilization research is an essential part of pharmacoepidemiology as it describes the extent, nature and determinants of drug exposure. Hence in recent years studies on drug utilization have become a potential tool to be used in the evaluation of health systems. The interest in drug utilization studies began in the early 1960s and its importance has increased since then because of increase in marketing of new drugs, wide variation in the pattern of drug prescribing and consumption, growing concern about delayed adverse effects and the increasing concern regarding the cost of drugs.[16]

Other terms considered synonymous with DUR include drug use evaluation (DUE), medication use evaluation (MUE), and medication use management. American Society of Health System Pharmacists (ASHP) currently espouses the nomenclature medication use evaluation (MUE).[17]

In addition, continual improvement in the appropriate, safe and effective use of drugs has the potential to lower the overall cost of care. DUR allows the pharmacist to document and evaluate the benefit of pharmacy intervention in improving therapeutic and economic outcomes while demonstrating the overall value of the pharmacist.[17]

Scope of drug utilization evaluation-

Studies on the process of drug utilization focus on factors related to prescribing, dispensing, administering and taking of medication, and its associated events, covering the medical and non-medical determinants of drug utilization, the effects of drug utilization, as well as studies of how drug utilization relates to the effects of drug use, beneficial or adverse. Drug use evaluation (DUE) or DU studies is an ongoing, authorized and systematic quality improvement process, which is designed to-

- Review drug use and/or prescribing patterns
- Provide feedback of results to clinicians
- Develop criteria and standards which describe optimal drug use
- Promote appropriate drug use through education and other interventions.They observe the patterns of drug use with current recommendations or guidelines for the treatment of a certain disease.
- They provide feedback of drug utilization data to prescribers.
- They relate the number of cases of adverse effects to the number of patients exposed. If it is possible to detect that the reaction is more common in a certain age group, in certain conditions or at a special dose level, then information on proper use of drug can be improved such as indications, contraindications, appropriate dose etc. so that withdrawal of drug may be avoided.
- They evaluate drug use at a population level, according to age, sex, social class etc.
- They include concept of appropriateness that must be assessed relative to the indication for the treatment, concomitant diseases (that might contraindicate or interfere with chosen drug therapy) and the use of other drugs (interactions). Thus

they document the extent of inappropriate prescribing of drugs and also the associated adverse, clinical, ecological and economic consequences. Thus DUE plays a key role in helping the healthcare system to understand, interpret and improve the prescribing, administration and use of medications.

The principal aim of DU research is to facilitate rational use of drugs, which implies the prescription of a well-documented drug in an optimal dose on the right indication, with correct information and at an affordable price. It also provides insight into the efficacy of drug use i.e. whether a certain drug therapy provides value for money. DU research can thus help to set priorities for the rational allocation of health care budgets.[16]

Sources of drug utilization data-

Drug utilization data are available from databases- computerized or otherwise. From these databases different types of information, qualitative or quantitative or referring to a particular population are available. Data may be diagnosis linked or nondiagnosis linked. Diagnosis linked data gives information about drug consumption for a particular condition and outcome while nondiagnosis linked data gives information only about drug consumption in a population. Some databases generate information about patterns of drug utilization and adverse drug reactions. Databases may also provide data in the form of drug sales, drug movement at various levels of the drug distribution chain, pharmaceutical and medical billing data or samples of prescription. Such data are helpful in measuring the economic impact of drug use but does not provide information on the amount of drug exposure in the population. Data or information about sales is available through pharmacy records. They provide detailed information on the drugs but data on consumer is very limited. Also the

data lacks information on morbidity. Data from general practitioners records of prescriptions can be more informative about the indications for drugs prescribed, diagnosis and other health related data, but these data are not always consistently completed. Data on drug utilization may also be obtained directly from the population through Health Surveys at National level or smaller surveys such as surveys conducted in specific settings such as among university students, female population, or elderly outpatients. Such studies provide information on drug use from consumer themselves and are a source of data on many other health related issues. Data obtained from medical practices and health facilities are used to measure specific aspects of health provision and drug use. Such data may be used to generate indicators that provide information on prescribing habits and aspects of patient care. These indicators may be used to determine where drug use problem exists, provide a mechanism for monitoring and supervision and motivate health care providers to follow established health care standards. Prescription and dispensing data are useful for determining some of the quality indicators of drug use recommended by WHO. These include-

(a) Average number of drugs per prescription (encounter)

(b) Percentage of drugs prescribed by generic name

(c) Percentage of encounters with an antibiotic prescribed

(d) Percentage of encounters with an injection prescribed

(e) Percentage of drugs prescribed from essential drug list or formulary

(f) Average drug cost per encounter

Types of drug use studies-

DU studies are either Qualitative or Quantitative

Qualitative DU studies are multidisciplinary operations which collect, organize, analyse and report information on actual drug use. They usually examine use of specific drugs or specific conditions. Qualitative DU studies include the concept of criteria. Criteria are predetermined elements against which aspect of the quality, medical necessity and appropriateness of medical care may be compared. Drug use criteria may be based upon indications for use, dose, dosing frequency and duration of therapy. Qualitative studies assess the appropriateness of drug utilization and generally link prescribing data to reasons (indications) for prescribing. Such studies are referred to as DU review or DU Evaluation. The process is a "therapeutic audit" based on defined criteria and has the purpose of improving the quality of therapeutic care.

Quantitative DU studies involve the collection, organization and display of estimates or measurements of drug use. This information is generally used for making purchase decisions or preparing drug budgets. But data from quantitative drug use studies are generally considered suggestive, not conclusive with respect to quality of drug use. It is possible to combine both quantitative and qualitative DU studies, which will yield information about pattern and amount of drug use as well as quality of drug use.

DU studies are also often **drug focused**, where the use of a single drug or class of drugs is examined. Less commonly DU studies are **indication focused**, where the use of a drug for a specific condition is examined.[16]

DUR is typically classified in three different categories:

• Prospective - evaluation of a patient's drug therapy before medication is dispensed

• Concurrent - ongoing monitoring of drug therapy during the course of treatment

• Retrospective - review of drug therapy after the patient has received the medication

1. Prospective DUR: Prospective review involves evaluating a patient's planned drug therapy before a medication is dispensed. This process allows the pharmacist to identify and resolve problems before the patient has received the medication. Pharmacists routinely perform prospective reviews in their daily practice by assessing a prescription medications dosage and directions while reviewing patient information for possible drug interactions or duplicate therapy. When part of an online claims adjudication process, prospective DUR often relies on computerized algorithms to perform key checks including drug interactions, duplications or contraindications with the patient's disease state or condition.

Issues Commonly Addressed by Prospective DUR:

• Clinical abuse/misuse

• Drug-disease contraindications (when a prescribed drug should not be used with certain diseases)

• Drug dosage modification

• Drug-drug interactions (when two or more different drugs interact and alter their intended effects, often causing adverse events)

• Drug-patient precautions (due to age, allergies, gender, pregnancy, etc.)

• Formulary substitutions (e.g., therapeutic interchange, generic substitution)

• Inappropriate duration of drug treatment

Example: Identification of drug-drug interactions are a common outcome of a prospective DUR. For example, a patient being treated with warfarin to prevent blood clots may be prescribed a new drug by another specialist to treat arthritis. If taken together, the patient could experience internal bleeding. Upon reviewing the patient's prescriptions, the pharmacist would note the potential drug interaction and contact the prescriber to alert him/her to the problem.

2. Concurrent DUR: Concurrent review is performed during the course of treatment and involves the ongoing monitoring of drug therapy to foster positive patient outcomes. It presents pharmacists with the opportunity to alert prescribers to potential problems and intervene in areas such as drug-drug interactions, duplicate therapy, over or underutilization and excessive or insufficient dosing. This type of review allows therapy for a patient to be altered if necessary.

Issues Commonly Addressed by Concurrent DUR:

• Drug-disease interactions and Drug-drug interactions

• Drug dosage modifications

• Drug-patient precautions (age, gender, pregnancy, etc.)

• Over and underutilization

• Therapeutic Interchange

Example: Concurrent DUR often occurs in institutional settings, where patients often receive multiple medications. Periodic review of patient records can detect actual or potential drug-drug interactions or duplicate therapy. It can also alert the pharmacist to the need for changes in medications, such as antibiotics, or the need for dosage adjustments based on laboratory test results. The key prescriber(s) must then be alerted to the situation so corrective action can be taken.

3. Retrospective DUR: A retrospective DUR reviews drug therapy after the patient has received the medication. A retrospective review aims to detect patterns in prescribing, dispensing or administering drugs. Based on current patterns of medication use, prospective standards and target interventions can be developed to prevent recurrence of inappropriate medication use or abuse. Outcomes of this review may aid prescribers in improving the care of their patients, either individually or within a certain target population (e.g., patients with diabetes, asthma, or high blood pressure).

Issues Commonly Addressed by Retrospective DUR:

• Appropriate generic use

• Clinical abuse/misuse

• Drug-disease contraindications

• Drug-drug interactions

• Inappropriate duration of treatment

• Incorrect drug dosage

• Use of formulary medications whenever appropriate

• Over and underutilization

• Therapeutic appropriateness and/or duplication

Example: An example of a retrospective DUR may be the identification of a group of patients whose therapy does not meet approved guidelines. For example, a pharmacist may identify a group of patients with asthma, who according to their medical and pharmacy history, should be using orally inhaled steroids. Using this information, the pharmacist can then encourage prescribers to utilize the indicated drugs.

Steps in Conducting a Drug Use Evaluation

Most authorities agree the following five steps are essential when conducting any quality-related DUR program.

1. **Identify or Determine Optimal Use**: An organization's established criteria are defined to compare optimal use with actual use. The criteria should focus on relevant outcomes within a delineated scope for DUR and identify the relevant drugs to be monitored for optimal use in advance. For example, if the use of a drug class prescribed to treat a patient with diabetes is being evaluated, then standards should be determined to identify all drugs within the drug class and to evaluate each drug's effectiveness, such as a decrease in blood glucose or A1c (glycosylated hemoglobin) levels to within normal limits.
2. **Measure Actual Use:** This step is where data are gathered to measure the actual use of medications. These data can be obtained from medical and prescription records or

electronic claim forms. It may require the organization to build an algorithm to identify all members who fit the criteria.

3. **Evaluate:** Acceptable thresholds (percent of patients meeting the indicator) should be determined prior to the comparison. This step involves applying the algorithm, identifying members who meet the DUR criteria and the comparison between optimal or appropriate and actual use. During this process, the evaluator determines causes for any discrepancies and whether findings are expected. In this process, patterns or aberrations can be identified and interpreted.
4. **Intervene**: This is the step where corrective action is implemented. Action should be targeted to areas of concern such as prescribing patterns, medication misadventures, and quality of drug therapy or economic consideration.
5. **Evaluate the DUR Program:** This step assesses the effectiveness of the DUR program. Efforts should be made to evaluate the outcomes and document reasons for positive and negative results. Implementing appropriate changes to the DUR program and continued observation should be undertaken.
6. **Report the DUR findings:** The final step is to report these findings to the appropriate team within the organization (e.g., the pharmacy & therapeutics committee) and/or individual prescribers when appropriate.

Role of Pharmacist and other Health Care Practitioners in DUE Studies

Prospective DUR: This process places responsibility on the health care practitioner to conduct a review of the drug order when it is presented for filling and proactively resolve potential drug- patient problems. It affords the pharmacist or other health care practitioner the opportunity to interact with patients and members of the health care team to work on a treatment plan for each patient. In the retail and institutional settings, a pharmacist can assess the prescription order at the time of dispensing and, using information from the patient's medical and/or pharmacy record, determine the appropriateness of the drug therapy prescribed. If the pharmacist identifies opportunities for improved patient care, he/she can contact the prescriber to discuss treatment alternatives.

Concurrent DUR: The pharmacist and other health care practitioners have the responsibility in the concurrent DUR process to assess the ongoing therapy of the patient and, when necessary, intervene to help modify the patient's treatment plan. When caring for those patients with multiple diseases, case managers may become actively involved in the management of the patient's condition. Through interaction with the prescriber, a health care practitioner within a managed care organization can better understand the care plan the prescriber would like to follow. Through patient counseling, health care practitioners can offer education on the proper use of medications and determine if there are specific patient needs.

