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UNIVERSITY OF THE WITWATERSRAND

MEDICAL SCHOOL

FACULTY OF HEALTH SCIENCES

DEPARTMENT OF PHARMACY AND PHARMACOLOGY

TOPIC

ASSESSING THE RATIONAL USE OF CEFOTAXIME AT QUEEN ELIZABETH II HOSPITAL

BY

TEBOHO MAPHASA

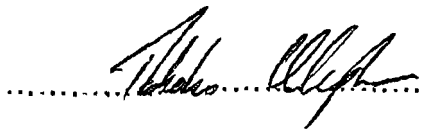
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A RESEARCH REPORT SUBMITTED TO THE FACULTY OF HEALTH SCIENCES, UNIVERSITY OF WITWATERSRAND, JOHANNESBURG, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PHARMACY IN CLINICAL PHARMACY

2004

DECLARATION

I Teboho Maphasa declare that this research report is my own work. It is being submitted for the degree of Master of Science in Clinical Pharmacy in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



..... Signature

09 Day of May 2005

ABSTRACT

The purpose of the study was to evaluate the use of cefotaxime with the idea of improving its use within the hospital. Improving the use of cefotaxime could result in a change in the proportion spent from the pharmacy budget. More importantly a change in prescribing patterns of this drug could also result in a reduction in resistant patterns of cefotaxime.

The use of cefotaxime amongst hospitalised patients is a major problem at Queen Elizabeth II Hospital in Maseru, Lesotho. It was not considered procedural to have available culture and sensitivity results before instituting cefotaxime therapy, as a result this lead to an alarming rate of consumption of the antibiotic.

The study seeks to assess the prescribing patterns; antimicrobial susceptibility patterns and indication for prescribing cefotaxime pre and post pharmacy intervention.

The study was conducted in two phases. In the first phase one hundred and fourteen patients participated and in the second phase, which was after the pharmacy intervention, thirty five patients participated. There was a significant reduction in the number of patient's participation in the second phase as the prescribers had narrowed down on prescribing cefotaxime in order to meet the required criteria.

The pharmacy intervention involved educating prescribers about the rational use of cefotaxime; distribution of guidelines for appropriate use of cefotaxime. The intervention had a positive influence on the prescribing patterns and indications for prescribing cefotaxime. The prescribers realised the importance of susceptibility testing in prescribing antibiotics and more specifically cefotaxime.

The most important recommendation was for the hospital to have in place Standard Treatment Guidelines and an Essential Medicines List.

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LIST OF ABBREVIATIONS/ACRONYMS

QE II	-	Queen Elizabeth II Hospital
WHO	-	World Health Organization
MIC	-	Minimum Inhibitory Concentration
RTA	-	Road Traffic Accident
STG	-	Standard Treatment Guidelines
EML	-	Essential Medicines List
SPP	-	Species
CRS	-	Cephalosporin resistant *Streptococcus*
CSF	-	Cerebrospinal fluid
SBP	-	Spontaneous Bacterial Peritonitis
IV	-	Intravenous
MDR	-	Multi-drug resistant
CRSP	-	Cephalosporin resistant *Streptococcus pneumoniae*

CHAPTER I

1.0 INTRODUCTION

1.1 BACKGROUND

Antibiotic use at Queen Elizabeth II Hospital (QEII) in Maseru, Lesotho, accounted for the largest proportion of the pharmacy budget (32%). The use of cefotaxime was increasing every year and its annual expenditure had accounted for the largest proportion of antibiotic use since 1995. In spite of its status as a restricted antibiotic the hospital spent approximately R108 291.94 and
R350 000.00 in the year 1995 and 2000 respectively, this represents an increase of almost 23% annually in a period of five years.

There has been irrational use of antibiotics in general in the hospital, which is probably due to the fact that the hospital does not have an Essential Medicines List and Standard Treatment Guidelines that adequately address the needs of the hospital. Antibiotics like amikacin were often used as first line antibiotics and there were no requirements for carrying out susceptibility test and once the pharmacy insisted on the availability of susceptibility patterns then the rate of using such antibiotics was reduced.

A clear problem exists at QEII (abbr.) as far as the use of cefotaxime is concerned. Procedurally before instituting cefotaxime therapy susceptibility

test results should be available to guide the prescriber unless circumstances call for empiric therapy of the antibiotic.

The existing problem in the hospital was that cefotaxime was generally used as first line antibiotic even before carrying out any culture and sensitivity test. It had been a great concern to the pharmacy department as there were instances where patients did not respond to the therapy and there was a general fear of building resistance to the antibiotic. Moreover the inappropriate use impacted negatively on the budget for drugs in the hospital.

This had been a problem generally in government hospitals in developing countries where patient care is solely the government's responsibility. A similar problem had been encountered in Thailand in a provincial hospital, where the annual expenditure of cefotaxime had accounted for the largest proportion of antibiotic expenditure since 1990 (Jakrawantana *et al.*, 1995).

It was also indicated by Dayani (1995) while assessing the use of cefotaxime in paediatric infections that in many institutions, cephalosporins in general, have been overused and abused resulting in the emergence of resistant organisms and an increasing burden on resources.

The isolation and identification of bacteria responsible in an infection involves a considerable time lapse, a surgical infection on the other hand can be fatal if not treated promptly and effectively. Specific antimicrobial therapy is not possible if the bacterial nature of the infection is not known. The logical solution is to use empiric therapy based on spectrum of activity of the selected

agent against the most likely infecting organisms (Wittman *et al.*, 1980).

The list of organisms, which are sensitive to cefotaxime with their degree of sensitivity, are as follows:

Streptococcus faecalis – cefotaxime has some activity but not useful

Staphylococcus aureus – quite sensitive

Streptoccocus pyogenes – quite sensitive

Streptococcus pneumoniae – quite sensitive

Neisseria meningitidis - quite sensitive

Neisseria gonorrhoeae – quite sensitive

Haemophilus influenzae – Usually very sensitive

Escherichia coli – Usually very sensitive

Klebsiella spp (abbr.) – Usually very sensitive

Proteus spp – Usually very sensitive

Pseudomonas aeruginosa – not useful

Bacteroides fragilis – sensitive but not very useful

(Grahame –Smith and Aronson 1994)

The conditions where cefotaxime is indicated are gonorrhoea, (long acting penicillin should not be used as adequate serum concentrations cannot be achieved), ampicillin resistant *H. Influenzae*, bacterial meningitis, bacterial osteomylitis and infectious arthritis. As a second- line agent for hospital acquired urinary tract infection and gram-negative septicaemia, where the first line agent is gentamicin.

Cefotaxime is not the drug of choice against infections caused by *Bacteroides fragilis* and *Staphylococcus epidermidis*. Abdominal (excluding biliary), and obstetric and gynaecological surgical procedures have *B. fragilis* as one of the most commonly isolated pathogens, and *S. epidermidis* is a pathogen isolated in neurological and cardiac procedures. One realises the possibility of treatment failure with cefotaxime, where the organism isolated cannot be effectively eradicated by the use of the antibiotic. Cefotaxime can be used successfully empirically in the treatment of bacterial meningitis caused by group *B streptococci* and *S pneumoniae*.

It is very important to note that even with empiric therapy, culture and sensitivity tests are still required to guide the prescriber in choosing the most appropriate drug for the patient, as it is possible that the organisms prevailing are not sensitive to the antibiotic chosen. This could result in the patient developing resistance to the drug and most importantly can be fatal. For example if *C. trachomatis* is a suspected pathogen appropriate anti-Chlamydia coverage should be added because cefotaxime has no activity against this organism. If enterococci are cultured ampicillin or/and gentamicin should be the antibiotic of choice.

1.2 STATEMANT OF THE PROBLEM

There was a great concern from the Department of Pharmacy at Queen Elizabeth II Hospital (QE II) about the manner in which cefotaxime was used in the hospital. Cefotaxime was prescribed without identifying the existing pathogens and for prolonged periods.

The study investigated the prescribing patterns, indications for cefotaxime and importance of sensitivity testing before and after pharmacy intervention. The perception was that there was irrational use of cefotaxime at QEII. This was based on the fact that about ninety percent of the time cefotaxime was administered without the knowledge of the causative organism. QEII Hospital had a high consumption rate of cefotaxime and the consumption of the drug was increasing at an alarming rate. Patients were often put on cefotaxime for 14 days without any apparent improvement.

The Pharmacy Department kept and controlled the use of cefotaxime in the hospital. In the past culture and sensitivity tests were requirements before the drug could be issued out. Empiric therapy was allowed when using cefotaxime but with the condition that culture and sensitivity test results were made available to the Pharmacy at least three days after starting therapy.

It was later not a requirement to produce any culture and sensitivity results at the Pharmacy before one could be issued with cefotaxime, for no apparent

reason. This condition led to erratic use of cefotaxime and it being used without the knowledge of the prevailing organism.

1.3 PURPOSE OF THE STUDY

The purpose of the study was to investigate the situation at QEII regarding the use of cefotaxime. The study also sought to find out whether there was any change in the use of cefotaxime after pharmacy intervention.

