Evaluation of Ceftriaxone Utilization and Prescriber's Opinion at Armed Forces Referral and Teaching Hospital, Addis Ababa, Ethiopia

Kelali Mehari (BPharm)

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This is to certify that the thesis prepared by Kelali Mehari, entitled: ‘’*Evaluation of Ceftriaxone Utilization and Prescriber’s Opinion at Armed Forces Referral and Teaching Hospital, Addis Ababa, Ethiopia’’* and submitted in partial fulfillment for the requirements of the Degree of Master of Pharmacy in Pharmacy Practice complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

Signed by the Examining Committee:

Internal Examiner: Dr.Workineh Shibeshi Signature_____ Date_____
(PhD, Associate Professor)

External Examiner: Dr.Bisrat Hailemeskel Signature_____Date_____
(PhD, Associate Professor)

Advisor: Ephrem Engidawork Signature_____ Date_____
(PhD, Associate Professor)

_____
Chair of Department

Abstract

Evaluation of ceftriaxone utilization and prescriber's opinion at Armed Forces Referral and Teaching Hospital:

Kelali Mehari

Addis Ababa University, 2017

Antimicrobial therapy demands an initial clinical evaluation of the nature and extent of the infective process and knowledge of the likely causative pathogen(s). This assessment should be supported, whenever practical, by laboratory investigation and its susceptibility to antimicrobial agents appropriate for treatment of the infection. The overuse and inappropriate use of antimicrobials has led to antimicrobial resistance. The aim of this study was therefore to evaluate the appropriateness of ceftriaxone use and prescriber's opinion at Armed Forces Referral and Teaching Hospital (AFRTH). A prospective cross-sectional study was conducted by reviewing medication records of patients who received ceftriaxone during hospitalization at AFRTH. Drug utilization evaluation (DUE) methods used were based on standards set forth by standard treatment guideline of Ethiopia 2014, American society of health system pharmacists. The DUE criteria used in this study were indication for use, dose, frequency of administration, duration of treatment, drug-drug interaction (DDI) and culture and sensitivity (C&S) test. Factors affecting inappropriate utilization of ceftriaxone were determined using regression analysis.

From a total of 300 patients, 54.3% were males. Ceftriaxone use was empiric in 62.7% cases. The most common indication for ceftriaxone use was surgical prophylaxis (34%). Most patients were dosed as 2 g/day (75.6%). The duration of therapy was found to be long in the range of 2-7 days (54.3%). Maintenance fluids were the most commonly co-administered medications (93.7%). Based on the interviewed physicians, the high utilization rate of ceftriaxone was due to its effectiveness and availability in the hospital. The use of ceftriaxone was appropriate only in 14.4% cases for the justification of use. Empiric and prophylactic treatment were found to have a significant association with inappropriate utilization of ceftriaxone. Majority of inappropriateness was seen with indication of ceftriaxone, duration of therapy and DDI. This may lead to emergence of resistant pathogens, which in turn compromises its effectiveness leading to treatment failure and increased cost of therapy. To avoid this inappropriate utilization of ceftriaxone, prescribers should prescribe by sticking to standard guidelines.

Key words: Ceftriaxone, drug use evaluation, antibiotic, rational use

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List of Abbreviations /Acronyms

AFRTH	Armed Forces Referral and Teaching Hospital
BL	Beta Lactams
BLBL	Beta Lactam with Lactamase Inhibitors
C&S	Culture and Sensitivity test
CI	Confidence Interval
DDI	Drug-Drug Interaction
DDD	Defined Daily Dose
DUR	Drug Utilization Review
ESB	Extended Spectrum Beta lactamase
ESC	Extended-Spectrum Cephalosporin
FMHACA	Food, Medicine and Health Care Administration and Control Authority
GYN and Obs	Gynecology and Obstetrics
ICU	Intensive Care Unit
MRSA	Methicillin-Resistant Staphylococcus Aures
OR	Odds Ratio
PBPs	Penicillin-Binding Proteins
PO	Per Oral
RTI	Respiratory Tract Infection
SD	Standard Deviation
STG	Standard Treatment Guideline
SPSS	Statistical Package for Social Science
UTI	Urinary Tract Infection
VRE	Vancomycin-Resistant Enterococci
WHO	World Health Organization

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1. INTRODUCTION

1.1. Background

The use of antimicrobial agents has become a routine practice for the treatment of many illnesses and antimicrobials are among the most commonly prescribed drugs in all indoor patients (Ghosh *et al* , 2014). It has been reported that antimicrobial costs constitute 20% to 50% of a hospital's total drug budget (Salama *et a*l, 1996).The parenteral third generation cephalosporins are among the most expensive antibiotics on a cost-per-day basis. Cephalosporins like all beta -lactam antibiotics, inhibit bacterial growth by interfering with the transpeptidation reaction of bacterial cell wall synthesis and classified by "generation"as first, second, third, fourth and fifth. In general, lower-generation cephalosporins have more gram-positive activity and higher-generation cephalosporins more gram-negative activity. They are now becoming a major part of hospitals formulary (Adu *et al.*, 1995).