Retrospective DUR: Due to their expertise in drug therapy management, health care practitioners play a leading role in describing the relationship between drug use and patient outcomes using retrospective DUR. When addressing population-based retrospective DUR

issues rather than individual patient care, the managed care pharmacist has a primary role in planning, organizing and implementing DUR activities. Pharmacists can educate health care professionals regarding drug use, participate in decision making within the context of the pharmacy and therapeutics (P&T) committee, and serve as members of DUR and other committees where input concerning drug use and drug policy development is required.

Pharmacists play a key role in this process because of their expertise in the area of medication therapy management. DUR affords the managed care pharmacist the opportunity to identify trends in prescribing within groups of patients whether by disease-state such as those with asthma, diabetes or high blood pressure, or by drug-specific criteria. Pharmacists can then, in collaboration with prescribers and other members of the health care team, initiate action to improve drug therapy for patients.[16, 17, 18]

Fluoroquinolones (FQs)

The fluoroquinolones are synthetic broad-spectrum antibacterial agents with bactericidal activity which are unusual among antimicrobials in that they were not isolated from living organisms, but rather synthesized by chemists. The first quinolone, nalidixic acid, discovered in 1962 by Lescher and colleagues was derived from the antimalarial drug chloroquine and subsequent agents were derived through side chain and nuclear manipulation. The newer fluoroquinolones have a wider clinical use including gram-positive and gram-negative aerobic and anaerobic organisms.[6, 10]

Gatifloxacin, moxifoxacin and trovafloxacin have all greatly improved the activity against gram-positive cocci, particularly pneumococci, and against anaerobes. Clinafloxacin, gemifloxacin and sitafloxacin have even better activity against gram-positive cocci and are as active as ciprofloxacin against most gram-negatives, though gemifloxacin is less active than the other new compounds against gram-negative anaerobes.[7]

Fluoroquinolones interfere with bacterial cell replication, transcription, and DNA repair by disabling two bacterial enzymes crucial to these processes, DNA gyrase (formerly topoisomerase II) and topoisomerase IV. These enzymes are necessary for bacteria to manage the topological challenge of containing their genetic material. Fluoroquinolones bind to the enzyme–DNA complex, causing a conformational change in the enzyme. This leads to DNA cleavage by the enzyme while the continued presence of the fluoroquinolone prevents ligation of broken DNA strands. The fluoroquinolones traps the enzyme on the DNA as a fluoroquinolone–enzyme–DNA complex, inhibiting further DNA replication. The process of complex-formation inhibits bacterial cell growth and is thus believed to be

bacteriostatic in nature. The bactericidal action of fluoroquinolones is attributed to DNA cleavage.[19, 20]

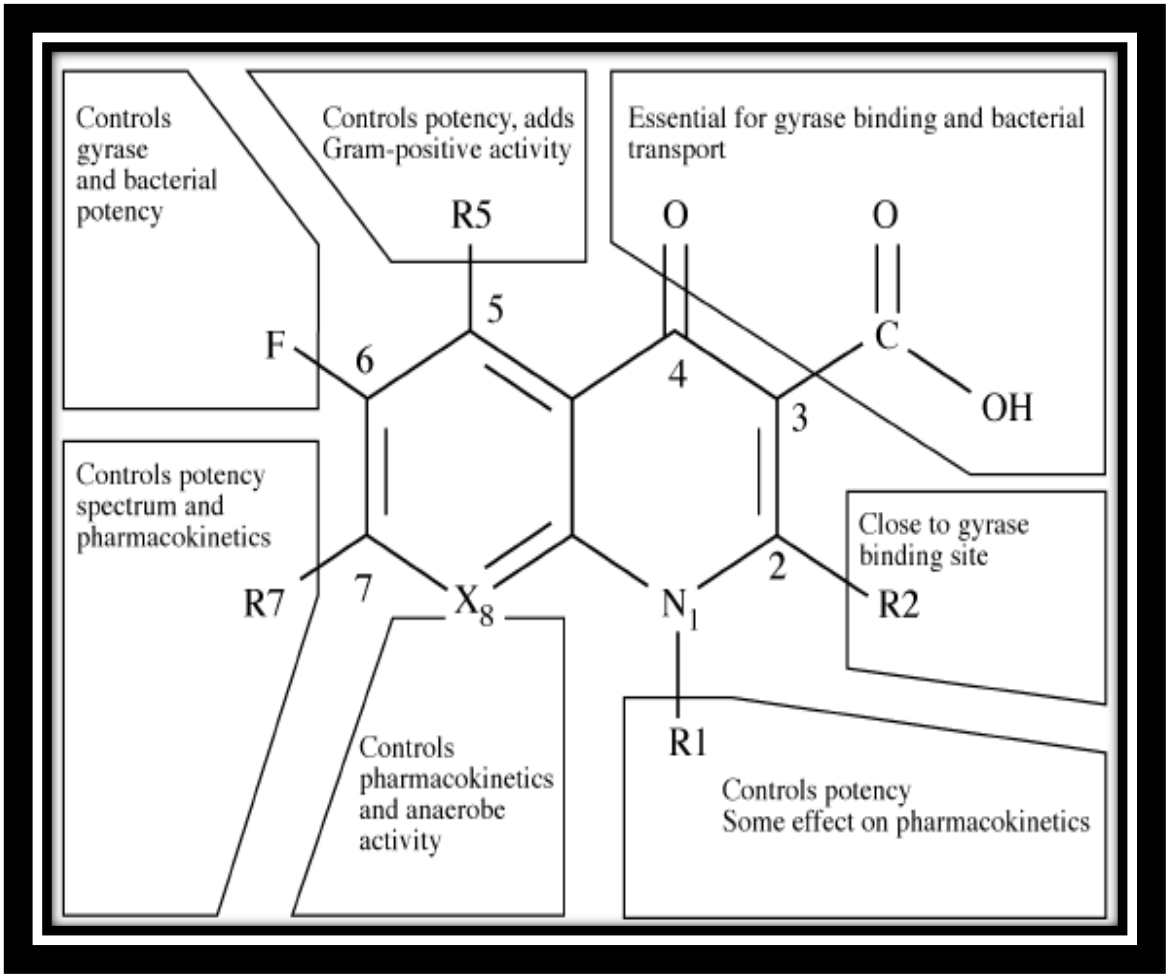

Figure 1. Structure of the quinolone and napthyridone molecule. In molecules where X is a carbon atom, the molecule is a quinolone (cinoxacin, norfloxacin, ofloxacin, ciprofloxacin, temafloxacin, sparfloxacin, grepafloxacin, levofloxacin, clinafloxacin, moxifloxacin, gatifloxacin). Where X is a nitrogen atom the molecule is a naphthyridone (nalidixic acid, enoxacin, tosufloxacin, trovafloxacin, gemifloxacin). Adapted from Domagala (1994).[21]

Fluoroquinolone advantages[6]

- Ease of administration
- Daily or twice daily dosing
- Excellent oral absorption
- Excellent tissue penetration
- Prolonged half-lives
- Significant entry into phagocytic cells
- Efficacy
- Overall safety

Fluoroquinolones disadvantages or side effects[6]

- Tendonitis or tendon rupture
- Multiple drug interactions
- Not used in children
- Newer quinolones produce additional toxicities to the heart that were not found with the older agents
- Gastrointestinal effects
- CNS effects: Headache, dizziness, and drowsiness have been reported with all fluoroquinolones.
- Phototoxicity: The degree of phototoxic potential of fluoroquinolones is as follows: lomefloxacin > sparfloxacin > ciprofloxacin > norfloxacin = ofloxacin = levofloxacin = gatifloxacin = moxifloxacin.
- Musculoskeletal effects.
- Hepatoxicity

- Cardiovascular effects
- Hypoglycaemia / Hyperglycaemia
- Hypersensitivity

Classification of fluoroquinolones

The classification of the fluoroquinolones is somewhat informal and unstandardized, but it does serve a clinical purpose to classify them by their spectrum of action and indication, so different generations of quinolones have been classified based on their antibacterial activity on gram positive and gram negative organisms with the first generation being the most narrow and the subsequent ones having an increase in spectrum of activity and on the novelty and complexity of the structures of quinolones. This classification has five generations.[10, 22, 23, 24]

First Generation

Nalidixic Acid, Cinoxacin

Second Generation

Norfloxacin, Ciprofloxacin, Lomefloxacin, Ofloxacin, Enoxacin, Fleroxacin, Rufloxacin

Third Generation

Levofloxacin, Sparfloxacin, Gatifloxacin, Temofloxacin, Tosufloxacin, Gemifloxacin, Grepfloxacin, Moxifloxacin

Fourth Generation

Trovafloxacin, Sitafloxacin, Prulifloxacin, Clinafloxacin, Garenoxacin, Alatrofloxacin

Fifth Generation

Delofloxacin

First Generation FQs

The first generation agents include cinoxacin and nalidixic acid, which are the oldest and least often used quinolones. These are active against gram-negative organisms but not against pseudomonas species because minimal serum levels are achieved and use of these drugs has been restricted to the treatment of uncomplicated urinary tract infections.

Cinoxacin and nalidixic acid require more frequent dosing than the newer quinolones, and they are more susceptible to the development of bacterial resistance. These agents are not recommended for use in patients with poor renal function because of significantly decreased urine concentrations. [10, 22, 23, 24]

Second generation FQs

The second generation quinolones have increased gram negative activity, as well as some gram positive and atypical pathogen coverage. Compared with first generation drugs and considered as a group, these agents have broader clinical applications in the treatment of complicated urinary tract infections and pyelonephritis, sexually transmitted diseases, prostatitis, selected pneumonias and skin and soft tissue infections.

Second generation agents include ciprofloxacin, enoxacin, lomefloxacin, norfloxacin and ofloxacin. Ciprofloxacin is the most potent fluoroquinolone against *P. aeruginosa*. Because of its good penetration into bone, orally administered ciprofloxacin is a useful alternative to parenterally administered antibiotics for the treatment of osteomyelitis caused by susceptible organisms.

Although the FDA has labeled some second generation quinolones for the treatment of lower respiratory tract infections and acute sinusitis, it should be stressed that *S. pneumoniae* is frequently resistant to agents in this class. Consequently, second generation

quinolones are not the drugs of first choice for lower respiratory tract infections and acute sinusitis.

Of the second generation agents, ofloxacin has the greatest activity against *Chlamydia trachomatis*. Ciprofloxacin and ofloxacin are the most widely used second generation quinolones because of their availability in oral and intravenous formulations and their broad set of FDA labeled indications. [10, 22, 23, 24]

Third generation FQs

Third generation fluoroquinolones have expanded activity against gram positive organisms, particularly penicillin sensitive and penicillin resistant *S. pneumoniae*, and atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.

Although the third generation quinolones retain broad gram negative coverage, they are less active than ciprofloxacin against Pseudomonas species. Because of their expanded antimicrobial spectrum, third generation quinolones are useful in the treatment of community acquired pneumonia, acute sinusitis and acute exacerbations of chronic bronchitis, which are their primary FDA labeled indications. Sparfloxacin carries a significant risk of phototoxicity. Grepafloxacin, sparfloxacin and moxifloxacin have been reported to cause prolongation of the QT interval; gatifloxacin has not. However, the FDA recommends that all of these drugs should be avoided in patients who are taking drugs that are known to prolong the QT interval. [10, 22, 23, 24]

Fourth generation FQs

Fourth-generation fluoroquinolones have same activities as that of third generation agents but with superior coverage against pneumococci and anaerobes. General clinical indications for fourth-generation fluoroquinolones are same as that of above generation

(except urinary tract infections and pyelonephritis) plus intra-abdominal infections, pelvic inflammatory disease (PID) and nosocomial pneumonia. [10, 22, 23, 24]

Pharmacokinetics and Pharmacodynamics

The newer fluoroquinolone antibiotics also have improved pharmacokinetic parameters compared with the original quinolones. They are rapidly and almost completely absorbed from the gastrointestinal tract. Peak serum concentrations obtained after oral administration are very near those achieved with intravenous administration. The bioavailability of fluoroquinolones ranges from 70% to greater than 90%.