1.4 SCOPE OF STUDY AND DELIMITATIONS

The study only focused on hospitalised patients who were on cefotaxime at the time of the study at Queen Elizabeth Hospital in Maseru, Lesotho. It did not include outpatients. The study did not analyse the views of prescribers of cefotaxime regarding its use and personnel administering the antibiotic to the patients.

1.5 OBJECTIVES

Objectives of the first part of the study;

1. Determine the prescribing patterns of cefotaxime in the hospital.
2. Determine the indications (diagnosis) for prescribing cefotaxime.
3. Determine the cost involved with cefotaxime use.
4. Determine the antimicrobial drug susceptibility patterns.

Objectives of the second part of the study;

1. Determine if the intervention had any change on the prescribing patterns of cefotaxime.
2. Determine if the intervention had any change on the indications for prescribing cefotaxime
3. Evaluate the effectiveness of the tools to control cefotaxime use.
4. Determine if the intervention had any effect on the cost of cefotaxime incurred
5. Determine if the intervention had any change on the susceptibility patterns.

1.6 RESEARCH QUESTIONS

1. What are the prescribing patterns for cefotaxime?
2. Does the pharmacy intervention have any influence on prescribing patterns of cefotaxime?
3. Does the pharmacy intervention have any influence on the indicators for prescribing cefotaxime?
4. Does the pharmacy intervention have any influence on the expenditure of cefotaxime

1.7 SIGNIFICANCE OF THE STUDY

The study would provide information to the prescribers at QEII hospital and other health institutions about the rational use of antibiotics and more specifically of cefotaxime.

The study would further assist the Therapeutics Committees in hospitals and the Therapeutics Committee at national level, of practices in the hospitals regarding drug use. The committees would therefore have an insight of the problems in the hospitals regarding the use of drugs and be able to plan and advice accordingly in drug management.

CHAPTER 2

2.0 LITERATURE REVIEW

The literature review is presented under the following subheadings: general problems in prescribing antibiotics; general information on cefotaxime and spectrum of activity; the empiric and maintenance use of cefotaxime; cost effective use of cefotaxime; background information and problems associated with the use of cefotaxime at QEII hospital; interventions to improve the prescribing of cefotaxime.

2.1 GENERAL PROBLEMS IN PRESCRIBING ANTIBIOTICS

It is common practice to use broad-spectrum antibiotics in order to have a wide coverage of organisms. Broad-spectrum cephalosporins especially cefotaxime and ceftriaxone are widely used with penicillin resistant strains. According to a study where a high dose of cefotaxime and ceftriaxone were used for the treatment of adult meningitis due to *Streptococcus pneumoniae,* failures with both these drugs have been reported. This is despite the fact that these cephalosporins have been widely used in the treatment of suspected pneumococal meningitis and considered the drugs of choice for meningitis caused by penicillin resistant *pneumococal* strains. (Viladrich *et al.*, 1996)

Furthermore, overcoming the problem of decreased cephalosporin susceptibility by increasing the dosage in order to achieve high antibiotic levels in cerebrospinal fluid (CSF) was reported to be a satisfactory option (Viladrich *et al.*, 1996).

In a multi-centre study where meropenem was compared with a combination of cefotaxime and metronidazole, meropenem monotherapy was considered a suitable alternative to the combination therapy in the empiric treatment of hospitalised patients with serious infections. Even though it is often the case that the choice of antibiotic for patients with serious infections is often empirical as the responsible pathogen has not been isolated prior to initiation of therapy. (Mehtar *et al.*, 1997)

According to Mehtar *et al.*, (1997) it is important to isolate the organism prevailing before initiating therapy even with serious infections as more susceptible antimicrobials can be used to lower the cost of treatment.

This prescribing of cefotaxime regardless of the condition and susceptibility test becomes a great concern as one found that in most cases cefotaxime was not really the drug of choice or should not have been used as first line therapy of a particular condition. It is possible to find a patient on an antibiotic for extended periods of time with no sign of improvement, which results in increased costs incurred for the treatment and all other services provided.

There is a growing economic pressure to reduce health care costs. The use of less expensive but equally efficacious pharmaceuticals is a well established strategy for controlling antibiotic expenditure. Haas and Bonczar (1996)

In the study where the effect of replacing cefotaxime with ceftizoxime in order for the hospital pharmacy to reduce costs, a policy was adopted whereby ceftizoxime was dispensed and administered whenever cefotaxime was ordered. No differences could be demonstrated between the two groups

except that cefotaxime treated patients received significantly more other antibiotics than did ceftizoxime treated patients. Haas and Bonczar (1996).

A study by Navasa *et al.*, (1999) where the effectiveness of oral ofloxacin was compared with intravenous cefotaxime in spontaneous bacterial peritonitis (SBP), showed that oral ofloxacin is as effective as intravenous cefotaxime in cirrhotic patients with uncomplicated SBP. Since uncomplicated hepatic encephalopathy in not a life threatening infection, it can be treated as outpatient with oral ofloxacin. This would result in an improvement in their quality of life and once again a marked reduction in the cost of treatment.

A study by Bhutta (1996) also compared the response to therapy using ceftriaxone compared with cefotaxime. The response to therapy in a series of 876 children consecutively admitted to The AGA Khan University Hospital, in Pakistan, with culture proven typhoid, including 281 cases infected with multi-drug-resistant (MDR) strains was evaluated. Of the 217 children with MDR typhoid who received therapy with the third generation cephalosporins, the outcome was significantly better with intravenous ceftriaxone compared with cefotaxime.

It was further indicated in the study that earlier recognition and introduction of appropriate second line therapy has allowed reducing the case of fatality rates of typhoid to less than 1%. Bhutta (1996)

It is very important for clinicians to observe closely the clinical and microbiological responses to antibiotics more specifically cephalosporins when patients presenting with resistant strains are treated with these antibiotics. A study by Ko *et al.*, (1998) where therapeutic challenges for antimicrobials are assessed, indicated the presence of a beta-lactam resistant *Aeromonas hydrophilia* strain.

Aeromonas species are susceptible to tetracycline, chloramphenicol, cephalosporins, aminoglycosides and fluoroquinolones. An increase in the level of resistance of clinical strains of *Aeromonas* to commonly used antibacterial agents has been observed. In this study it was verified that a strain of *A. hydrophilia*, the most common *Aeromonas sp* causing human infections, acquired resistance to extended spectrum beta- lactam agents during antibiotic therapy with cefotaxime but remained susceptible to fluoroquinolones. The study demonstrated the emergence of cephalosporin resistant mutants, which might cause therapeutic failure in the treatment of invasive *Aeronomas* infections. (Ko *et al.*, 1998)

According to a research report by Collingnon and Bell (1996) on antibiotic resistance with a specific focus on *Streptococcus pneumoniae*, there was an indication that this particular organism continues to be a common cause of serious and life threatening infections including pneumonia, bacteraemia and meningitis. *Streptococcus pneumoniae* was one of the organisms isolated in the study conducted by the QEII Pharmacy Department, whereby prevalent organisms in the wards were being isolated.

Collingnon and Bell (1996) reported in this study that the level of penicillin resistance among *S. pneumoniae* isolates was six times higher than that found in 1989 in Australia. In meningitis caused by organisms with any level of penicillin resistance, penicillin treatment is likely to fail. Penicillin resistance has consequences for other related drugs. Penicillin resistance in *S. pneumoniae* is not due to beta-lactamase production but to changes in the target sites for penicillin. This change increases the MICs (abbr.) for all beta-lactams including the third generation cephalosporins. However, the levels of third generation cephalosporins achieved in CSF are still high enough to eradicate organisms with intermediate penicillin resistance. Alternative regimens include a combination of vancomycin with third generation cephalosporin and rifampicin as well as the newer agents such as the carbapemens and quinolones.

A great concern is the implication of rapid rise in resistance to third generation cephalosporins noted in the United States. It is reported that in some areas up to 27% of penicillin resistant pneumococci have high levels of resistance to cefotaxime. Collignon and Bell (1996). This leads to failure of these agents, yet they are the main treatment for the increasingly common intermediate penicillin resistant strains. In life threatening infections other than meningitis high dose intravenous penicillin appears sufficient to eradicate organisms with intermediate resistance. The report further states that there is however controversy of whether cefotaxime or ceftriaxone should be used instead of vancomycin. In non-life-threatening infections the most appropriate antibiotic is less clear. In otitis media, amoxycillin still appears the best choice, as drug

levels achieved in the middle ear can still exceed the MIC of strains with intermediate resistance. When assessing the oral agents (i.e. cefaclor, trimethoprim, erythromycin and cefpodoxime) for use in children the report stated that they do not reach adequate levels to eradicate resistant isolates. Combining clavulanic acid with amoxycillin is no advantage, as the resistance is not due to beta-lactamase. For high level penicillin resistant isolates there does not appear to be a satisfactory oral agent.