The parenteral third generation cephalosporins include cefotaxime, ceftriaxone, ceftazidime, cefoperazone, ceftizoxime , latamoxef , ceftibuten and cefixime (Brunton *et al.*, 2011). Ceftriaxone is a white to yellowish-orange crystalline powder, which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. It must be reconstituted with sterile water for injection or parenteral solutions at the time of using. Study results involving liquid chromatography showed that the stability of reconstituted ceftriaxone for injection is higher at lower temperature. Accordingly, ceftriaxone for injection reconstituted with water to a concentration of 100 mg/mL, is chemically stable for at least 4 days when stored at 23 ± 2 °C in the presence or absence of light; for at least 41 days at 8 ± 1 °C; and for 76 days at - 20 °C ± 0.5 °C (Diego *et al.*, 2010). The chemical formula of ceftriaxone sodium is C18H16N8Na2O7S3•3.5H2O and has a calculated molecular weight of 661.60. Ceftriaxone sodium is (6R,7R) - 7 - [2 - (2 - Amino - 4 - thiazolyl)glyoxylamido] - 8 - oxo - 3 - [[(1,2,5,6 - tetrahydro - 2 - methyl - 5,6 - dioxo - as-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 72-(Z)-(O-methyloxime), disodium salt, sesquaterhydrate (Figure1) (Trevor, 2010).

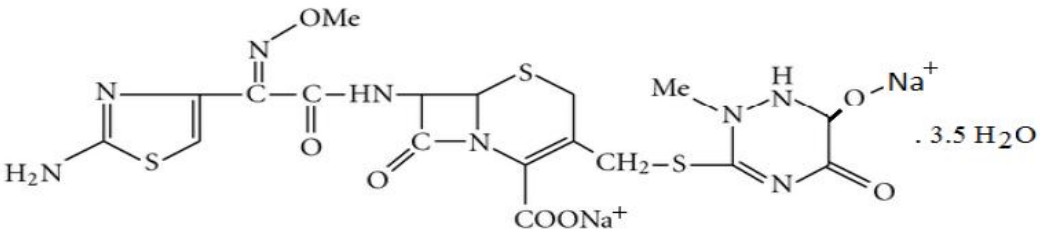

Figure 1: Chemical structure of ceftriaxone

Ceftriaxone for injection is a sterile, semi-synthetic, broad-spectrum third generation cephalosporin antibiotic for intravenous or intramuscular administration and lasted for more than 30 years since its development (Diego *et al.,* 2010). It has activity in vitro very similar to that of ceftizoxime and cefotaxime and a $t_{1/2}$ of ~8 h is its outstanding feature. Administration of the drug once or twice daily has been effective for patients with meningitis, whereas once a day dosage has been effective for other infections. About half the drug can be recovered from the urine and the remainder appears to be eliminated by biliary secretion (Brunton *et al.*, 2011). It is one of the most commonly used antibiotics due to its high anti bacterial potency, wide spectrum of activity and low potential for toxicity (Abebe *et al*., 2012).In Ethiopia, this drug is being most frequently used at different hospitals throughout the country. The most likely reason for its widespread use is due to its effectiveness in susceptible organisms in complicated and uncomplicated urinary tract infection, respiratory tract infections (RTIs), skin, soft tissue, bone and joint infections, bacteraemia/septicemia (Finkel *et al.,* 2009; Brunton *et al.*, 2011), meningitis (Delangle *et al.*, 2013), pelvic inflammatory disease, infections in immunosuppressed patients, acute bacterial otitis media (Leibovitz *et al*., 2000), genital infections, disseminated Lyme's disease and in surgical prophylaxis of infections (Pichichero, 2006; Longo *et al.*, 2012).

Antimicrobial resistance is now a global threat. Its emergence rests on antimicrobial overuse in humans and food-producing animals, and globalization and suboptimal infection control facilitate its spread (Huttner et al., 2013).Emergence of antimicrobial resistance is a result of the use, over use and misuse of antibiotics (Ayinalem *et al*., 2013). Bacteria can acquire resistance to antibiotic as a result of chromosomal mutation, expression of a latent chromosomal gene, by exchange of genetic material through transformation, transduction or conjugation by plasmids (Abdelhalim et al., 2013). The wide spread use of expanded spectrum beta-lactam antibiotic, in particular the third generation cephalosporin for nosocomial infection has led to emergence of *B* - lactamase capable to efficiently destroy these compounds the so-called extended spectrum beta lacatmases (ESBs). ESBs are defined

as beta lactamases capable of hydrolyzing oximino cephalosporins (cefuroxime, ceftatoxime, ceftriaxone, ceftazidime) and are inhibited by claviulanic acid (Kheder *et al*., 2011). Bacteria can be resistant to more than one antimicrobial agent. These highly multi-resistance bacteria have made many currently available antimicrobial drugs ineffective, also in certain instances, have already posed an important public health problem. When microorganisms become resistance to first line antibiotics more expensive antibiotics are prescribed which increase cost of the therapy and increase hospital stay (Abdelhalim et al., 2013).

Drug Use Evaluation (DUE) is performed in patient settings to identify trends of overuse and inappropriate prescribing. Surveys have shown that 22-65% antibiotic prescriptions either are inappropriate or in correct. When considering this, targeting antibiotics that are prescribed frequently for DUE would be important to extend the useful life of the antimicrobial agents (Abebe *et al*., 2012). The World Health Organization (WHO) defined drug utilization research as the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences (Shalini et al., 2010). Periodic evaluation of drug utilization studies needs to be done to enable prescription of suitable medications, to improve the therapeutic benefits and reduce the adverse effects. Prescribing pattern studies are powerful exploratory tools to ascertain the role of drugs in the society. They seek to monitor, evaluate and if necessary suggest modifications in prescribing practices (Dinesh *et al*, 2011).