The only disadvantage of an oral administration is that the absorption of the drug is affected by cations like aluminium, magnesium, zinc, iron and calcium because of the formation of insoluble drug–cationic chelate complexes in the gastrointestinal tract.

Fluoroquinolones have shown to have higher protein binding and large volume of distribution which results in higher concentration of the drugs in the tissues and fluids. Penetration of the fluoroquinolones into various tissues like kidney, lung, bronchial mucosa, gallbladder, genital tract and prostate are found to be very high.

All the fluoroquinolones undergo either renal or non-renal pathway for their elimination. Only ofloxacin and levofloxacin are exclusively eliminated by the kidneys which are hydrophilic drugs and other lipophilic fluoroquinolones, mainly third and fourth generation, undergo non-renal pathway for elimination. Dosage adjustments based on estimated creatinine clearance values must be made for the agents with significant renal elimination. In most instances, administering the usual dose at an extended interval is recommended. [23, 24]

Pharmacodynamics deals with the relationship between the drug concentration and the antimicrobial activity. At concentrations above the MIC, all fluoroquinolones exhibit both post antibiotic effect and concentration-dependent bactericidal activity. Fluoroquinolones like ciprofloxacin and fleroxacin at high concentrations act on the cell membrane of bacteria and disintegrate the inner and outer membranes of the bacteria. They act as a chelating agent and remove cations, majorly magnesium ions. But the maximum concentration of fluoroquinolones must be 10 times that of the MIC when treating gram-positive bacteria. To calculate it another way, for gram-negative organisms the AUC-to-MIC ratio desired is greater than 125; for gram-positive organisms the AUC-to-MIC ratio should be at least 30.[10, 23, 25, 26]

Indications for Fluoroquinolone Antibiotics Labelled by the U.S. Food and Drug Administration (Table 1).[24]

Indications	Agents
Uncomplicated urinary tract infections	Nalidixic acid, cinoxacin, norfloxacin, lomefloxacin, enoxacin, ofloxacin, ciprofloxacin, levofloxacin, gatifloxacin, trovafloxacin*
Complicated urinary tract infections and pyelonephritis	Norfloxacin, lomefloxacin, enoxacin, ofloxacin, ciprofloxacin, levofloxacin, gatifloxacin
Lower respiratory tract infections (limited)	Lomefloxacin, ofloxacin, ciprofloxacin, trovafloxacin*
Skin and skin structure Infections	Ofloxacin, ciprofloxacin, levofloxacin, trovafloxacin*

Urethral and cervical gonococcal infections	Norfloxacin, enoxacin, ofloxacin, ciprofloxacin, gatifloxacin, trovafloxacin*
Urethral and cervical chlamydial and gonnococcal infections	Ofloxacin, trovafloxacin*
Bone and joint infections, gram-negative bacterial infections	Ciprofloxacin
Infectious diarrhea	Ciprofloxacin
Typhoid fever	Ciprofloxacin
Prostatitis	Norfloxacin, ofloxacin, trovafloxacin*
Acute sinusitis	Ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, trovafloxacin*
Acute exacerbations of chronic bronchitis	Levofloxacin, sparfloxacin, gatifloxacin, moxifloxacin, trovafloxacin*
Community-acquired pneumonia	Levofloxacin, sparfloxacin, gatifloxacin, Moxifloxacin, trovafloxacin*
Intra-abdominal infections	Trovafloxacin*
Gynaecologic and pelvic infections	Trovafloxacin*
Nosocomial pneumonia	Trovafloxacin*
*	Treatment with trovafloxacin is reserved for life- or Limb-threatening infections

The drugs can be further differentiated based on available formulations, required dosage adjustments in renal or hepatic disease, significant adverse effects and significant drug interactions (Table 2).

Table 2: Distinguishing characteristics of fluoroquinolones antibiotics[6]

Class and agent	Half life	Route of administration	Dosage adjustment required	Significant adverse effects	Significant drug interactions
First generation					
Nalidixic acid	60 to 90 Mins	Oral	Renal impairment		Warfarin
Cinoxacin	1.1 to 2.7 hrs	Oral	Renal impairment	Hypersensitivity (fewer than 3% of recipients)	
Second generation					
Norfloxacin	2.3 to 5.5 hrs	Oral	Renal impairment		Warfarin, ciclosporine
Lomefloxacin	7 to 8.5 hrs	Oral	Renal impairment	Phototoxicity, headache (3 to 44% of recipients), abdominal pain (11%), nausea (5.6%)	
Enoxacin	3.3 to 7 hrs	Oral	Renal or hepatic Impairment (patients with advanced cirrhosis)	Phototoxicity (mild)	Warfarin, ranitidine, bismuth subsalicylate, theophylline, caffeine

Ofloxacin	5 to 8 hrs	Oral, intravenous	Renal or hepatic impairment (patients with severe disease)	Insomnia (13% of recipients)	Warfarin
Ciprofloxacin	3 to 5.4 hrs	Oral, intravenous	Renal impairment	Nausea, vomiting, abdominal pain	Warfarin, theophylline, caffeine, cyclosporine, glyburide
Third generation					
Levofloxacin	6 hrs	Oral, intravenous	Renal impairment	Headache, nausea (6.6% of recipients), diarrhea	
Sparfloxacin	21 hrs	Oral	Renal impairment	Phototoxicity (8% of recipients), QTinterval prolongation, torsades des pointes	Drugs that prolong the QT interval, including class I antiarrhythmics, tricyclic antidepressants, phenothiazines, cisapride, pentamidine and erythromycin
Gatifloxacin	7 hrs	Oral, intravenous	Renal impairment		Same as for sparfloxacin
Fourth generation					
Moxifloxacin	12 hrs	Oral	Hepatic impairment	QT-interval prolongation	Same as for sparfloxacin

Trovafloxacin, Alatrofloxacin	7.8 hrs	Oral, Intravenous	Hepatic impairment (patients with mild to moderate cirrhosis)	Dizziness (2.4 to 11% of recipients), severe hepatotoxicity (rare), candidal vaginitis (1 to 10%)	Morphine, Citric acid-Sodium citrate

Indication of most commonly use fluoroquinolones with oral dose, frequency and duration (Table 3).[10, 22]

Drug	Indication	PO dose (mg)	Interval	Duration (day/s)
Ciprofloxacin	Uncomplicated UTI	250	BD	3
	Complicated UTI; Acute pyelonephritis	250-500	BD	7-14
	Uncomplicated N. gonorrhoea	500	1-dose	1
	AECB; CAP	500-750	BD	10-14
	Acute prostatitis	500	BD	14-28
	Infectious diarrhoea; typhoid fever	500	BD	3-5
Gatifloxacin	Uncomplicated UTI	400	OD	3
	Uncomplicated N. gonorrhoea	400	1-dose	1
	Complicated UTI; AECB; CAP; Acute pyelonepritis	400	OD	7-14

Levofloxacin	Uncomplicated UTI; Acute pyelonephritis	250	OD	10
	AECB; CAP	500	OD	7-14
Moxifloxacin	AECB; CAP	400	OD	5-10
Norfloxacin	Uncomplicated & Complicated UTI; Acute pyelonephritis	400	BD	3-10
	Acute Prostatitis	400	BD	14-28
Ofloxacin	Uncomplicated & Complicated UTI; Chlamydia	200	BD	3-10
	Uncomplicated N. gonorrhoea	400	1-dose	1
	AECB; CAP	400	BD	7-10
sparfloxacin	AECB; CAP	400 x1, then 200	OD	10
CAP = community acquired pneumonia; AECB = acute exacerbations of chronic bronchitis; UTI = urinary tract infection.				

Fluoroquinolones resistance

The problem with fluoroquinolones usage is that they are largely prescribed for the wrong indications. Even if prescribed correctly, the patients are given wrong dose levels or

the drug is given for the wrong duration of therapy. This results in the development of resistance in the micro-organisms or the prevalence of adverse effects.[23]

Resistance develops to fluoroquinolones due to three possible mechanisms; alterations in topoisomerase enzymes, decreased permeability and efflux mechanisms. No quinolone degrading enzyme has been identified. Resistance patterns have been show in strains of *Escherichia coli, Klebsiella pneumoniae; Pseudomonas aeruginosa; Chlamydia trachomatis* and *Mycoplasma pneumoniae; Campylobacter jejuni; Burkholderia cepacia; Stenotrophomonas maltophilia; Neisseria gonorrhoeae; Staphylococcus aureus* (especially oxacillin-resistant strains); *Enterococcus faecium*; and *Streptococcus pneumoniae*. Resistance to one quinolone usually confers resistance to the entire class. It has been shown that when there is a methyl or methoxy group in position number eight the topoisomerase enzymes must undergo mutations in two sights for there to be an effect on binding affinity.[22]

Pregnancy and lactation

Fluoroquinolones are relatively contraindicated in pregnancy. Fluoroquinolones administration is often discouraged in pregnant women because they can easily traverse the placental barrier or through milk and get distributed in the foetus. This may cause abortions as well as birth defects and arthropathy in the immature child.[23] Use if potential benefit outweighs risk. In case of lactation, controversial data available so caution while use.[27]

PREVIOUS STUDIES

- A study was conducted by **P. Ravi Shankar et al.,** on Fluoroquinolones utilization among inpatients in a teaching hospital in Western Nepal over a period of five months in which inpatients prescribed with one or more fluoroquinolones along with other drugs present in the prescription are recorded for further analysis. The mean ±

SD for number of drugs and duration was calculated noting the duration where the day of admission was included while the day of discharge was excluded. Specimens sent for culture and sensitivity testing, organisms isolated and their sensitivity patterns were detailed. The cost of drugs prescribed was calculated using the price list supplied by the hospital pharmacy. Fluoroquinolones were prescribed to 263 patients during the study period in which 160 are females and 103 are males. Mean ± SD number of drugs prescribed and duration of hospitalization were 6.5 ± 3.3 and 6.2 ± 5.4 days respectively. Fluoroquinolone utilization was 7.76 DDD/100 bed-days. Fluoroquinolones were used for prophylaxis in 110 patients (41.8%). Other indications were urinary tract infections and acute gastroenteritis. *E.coli, S.aureus* and *P. aeruginosa* were common organisms isolated and the mean cost of drugs was 13.1 US$ where fluoroquinolones contributed to 36.7% of the total drug costs.[28]

- **Juno J. Joel et al.,** carried out drug utilization study of fluoroquinolone antibiotics in a university teaching hospital for a period of seven months in the medicine and surgery wards after obtaining the ethical clearance. The data were collected from patients of all age groups from either sex, who got admitted to the medicine and surgery wards of the hospital. Total of 100 patients were enrolled in which 67 were male and 33 were female and the FQ utilization was measured in term of DDD/100 bed days. Mean ± SD number of drugs prescribed and length of hospital stay were 8.23 ± 3.33 and 11.54 ± 7.57 respectively. Ciprofloxacin was the most commonly prescribed drug. Overall Fluoroquinolone utilization was found to be 33.55 DDD/100 bed-days.[29]

- **Luigi Guglielmo et al.,** studied Antibiotic Prescribing Patterns in Italian Hospital Inpatients with Pneumonia, Chronic Obstructive Pulmonary Disease, and Urinary Tract Infections involving 1609 patients for a period of 6 months and the study reported that Sixty-three antimicrobial agents were used. The most frequently used drugs were third-generation cephalosporins (24.6%), fluoroquinolones (15.4%), aminopenicillins (15.0%), and ureidopenicillins (9.7%). Results showed that the use of broad-spectrum antibiotics probably was excessive and treatment seemed to be based more on the opinion of the treating physician and the local habits rather than objective criteria. [30]
- **Curtis J Donskey et al.,** conducted the prospective, observational study to determine the frequency of, reasons for, and adverse effect of unnecessary fluoroquinolone use in a tertiary care medical centre in hospitalized patients considering that longer than necessary treatment duration would account for a significant proportion of unnecessary fluoroquinolones use. Patient receiving fluoroquinolones were identified through daily review of pharmacy records and results shows that two hundred twenty six study subjects received 227 fluoroquinolone regimens during the study period of 6-weeks. Therapy was determined to be necessary or unnecessary based on published guidelines or standard principles of infectious diseases. Adverse effects were determined based on chart review 6 weeks after completion of therapy. Of 1,773 days of fluoroquinolone therapy, 690 (39%) were deemed unnecessary. The most common reasons for unnecessary therapy included administration of antimicrobials for non-infectious or non-bacterial syndromes (292 days-of-therapy) and administration of antimicrobials

for longer than necessary durations (234 days-of-therapy). The most common syndrome associated with unnecessary therapy was urinary tract infection or asymptomatic bacteriuria (30% of all unnecessary days-of-therapy). Twenty-seven percent (60/227) of regimens were associated with adverse effects possibly attributable to therapy, including gastrointestinal adverse effects (14% of regimens), colonization by resistant pathogens (8% of regimens), and CDI (4% of regimens).[31]