The reasons for increasing resistance in *S. pneumoniae* worldwide are not completely understood, although antibiotic pressure appears to be a major factor. Collignon and Bell (1996)

As it was common practice at QE II to prescribe cefotaxime without any sensitivity tests done, which is just blind therapy, it follows that assessing whether the infecting organism had been eradicated after therapy was not considered as one of the monitoring parameters as the organism was not known in the first instance.

Once antimicrobial therapy has been instituted the patient must be monitored carefully for therapeutic response. Clinical assessment of the patient on a regular basis is clearly the most effective.

The monitoring could be by determining the serum (or other fluid) levels of antimicrobials, which may be useful in assuring outcome and/or preventing toxicity. There are a few antimicrobials that require serum concentration monitoring, and in selected situations. These include aminoglycosides, flucytosine and chloramphenicol. Aminoglycosides are commonly prescribed

at QEII hospital with little or no monitoring parameters in place. It is important to monitor for failure of antimicrobial therapy. It does not necessarily mean that serum levels are required for cefotaxime, but what is important is to assess the susceptibility of the prevailing organisms to cefotaxime.

One continues to emphasise the importance of having culture and sensitivity results available before instituting cefotaxime therapy because of possible presence of resistant pathogens. Perlino and Lichtenberger (1991) also indicate the importance of having available susceptibility results prior to treatment with cefotaxime. They also observed while assessing the possible role of cefotaxime as a primary agent for empiric therapy of infections due to gram- negative bacilli, that a majority of isolates were obtained from urine cultures, the remainder were from blood, sputum, pus or wounds, *E.coli* was the most common organism. *Pseudomonas aeruginosa* was found in 35 isolates 88% were sensitive to cefotaxime. There was a subgroup of organisms isolated from sites other than the urinary tract which when tested only 63% of the organisms in this subgroup were sensitive to cefotaxime whereas sensitivity to tobramycin was 96%; gentamicin 92%.
It was then concluded, in the hospital where the study was conducted, that cefotaxime used alone would be inappropriate therapy for suspected gram-negative bacterial infection especially if the site of infection were isolates from sites other than the urinary tract, which were less sensitive to cefotaxime in comparison with other antimicrobials namely tobramycin and gentamicin. Furthermore the recommendations of Perlino and Lichtenberger (1991) were

that the local sensitivity patterns of gram-negative bacilli to cefotaxime are assessed before cefotaxime is used as empiric therapy.

A study was conducted at QEII Hospital, assessing the patterns of antibiotic prescribing for hospitalised patients. According to this study Marabe (1994) assessed the following specific areas for all the antibiotics in the study:

- The number of cases prescribed
- The number of cases where gram stain was performed
- The number of cases where monitoring of patient response was identified
- The number of cases where treatment period exceeded 7 days without identification of the pathogen(s) prevailing
- The number of cases where patients responded positively indicating success of antimicrobial treatment
- The number of treatment failures

The results of the study indicated that in general the success rate of antibiotic therapy used was 22% and the failure rate was 60%, while 16% of the cases had their sensitivity tests performed. 44% of the cases had treatment periods over 7 days without identification of the infecting organism.
The antibiotics assessed in the study were ampicillin, amikacin, cefotaxime, co-trimoxazole (sulphadiazine/trimethoprim), chloramphenicol, cloxacillin, erythromycin, gentamicin, metronidazole, nalidixic acid, nitrofurantoin, penicillin and tetracycline. Marabe (1994)

2.2 GENERAL INFORMATION ON CEFOTAXIME AND ITS SPECTRUM OF ACTIVITY

When concentrations of deacetyl- cefotaxime and cefotaxime were determined by high liquid chromatography it was shown that plasma concentrations of cefotaxime exceed those of deacetyl-cefotaxime for about two hours after a single dose with concentrations of metabolite higher for the remaining six hours of the observation period.

Cefotaxime can be used as a single agent or in combination with other antimicrobials. The indications for cefotaxime include:

- Use for surgical prophylaxis in paediatrics – an example is a pre-operative dose of cefotaxime + metronidazole and then a single dose after 12 hours (in neonates < 1wk; 1< 4wks and infants 4wks up to 12 years)
- Use as an alternative in peritonitis in adults caused by resistant *Enterobacter*, a third generation cephalosporin IV – cefotaxime can be used depending on sensitivity at dose of 1 –2g hourly up to 12g per day in life threatening disease
- Use in septicaemia in the newborn – especially when an antibiotic that crosses the blood brain barrier is needed for example in complicated meningitis- cefotaxime 50-100mg/kg/24 hours in three divided doses for 7 – 10 days.
- Use in acute bacterial meningitis in paediatrics- either as empiric treatment for those aged 3 months to 16 years- cefotaxime IV 200mg/kg/24 hours in 3 divided doses for 10 to 14 days. In neonates

and infants < 3 months one of the options is cefotaxime, IV, 200mg/kg/24 hours in three divided doses for 14 days (if the organism is gram-negative then for 21 days) plus ampicillin, IV, 200mg/kg/24 hours in 4 divided doses for 14 days

- Use for septic or pyogenic arthritis in paediatrics cause by ampicillin resistant *H. influenzae* - cefotaxime, IV, 500mg/kg/24 hours in three divided doses for 10 – 14 days.
- Use as part of an antibiotic option in shock in paediatrics (vancomycin + cefotaxime + metronidazole) – cefotaxime, IV, 200mg/kg/24 hours in divided doses for 10 days.
- Use for *H. influenzae* chest infection in cystic fibrosis in paediatrics – cefotaxime, IV, 50 –100mg/kg 8hourly for 10 to 14 days.
- Use for bacterial meningitis in adults but only where the bacterial aetiology is unknown, and if it is known that there is significant resistance of *pneumococci*, the addition of a third cephalosporin is suggested- cefotaxime, IV, 4g/day divided doses, 6 hourly.

(Standard Treatment Guideline Committee, 1998)

Cefotaxime is also indicated for serious infection in organisms in the following areas:

1. Lower respiratory infection including pneumonia
2. Gynaecologic infections
3. Bacteraemia/ septicaemia

4. Skin infection
5. Intra abdominal infection
6. Bone and joint infection
7. Central nervous system infection

(Hoechst-Roussel Pharmaceuticals, 1996)

Since the antibiotic has a wide coverage for microorganisms there is a tendency of being over utilized and ultimately misused. This in most cases results in resistant strains developing.

Organisms susceptible to cefotaxime are gram-positive *Streptococci.* Most gram-negatives except *Pseudomonas aeruginosa* are sensitive. Organisms not susceptible are Enterococcus spp and *B. fragilis.*

2.3 THE EMPIRIC AND MAINTENANCE USE OF CEFOTAXIME

The severity and/or acuity of infectious process dictates the necessity for so called "empiric" antimicrobial therapy. Empiric therapies are directed at organisms that are frequently known to cause the infection in question (Mehalik and Allen 1996).

The need for prompt antimicrobial therapy was emphasized by the rate of mortality within hours in patients with an acute presentation of meningitis or any other life threatening condition. In this situation it is not appropriate to wait for culture results to initiate therapy. After taking the patient history, carrying out physical examination and collecting specimens for appropriate laboratory tests the patient should be started on intravenous antibiotics. The choice of

empiric therapy should be based upon the patient's age, history and any specific underlying diseases and tailored further by the results of the gram-stain. Once the culture results are known and the antimicrobial sensitivity has been performed more specific antibiotic therapy can be initiated.
Empiric cefotaxime therapy is needed in treating amongst many conditions bacterial meningitis, bacterial osteomylitis, and infectious arthritis. (Butler *et al.*, 1992)

According to Butler *et al.*, (1992) selection of empiric antimicrobial therapy should follow careful consideration of suspected site(s) and source of infection and the most likely pathogens. Empiric therapy should be chosen to cover as narrowly as possible, only the suspected organisms.

Using antibiotic(s) with narrowest spectrum reduces the rate of secondary drug resistance, superinfection and confusion when assessing clinical response. The unique pharmacologic response of each potential antimicrobial must next be considered with regards to the following properties:

- Ability to penetrate the site of infection
- 'Inoculum effect' (stability toward beta- lactamases produced by large bacterial inocula)
- Activity in an environment of potential low metabolic activity (as in abscesses) or a low pH or $P0_2$ as in necrotic tissue disease.
- Lastly antimicrobial selection is based upon consideration of potential adverse reactions, drug- disease interactions, ease of dosing and overall therapy costs. (Butler *et al.*, 1992)

The dosage, route and frequency of administration of cefotaxime should be determined by severity of infection, susceptibility of the documented or suspected pathogen and the health status of the patient. The dose and frequency are important factors determined by the half-life, however determinants of effective antimicrobial therapy include other pharmacokinetic properties (residence time; penetration into the infection site; binding characteristics to intravascular, extra-vascular and membrane bound proteins; influence of disease as well as the pharmacokinetic aspects.)

According to the WHO (abbr.) model prescribing information: Drugs used in bacterial infections 2002, the antimicrobial susceptibility of an organism should be known, and the most effective and safe agent targeted to the organism should be used. This practice reduces the likelihood of selection of resistant microorganisms and superinfection. The study questioned the rational use of cefotaxime by assessing whether the general principles of antibiotic use are being followed, more specifically determining the organism present before instituting appropriate therapy as a general rule to follow.