1.2. Statement of the problem

Worldwide, it is estimated that over 50% of all medicines are prescribed, dispensed or sold inappropriately (Holloway *et al*., 2011). Ethiopian hospitals use 50% of their total budget for drug, which is considered high drug budget compared to the population segment using these health facilities. However, very little is known how drugs (particularly antibiotics) are used in hospitals like in other health facilities (Woldu *et a*l., 2013). The antibiotics usage in developing countries is alarming because more than 90% of antibiotics used in surgical prophylaxis were found to be inappropriate (Ullah *et al*., 2013).

Continued empiric use for presumed infections, prophylactic injection in surgery and empiric therapy for fever can lead to inappropriate usage of Cephalosporins (MP *et al*., 2013). Antimicrobial therapy and prophylaxis in hospitals has been reported to be incorrect in 9 to 64% (Woldu *et al*, 2013). Majority of hospitalized patients receive antibiotics for therapy or prophylaxis during their inpatient stay. It has been estimated that at least 50% of patients receive antibiotics without clear indications (Rehm *et al*., 2009). In addition to overuse, frequency and extended duration of use of antibiotics, use of suboptimal doses and longer stay in hospitals are additional risk factors that have contributed to the emergence and dissemination of antimicrobial resistance (MP *et al*., 2013: Sweileh *et al*., 2007). Apart from emergence of resistance, such factors may lead to infections that are worse than the originally diagnosed one which increase duration of hospital stay and cost of treatment (Ghosh *et al*., 2014).

The extraordinary therapeutic effects of antimicrobials, the problems of resistant microorganisms, irrational prescribing, different untoward toxic-effects and high cost involved – up to 40% of a hospital's drug expenditure–are compelling reasons for concern about optimizing and appropriate use of antimicrobials (Akter et al., 2012). Studies conducted in USA have found that antimicrobial drug resistance has been projected to add between $100 million and $30 billion annually to health-care costs (Lee et al, 2009). In line with this, the inappropriate use of ceftriaxone caused, worldwide, an annual cost of $4-5$ million pertaining to infection caused by antibiotic resistant bacteria (Ayinalem et al, 2013). During the past several years, the problem of antibiotic resistance has noticeably worsened in Ethiopia and assessments have shown that there is not only higher consumption but also irrational use (FMHACA, 2009).

Despite strenuous efforts to control their use and promote optimal prescribing, practitioners still continue to prescribe excessively. However, the inevitable consequence of the widespread use of

antimicrobial agents has been associated with the emergence of antibiotic-resistant pathogens. As a general 'rule of thumb', the more frequently an antibiotic is used, the higher will be the rate of bacterial resistance. That is, higher utilization is associated with higher resistance rate (Sileshi *et al.,* 2016).

Rational use of drugs is defined by WHO as "patients receive medicines appropriate to their clinical needs, in doses that meet their own requirements for an adequate period of time and at the lowest cost to them and their community" (Kaliamoorthy et al., 2012). The present study performed a DUE for a specific antibiotic and attempted to gather basic data to examine the appropriate use of antibiotics.

1.3. Literature review

Antibiotics are powerful and effective drugs in the fight against infectious diseases caused by bacteria and have been frequently used for decades worldwide for effective treatment of a variety of bacterial infections. Antibiotics have saved millions of lives since their first appearance about fifty years ago (Woldu *et al*., 2013).Bacterial resistance to antimicrobial agents due to the increasing use of antimicrobial agents has become a worldwide concern (Lee *et al*., 2009). The relationship between antimicrobial use and antimicrobial resistance is complex, with a growing body of data strongly suggesting that higher levels of antimicrobial usage are associated with increased levels of antimicrobial resistance (Chelkeba *et al.*,2013**).**The beta-lactam stability of the third generation cephalosporins seems to have been reduced by the increased use of these agents. Increased use of the third generation cephalosporins has been associated with outbreaks of resistant pathogens (Adu *et al.*, 1995).The use of third generation cephalosporins has been linked with infection with *Methicillin-resistant Staphylococcusaureus* (MRSA), *Clostridium difficile*, Enterococci and resistant gram-negative bacilli. Periods of increased cephalosporin use have coincided with increased rates of isolation of vancomycin-resistant enterococci (VRE) (Shankar *et al*., 2005).

Studies investigating antibiotic utilization rate have found that ceftriaxone was the most frequent antibiotic prescribed. Several studies showed the proportion to range from 19%to 66%.These include studies done in Bangalore, India (23.77%) (Sapna *et al.*, 2012), Spain (66%) (Pereira *et al.*, 2004), Brazil (23.4% and 21.6%) (Rodrigues *et al.*, 2013), USA (19%), (Mylotte & Weislo, 2000), West India (31.7%) (Chin *et al.*, 2010) and Arba Minch, Ethiopia (19.3%) (Chelkeba *et a*l., 2013). Another study conducted to establish a relationship between ceftriaxone use and resistance to third-generation cephalosporins among clinical strains of *Enterobacter cloacae* in Besancon hospital of France (Muller et al, 2004). Accordingly, the consumption rate of ceftriaxone which is expressed in DDD/1000 patient days shows increment from 22.02 in 1999 to 32.03 in 2002. European surveillance of antimicrobial consumption project which collected data for 13 years of outpatient cephalosporin use (from 1997-2009), revealed the presence of substantial parenteral use of third-generation cephalosporins (mainly ceftriaxone) in France, Italy and the Russian Federation (Versporten *et al.*, 2011).