- A study on antibiotic-prescribing practices of primary care prescribers for acute diarrhoea was conducted in New Delhi, India by **Anita Kotwani et al.,** for the period of one year by using patients' exit interviews at 10 public sector facilities and 20 private clinics form four residential localities. The percentage of patients receiving antibiotics and the prescribing pattern of antibiotics were analysed by using the anatomical therapeutic chemical classification and the defined daily dose. At public facilities 43% (171 of 398) and at private facilities 69% (76 of 110) of the patients with acute diarrhoea were prescribed at least one antibiotic. The main antibiotic class that was prescribed in both public and private sector facilities was fluoroquinolones, J01MA (91.5% and 96%, respectively). At public facilities, the most commonly prescribed fluoroquinolone was norfloxacin, followed by ofloxacin and ciprofloxacin. At private clinics, it was ofloxacin followed by ciprofloxacin**.**[32]
- To measure the changes in the rate and type of fluoroquinolones prescribed in the United States from 1995 to 2002 **Jeffrey A. Linder et al.,** performed a longitudinal analysis of the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey of adult visits to physicians in ambulatory clinics and emergency departments throughout the United States from 1995 to 2002 where

fluoroquinolones became the most commonly prescribed class of antibiotics to adults in the United States. Fluoroquinolone prescribing rose threefold, from 7 million visits in 1995 to 22 million visits in 2002 ($P < 0.0001$). Fluoroquinolone prescribing increased as a proportion of overall antibiotic prescribing (from 10% to 24%; $P < 0.0001$) and as a proportion of the U.S. population (from 39 to 106 prescriptions per 1000 adults; $P < 0.001$). These increases were due to the use of newer fluoroquinolones with activity against *Streptococcus pneumoniae*. For nonapproved diagnoses 42% of fluoroquinolone were prescribed. Among patients receiving antibiotics, nonapproved fluoroquinolone prescribing increased overtime.[33]

- A case control study on FQ utilization in the emergency departments (ED) of 2-academic medical centres was carried out by **Ebbing Lutenbach et al.,** from August 23, 1999 to November 19, 1999 to identify the prevalence of, and risk factors for, inappropriate FQ use by using existing health care system guidelines established by the university of Pennsylvania Antimicrobial Management Programme (AMP). Total of 100 patients were enrolled in which 81 received FQ for an inappropriate indication. Of these cases, 43 (53%) were judged inappropriate because another agent was considered first line, 27 (33%) because there was no evidence of infection based on the documented evaluation, and 11 (14%) because of inability to assess the need for antimicrobial therapy. Of the 19 patients who received FQ for an appropriate indication, only 1 received both the correct dose and duration of therapy.[34]

- A study conducted by **Elbert S. Huang et al.,** on National patterns in the treatment of Urinary Tract infections in women by ambulatory care physicians was the sample survey of practicing physicians participating in the National Ambulatory Medical Care Survey from 1989 to 1998 in women aged 18 to 75 years diagnosed with uncomplicated acute cystitis or urinary tract infection. In this study 1478 prescriptions were collected and assessed. The most frequently prescribed antibiotics were trimethoprim – sulfamethoxazole, fluoroquinolones and nitrofurantoin. Prescriptions containing trimethoprim – sulfamethoxazole declined from 48 %(1989-90) to 24% 1997 whereas fluoroquinolone increased from 19% to 29% and nitrofurantoin from 14% to 30%. Among primary care physicians, interns were the most likely to prescribe fluoroquinolones while obstestricians were most likely to use nitrofurantoin. Study showed that ambulatory care physicians are increasing their use of nitrofurantoin and fluoroquinolones even though they are not highly therapeutic and not cost effective.[35]
- A study conducted by **Gupta N et al.,** for auditing the prescription to study utilization of antimicrobials in a tertiary hospital to determine the frequency of prescribing antimicrobials in an Indian hospital. A total of 289 prescriptions were collected during the study period and analyzed for the number of antibiotics, prescribed frequency of individual drug, defined daily dose, age, sex frequency. The frequency of prescribing penicillins and cephalosporins was 67.82%, quinolones 34.25%, aminoglycosides 31.83%, metronidazole 25.25%, tetracycline and chloramphenicol 4.84% and vancomycin 1.03%. The prescribing frequency of penicillins and cephalosporins was significant ($P<0.01$) in males while compared

with females. This study showed that the frequent use of expensive antibiotics like cephalosporins, quinolones and vancomycin was without any microbiological confirmation.[36]

- **Sahar I. Al-Niemat et al.,** conducted the retrospective survey taking sample of 187,822 prescriptions obtained from 5 outpatients pharmacies in King Hussein Medical College written over the period of 3 consecutive months. The percentage of antibiotic prescribed along with the percentage share of different antibiotics was also calculated using the methodology recommended by the WHO. Study showed that average percentage of prescriptions involving antibiotics was 35.6%. Penicillins (most frequently amoxicillins) and Quinolones (most frequently ciprofloxacin and norfloxacin) were the most commonly prescribed antibiotics with an average percentage of 31.8% and 27.5%. The average prescribing rate for other antibiotic categories was as follows: macrolides (5.2%), cephalosporins (16%), and amoxicillins / clavulanate (5.4%).[37]
- **Joseph Feliciano et al.,** conducted the retrospective evaluation of 1,273 patients who underwent prostate biopsy at New York Harbor Veterans Affairs Hospital from January 2004 to December 2006 where patients received levofloxacin or gatifloxacin. Using the Veterans Affairs computerized patient record system, all patients was viewed who visited within 1 month after prostate biopsy. Visits were queried for infective symptoms and positive cultures were evaluated for resistance patterns. The annual and overall incidence of infective complications and fluoroquinolone resistant infections was calculated and out of 1,273 patients 31 (2.4%) presented with infective symptoms after biopsy. The overall incidence of

fluoroquinolone resistant infections was 1.2% (15 cases). When stratified by year, there were statistically significant increases in the incidence of infective complications and fluoroquinolone resistance from 2004 to 2006. Cultures from 89% of patients are positive to Escherichia coli and out of which 90% were fluoroquinolone resistant. Fluoroquinolone resistant E. coli were also resistant to gentamicin in 22% of cases, trimethoprim/sulfamethoxazole in 44%, piperacillin in 72% and ampicillin in 94%. However study showed that fluoroquinolones are still effective as antibiotic prophylaxis for prostate biopsies but there is an increase in infective complications and fluoroquinolone resistance.[38]

- A prospective questionnaire based cross-sectional survey was conducted by **M.V. Srishyla et al.,** to study the antimicrobial prescribing pattern in the in-patient setting of an 800-bedded tertiary hospital. The prescribing pattern was assessed on the basis of type of use, specialty, site of infection, route of administration and the antimicrobial agent used. Total of 556 inpatients in the study concluded that 56% of in-patients were prescribed with antimicrobial agents, and 44% of them received a combination of antimicrobials. A total of 36 different antimicrobial agents were prescribed. Gentamicin (17%), metronidazole (9%) and ciprofloxacin (8%) were the most commonly used antimicrobial agents. Study showed that Lower respiratory tract infection was most common cause for the use of antimicrobial and also it was used 34% empirically, 27% therapeutically and 32% prophylactically during the study period.[39]

- A prospective cross sectional and observational study carried out by **Mahadevamma L et al.,** on patients diagnosed with UTI and who were above age group of 15-years in the OBG and Urology departments of both in-patients and out-patients, for a period of 5 months to analyse the prescribing pattern of antibiotics in Urinary Tract Infection (UTI). Among 162 patents, 54 were in-patients and 108 were out-patients. Most of the in-patients were prescribed with Ciprofloxacin 13(22.8%), and Ceftriaxone 19(33.3%). In out-patients, Ciprofloxacin 25(23.8%), Norfloxacin 15(14.3%) and Ceftriaxone 14(13.3%) were prescribed frequently. The study found that gram negative organisms like *E. coli* and *Klebsills* was the most predominant organisms associated with infection. It was also found that Cephalosporin's were most commonly used and Quinolones were the second most commonly used drugs for the treatment of UTI.[40]
- **Karel Urbane et al.,** conducted the study to evaluate the dependence of Escherichia coli resistance to fluoroquinolones on their use in the outpatients and inpatients in the Olomouc region of the Czech Republic. Data on inpatient antibiotic use were obtained from the database of the Department of Pharmacology and expressed as defined daily dose per 100 bed-days (DBD). Data on outpatient prescriptions were obtained from the database of General Health Insurance Company and expressed in defined daily doses per 1000 clients per day (DBD). Escherichia coli strains were isolated from samples of urine of both community and hospitalized patients suffering from acute bacterial urinary tract infection, examined using aerobic cultivation, and determined by standard biochemical procedures. Results of this

study show the impact of fluoroquinolone utilization on E. coli resistance and support the need of controlled use of these effective antibiotics.[41]

- **Jimmy Jose et al.,** studied and analyzed the pattern of ADRs implicated to fluoroquinolone antibiotics reported over a period of 4 years and 6 months which were spontaneously reported in the ADR reporting unit of a tertiary care teaching hospital in India. Analysis for causality, severity and preventability was also done. Eighty ADRs associated with fluoroquinolones were notified during the evaluation period, which accounted for 5.4% of the total ADRs reported and 30.2% of all reports to antibacterials. Type A reactions (58.8%) accounted for majority and more were described to be common (48.8%) in the literature. Levofloxacin (48.8%) occupied the major share of the reactions reported. The most commonly affected organ system was skin and appendages (32.5%) and the most frequently reported reaction was skin rash (21.3%). No report of reactions affecting musculoskeletal system was observed while rare reaction like nephrotoxicity was noticed. The proportion of nervous system adverse reactions noticed were higher than that observed with antibacterial agents in general. Drug dechallenge was instituted in majority (73.8%) for management of the reactions, while additional treatment was instituted in 50% of the reactions. In which most of the reactions were probable (52.5%) in nature on causality assessment and (72.5%) were of moderate severity. Many (23.8%) of the reactions were deemed to be preventable on evaluation. Drug–drug and drug–disease interaction were the most important factors which contributed to preventability.[42]

Chapter- IV

Methodology

Materials and Methods:

STUDY DESIGN: Prospective and observational study.

STUDY PERIOD: This study was conducted for a period of 7 months

STUDY SITE

The present study was conducted in the medicine units of Adichunchanagiri Hospital and research center, B.G. Nagara. It is a 1050-bedded tertiary care teaching hospital having different specialties like medicine, surgery, orthopedics, pediatrics, obstetrics and gynecology. This hospital provides specialized health care services to all strata of people in and around B.G. Nagara.

STUDY APPROVAL

Ethical clearance was obtained from the ethical committee of AH & RC, B.G. Nagara. Copy enclosed in annexure.

STUDY CRITERIA

Inclusion Criteria:

- Patients of either sex prescribed with fluoroquinolones on inpatient basis in medicine department.

Exclusion Criteria:

- Patient below 18 years of age.
- The patients who are treated with fluoroquinolones other than medicine department.
- Patients with immune compromised disease.

SOURCE OF DATA

Data was obtained from the patient's case sheets, treatment charts, and investigation reports.

MATERIAL USED

A well designed patient data collection form was developed and used for this study (enclosed in Annexure).