World Health Organisation guidelines further stated that microbiological investigation should always be carried out before treatment especially when the aetiology is uncertain in severe infections, or when patients fail to respond to empirical therapy or develop a new infection during the cause of treatment. This has not been the case at QEII hospital hence the rational use of this antibiotic becomes questionable.

The concept of rational use covers a number of areas in drug use just to name a few; the relevance of the drug prescribed, the appropriateness of the dose regimen, other prevailing conditions, and several other pharmacokinetics aspects. There is also the pharmacoeconomic aspect, which is important when looking at the rational use of the drug. Antibiotic agents constitute a significant proportion of the hospital budget. Parenteral agents are generally several fold more expensive than their counterparts and account for the bulk of the antimicrobial budget (WHO model for prescribing information 2002).

2.4 COST EFFECTIVE USE OF ANTIBIOTICS

Ploster *et al.*, (1998) indicated that factors that produce unfavourable clinical outcomes would adversely affect the cost effectiveness of the antimicrobial agent. Therefore the efficacy of drug therapy and the cost of treatment failure are important aspects of pharmacoeconomic evaluation of antimicrobial agents.

Considering the fact that there are organisms resistant to cefotaxime it becomes cost-effective to carry out culture and sensitivity tests before treatment with cefotaxime. The susceptibility assessment is even more important especially where the causative organism is not known, unlike in bacterial meningitis, pneumococal arthritis and several other life threatening conditions where empiric therapy may be critical.

Ploster *et al.*, (1998) continued to emphasize the importance of determining and monitoring local patterns of microbial resistance. Empirical antimicrobial

therapy of serious infections will be affected by such patterns and these in turn will influence the cost effectiveness of antimicrobial regimens.

Once again, according to Ploster *et al.*, (1998), inappropriate selection of antimicrobials can result in increased cost associated with prolonged hospitalisation. Sub-optimal antimicrobial selection can also necessitate additional antimicrobial drug therapy and consultation with infectious disease specialists.

The dose and frequency of administration are important components in determining the prescribing patterns hence important factors in assessing the rational use of a drug. Brogden and Spencer (1996) reported in a retrospective study conducted in United States comparing cost outcomes amongst 495 hospitalised patients treated with cefotaxime twice daily with those treated with other antibiotic regimen in 3949 matched controls. Twice daily cefotaxime was found to be associated with slightly shorter hospital stay and consequently lower hospitalisation costs than the matched case.
One wonders if it is rational to continue using cefotaxime three times daily as had been the practice at QEII when as indicated from the above-mentioned study that it is more cost effective to use twice daily.

The cost of antibiotic used as blind therapy was alarming in such circumstances. The cost incurred by the hospital at large was enormous as it takes into consideration the laboratory assessments, hospitalisation and consultations.

2.5 BACKGROUND INFORMATION AND PROBLEMS ASSOCIATED WITH THE USE OF CEFOTAXIME AT QEII HOSPITAL

The available Standard Treatment Guidelines are fragmented, and the Essential Medicines List is outdated; therefore antimicrobials were amongst drugs, which were used without any guiding principle at QEII.

Queen Elizabeth II Hospital is the only referral hospital in Lesotho and the bed capacity is 420 beds. The hospital has the capacity to offer all the essential services but the more specialised services are outsourced. There are specialists in different medical fields and with different backgrounds in terms of practice hence the need to have a standard manner of treatment.

At QEII hospital cefotaxime is administered 12hrly, 8hrly, and 6hrly. The most common dosage interval is the 8hrly regimen for both medical and surgical wards.

Raddith *et al.*, (1995) indicated in their study that clinical studies of cefotaxime administered every 8 and 12 hours have demonstrated comparable clinical and microbiological success when compared to the traditional 6hrly regimen. This phenomenon may be explained in part by the pharmacokinetic and pharmcodynamic properties of cefotaxime and the antimicrobially active metabolite deacetyl-cefotaxime. Infections caused by bacteria with MIC 90 values < 1 or = 1 microgram/ml usually respond to 8 to 12 hourly dosage interval. Less susceptible organisms with MIC 90 values between 2 and 8 micrograms/ml such as *a Serratia marcescens* may initially require cefotaxime

administered every 6 or 8 hours. The practice at QEII hospital tends to be that one common dosage regimen is used without any evidence of clinical or microbiological response.

There were situations where patients were on cefotaxime for more than fourteen days without the prescriber knowing the causative organism. It is important for the prescribers to be aware that prolonged use of cefotaxime may result in overgrowth of non-susceptible organisms. As with other beta-lactam antibiotics, granulocytopenia and, more rarely, agraulocytosis may develop during treatment with cefotaxime, particularly if given over long periods. Courses of treatment lasting longer than 10 days, blood counts should therefore be monitored, according to the claforan® prescribing information Hoechst-Roussel (1996).

At QEII hospital the majority of infections were treated initially on the basis of clinical evidence, without full knowledge of the causative organisms or their susceptibility. In most cases the choice of antimicrobial which could be due to highly resistant strains or if it is pathogens with intermediate resistance being targeted then the dose of antibiotic could be lower than MIC required.

There are limitations with cefotaxime like any other pharmacological agent. The important point to note was, with the continuous irrational use of this antibiotic at QEII, there will develop resistant strains. This was why the importance of culture and sensitivity testing is over emphasized. At QEII hospital amongst patients who had been on cefotaxime there are a

percentage of those who have not responded. This could either be due to the development of resistant strain or the organism targeted was not susceptible The selection of resistant antibacterial is minimised by adherence to the basic few principles namely: use of antimicrobials that are most appropriate for the cause of infection and prevalence of local resistance; use of adequate doses; ensuring that the treatment course is complete.

According to WHO guidelines, the basic principle to follow for prescribing antimicrobials is to determine the causative pathogen and target such a pathogen with the sensitive antimicrobial.
Objective data and evidence of clinical efficacy should provide the basis for decisions for selection of antimicrobials like all other drugs in drug formularies

Unfortunately, since microbiological investigations were not carried out as an initial procedure prior to treatment with antimicrobials and more so with cefotaxime, the use of cefotaxime had increased. At the same time there was also a lack of stringent controls from the pharmacy. As microbiological investigations were not available and stringent control not enforced the prescribers opted for easy solutions by choosing antibiotics with broad coverage of microrganisms as first line antimicrobial treatment even where the respective antibiotic is not the drug of choice.

As has been shown by Collignon and Bell (1996) even though extended spectrum cephalosporins are widely used for empiric therapy of meningitis, there has been an emergence of cephalosporin resistant *Streptococcus*

pneumoniae (CRSP), which has led to treatment failure in children with pneumonia.

It was further indicated that where CRSP (abbr.) occurs with the same frequency (i.e. >5%) empiric therapy with the combination of cephalosporin and vancomycin is recommended. Furthermore the importance of susceptibility testing of strains from all patients with pneumococal meningitis is emphasized. A pharmacoeconomics review of cefotaxime by Ploster *et al.*, (1981) reported that *Enterobacter* spp *Serratia* spp and *C. freundii* are some of the organisms, which have reduced sensitivity to cefotaxime.

An investigation that further supports failure of treatment due to organism resistance, as has been indicated, is by Perlino and Linchtenberger (1991). This report also emphasizes the importance of culture and sensitivity testing before instituting cefotaxime therapy. Treatment failures of meningitis caused by organisms with MIC of cefotaxime as low as 0.5 µg/ml and treatment successes with MIC as high as 2 µg/ml have been reported.

According to Brogden and Spencer (1996), the usefulness of cephalosporins had been threatened by the emergence of beta-lactam resistant enteric bacilli producing extended spectrum beta-lactamases, which was usually in serious hospitalised patients. They further emphasized that resistant bacteria were generally frequently found in hospitals where the selective pressure of antibiotic usage patterns contributes to the development of resistance.

One should acknowledge that the patterns of bacterial resistance vary widely between countries, between hospitals and between wards (WHO, Geneva 2002).

Choosing an antibiotic without knowledge of the prevailing pathogen is an expensive manner of clinical practice, potentially more harmful and will lead to spread of resistant strains and superinfection which is difficult to treat. (WHO, Geneva.2002)

It is clear then, after assessing several investigations about the use of cefotaxime that its use at QEII hospital is questionable and not cost effective, as the basic principle of using antimicrobials was not followed.

Once again the above-mentioned studies are amongst many that further indicate the importance of carrying out culture and sensitivity tests prior to instituting cefotaxime therapy. This is the case more especially as there has been strains isolated which are resistant to cephalosporins.

Queen Elizabeth II Hospital is one of the hospitals, which needed to be highly sensitised about the difference between empiric therapy using cefotaxime and misuse of cefotaxime.

2.6 INTERVENTIONS TO IMPROVE THE PRESCRIBING OF CEFOTAXIME

There had been several initiatives by the Pharmacy Department to control the use of antibiotics. One of them being the cefotaxime intervention whereby the pharmacy together with the relevant physicians were educating the other

prescribers on the use of cefotaxime to enable the prescribers to make informed decisions.