Almost 50% of all antibiotic prescriptions are inappropriate based on clinical and economic criteria (El-shamshy*et al*., 2011). Approximately 30–50% of antibiotic use in hospital practice is now for surgical prophylaxis. However, between 30% and 90% of this prophylaxis is inappropriate

(Dettennkofer *et al.,* 2002). Inappropriate antimicrobial use has negative effects beyond increased rates of mortality and morbidity. Treatment failures can require extra hospital days, additional laboratory costs, and other infection control measures, and may affect subsequent empirical antibiotic choices, resulting in higher drug costs. Additional costs also stem from the need to develop new antimicrobial agents and to implement educational programs on antimicrobial resistance (Howard *et al*., 2001).

Studies done to evaluate appropriate use of ceftriaxone have obtained different results, with its inappropriate use ranging from 34.5-87.9%. The proportion was 34.5 % in Korea (Lee *et a*l., 2009), (41.7%) in Thailand (Phuphuakrat *et al.,* 2013) and 85.3% in Iran (Shohrati *et al*., 2010). Among studies done in different areas of Ethiopia, the proportion was shown to be 46.2% in Dessie (Ayinalem *et al.*, 2013), 64.2% in Mekelle, (Abebe *et al.*, 2012) and 87.9% in Addis Abeba, Tikur Anbesa Specalized Hospital (Sileshi *et al*., 2016). Studies investigating to determine factors affecting appropriate utilization of ceftriaxone found significant positive association between empiric treatment and inappropriate utilization of ceftriaxone (Sileshi et al., 2016).

Inappropriate chemoprophylaxis is associated with higher surgical site infection rate leading to prolongation of hospital stay and increased number of drug usage (Rana *et al*., 2013). It is important to select an antibiotic with the narrowest antibacterial spectrum, to reduce the emergence of multi-resistant pathogens and because broad-spectrum antibiotics may be required later if the patient develops serious sepsis. The use of 'third generation' cephalosporins such as ceftriaxone and cefotaxime should therefore be avoided in surgical prophylaxis (Dellinger *et al.,* 1994 and MP *et al*., 2013). However, several studies showed that ceftriaxone was used for surgical prophylaxis. The prevalence being 50.64% (pre-operatively) and 36.93% (post-operatively) in Brazil (Rana *et al*., 2013) and 68.2% (Mistry *et al*., 2013) and (23.77%) (Sapna *et al*., 2012) post operatively in India. Similar studies done in Ethiopia reported a prevalence of 11.1% at Tikur Anbesa Specialized Hospital, Addis Ababa (Sileshi *et al.,* 2016) and 38.8% pre-operatively in Mekelle (Abebe *et al*., 2012).

The other major contributing factors for emergence of resistance and treatment failure due to inappropriate use of antimicrobials is irrational prescribing with respect to dose, frequency, and duration and not considering compatibility and drug interaction effect of co-administered drug (Ghosh *et al.,* 2014). In one study, antimicrobial therapy was administered to 25% to 40% of hospital inpatients and it was inadequate in 50% of cases in terms of dosage, route of administration, or indication (Salgado *et al*., 2014). In order to be rational, use of a drug must be effective, safe,

prescribed for the proper therapeutic indication and the correct dosage in an appropriate formulation, easily available and of a reasonable cost (Suman *et al*., 2014).

Different treatment guidelines recommend ceftriaxone for treatment of different infectious diseases. Studies done in Ethiopia found that ceftriaxone was prescribed for its inappropriate indications, the proportion was shown to be 8.6% at Tikur Anbesa Specialized Hospital, Addis Ababa (Sileshi *et al.*, 2016) and 8% in Bahir Dar (Bantie et al., 2014). Concomitant administration of ceftriaxone with ringer lactate constituted major drug-drug interaction (Gin et al., 2009). Different studies done in Ethiopia found that ceftriaxone was prescribed with ringer lactate in 6.7%cases at Tikur Anbesa Specialized Hospital, Addis Ababa (Sileshi *et al.*, 2016) and 33.1% cases in Mekelle (Abebe et al., 2012).

Several studies demonstrated that ceftriaxone was prescribed for inappropriate duration of treatment. The prevalence was reported to be 42.8% in Korea (Lee *et al.*, 2009), 50.0% in Addis Ababa, Ethiopia (Sileshi *et al*., 2016) and 43.3% in Dessie, Ethiopia (Ayinalem *et al.*, 2013) in case of pneumonia. Ceftriaxone was also prescribed in inappropriate frequency in Dessie, Ethiopia (24%) (Ayinalem *et al.*, 2013) in case of meningitis and at Tikur Anbesa Specialized Hospital, Addis Ababa, Ethiopia (80.3%) (Sileshi *et al*., 2016).

Antimicrobial therapy demands an initial clinical evaluation of the nature and extent of the infective process and knowledge of the likely causative pathogen(s). This assessment should be supported, whenever practical, by laboratory investigation and its susceptibility to antimicrobial agents appropriate for the treatment of the infection (Ghosh *et al*., 2014). It was observed that ceftriaxone was prescribed for its indications without culture and sensitivity test in 36.3% cases in Korea (Lee *et al.*, 2009) and 89.5% cases at Tikur Anbesa Specialized Hospital, Addis Ababa, Ethiopia (Sileshi *et al*., 2016).