COLLECTION OF DATA

Inpatients who met the study criteria were enrolled to the study for assessing drug utilization pattern after obtaining their written consent. A suitably designed data collection form was used to record all the necessary data including patient demographic details, patient medication history, and reason for admission, medication details and lab investigations.

STUDY PROCEDURE

Clinical pharmacist routinely monitored the patient's drug therapy and interview with physician as well as patient when necessary and a total of 108 cases prescribed with fluoroquinolones were enrolled for the study. The incidence of fluoroquinolones use was

studied based on gender and age of patients. The total prescriptions were analyzed for number of drugs per prescription and then the prescriptions were screened/evaluated for the common category of drug prescribed on the basis of essential medicine list 2013 for the disease condition , number of fluoroquinolones antibiotics per prescription, type of therapy (Empirical or Specific), gender, dose, and route of administration, frequency of administration, culture and sensitivity (C&S) results, and duration of antibiotic therapy, also any major/potential drug interaction and ADRs if any using standard textbooks/ tertiary sources (Drug interaction facts, The pharmacological basis of therapeutics by Goodman and Gilman, Pharmacotherapy handbook by Dipiro, Handbook of Applied therapeutics by Koda-Kimble) and software available in the department (MICROMEDEX.COM, LEXI.COM). The identified drug related problems was discussed with the physicians for further management. The data was collected, documented and analyzed by using suitable statistical method.

Statistical methods

The data were subjected to descriptive statistical analysis using Microsoft Excel. Microsoft word and Excel have been used to generate bar graph, pie charts and tables.

Chapter -V

Results

RESULTS

A total of 108 inpatients treated with at least one fluoroquinolone in medicine units were reviewed over a period of 7 month from July 2014 to February 2015. A total of 1091 drugs were prescribed to 108 patients with a mean ± SD of drugs prescribed 10.10 ± 3.16. During the study period it was found that total of 115 Fluoroquinolones were prescribed to the study population with an average of 1.06 of Fluoroquinolones per prescription. The incidence of Fluoroquinolones was calculated based on gender and age of the patients.

PATIENTS DISTRIBUTION

Result shows that out of 108 patients, males were 60 (55.56%) and females were 48 (44.44%) (Table 4, Fig 3). The majority of the patients (48.15%) were in the age group of 60-80 years followed by (30.56%) the age group of 40-60 (Table 4, Fig 2).

Table 4: Age distribution of patients

Age in years	Number of patients	Percentage (%)
<20	2	1.85
20-40	13	12.03
40-60	33	30.56
60-80	52	48.15
>80	8	7.41

Table 5: Gender distribution of patient

Gender	Number of patients	Percentage (%)
Male	60	55.56
female	48	44.44

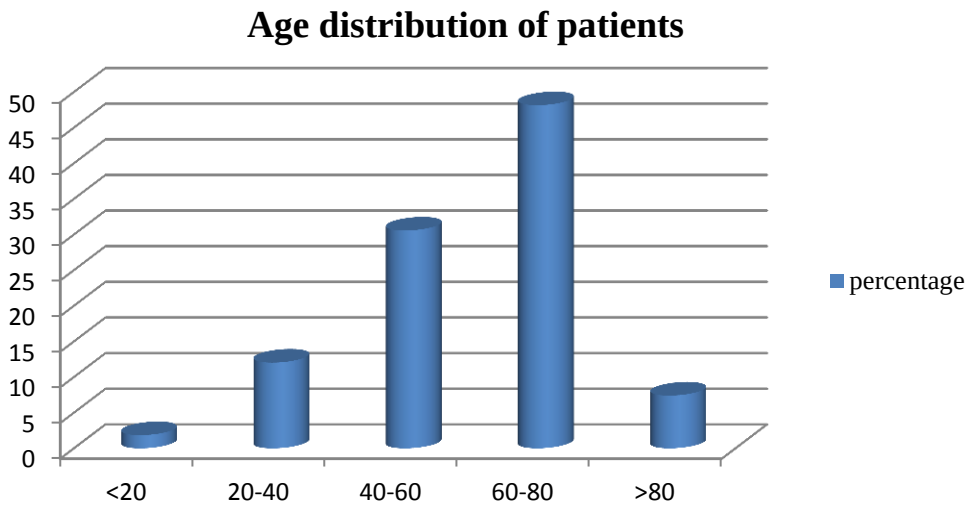

Fig 2: Age distribution of inpatients

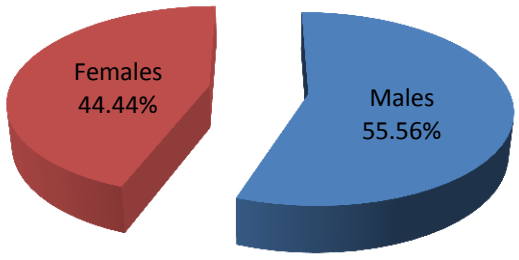

Fig 3: Gender distribution of patients

TYPE OF TREATMENT DURING HOSPITAL STAY

In the present study maximum number of patients 102 (94.44%) received empirical therapy and 6 (5.56%) patients received specific therapy of treatment (Table 6, Fig 4).

Table 6: Type of treatment

Treatment	Number	Percentage (%)
Empirical	100	92.59
Specific	8	7.41

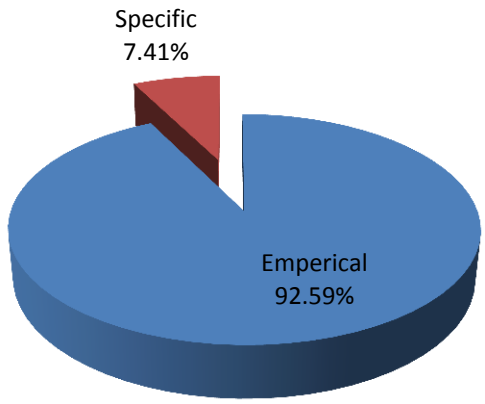

Fig 4: Type of treatment

CO-MORBIDITY CONDITION OF PATIENTS

Out of 108 patients enrolled in the study, 71 (65.75%) were having at least one co-morbidity condition whereas 37 (34.25%) were not having co-morbidity condition (Table 7, Fig 5).

Table 7: Co-morbidity condition of patients

Co-morbidity condition	No. of patients	Percentage (%)
Yes	71	65.74
No	37	34.25

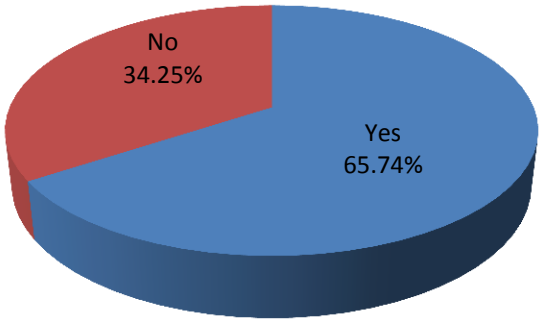

Fig 5: Co-morbidity condition of patients

Out of 71 patients having at least one co-morbidity condition, 44 (61.97%) patients were having only one co-morbidity condition along with infectious disease followed by 18 (25.35%) were having two co-morbidity and 9 (12.68%) were having three or more than three co-morbidity condition (Table 8). In study, 10 (14.08%) patients were having only hypertension as the single co-morbidity condition followed by 9 (12.68%) patients with diabetes mellitus and also as a double co-morbidity condition 10 (140.8%) patients were having both hypertension and diabetes mellitus as a co-morbidity condition.

Table 8: Distribution of co-morbidity condition

No. of co-morbidity condition	No. of patients	Percentage (%) (n=71)
1	44	61.97
2	18	25.35
≥3	9	12.68

SITE OF INFECTION FOR FLUOROQUINOLONES USE DURING STUDY PERIOD

Maximum number of patients admitted in medicine units who were prescribed with fluoroquinolone have infection in respiratory tract 48 (44.44%) followed by gastrointestinal tract 23 (21.29%) and urinary tract 14 (12.96%) (Table 9).

Table 9: site of infection for fluoroquinolone use

Site of infection	No. of patients	Percentage (%) (n= 108)
Eye	3	2.78
Eye / Respiratory tract (RT)	1	0.93
Respiratory tract (RT)	48	44.44
Gastrointestinal tract (GIT)	23	21.29
Urinary tract (UT)	14	12.96
Gastrointestinal tract / Respiratory tract	3	2.78
Gastrointestinal tract / Urinary tract	1	0.93
Respiratory tract / Urinary tract	7	6.48

Liver	5	4.63
Head	1	0.93
Foot	2	1.85

DISTRIBUTION OF THERAPEUTIC CLASSES OF DRUGS PRESCRIBED TO STUDY POPULATION DURING HOSPITAL STAY

Out of 1091 drugs prescribed, the mostly prescribed therapeutic class of drugs during hospital stay were anti-infectives 271(24.84%), followed by respiratory system drugs 222 (20.35%) and alimentary tract drugs 157 (14.39%) (Table 10).

Table 10: Distribution of therapeutic classes of drugs prescribed during hospital stay

Therapeutic classes	Percentage (%) (n=1091)
Anti-infectives	24.84
Alimentary tract drugs	14.39
Hormones and other endocrine medicines	3.57
Cardiovascular drugs	7.24
Diuretics	2.57
Vitamins, minerals and proteins	4.58
Respiratory system drugs	20.35
Antiallergic and medicine used in anaphylaxis	1.28

Analgesics, antipyretics, NSAIDS, medicines for gout, rheumatoid disorders and migraine	8.07
Medicine affecting blood	0.73
Central nervous system drugs	1.83
Miscellaneous	10.54

NUMBER OF DRUGS PRESCRIBED DURING HOSPITAL STAY

In 108 patients total of 1091 drugs were prescribed with mean ± SD of 10.10 ± 3.16 in which maximum number of patient i.e. 64 (59.26%) were prescribed with 6 to10 numbers of drugs followed by 31 (28.70%) patients with 11 to 15 numbers of drugs (Table 11).

Table 11: Number of drugs prescribed during hospital stay

Number of drugs in the prescription	Number of patients received	Percentage (%)
1-5	6	5.56
6-10	64	59.26
11-15	31	28.70
>15	7	6.48

DURATION OF HOSPITAL STAY AND DURATION OF FLUOROQUINOLONE PRESCRIBED

Number of patients admitted for a period of 1 to 5 days was 56 (51.85%) followed by 39 (36.11%) patients for 6 to 10 day and 10 (9.26%) patients for 11 to 15 days. Mean ± SD duration of hospital stay was 6.84 ± 3.77 days (Table 12).

Table 12: Duration of hospital stay

Number of days of hospital stay	Number of patients	Percentage (%)
1-5	56	51.85
6-10	39	36.11
11-15	10	9.26
>15	3	2.78

During the study period 60 (55.56%) patients received Fluoroquinolones for 5 days followed by 20 (18.51%) patients for 3 days (Table 13).

Table 13: Duration of Fluoroquinolones prescribed

Number of days Fluoroquinolones prescribed	Number of patient	Percentage (%)
1	1	0.93
2	7	6.48
3	20	18.51
4	9	8.33
5	60	55.56
6	1	0.93
7	8	7.40
9	1	0.93
15	1	0.93

COMPARISION OF ANTIBIOTICS CO-PRESCRIBED WITH FLUOROQUINOLONES

The most commonly prescribed anti-infectives along with Fluoroquinolones in medicine units in study population was ceftriaxone 36 (33.33%) followed by metronidazole 31(28.70%) (Table 14, Fig 6).