After realising serious erratic prescribing of antibiotics like amikacin for hospitalised patients the pharmacy department intervened by assessing prescriptions where the suspected antibiotic was prescribed. The Pharmacy Department raised their concern in the regular meeting with the department concerned. The respective cases were discussed further in that forum. The main problem as sighted by the pharmacy was there was a lot of empiric treatment when using antibiotics, and culture and sensitivity testing was hardly carried out. The senior medical officers were always complaining that they are aware of the importance of using susceptibility results to enable them to choose the most appropriate antibiotic but unfortunately they were always ordering for tests to be done but it seemed like the results were never available. Part of the problem was identified to be more administrative than clinical.

As control measures the pharmacy department insisted on seeing the patient charts before issuing certain antibiotics like aminoglycosides and cephalosporins.

The Pharmacy Department insisted that certain test results be made available prior to issuing out the respective antibiotics and also making sure the monitoring parameters are followed.

The Pharmacy Department together with the Laboratory Department at QEII Hospital were also engaged in a study determining the pathogenic isolates prevalent in the different wards, more specifically theatre and the surgical wards. The purpose of this study was to determine the extend of hospital acquired infections and the sensitivity characteristics of the bacterial isolates found in the hospital. It was realised that most prevalent infections were hospital acquired.

The findings of the study indicated that *Staphylococcus albicans* and *Bacillus* spp were the most common isolates. Culture and sensitivity tests carried out showed that staphylococcal isolates were most sensitive to ampicillin, tetracycline and erythromycin, suggesting the use of these antibiotics even in empiric therapy of staphylococcal infection.

Staphylococcus aureus demonstrated less sensitivity to penicillin. The *Pseudomonas* spp isolated were more sensitive to aminoglycosides, cephalosporins and ciprofloxacin. The antibiotic with the highest level of sensitivity for *Pseudomonas* and *E.coli* isolates was gentamicin, while, *Klebsiella* was more sensitive to cefotaxime.

It was concluded in this study that gentamicin could be used as the drug of choice for hospital acquired *Pseudomonas* and *E. coli* (Tema 2001).

The Pharmacy Department was able to use data from this study to indicate to the prescribers at least the most prevalent isolates within the hospital and most importantly their sensitivity profiles in order to avoid the use of antibiotics which seemed to be less sensitive to such isolates.

The Pharmacy was also involved in assessing the rate at which antibiotics are prescribed in minor ailments for outpatients. The study was looking at specifically the consumption level of antibiotics amongst patients with common cold. The idea with these studies was to create awareness amongst prescribers of the rate or extent at which antibiotics are used in minor ailments and thereby improve their rational use Tlali (2001).

The Pharmacy Department was also actively involved in the development of the Standard Treatment Guidelines as well as the Essential Medicines List for the hospital as an initiative to improve the rational drug use at large but more specifically rational antibiotic use.

The assessment of the rational use of cefotaxime, as has been indicated, was one of the pharmacy initiatives and intervention towards improving the rational use of drugs. The following chapter indicates the methodology used and the findings of the research.

CHAPTER 3

3.0 METHODOLOGY

3.1 RESEARCH DESIGN

The study used a quantitative and qualitative design. It was a one group before – after design, where the same measuring instrument was used for the before and after measures. The design enabled the researcher to interpret the responses in order to conclude on how cefotaxime was used before and after the intervention.

3.2 DATA COLLECTION

The study was conducted in two phases. The researcher and pharmacists collected data from QEII.

Data were collected from the patient's charts by the researcher with the assistance of three other pharmacists. Informed consent was obtained from the patients. Data were collected over a period of two months before the intervention followed by a period of intervention of six months, after which data were collected once again for a period of two months. Phase II used the same criteria to evaluate the impact of the interventions.

PHASE 1

- The phase involved assessing cefotaxime use before pharmacy intervention. Data were collected over a period of two months before intervention.

Phase 1 of the study was as follows

- Hospitalised patients on cefotaxime were identified and information from their charts was recorded.

  List of information collected

  - Demographic information
  - Indication(s) for the use of cefotaxime
  - Sensitivity test results
  - Dose of cefotaxime
  - Duration of therapy

- Prescribing patterns for cefotaxime were determined according to the dose, duration of therapy, and indication for prescribing.

- Prescribing patterns were also determined in relation to the cost. The expenditure for cefotaxime was determined over a period of time before and after the intervention.

The Pharmacy intervention was as follows:

- Guidelines for appropriate use of cefotaxime availed to prescribers.

- Influential speakers (physicians) explained and indicated the importance of changing prescribing patterns in the use of cefotaxime.

- Tool designed by pharmacy to control use of cefotaxime.

- Information on cefotaxime therapy published on hospital circulating clinical information.

The period of intervention was six months.

PHASE 2

This phase involved determining the effectiveness of the intervention.

Phase 2 of the study was as follows:

- The same information as in Phase 1 was recorded

- Prescribing patterns were monitored after the intervention to note any changes.

- Any change in indications for prescribing cefotaxime, which may be influenced by the availability of sensitivity results was recorded.

(It was assumed that the change in prescribing was due to the available susceptibility results. The general practice was the therapy chosen was according to the sensitive organism prevailing as opposed to just being guided by the presenting signs and symptoms.)

- It was determined if the study tool had been effective by monitoring whether the prescribers had adopted the requirements for prescribing cefotaxime after the intervention, which was a way of assessing the effectiveness of the tool.

3.3 POPULATION AND SETTING

All hospitalised patients, at QEII hospital, who received cefotaxime during the study period, regardless of age and condition were included in the study. The charts of all study patients were reviewed for demographic, clinical, and microbiological and drug data.

3.4 RESEARCH INSTRUMENT AND ETHICAL CONSIDERATION

The research instrument used for the study was the questionnaire referred to as Annexure I. Confidentiality on information was dealt with by making the respondents anonymous. The Therapeutics and Ethical Committee of the hospital approved the study (Annexure II). Ethics approval was obtained from the Committee for Research on Human subjects of the University of Witwatersrand (Annexure III).

3.5 DATA ANALYSIS

Data were analysed to provide answers to all the research questions which were about prescribing patterns; indications for prescribing cefotaxime; and if the pharmacy interventions had any influence on these indications and prescribing patterns.

Data were analysed using descriptive statistics. Calculations of descriptive measures such as percentages were used. The results were presented in the form of graphs and a table.

CHAPTER 4

4.0 RESULTS

4.1 INTRODUCTION

Data were analysed to provide answers to all research questions which were about the following issues

- The prescribing patterns of cefotaxime across different age groups, gender and disease patterns.
- The indication for the use of cefotaxime.
- The rationale for the dosing patterns.
- The rational use in relation to concomitant administration of cefotaxime with other antibiotics.
- How often prescribers used susceptibility patterns to determine the choice of cefotaxime.
- The use of monitoring parameters to assess the effective use and/ or adverse reactions in the use of cefotaxime.
- Whether the intervention had any significant change on the prescribing patterns and indications for which cefotaxime is prescribed.

The findings are presented under three main parts. Part I presents the patient categorisation and disease conditions for which cefotaxime was prescribed. Part II presents the prescribing patterns. Part III indicates the use of susceptibility analysis in determining the choice of antimicrobial (which was used to assess the rational for the use of cefotaxime); the extend at which

monitoring parameters were used. All the three parts presented findings prior to and after pharmacy intervention.

4.1.1 PART I

This part gives an analysis of the demographic data of patients on cefotaxime and findings are presented in Table 4.1. Before pharmacy intervention 114 patients received cefotaxime during the two month study period. During the two months study period. During the two months post intervention 35 patients received cefotaxime. Before pharmacy intervention 30% of patients receiving cefotaxime were over 51 years of age, while 26% of the population was paediatrics between the ages of 0 – 12 years.

The adult population was mostly male (64%). The most prevalent disease condition was trauma (gunshots, stab wounds, road traffic accidents). The most prevalent medical condition was pneumonia (17%). Five percent of patients with meningitis received cefotaxime.

After the intervention only 8% was over 51 years of age and 34% paediatrics between the ages 0 – 12 years. The highest percentage of patients administering cefotaxime was between the ages 13 – 30 years with a percentage of 43%. The most common condition for which cefotaxime was used after the intervention was meningitis with 71% of the patients, followed by 23% with pneumonia. Male patients were still more than the females even after the intervention.