The recent emergence of resistance against third-generation cephalosporins is of great concern, although neither the risk factors for resistance nor its real impact on mortality have been well defined (Ariza *et al*., 2012). Studies assessing the overall resistance rate of ceftriaxone have reported variable prevalence across the world. It was 31.4% in Pakistan (Iqbal *et al.*, 2008), 47.4% in Nepal (Bajimaya *et al*., 2010), 77% in Bangladesh (Furqan & Paracha, 2014), 64% in Sudan (Ibrahim *et al*., 2012), 21.7% in Singapore (Hsu *et al.*, 2010) for *E. coli* isolates. In the study done in the USA from 1996 - 1998, it was found out that the prevalence of ceftriaxone-resistant Salmonella increased from 0.1% in 1996 to 0.5% in 1998 (Dunne *et al.*, 2000). Similar studies done in Ethiopia reported a prevalence of

82% in Bahirdar (Mulu *et al.,* 2012) and 9.8% in Gonder (Anagaw *et al*., 2013) for *streptococcus pneumoniae*. Over the past several decades, the increased prevalence of known resistant organisms and the emergence of newly resistant organisms such as penicillin-resistant pneumococci, methicillin-resistant *Staphyloccus aureus*, vancomycin-resistant enterococci, EBS-producing *Escherichia coli*, *Klebsiella pneumoniae*, and imipenem-resistant gram-negative bacilli, have resulted in delays in effective therapy and increase in the length of hospitalization, which have led to increased costs for patients. Compared to infections caused by susceptible pathogens, those caused by resistant pathogens are associated with higher rates of morbidity and mortality (Lee *et al*., 2009). Rational use refers to the same obstacles as for rational selection, meaning only using antibiotics if necessary and avoiding use for viral infections and infections that are self-limited. Rational use of antibiotics would decrease the pace of resistance development and costs for health care systems and individuals (Azhar *et al*., 2010).

2. OBJECTIVES

2.1. General Objective

The objective of this study was to evaluate the rational use of ceftriaxone at Armed Force Referral and Teaching Hospital Addis Ababa, Ethiopia

2.2. Specific objectives

- To assess the appropriateness of ceftriaxone use in terms of its:
    - Indication for use
    - Dosage and frequency of administration
    - Duration of treatment
    - Interaction with other drugs (DDI)
    - Implementation of culture and sensitivity test
- To assess the reasons behind inappropriate utilization of ceftriaxone
- To assess determinants of ceftriaxone inappropriate use
- To assess the prescriber's opinion on the utilization of ceftriaxone

3. METHODS

3.1. Study setting

The study was conducted at AFRTH, which is the only referral and teaching military hospital of the country. AFRTH is located in Addis Ababa, Ethiopia. It is organized under Health Main Directorate, Ministry of Defense. It provides medical services to members of the Ethiopian defense forces, their family and civil workers at the Ministry of Defense. AFRTH accepts referral cases from all the command referral hospitals including the Air force hospital. This hospital offers diagnosis and treatment for approximately 85,872 outpatients, 3723 inpatients and 789 deliveries per year. It is one of the biggest hospitals in the city where medical and other health science students get their attachment for clinical practice. The hospital has 541beds and offers 24 hours service.

3.2. Study design and period

Prospective cross-sectional study was conducted to carry out DUE by reviewing medical records for patients who received ceftriaxone between July and September 2015.

3.3. Source and Study Population

The source population was all patients admitted to medical, surgical, GYN and Obs, orthopedic and ICU wards of AFRTH who received ceftriaxone. In addition, those patients who satisfied the inclusion criteria during the study period formed the study population.

3.4. Inclusion and Exclusion Criteria

Inclusion criteria

- Age ≥ 18 years
- Patient's chart with complete records

Exclusion Criteria

- Patients who refused to participate in the study and with medical records of insufficient or illegible information

3.5. Sample Size and sampling procedure

The minimum sample size was calculated using a formula used to estimate the sample size for a single population.

$$n = \frac{Z\left(1-\frac{a}{2}\right)^2(\text{p x q})}{\text{d}^2}$$

Where:

- n = the desired sample size when population is >10,000
- Z($1-\frac{a}{2}$)= the standard normal variable a $(1-a)$ % confidence level and a is the level of significance. At a 95% confidence level, the value of this parameter is 1.96 that was used in the study.
- p = the positive character (expected prevalence)
- q = the negative character
- d = the degree of accuracy (absolute precision) required, usually set at 0.05

Even though there was a similar study done at Tikur Anbesa Specalized Hospital (selishi et al., 2016), a conservative sample estimate was used to bring about a better outcome and strong association by assuming that the sample was independent and randomly selected.

$$n = \frac{Z\left(1-\frac{a}{2}\right)^2(\text{p x q})}{\text{d}^2} = \frac{(1.96)^2(0.5 \text{ x } 0.5)}{0.05^2} = 384.6 \approx 384$$

When the above sample size was adjusted based on the total number of patients who were estimated to take ceftriaxone during the study period was 900(N)(387from medical ward , 216 from surgical ward , 180 from Gynecology and obstetrics ward , 63 from orthopedic ward and 54 from ICU ward). The estimated study population is less than 10,000 the sample size was adjusted by using the following formula to get minimum sample size required for the study.

$$\text{Corrected sample size} = \frac{\text{n x N}}{\text{n+N}}$$

Substituting the values in the above formula produced an adjusted sample size of 269. Taking 10% for contingency (27), the final sample size was 296. All patients who received ceftriaxone at AFRTH (in medical, surgical, GYN and obs, orthopedic and ICU wards) during the study period and fulfilling

the inclusion criteria were included in the study. The issue of representativeness was well addressed as on the one hand, all wards (medical, surgical, GYN and obs, orthopedic and ICU) were included and a large sample size of 300 was considered to ensure representativeness.