Table 14: Comparison of anti-infectives co-prescribed with Fluoroquinolones

Anti-infectives co-prescribed	Number of patients	Percentage(% in total patients)
Amoxicillin/clavulanate	4	3.70
Cefixime	3	2.78
Ceftriaxone/salbactum	4	3.70
Ceftriaxone	36	33.33
Azithromycin	5	4.63
Piperacillin/tazobactum	10	9.26
Doxycyclin	9	8.33
Amikacin	4	3.70
Gentamicin	1	0.93
Clindamycin	1	0.93
Linezolid	1	0.93
Meropenem	1	0.93
Metronidazole	31	28.70
Tinidazole	9	8.33
Nitrofurantoin	6	5.56
Isoniazid	3	2.78
Ethambutol	3	2.78
Rifampicin	3	2.78
Pyrazinamide	3	2.78
Mefloquine	5	4.63

Artesunate	7	6.48
Primaquine	1	0.93
Ornidazole	1	0.93
Albendazole	4	3.70
Oseltamavir	1	0.93

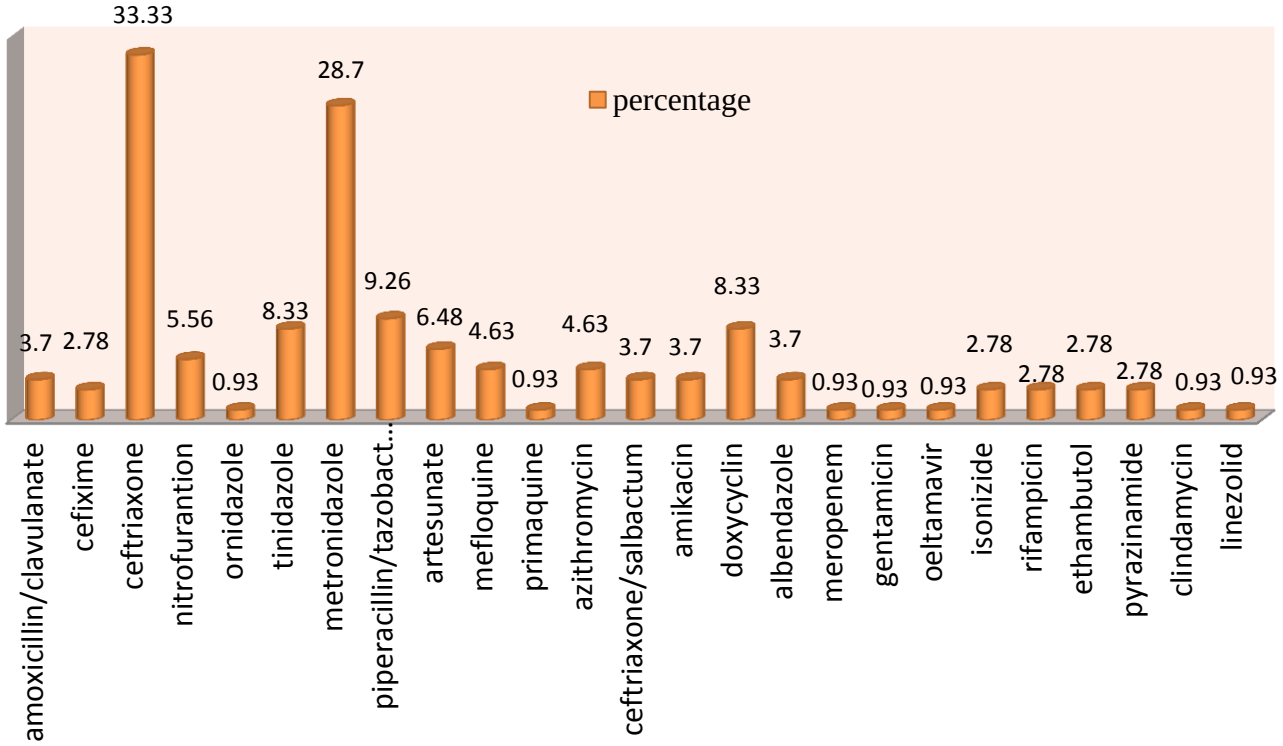

Fig 6: Comparision of anti-infectives co-prescribed with Fluoroquinolones

NUMBER OF FLUOROQUINOLONES PERSCRIBED IN PATIENTS

In total of 108 patients only one fluoroquinolone was prescribed in 101 (95.37%) patients whereas only 7 (6.48%) patients were prescribed with two Fluoroquinolones during hospital stay (Table15).

Table 15: Number of fluoroquinolone prescribed per patients

No. of Fluoroquinolones	No. of patients	Percentage (%)
One	101	95.37
Two	7	6.48

INDIVIDUAL FLUOROQUINOLONE USE DURING STUDY PERIOD

Out of 115 Fluoroquinolones prescribed to the study population Ciprofloxacin 50 (43.48%) was the most commonly prescribed fluoroquinolone followed by Levofloxacin 48 (41.74%). Ciprofloxacin was the most commonly prescribed parenteral fluoroquinolone whereas Levofloxacin was the most commonly prescribed oral fluoroquinolone. Moxifloxacin was the only fluoroquinolone use as eye drops (Table 16, Fig 7).

Table 16: Individual Fluoroquinolones use

Fluoroquinolones (ATC Code)	Number			Percentage (%) (n=115)			Total (%)
	Parenteral	Oral	Eye drops	Parenteral	Oral	Eye drops	
Ciprofloxacin (J01MA02)	22	28	0	19.13	24.35	0	50 (43.48%)
Levofloxacin (J01MA12)	12	36	0	10.43	31.30	0	48 (41.74%)
Moxifloxacin (S01AE07)	0	0	4	0	0	3.48	4 (3.48%)
Norfloxacin (J01MA06)	0	9	0	0	7.83	0	9 (7.83%)
Ofloxacin (J01MA01)	0	4	0	0	3.48	0	4 (3.48%)
Total	34	77	4	29.56	66.96	3.48	115 (100%)

As moxifloxacin was only used as the eye drops, Ciprofloxacin 50 (43.48%) was used twice a day (BD) whereas Levofloxacin 45 (39.13%) was used once a day (OD) and 3 (2.61%) was used twice a day (BD) followed by Norfloxacin 9 (7.83%) for BD, Ofloxacin 1 (0.87%) for OD and 3 (2.61%) for BD. Fluoroquinolones were mainly used as OD for respiratory diseases and as BD they were used for gastrointestinal diseases followed by respiratory diseases.

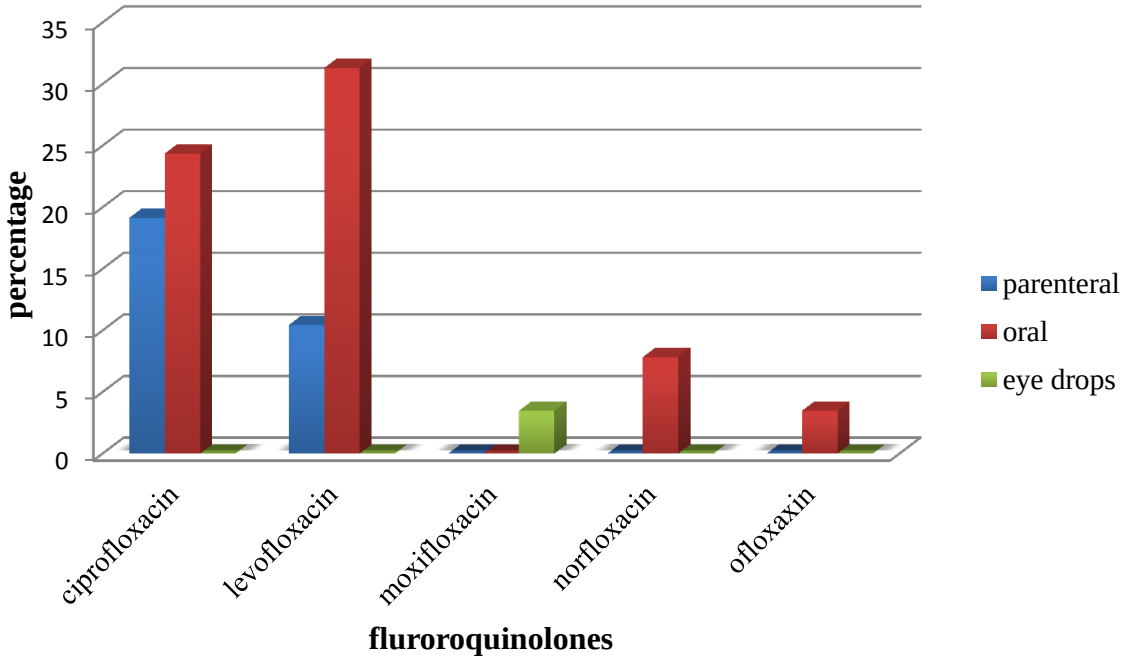

Fig 7: Individual Fluoroquinolones use

FIXED DOSE COMBINATION OF FLUOROQUINOLONES WITH OTHER ANTI-INFECTIVES

Out of 115 Fluoroquinolones 11(9.57%) were prescribed in fixed dose combination with other anti-infectives. Ciprofloxacin+Tinidazole was the most commonly prescribed combination which account for 72.73% of total fixed dose combination prescribed (Table 17).

Table 17: Fixed dose combination of Fluoroquinolones

Combination of Fluoroquinolones	Percentage (%) (n=11)
Ciprofloxacin+Tinidazole	72.73
Ofloxacin+Ornidazole	9.09
Ofloxacin+Cefixime	9.09
Norfloxacin+Tinidazole	9.09

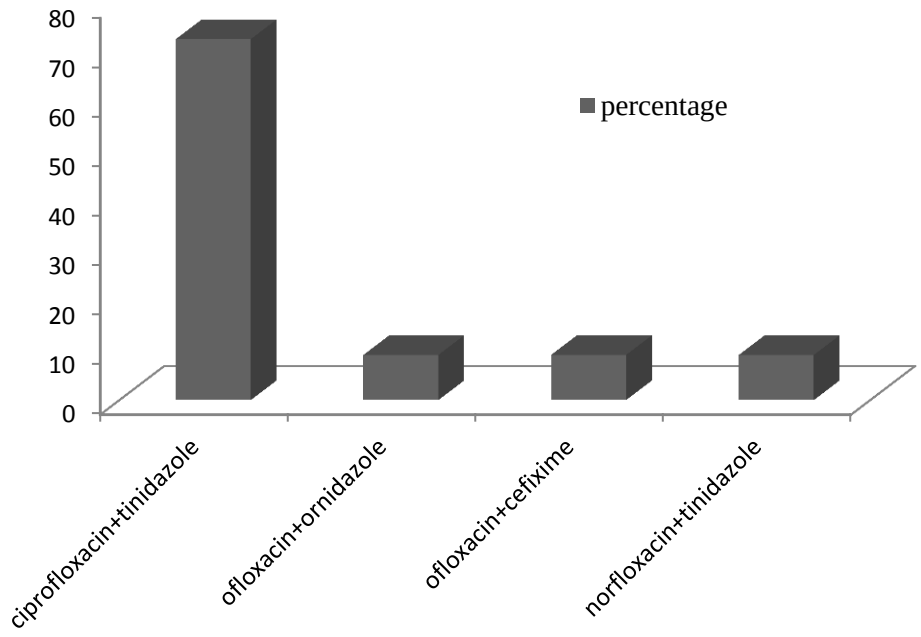

Fig 8: Fixed dose combination of Fluoroquinolones

DRUG-DRUG INTERACTIONS (DDIs)

Table 18: Patients distribution on drug-drug interactions

DDI (Major)	No. of patients	Percentage (%)
Yes	54	50.00
No	54	50.00

Table 19: DDIs identified during study period

Interacting drugs	No. of DDIs (Total =72)	Classification of DDI	
Levofloxacin + Ondansetron	7	pharmacodynamic	Synergistic
Levofloxacin + Insulin	6	pharmacodynamic	Synergistic/Antagonist
Ciprofloxacin + Ondansetron	15	pharmacodynamic	Synergistic
Furosemide + Amikacin	1	Pharmacokinetic	Synergistic
Levofloxacin + Glibenclamide	2	pharmacodynamic	Synergistic/Antagonist
Levofloxacin + Metformin	4	pharmacodynamic	Synergistic/Antagonist
Ciprofloxacin + Insulin	10	pharmacodynamic	Synergistic/Antagonist
Ciprofloxacin + Metformin	6	pharmacodynamic	Synergistic/Antagonist
Levofloxacin + Mefloquine	2	pharmacodynamic	Synergistic

Rifampicin + Phenytoin	1	Pharmacokinetic	Antagonist
Norfloxacin + Metformin	1	pharmacodynamic	Synergistic/Antagonist
Norfloxacin + Glimipride	1	pharmacodynamic	Synergistic/Antagonist
Atorvastatin + Carbamazepine	1	Pharmacokinetic	Antagonist
Atorvastatin + Fenofibrate	1	pharmacodynamic	Synergistic
Ofloxacin + Insulin	1	pharmacodynamic	Synergistic/Antagonist
Norfloxacin + Mefloquine	1	pharmacodynamic	Synergistic
Norfloxacin + Ondansetron	1	pharmacodynamic	Synergistic
Mefloquine + Ondansetron	2	pharmacodynamic	Synergistic
Ciprofloxacin + Gliclazide	1	pharmacodynamic	Synergistic/Antagonist
Ciprofloxacin + Theophylline	2	Pharmacokinetic	Synergistic
Levofloxacin + Glimipride	1	pharmacodynamic	Synergistic/Antagonist
Levofloxacin + Theophylline	4	Pharmacokinetic	Synergistic
Alprazolam + Digoxine	1	pharmacodynamic	Synergistic

All the identified DDIs were reported to physicians and documented. Among 72 DDIs reported to the physician 33 (45.83%) were accepted and necessary action was taken to minimize the severity of interaction (Table 20, Fig 9).