TABLE 4.1: Represents the demographic data and disease patterns in relation to the use of cefotaxime

Variables		Before Pharmacy intervention		After Pharmacy intervention	
		Frequency n =114	(%)	Frequency n = 35	(%)
Age	0 – 12	30	26	12	34
	13 – 30	20	17	15	43
	31 – 50	32	28	6	17
	51<	34	30	2	8
Gender	Male	73	64	20	57
	Female	24	21	15	43
Diagnosis	Meningitis	6	5	25	71
	Pneumonia	20	17	8	23
	Gangrene	15	13	-	-
	Carcinoma	8	7	-	-
	Abscess	4	3	-	-
	Trauma (post-op)	7	6	-	-
	Trauma	29	25	-	-
	Septicaemia	2	2	2	6
	Other	13	10	-	-

4.1.2 PART II

Part II of the results gives an analysis of the prescribing patterns of cefotaxime

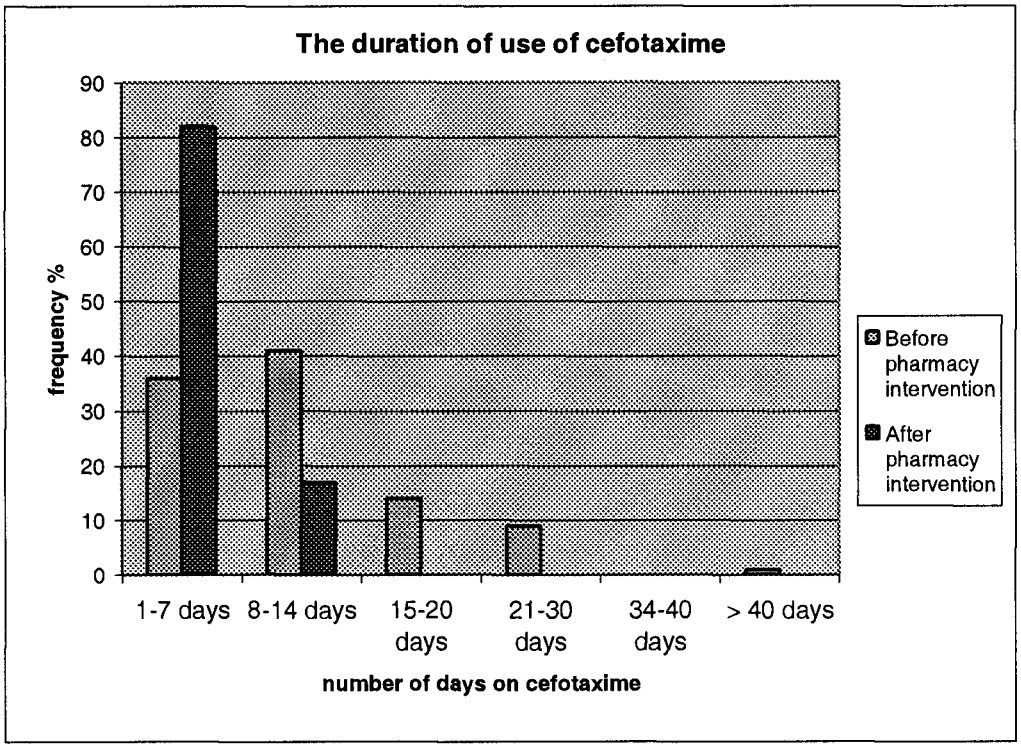


Figure 4.1. Duration of cefotaxime use

Prior to the intervention the most common duration of use for cefotaxime was 8 – 14 days with 41% of the patients (n= 47). Fourteen percent (n=16) of the patients received cefotaxime for 15 –20 days; 9% (n=10) over 21 –30 days, and 1% (n=1) over 40 days. After intervention the most common duration of use was 1-7 days at 82%. No patients received cefotaxime for longer than 14 days.

The rationale for the dosing patterns prior to the intervention were different, for most prescribers it was past experience and others it was practice followed from influential senior medical practitioners.

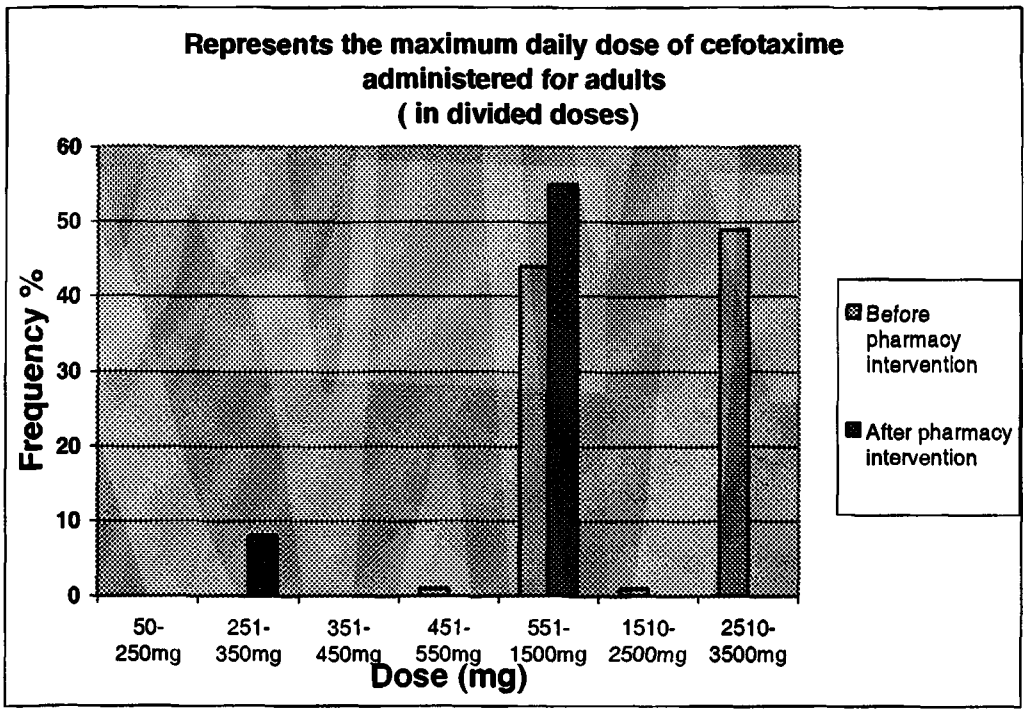


Figure 4. 2. Daily dose of cefotaxime administered for adult

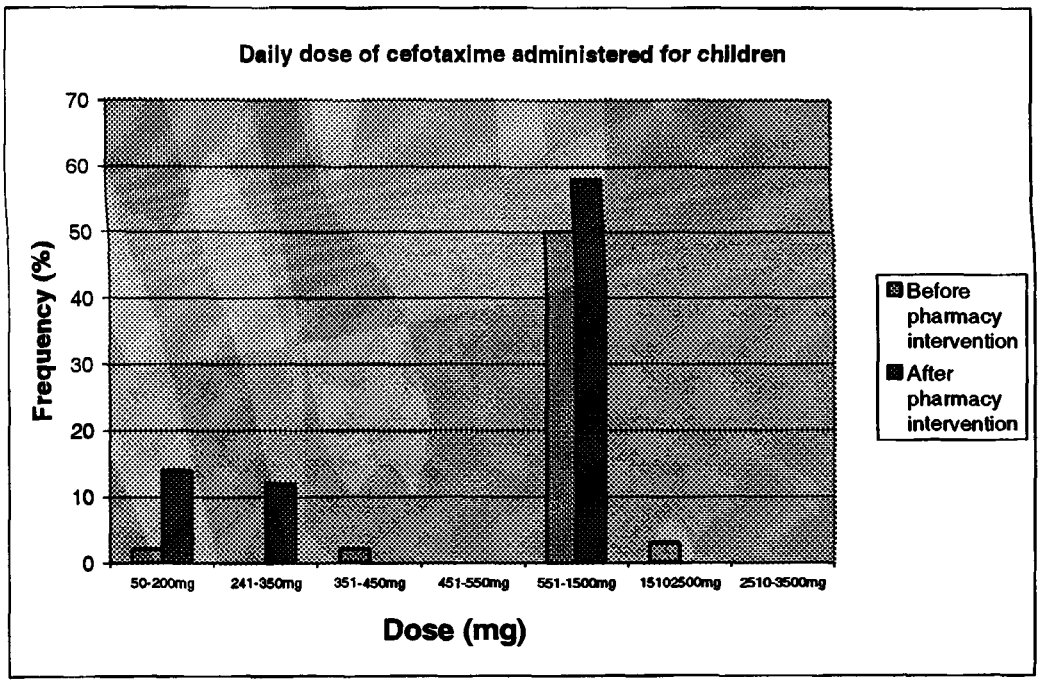


Figure 4.3. Daily dose of cefotaxime administered for children

The most common maximum daily dose before intervention for adults was between 2510 –3500mg (49%) given in divided doses. This shows a trend of prescribing high doses. The most common maximum daily dose for adults

after intervention was 551-1500mg at 55%. After the intervention, for adults, there was a trend of prescribing comparatively lower doses as indicated by the 0% for the 2510-3500mg daily doses, which was 49% before intervention for the same daily dose. After the intervention the dose prescribed was generally comparatively lower but still within the recommended dose.

The maximum daily dose for children before and after the intervention was 551-1500mg at 50% and 58% respectively. Even though there did not seem to be much change before and after the intervention, there was also a general tendency towards prescribing comparatively lower doses for children after the intervention as shown on Figure 4.3. The differences noticed could be due to the differences in weight of the patients enrolled.