3.6. Study Variables

3.6.1. Independent Variables

- Socio-demographic characteristics (age, sex)
- Disease related factors (ward type, treatment type, diagnosis type)
- Drug related factors (C&S test, indication for use, dose, frequency of administration, duration of treatment and DDI with ceftriaxone)

3.6.2 Dependent Variables

- Appropriateness of ceftriaxone utilization

3.7. Data Collection

3.7.1 Instruments

i). Data abstraction format:

The data were collected by reviewing medication charts of patients admitted during the study period by making use of a well-designed patient data collection format (Annex II) which was prepared for the purpose of this study. The content of the data collection format was designed to record ward type, patient demographics, patient chart number, admission and discharge dates, working diagnosis, C&S results, information regarding administration of ceftriaxone including its indication, dose, frequency of administration, duration of therapy and DDI with ceftriaxone

II. Key informant interview:

Data were also collected by interviewing 17 physicians practicing in the medical, surgical ,GYN and obs, orthopedic and ICU wards of AFRTH .Additionally, 1 microbiologist practicing in the microbiology laboratory unit of the hospital were interviewed. They were selected based on their long time professional experience in the study area. Accordingly, senior physicians, GPs and microbiologist were selected. The interview was made through self-administered questionnaire (Annex III) supplemented with clarification by the principal investigator. The interview revolved around issues that stood out during chart review and patient follow-up, including among others, C&S

test, frequency of administration, co-administration with potentially interacting agents, IV to oral switching and utilization rate. Similarly, the experiences of microbiologist regarding the quality of microbiology laboratory, causes of negative culture results, the number of days it would take for C&S test result to come back and the responsible body who would take such results were also assessed(Annex IV)

3.7.2. Data collectors recruitment and training

Data was collected by three clinical pharmacists. The data collectors were trained for one day on how to familiarize them with the data abstraction format thereby to facilitate the data collection process.

3.7.3. Data quality assurance

To assure quality of the data, the following measures were undertaken. Data collectors were trained on how to use such formats and how to approach other health care workers .The data collection format was also pretested on 15 patients (5% of the sample size). This was conducted on the medical records of patients other than those included in the study. Furthermore, the principal investigator on daily basis for its completeness and accuracy checked the data collection process continuously.

3.8. Data Analysis

The data were checked for completeness and then entered and analyzed using Statistical Package for Social Sciences (SPSS®Statistics) program version 21 (SPSS; Chicago, IL, U.S.A.). Descriptive statistics such as frequency, percentage, mean and standard deviation (SD) were employed to summarize study variables.

The data was processed and analyzed by using six criteria (indication for use, dose, frequency of administration, duration of treatment, DDI with ceftriaxone and C&S test) for DUE as per zonal standard treatment guideline of Ethiopia 2014, American society of health system pharmacists and rational use of ceftriaxone prepared by, College of Health sciences, Addis Ababa University. In computing the overall appropriateness of ceftriaxone utilization, the appropriateness of ceftriaxone use with respect to each of the six criteria was first determined for each patient as per the protocol. Then, another variable linking the outcomes of these evaluations were created in the SPSS software by “AND condition”. Finally, the descriptive analysis of this variable was carried out in determining the overall appropriateness of ceftriaxone utilization. To this end, the appropriate use of ceftriaxone could be computed by dividing the number of cases considered appropriate with respect to all the six criteria to the total number of cases (300 cases). But, in computing the appropriateness of a given

criteria, say the appropriate use of ceftriaxone with respect to dose, the number of cases with appropriate dosing was divided by the total number of cases (300 cases). The responses of key informants were also analyzed using content thematic analysis Accordingly, the collected dataset was first well identified that cause a significant inappropriate utilization of ceftriaxone and analysis of the result were mad contextualized in relation to existing literature.

Univariable binary logistic regression analysis was performed to relate each variable to inappropriate utilization of ceftriaxone. From the univariable analysis, those variables with $p<0.25$ were selected for multivariable binary logistic regression analysis. Multivariable binary logistic regression analysis was used to assess predictability of the independent variables of inappropriate utilization of ceftriaxone and to estimate the odds ratios (OR), 95% confidence intervals (CI) and p-values. The association was declared significant at $p<0.05$.

3.9. Ethical Consideration

Approval and permission was sought from Ethical Review Board of School of Pharmacy, AAU and AFRTH medical health directorate Ethical Review Committee. The issue of assuring privacy and confidentiality was given more attention. The confidentiality of data collected, from the patients as well as prescribers perspectives, was maintained. As part of this, the identifiers (name and address) of both the patients and prescribers were omitted from the data collection format. Besides, a written consent was obtained for each patient during data collection.

3.10. Operational Definition

Appropriate: The indication for use, dose, frequency of administration, duration of treatment, C&S investigation, and DDI with ceftriaxone were according to the recommendations in the current treatment guidelines.