Table 20: DDIs accepted by physician

Physician acceptance	DDI (n=72)	
	Number	Percentage (%)
Yes	33	45.83
No	39	54.17

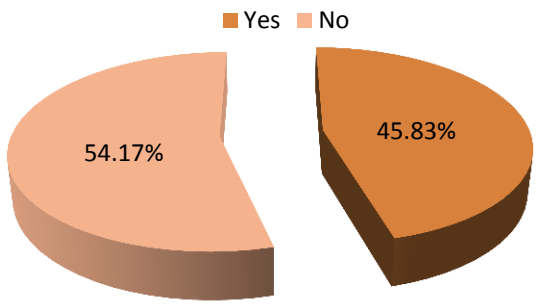

Fig 9: Physician acceptance of Drug-Drug interactions

Table 21: Physician acceptance and action taken

Action taken	Number	Percentage (%) (n=33)
Dose altered	2	6.06
Frequency changed	7	21.21
Monitored therapy	23	69.70
Drug stopped	1	3.03

Chapter-VI

Discussion

The study provides the data on the incidence of fluoroquinolone use and also nature and extent of fluoroquinolones use in patients admitted to medicine units of AH&RC. A total of 108 patients prescribed with fluoroquinolones were enrolled in the study after obtaining their written consent.

Gender and Age

In the present study male population was more (55.56%) than the female (44.44%) (Table 5, Fig 3).This finding is similar to a study conducted by Shankar et al[28] that showed a male predominance (61.6%) compared to females (38.8%).[43] A study conducted in university teaching hospital by Joel et al also showed that greater proportion of study population was male (67%) than female (33%).[29]

The majority of the patients (48.15%) were in the age group of 60-80 years followed by (30.56%) the age group of 40-60 (Table 4, Fig 2). The clinical research study on fluoroquinolone prescribing and drug utilization study of fluoroquinolone antibiotics also showed that age ranged from 40-80 years were more likely to be prescribed with fluoroquinolones.[29, 33]

Types of treatment

It was observed that 100 (92.59%) patients received fluoroquinolone for empirical treatment whereas 8 (7.41%) received it for specific treatment (Table 6, Fig 4). In another study it was found that only 35% patients were treated empirically.[29] This study showed that treating of patients specifically after culture and sensitivity test is relatively low than empirical treatment. In this study it was observed that Levofloxacin was used in more number of patients than other fluoroquinolones for empirical treatment followed by

Ciprofloxacin. The most common clinical conditions that were treated empirically with FQs were lower respiratory tract infections {21 (20.59%)}, acute exacerbation of COPD {21 (20.59%)}, followed by acute gastroenteritis {20 (19.61)} and urinary tract infection {15 (14.71%)}. In the study conducted by Joel et al., showed that FQs were empirically used in acute gastroenteritis (42.86%), lower respiratory tract infections (17.14%).[29]

Out of 8 specific treatment after culture and sensitivity test, 3 (37.5%) were for treating *pseudomonas aeruginosa*, 2 (25%) were for treating *Escherichia coli* infections followed by 1 (12.5%) for *klebsiella species*, 1 (12.5%) for *Streptococcus pneumoniae* and 1 (12.5%) for *staphylococcus aureus*. Levofloxacin 6 (75%) was the most commonly used fluoroquinolone for specific treatment followed by Ciprofloxacin 2(25%). Out of 10 Culture and sensitivity test 2 cases of E. coli were found resistant to Ofloxacin and Ciprofloxacin.

Co-morbidity condition

In the present study about 65.57% of study population has been presented with at least one co-morbidity condition (Table 7, Fig 5). Out of 71 patients 61.97% of patients were having only one co-morbidity, 25.35% were having two and 12.68% were having three or more than three co-morbidity condition along with other infectious diseases (Table 8). The most common co-morbidity condition observed was hypertension and/or diabetes. As a single co-morbidity condition hypertension account for 14.08% of total co-morbidity condition followed by diabetes mellitus 12.68% where as a double co-morbidity condition combination of hypertension and diabetes mellitus account for

14.08% of total co-morbidity condition. These co-morbidity leads to the poly pharmacy and thus increases the chance of more drug related problems.

Site of infection

Among the site of infections presented in the study population, respiratory tract (44.44%) were the most common site, followed by gastrointestinal tract (21.29%) and urinary tract (12.96%). The study showed that more percentage of fluoroquinolone was used for FDA-approved indication and also study conducted by Shankar et al[28] and Linder et al[33] showed that greater number of fluoroquinolone were used for infection in respiratory tract, urinary tract and gastrointestinal tract.

Distribution of therapeutic classes of drugs

Among the drugs prescribed to the study patients, anti-infective drugs (24.84%) were the most commonly prescribed class of drugs, followed by respiratory system drugs (20.35%) and alimentary tract drugs (14.39%), analgesics and antipyretics (8.07) (Table 9). In a study conducted by Srishyla et al[44] in Bangalore showed that cardiovascular drugs, NSAIDs and antiulcer drugs were most commonly prescribed whereas drugs for blood and blood forming agents followed by anti-infective for systemic use, drugs for alimentary tract and metabolism and central nervous system drugs was observed in study conducted by Karin et al[45]. The use of drugs depends on the morbidity patterns and other factors and may not be comparable between different studies. It is obvious that the increased use of anti-infective agents and respiratory system drugs were due to the reason that most of the study population were presented with infectious disease of respiratory tract.

Number of drugs prescribed during hospital stay

In 108 patients total of 1091 drugs were prescribed with mean ± SD of 10.10 ± 3.16 in which maximum number of patient i.e. 64 (59.26%) were prescribed with 6 to10 numbers of drugs followed by 31 (28.70%) patients with 11 to 15 numbers of drugs (Table 11). It was found that mean ± SD of drugs prescribed were 6.5 ± 3.3 and 8.23 ± 3.33 in study conducted by the Shankar et al[28] and Joel et al[29] .

Duration of hospital stay

The mean ± SD duration of hospital stay by study population was found to be 6.84 ± 3.77 days ranging from 2 to 22 days. This was similar to the study conducted in a teaching hospital in Nepal where mean ± SD duration of hospital stay was 6.2 ± 5.4 days[28] whereas very less than that study conducted by the Joel et al [29]. In this study it was found that majority of the patients i.e. 56 were admitted for a period of 1 to 5 days followed by 39 patients for 6 to 10 day and 10 patients for 11 to 15 days whereas study conducted by the Joel et al[29] showed that maximum number of patients 37 were admitted for the period of 6-10 days followed by 21 patients for 11-15 days. In this study maximum number of patient admitted only for 1-5 days may be because the study site is situated in the rural area and maximum patients were of agricultural background and they demand for early discharge.

Antibiotics co-prescribed with fluoroquinolones

The most common anti-infectives co prescribed in medicine units was found to be ceftriaxone (33.33%) followed by metronidazole (13.86%) and piperacillin/tazobactum (9.26%) (Table 14). In a previous study conducted by Babu et al.[2], also showed that

mostly prescribed anti-infective was ceftriaxone (48.51%) followed by metronidazole (17.82%) and ciprofloxacin (13.86%). In a cross sectional study of antibiotic prescribing pattern in two private sector hospitals by Sharma et al.,[4] also showed the similar result in non-teaching hospital than in teaching hospital where ceftriaxone was mostly prescribed antibiotics followed by metronidazole. The study conducted by Gupta N et al.,[36] in prospective prescription audit, where prescribing frequency for Penicillins and Cephalosporins was more followed by metronidazole.

Fluoroquinolones

During the study period total of 115 fluoroquinolones were prescribed to the 108 study population with an average of 1.06 fluoroquinolones per prescription. In 27 (25%) patients only fluoroquinolones were prescribed as a single anti-infective agent. The effective use of single anti-infectives in patients indicates the improved prescribing skill of the clinicians and also avoids the possible drug related problems.

The length of fluoroquinolone prescribed to the patients was varied from 1 to 15 days (Table 13). The maximum numbers of fluoroquinolones 55.56% were prescribed for 5 days and relatively less 18.51% were prescribed for 3 days. Out of 55.56% FQs prescribed for 5 days 53.33% were mainly for respiratory diseases followed by 16.67% for urinary tract infections and out of 18.51% FQs prescribed for 3 days 45% were for respiratory diseases and 25% for acute gastroenteritis.

Out of 108 patients, only one FQ was prescribed to 101 (95.37%) patients and 7 (6.48%) patients were prescribed with 2 FQs. In a study conducted by Joel et al., 87% patients were prescribed with one FQ and 13% were prescribed with 2 FQs.

Out of 115 FQs prescribed 43.48% was Ciprofloxacin and 41.74% was Levofloxacin followed by 7.82% of norfloxacin. Total 34 (29.56%) FQs were given by parenteral route and 77 (66.96%) were given by oral route. In this study parenteral Ciprofloxacin (19.13%) was prescribed more than the parenteral Levofloxacin (10.43%) (Table 16). In another study also it was found that parenteral Ciprofloxacin was prescribed more than parenteral Levofloxacin.[46] The study conducted by Joel et al., showed that parenteral Levofloxacin was more than parenteral Ciprofloxacin.[29]

In term of frequency, FQs were mainly used BD and OD. Moxifloxacin used in the study were only eye drops, so out of 115 FQs 56.52% were used BD and 40% were OD. In this Ciprofloxacin 50 (43.48%) was used twice a day (BD) whereas Levofloxacin 45 (39.13%) was used once a day (OD) and 3 (2.61%) was used twice a day (BD) followed by norfloxacin 9 (7.83%) for BD, Ofloxacin 1 (0.87%) for OD and 3 (2.61%) for BD. Fluoroquinolones were mainly used as OD for respiratory diseases and as BD they were used for gastrointestinal diseases followed by respiratory diseases.

Out of 115 fluoroquinolones 11(9.57%) were prescribed in fixed dose combination with other anti-infectives. Ciprofloxacin+Tinidazole was the most commonly prescribed combination which account for 72.73% of total fixed dose combination prescribed (Table 17).

Drug-Drug Interaction (DDI)

Out of 108 patients, total of 72 major/potential DDIs were occurred in 54 (50%) patients. It was found that majority of DDIs were pharmacodynamics and synergistic in nature (Table 19). Most common drug interaction was observed between Ciprofloxacin and Ondansetron i.e. 15 (20.83%) out of 72 DDIs followed by Ciprofloxacin and Insulin 10 (13.89%).

Drug interactions accepted by physicians

Out of 72 major/potential DDIs, 33 interactions (45.83%) were accepted by the physicians (Table 20, Fig 9) and took necessary action for the further management after clinical pharmacist recommendation. The further action taken was dose altered (60.6%), frequency changed (21.21%), monitored therapy (69.70%) and drug stopped (3.03%).

Clinicians and pharmacists should use their best judgments while prescribing or assessing drug therapy. The study opens door for larger studies to emphasize the role of clinical pharmacist in identifying and preventing DDIs and provide safe advice on interaction management which can greatly add to patient safety and wellbeing.