The dosage regimen recommended in the intervention for adults was 500mg – 1g in two to three divided doses for moderate to serious infection, and 2g every 8 hours for life threatening infection. The recommended dose for children was 50mg – 200mg /kg/day in three divided doses.

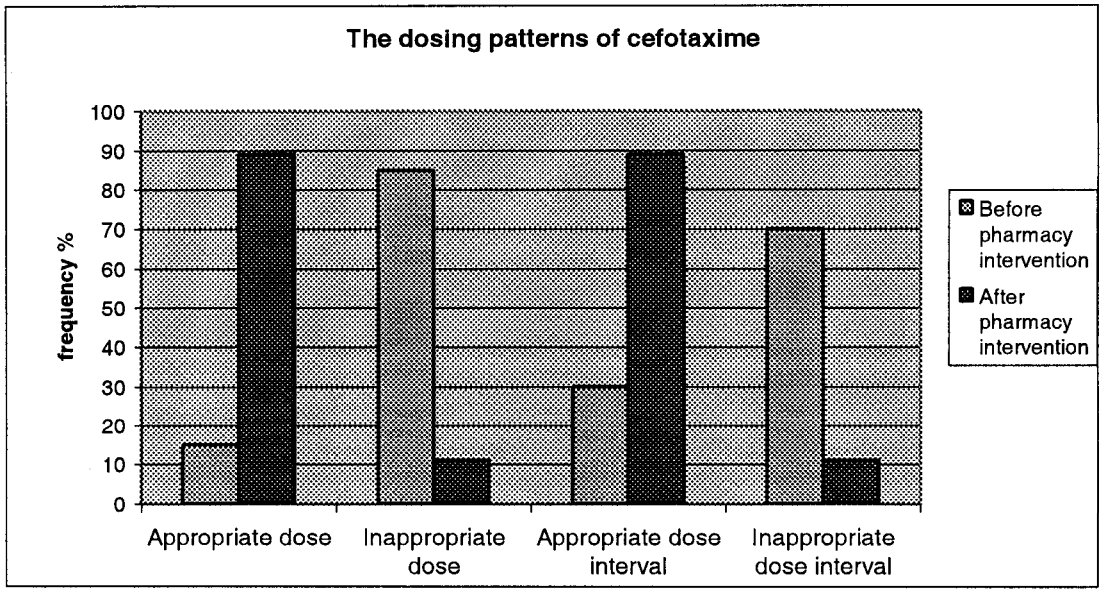


Figure 4.4. The dosing patterns of cefotaxime

Before the intervention only 11% of the patients had their dose prescribed appropriately and 30% had the appropriate dosing interval.

After the intervention 89% of the patients had the appropriate dose and dose interval for cefotaxime prescribed.

The appropriate dosing interval for adults and children was taken to be 12 and 8 hours respectively.

4.1.3 PART III

This part of the results gives an analysis of the rationale for the choice of antibiotic and also assessing the use of cefotaxime with other antimicrobials. The rational for the choice of antibiotic is analysed by the frequency of using indicator parameters such as susceptibility tests. It further gives an analysis of the use of monitoring parameters in the use of cefotaxime, and finally the significance of the pharmacy intervention in the use of cefotaxime.

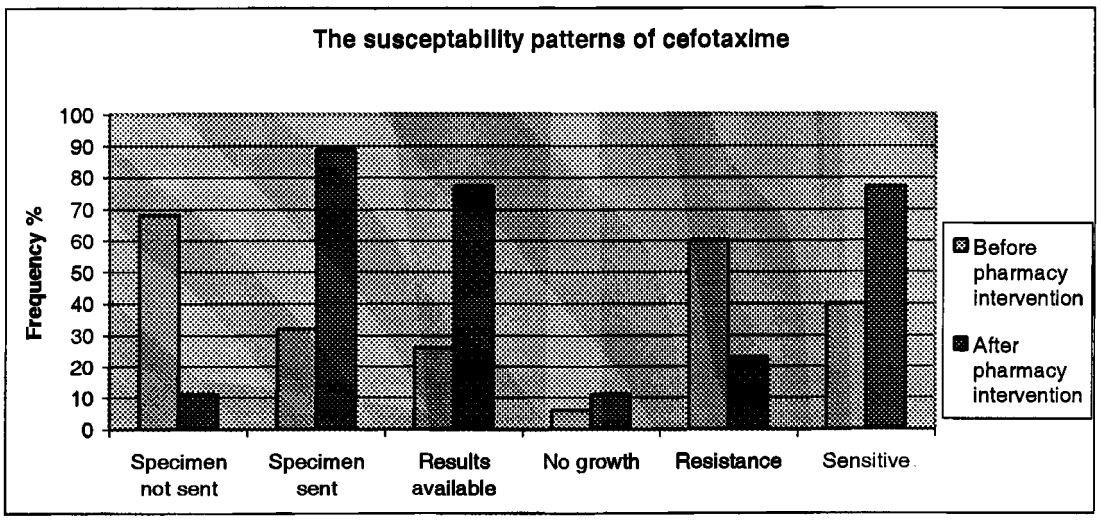


Figure 4. 5. Culture and sensitivity investigations

Before the intervention the frequency of sending specimens for susceptibility testing and identification was low (10%). The findings indicated that 68% of patient charts did not have susceptibility results, as specimen were never sent to the laboratories. Out of the 36 specimens sent only 6% of them did not have any growth. Out of the 30 susceptibility results available 60% were resistant and another 40% sensitive.

The organisms found to be resistant were 33% (n = 6) *Staphylococcus spp*, 28%(n = 5) *Pseudomonas aeruginosa,* 17% (n = 3) *Streptococcus pyogenes,* 11%(n = 2) *Bacteriodes fragilis*, 6% (n = 1) *Haemophilus influenzae* and 6% (n = 1) Enterococci *according* to the laboratory results.

In cases where an additional antibiotic was used, gentamicin (34%) was the most common prescribed followed by metronidazole at 32%.

The findings indicated that 86% of the patients did not have their renal clearance monitored before or after the use of cefotaxime as opposed to 14% who did. The most common outcomes recorded were Urine & Electrolyte and full Blood Count for 54% and 53% of the patients respectively and 3% of the patients had liver function test results recorded.

The monitoring parameters were necessary to assess whether the patients were responding to therapy.

After pharmacy intervention, 89% of the patient charts had documented susceptibility results as specimens were sent to the laboratory for assessment, compared to the 11% before the intervention. Out of the specimen sent 11% indicated no growth. There was resistance in 23% of the 26 specimen sent. While the susceptibility showing sensitive organisms were 77%.

In cases where there was an additional antibiotic to cefotaxime, gentamicin was still the most common antibiotic used at 34%.
As the use of cefotaxime reduced after the intervention at QEII hospital the antibiotic used in place was gentamicin and in some cases a combination of gentamicin and penicillin.

The use of cefotaxime decreased by 69%. Following the decrease in the use of the cephalosporin there was general increase in the use of aminoglycosides.

The combination of penicillin and gentamicin compares with some second and third cephalosporins i.e. cefoxitin with regard to susceptibility of aerobic gram-positive Streptococci. Also the combination of penicillin and aminoglycoside provides bactericidal activity against Enterococcus spp, while no cephalosporin has antimicrobial activity against Enterococci.
The toxicity of aminoglycosides remains the limiting factor. (Butler *et al.*, 1992)

Greater attention is being paid to the pharmacoeconomics of drug therapy, where patient outcomes are valued and the costs to arrive at those outcomes are estimated. It was important to understand the true cost of cefotaxime therapy, especially as the number of patients on the antimicrobial is relatively high. The total cost of antimicrobial therapy includes much more than just the acquisition cost of drugs.

The total economic impact of antimicrobial therapy include the cost of drug acquisition, storage and inventory costs, preparation, distribution,

administration, monitoring, adverse effects, impact on length of stay, cost of control systems.

The use of cefotaxime in particular has had a negative impact on the cost, more specifically the acquisition cost, length of stay of patients and control systems put in place to control the antibiotic.

The budget for drugs was 12 million Rands and the acquisition cost of cefotaxime was 2.06% of the total budget before the intervention and 1.44% after the intervention. This cost does not include all other costs incurred in the treatment.

The total cost of using cefotaxime reduced after the intervention as the consumption levels and duration within which cefotaxime also showed a relative reduction.

Before the intervention, expenditure of cefotaxime over 6 months was R130, 680.00 for 1g dosage form and R110,280.00 for 500mg dosage form, which was a total of R240, 960.00. After the intervention, which was over 6 months, the expenditure was R61,420.59 for 1g and R101,455.60 for 500mg. The total expenditure after the intervention was R162,876.19. There was a 53% reduction in expenditure for 1g and 8% reduction for 500mg cefotaxime.

The differences in expenditure were found to be due to changes in prescribing patterns after the intervention. There was generally high doses prescribed before the intervention where more of the 1g dosage forms were used compared to the period after the intervention,

The results of the study are discussed in Chapter 5.