Inappropriate: The indication for use, dose, frequency of administration, duration of treatment, C&S investigation, and DDI with ceftriaxone were not according to the recommendations in the current treatment guidelines

Specific Therapy: Refers to the ability of antibiotics to kill or suppress the growth of infecting microbes by accurate diagnose of bacterial infection. Therefore, it is important to take the sample first from either blood, fluid secretion and tested it based on clinical testing i.e. culture and sensitivity test testing microorganisms should be recognized.

Empirical Therapy: choosing an antibiotic using clinical considerations (the history and physical examination) and what is known about the organisms likely to account for those signs and symptoms as well as their local antibiotic susceptibilities rather than waiting for a culture to grow the organism and identify its susceptibilities.

Prophylaxis: refers to the prevention of an infection after surgery

Suspected diagnosis: Diagnosis made by the judgment of clinicians without adequate evidence such as imaging results, laboratory findings or clinical manifestations

Dose: The quantity of ceftriaxone administered to a patient at once or per administration.

Major drug-drug interaction: The interaction may be life threatening and/or require medical intervention to minimize or prevent serious adverse effects.

Moderate drug-drug interaction: The interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy.

Minor drug-drug interaction: The interaction would have limited clinical effects. Manifestations may include an increase in the frequency or severity of the side effects but generally would not require a major alteration in therapy.

4. RESULTS

4.1 Socio-demographic characteristics of patients

A total of 300 admitted patients treatment chart containing ceftriaxone injection were analyzed in the study. Among the 300 patients, 137 (45.7 %) were female and 163 (54.3%) male. The mean age of the study population was 36.4 years (SD ±13.2 years; range 18 to 81 years). Almost all of the study participants were in the age group 18-65.(Table1).

Table 1: Socio-demographic characteristics of patients included in the study at Armed Forces Referral and Teaching Hospital from July to September 2015

Characteristics	Category	Frequency (%)
Sex	Female	137(43.3
	Male	163(54.3)
Age	18-65	288 (96)
	≥ 65	12 (4)

4.2 Prescription pattern

It was found out that around 50% of the cases had received ceftriaxone for diseases where it is indicated as primary (first-line) therapy according to current evidence-based guidelines. Among the ceftriaxone prescriptions, majority of the prescriptions were for empiric therapy, which accounted for more than 60% of ceftriaxone prescriptions (Table 2).

Table 2: Types of treatment with ceftriaxone received by the study participants at Armed Forces Referral and Teaching Hospital

Characteristics	Category	Frequency (%)
Indication of Ceftriaxone	Primary	145(48.3)
	Alternative	126 (42.0)
	Not-indicated	29(9.7)
Type of treatment with ceftriaxone	Therapeutic	198 (66)
	Empiric	188(62.7)
	Specific	10(3.3)
	Prophylactic	102(34)

4.3. Dosage and frequency of administration

The prescribed dose (amount per administration) was 1g or 2g for all types of ceftriaxone indications. The most frequently prescribed dose was found to be 1g and daily dosage with 2g accounting for 75.7% of the cases. Among the frequency of ceftriaxone administration, twice daily appeared to be the most common frequency of administration (Table 3).

Table 3: Dosage and frequency of ceftriaxone administration to the study participant at Armed Forces Referral and Teaching Hospital

Characteristics	Frequency n	Percent %
Dose (amount given once)		
1g	293	97.7
2g	7	2.3
Dosage per day(g)		
1g	14	3.3
2g	224	75.7
3g	55	18.3
4g	7	2.3
Frequency of administration		
Once daily	14	3.3
Twice daily	231	77
Three times daily	55	18.3

4.4. Duration of treatment

The mean duration of treatment with ceftriaxone was found to be 5.17 days (ranging from 1 -18 days) and over half of the patients received for 2-7 days (54.3%). Analysis of the specific duration of treatment with ceftriaxone revealed that it was most commonly given for 1 day (24.7%) followed by 7days (19%) (Table 4).

Table 4: Duration of treatment with ceftriaxone for the study participants at Armed Forces Referral and Teaching Hospital

Duration (days)	Number of patients	Percent %
1	74	24.7
2-7	164	54.7
7-14	56	18.7
>14	6	2

4.5. Indications of ceftriaxone

RTI was the most common indication of ceftriaxone, which accounted almost for quarter of the indications. The second most common indication of ceftriaxone, was pre and postoperative prophylaxis (20%). The ceftriaxone was not justified in 9.7 % of patients based on current evidence based guidelines (Table 5).

Table 5: Indications for which ceftriaxone was prescribed to the study participant at Armed Forces Referral and Teaching Hospital[1]

Indication by system	Frequency (%)
Respiratory tract infection (RTI)	71 (23.7)
Pre and post operative prophylaxis(PI)	60 (20.0)
Post operative prophylaxis (POP)	42(14.0)
Skin , soft tissue and bone infection (SSBI)	37(12.3)
Cirrhosis related infection (CRI)	13(4.3)
Urinary system infection (USI)	10(3.3)
Preoperative treatment (POT)	9(3.0)
Gynecology and obstetrics (GB)	9(3.0)
Central nervous system infection(CNSI)	8 (2.7)
Gastro intestinal infection (GII)	8(2.7)
Sepsis and septic shock (SSS)	4(1.3)
Non –indications(NI)	29(9.7)