But no any adverse drug reactions were found in the study population during the study period.

Chapter -VII

Conclusion

Conclusion

The study concludes that, males are more likely to be prescribed with FQs and also the age group more than 40 years has shown the greater incidence for FQs prescribed.

The number of patients receiving specific treatment based on culture and sensitivity test was less than that reported in the previous studies and for empirical treatment broad spectrum FQ, Levofloxacin, was used more. So there should increase in the specific treatment depending upon culture and sensitivity test which will also further helps to decrease the irrational prescribing practice among the clinicians.

The average number of drugs per prescription in this study site was higher than that reported in the previous studies. The mean duration of hospital stay was 6.84 ± 3.77 days ranging from 2 to 22 days.

Respiratory system followed by digestive system and urinary tract disorders were the most frequent primary disease condition observed in the study population of medicine units. Among the drug received by study patients, anti-infective drugs were the most commonly prescribed class of drugs, followed by respiratory system drugs and alimentary tract drugs. The most common anti-infectives co prescribed with FQs in medicine units was found to be ceftriaxone followed by metronidazole and piperacillin/tazobactum.

The most common FQs prescribed were found to be ciprofloxacin followed by levofloxacin. An average of 1.06 fluoroquinolones per prescription was prescribed where oral route account more than the parenteral route. This is a good sign as injections are expensive, need of trained manpower and may also carry the risk of transmission of

infections. Mostly FQs were used BD during the study period and that is also for gastrointestinal diseases followed by respiratory diseases. During the study period 2 cases of E. coli were found resistance to ofloxacin and another with ciprofloxacin.

The total of 72 potential/serious drug-drug interactions were identified during study period in which Ciprofloxacin+Ondansetron was the most common interaction found that was 15 out of 72 but no any adverse drug reaction were identified in study population during study period.

Chapter-VIII

Summary

Summary

The assessment of medicine utilization is important for clinical, educational and economic purpose. Since the impact of drug utilization programs are not long lasting, periodic audits with adequate corrective measures need to be implemented.

The study was aimed to obtain the information on drug utilization pattern of FQs in medicine units of a tertiary care teaching hospital. The study of drug utilization pattern is essential so that necessary modifications in the prescribing practices of the prescribers can be made and rational and cost effective medical care can be achieved.

This prospective and observational study provides the data on the incidence, nature and extent of FQs use in patients admitted to medicine units of AH&RC during the study period of 7 months. A total of 108 patients prescribed with FQs were enrolled in this study in which 60 were male and 48 were female. Mean ± SD number of drugs prescribed and duration of hospitalization were 10.10 ± 3.16 and 6.84 ± 3.77 days respectively. An average of 1.06 fluoroquinolones per prescription was prescribed where oral route account more than the parenteral route. Ciprofloxacin was the most commonly prescribed FQs and it was mostly used BD. FQs were most commonly used for respiratory disorders followed by digestive disorders and urinary tract infections. Total of 72 potential/major DDIs were identified in 54 patients but no any adverse drug reactions were identified where 45.83% of total potential/major DDIs identified were taken for further management. It is recommended that a pharmacist in collaboration with prescribers and other members of the health care team can initiate the action to improve drug therapy for patients to optimize treatment outcome. Pharmacist intervention in drug therapy is beneficial for better patient care.

Chapter- IX

Limitations

Limitations

- The sample size of the study population was less.
- The study period was short and seasonal variations were not considered.
- Reasons behind more empirical use were not investigated.

Chapter- X

Future Directions

Future Direction

- Similar study can be carried out in other department of the study site.
- To Improve the type of specific treatment based on culture and sensitivity test is important because wide spread antimicrobial use may increase healthcare costs, increase adverse drug events, and encourage the emergence of antimicrobial resistant organisms.
- Antibiotic resistance pattern studies can be done.
- Safety and efficacy of Fluoroquinolones can be studied comparatively as a separate research.
- Pharmacoeconomic study can be done.
- The DUE study can be conducted for longer period.

Chapter- XI

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Chapter- XII

Annexure

|| Jai Sri Gurudev ||
Sri Adichunchanagiri Shikshana Trust (R)
Adichunchanagiri Institute of Medical Sciences
(Recognised by Medical Council of India, New Delhi, General Medical Council, London (U.K.) &Affiliated to Rajiv Gandhi University of Health Sciences, Karnataka)

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No. AIMS/IEC/ /2014-15 **Date: 16-07-2014**

CERTIFICATE

This is to certify that the M. Pharm. research project titled **"A study on drug utilization evaluation of fluoroquinolones in medicine units of rural tertiary care teaching hospital"** to be submitted to the Rajiv Gandhi University of Health Sciences, Bengaluru, and to be conducted by the research scholar Mr. Bipin Kafle, under the guidance of Mr. M Kumaraswamy, Associate Professor, Department of Pharmacy practice, SAC College of Pharmacy, BG Nagara, Mandya, Karnataka - 571448 has been discussed and approved by the Institutional Ethical Committee, Adichunchanagiri Institute of Medical Sciences, BG Nagara, Mandya, Karnataka - 571448 on 14th July 2014.

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DATA COLLECTION FORM

"A STUDY ON DRUG UTILIZATION EVALUATION OF FLUOROQUINOLONES IN MEDICINE UNITS OF RURAL TERTIARY CARE TEACHING HOSPITAL"

PATIENT NAME:			**IP NO:**		**DOA:**
AGE:	**SEX: M/F**	**WEIGHT:**	**UNIT:**		**DOD:**
COMPLAINTS ON ADMISSION:					
MEDICAL HISTORY: **MEDICATION HISTORY:** **SOCIAL HISTORY:** **FAMILY HISTORY:**					
PHYSICAL EXAMINATION: **GENERAL:** **CVS:** **RS:** **CNS:**				**OTHERS:**	
PROVISIONAL DIAGNOSIS:					
LABORATORY INVESTIGATION:				**HAEMATOLOGY:**	
Urea: S.Cr: Na^+: K^+: Cl: Bili T: D: C:	RBS: FBS: PPBS: T.Chol: TGs: LDL: VLDL: HDL:	Alb: Glob: AST: ALT: ALP:		RBC: Platel: WBC: L: M: E: B: N:	Retics: Hb: PVC: MCV: MCH: MCHC: TC: ESR:
URINE ANALYSIS:				**OTHERS:**	
Blood: Protein: Sugars: Casts:	WBC: RBC: EP.Cells: Crystals:				
FINAL DIAGNOSIS:					

DETAILS OF DRUG THERAPY

S. No.	Drugs	Dose	Route	Freq	Started Date	End Date	No. of days parenteral	No. of days of oral	Remarks

TREATMENT

☐ EMPIRICAL THERAPY ☐ SPECIFIC THERAPY

SUSPECTED PATHOGENS.....

DRUG INTERACTION IF ANY:

Is there any drug interaction? Yes ☐ No ☐

INTERACTING DRUG1	INTERACTING DRUG 2	CLASSIFICATION	SEVERITY

No. of drug interactions/prescription: _____

ADVERSE DRUG REACTIONS IF ANY:

Is there any adverse drug reaction identified? ☐ Yes ☐ No

Naranjo's scale score:

Interpretation: definite/probable/possible/doubtful

S.NO	**Associated Drug**	**Description of ADR**

Is the prescribed fluoroquinolones are safe and effective? Yes ___ No ___

If No, Why Not?

Name and Signature of the student: Bipin Kafle

PATIENT CONSENT FORM

I, …… have been explained by the investigators Mr. M. Kumaraswamy/Mr. Bipin Kafle about the **"A STUDY ON DRUG UTILIZATION EVALUATION OF FLUOROQUINOLONES IN MEDICINE UNITS OF RURAL TERTIARY CARE TEACHING HOSPITAL".**

I am above 18 years of age and hereby give my consent to be included as a participant in this study.

1. I have been explained about the nature of the study.
2. I have informed the investigator of all the treatments I am taking or have taken in the past…… months including any alternative treatments.
3. I have the option to withdraw from the trial at any stage.
4. I have been answered to my questions by the investigator about the study.
5. I have decided to be in the research study.

I am aware, that if I have any questions during this study, I should contact at any of the above investigators.

Place: - Name:-

_____

Thumb impression/Signature:-

Date:-

॥ ಜೈ ಶ್ರೀ ಗುರುದೇವ್ ॥

ಫಾರ್ಮಸಿ ಪ್ರಾಕ್ಟಿಸ್ ವಿಭಾಗ

ಶ್ರೀ ಆದಿಚುಂಚನಗಿರಿ ಔಷಧ ವಿಜ್ಞಾನ ಮಹಾವಿದ್ಯಾಲಯ

ರೋಗಿಯ ಸಮ್ಮತಿ ಪತ್ರ

..... ಆದ ನನಗೆ ಸಂಶೋಧಕರಾದ ಶ್ರೀ ಎಂ.ಕುಮಾರಸ್ವಾಮಿ/ ಶ್ರೀ ಬಿಪಿನ್ ಕಾಫಲೆ ನಡೆಸುತ್ತಿರುವ "ಗ್ರಾಮೀಣ ತೃತೀಯ ಆರೈಕೆ ಬೋಧನ ಆಸ್ಪತ್ರೆಯ ವೈದ್ಯಕೀಯ ಘಟಕಗಳಲ್ಲಿ ಫ್ಲೂರೋಕ್ವಿನೋಲೊನ್ಸ್ ಔಷಧ ಬಳಕೆಯ ಮೌಲ್ಯಮಾಪನದ ಬಗ್ಗೆ ಒಂದು ಅಧ್ಯಯನ" ಎಂಬ ಸಂಶೋಧನೆಯ ಬಗ್ಗೆ ಸಂಪೂರ್ಣವಾಗಿ ತಿಳಿಸಿಕೊಟ್ಟಿರುತ್ತಾರೆ.

ನಾನು 18 ವರ್ಷ ಮೇಲ್ಪಟ್ಟವರಾಗಿದ್ದು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಯಿಸಲು ಒಪ್ಪಿಗೆ ನೀಡಿರುತ್ತೇನೆ.

1. ನನಗೆ ಈ ಮೇಲಿನ ಅಧ್ಯಯನದ ಸ್ವಭಾವ/ಲಕ್ಷಣದ ಬಗ್ಗೆ ತಿಳಿಸಿರುತ್ತಾರೆ.
2. ನಾನು ಸಂಶೋಧಕರಿಗೆ ತೆಗೆದುಕೊಳ್ಳುತ್ತಿರುವ /ತೆಗೆದುಕೊಂಡಿರುವ ಚಿಕಿತ್ಸೆಗಳ ಬಗ್ಗೆ ತಿಳಿಸಿರುತ್ತೇನೆ.
3. ನನಗೆ ಈ ಅಧ್ಯಯನದ ಯಾವ ಭಾಗದಲ್ಲಿಯೂ ಪ್ರಯೋಗದಿಂದ ಹಿಂದೆ ಸರಿಯಲು ಅವಕಾಶವಿರುತ್ತದೆ.
4. ನಾನು ಅಧ್ಯಯನದ ಬಗ್ಗೆ ಸಂಶೋಧಕರು ಕೇಳಿದ ಎಲ್ಲಾ ಪ್ರಶ್ನೆಗೆ ಉತ್ತರಿಸುತ್ತೇನೆ.
5. ನಾನು ಸಂಶೋಧನೆಯ ಭಾಗಿಯಾಗಿರಲು ನಿರ್ಧರಿಸಿರುತ್ತೇನೆ.

ಸಂಶೋಧನಾ ಸಮಯದಲ್ಲಿ ನನ್ನಲ್ಲಿ ಉದ್ಭವಿಸುವ ಪ್ರಶ್ನೆಗಳಿಗೆ ಸಂಶೋಧಕರನ್ನು ಸಂಪರ್ಕಿಸಬೇಕೆಂಬ ಜ್ಞಾನ ಹೊಂದಿದ್ದೇನೆ.

ಸ್ಥಳ:

ಹೆಸರು

ದಿನಾಂಕ:

ಸಾಕ್ಷಿ:

ಹೆಬ್ಬೆರಳಿನ ಗುರುತು/ಸಹಿ