CHAPTER 5

5.1 DISCUSSION

Cefotaxime use after the intervention had decreased by 69%. It was apparent that physicians had critically evaluated the appropriateness of cefotaxime before prescribing hence resulted in the 69% reduction in use. The use of cefotaxime in Phase II of the study indicated the appropriateness of the intervention or persuasion strategies. A similar study was conducted in Lampang Hospital in Thailand, where cefotaxime use was evaluated. Similar results were seen in that study where cefotaxime use was evaluated. (Jakrawatana *et al.*, 1995)

At Lampang Provincial Hospital, an 800 bed tertiary hospital, the level of expenditure of cefotaxime was increasing every year. A multiple intervention strategy was used to improve the use of cefotaxime in the hospital. Post – intervention results showed a significant increase in the overall appropriate justification for use. Although some process indicators for instance culture and sensitivity test, renal function monitoring showed a higher percentage of appropriateness in the post- intervention phase, overall drug monitoring for both periods were comparable. (Jakrawatana *et al.*, 1995)

According to Jakrawatana *et al.*, (1995), the percentage of appropriate indication according to criteria was 65% and 85% of the cases during the pre- and post- intervention period respectively. This study further showed that the majority of use was in the medicine service with 62% and 95% of the cases appropriately prescribed in the pre- and post- intervention period respectively.

In Phase II of the QE II study, 71% of patients were on cefotaxime for meningitis as opposed to 5% in Phase I. This is an indication that there were more cases which required treatment with cefotaxime as guided be the susceptibility assessments as opposed to Phase I, where it was more blind treatment.

In Phase I cefotaxime was used in a number of conditions even where it was not the drug of choice. These findings once again are a reflection of critical evaluation of the choice of antibiotic, making use of indicators like culture and sensitivity testing.

The most common duration of treatment after the intervention was 1 – 7 days for 82% of the patients, which showed an improvement from 8 – 14 days prior to intervention. The percentage of patients who were on cefotaxime for more than 10 –14 days had reduced by over 60%. This was an indication that prescribers were more cautious about using cefotaxime.

After the intervention the most common maximum daily dose administered in divided doses was 551 – 1500mg. There was a general trend for both adults and children to lower the dose as seen after the intervention. What was most important was to see patients responding positively to the therapy after the change. Seventy seven percent of the patients had their specimen collected and examined to determine the susceptible pathogen as opposed to 26% prior to intervention. The results indicating no growth even after the intervention was 11%, which was still relatively high, compared to 6% before intervention. The reason for this high percentage could be that patients were

still given intravenous antibiotics on admission prior to carrying out culture and sensitivity tests, as the pharmacy intervention was not able to change the manner of operating at casualty. The resistant isolates found were 23% (n = 8) as opposed to 60%(n = 68) prior to intervention, which showed that the patients identified for assessment to whom cefotaxime would be prescribed were highly streamlined such that those with resistant isolates were very few.

The recommended dosage schedule is based on information from the treatment protocols. The duration of treatment is decided by knowing the pathophysiology and prognosis of the infection. The monitoring of treatment is also very important. Eighty nine percent of the patients had the appropriate dose prescribed and also the dosage interval correct after the intervention compared to a relatively low percentage of 15 and 30 respectively.

According to the findings, the persuasion strategies employed had a positive influence on the use of cefotaxime. It is important though to note that since the manner of prescribing cefotaxime has been influenced greatly by the intervention, it is possible that after sometime the prescribers may change back to initial way of prescribing cefotaxime, especially as the attendance for the lectures (as part of the intervention) were voluntary. It is therefore important to have available STG and EML and other guiding policies for the hospital so that if after a while the effect of the persuasion strategies declines the control systems for the use of drugs, cefotaxime included, are in place.

The Pharmacy intervention had a positive impact on the prescribing patterns of cefotaxime. It is important though for one to note that to maintain the rational use of cefotaxime in the hospital, the Pharmacy Department has to maintain the control systems.

Prescribers were generally indicating that following the basic principles of susceptibility testing as a guide to the choice of antibiotic is rational but unfortunately the time it takes to get such test results from the laboratory due to other administrative hindrances may result in them not acknowledging the usefulness of such tests in making an antibiotic selection. Therefore the involvement of several departments would result in positive collaborative efforts, which would lead to rational prescribing of antibiotics. For example there was a misunderstanding within the wards of who should collect specimen for testing, the junior doctors, nurses, laboratory technicians, which in some wards would result in specimen not collected and tested as has been directed by senior doctors. In other instances, which are not necessarily very common, the susceptibility results would be available but the nurses would not administer all the stated doses for patients or in worse situations chart that they have administered when they have not. All these problems would ultimately affect the effectiveness of the therapy, resulting in a decision to change therapy with the understanding that the patient is not responding to the specific therapy.

The adherence to the specified manner of using cefotaxime had a positive impact on the acquisition cost of the antibiotic. There was a reduction in the

consumption levels of cefotaxime and its use was according to the stated protocols hence reduction in duration of therapy. All these aspects resulted in reduced expenditure for cefotaxime.

The Pharmacy Department was criticised when instituting control systems, that it was focusing more on the cost of therapy than therapeutic efficacy. The issue was later resolved as the department clarified the importance and relevance of cost in relation to therapy especially as QEII is a state hospital and the limited funds must be spent rationally.

5.2 CONCLUSION

The use of cefotaxime after the intervention had improved. The improvement was evident with the prescribing patterns and the indications or appropriateness for prescribing cefotaxime. A high percentage of patients had their antimicrobial susceptibility patterns assessed prior to cefotaxime use, which was not the case before the intervention. A more procedural approach was adopted in selecting cefotaxime as a drug of choice.

The findings indicate that the intervention had a positive change on the manner in which cefotaxime was prescribed; and a positive impact on the manner of determining the indications for prescribing cefotaxime at Queen Elizabeth II Hospital. This was evident in the findings where it was indicated that there were fewer patients on cefotaxime in Phase II, as patients were critically assessed to determine the appropriateness of using cefotaxime, making use of indicators like susceptibility assessments for renal function tests.

Empiric antimicrobial regimen is selected based upon patient – specific considerations. Thus every clinician must be aware of the differences in the microflora at various areas of infection, along with their usual antimicrobial susceptibilities. These data are then used to formulate empiric therapy regimens.

Considering patient-specific issues such as concurrent medical problems and concomitant drug therapies further refines antimicrobial selection. Next the

practical issues surrounding drug administration and overall therapy costs must be considered. (Butler *et al.*, 1992)

5.3 LIMITATIONS OF STUDY

The researcher was conducting the project on a part time basis while engaged in a full time job in Maseru. This situation made it difficult to conduct the research as the reference material could only be accessed at the University of Witwatersrand and other institutions, which were not easily accessible.

It was difficult conducting research where the researcher was part of the office, which was concerned with the use of cefotaxime, as some prescribers did not consider the importance of the research but rather their relation with the department in question.

The study did not assess the performance of the nursing staff in administering cefotaxime to the patients, as infrequent administration of cefotaxime could also lead to poor response to antibiotics.

5.4 RECOMMENDATIONS

An updated national treatment guidelines and national medicines list need to be made available to prescribers at Queen Elizabeth II hospital.

Queen Elizabeth II hospital should have its specific treatment guidelines to specifically address the hospital's needs.

There should be continuous education programmes involving different professionals and creating a forum for imparting knowledge and building capacity not only amongst prescribers but also with all other related health professionals who are to take part in the health care system.

The pharmacy to engage in an exercise to closely monitor the rational use of drugs, more specifically antibiotics.

Encourage pharmacy department's involvement in therapeutic management of hospitalised patients.

Culture and sensitivity testing to be carried out for all patients prior to antibiotic administration as a matter of policy.

Empiric treatment should also be allowed with antibiotics, but only with very strong justification as a matter of policy.

To encourage adherence to improved prescribing patterns and indications for prescribing cefotaxime at Queen II hospital.

To maintain reduction in expenditure of cefotaxime.

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ANNEXURES

Annexure 1

ASSESSING THE USE OF CEFOTAXIME AT QEII HOSPITAL

SECTION I

1. Age ☐
2. M | F

3. Diagnosis

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4. Date when cefotaxime started .....
5. Date when cefotaxime discontinued.....
6. Date if re-continued.....
7. Date if re-discontinued .....
8. If specimen were sent for C & S YES / NO

9. Sensitivity test results (R) Resistant

(S) Sensitivity

Organism Present

Sensitive	Resistant

10. The dose prescribed for the patient

.....

.....

.....

.....

11. The number of days the patient is on cefotaxime .....

12. Any other antibiotics the patient is administering

.....

.....

ASSESSMENT AFTER PHARMACY INTERVENTION

SECTION II

a. Has the use of cefotaxime been appropriate

b. Culture and Sensitivity results available prior to prescribing

Yes	No

c. Is the dose prescribed correct (based on clinical indications and renal function)

Yes	No

d. Is the dosing interval correct?

Yes	No

e. In order to monitor the use of the drug was the renal clearance obtained 48 hours prior to or 12 hours after initial cefotaxime use

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f. Are there any adverse drug reactions recorded after the intervention?

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g. Were there any patient outcomes recorded while using cefotaxime?

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