[1] RTI: community acquired pneumonia, hospital acquired pneumonia, aspiration pneumonia, otitis media; PI: Ceasarean section/hysterectomy,acute appendicitisPOP**:** Trauma and orthopedic surgery **POT:**maxillo facial trauma, perianal fistula abscess, squamose cell super imposed infection etc SSBI: diabetic foot ulcer, cellulitis, wet gangrene, osteomyelitis, pomposities; CNSI: pyogenic meningitis, brain abscess; SSI: sepsis and septic shock; UTI: pyelonephritis, other UTI; GII: acute bacterial gastroenteritis, cholangitis,; CRI: spontaneous bacterial peritonitis, primary bacterial peritonitis GB: pelvic inflammatory disease, STI, threatened abortion

4.6. Concomitant administration of drugs with ceftriaxone

The top five most commonly co-prescribed drugs with ceftriaxone were maintenance fluids (93.7%), Diclofenac (36.7%), Pethidine (27.3%), Metronidazole (22.3%) and Gentamycin (9.3%) (Figure 2).

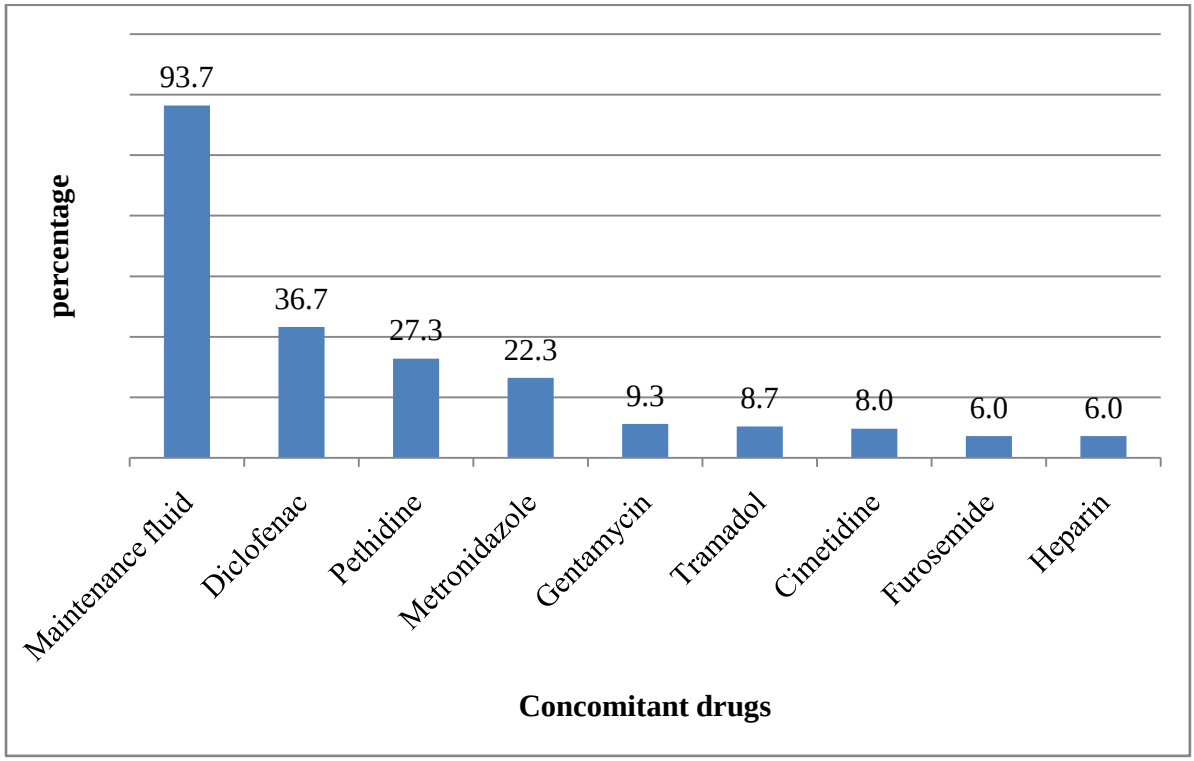

Figure 2: Concomitant administration of drugs with ceftriaxone at Armed Forces Referral and Teaching Hospital

Analysis of the present study also showed that the probability of intravenous incompatibility was observed between ceftriaxone and ringer lactate in 36 % cases and this was identified as major DDI (Table 6).

Table 6: Co-administered drugs with potential drug - drug interaction with ceftriaxone at Armed Forces Referral and Teaching Hospital

Co administered drug	Severity of DDI	frequency (n=300)	percentage
Ringer lactate	Major	108	36 %
Gentamycin	Minor	28	9.3%
Heparin	Moderate	18	6.3 %
Furosemaide	minor	18	6.3 %

4.7. Culture and sensitivity test

Only 3.3% cases were sent for C and S test. From the ten C and S tests, half was done before initiating ceftriaxone and almost one third of the tests were done within 48h. However, the other 20% of the C and S tests were done after 48 h of initiating ceftriaxone (Table 7).

Table 7: Culture and sensitivity tests in patients prescribed with ceftriaxone at Armed Forces Referral and Teaching Hospital

	Frequency N	Percent %
Culture and sensitivity test		
Done	10	3.3
Not done	290	96.7
Growth		
Yes*	2	20
No	8	80
Sensitivity to Ceftriaxone		
Sensitive	-	-
Resistant	2	100

*The microorganisms isolated included *E. coli, Klebsiella spp, Staphylococcus aureus*

4.8. Practice of ceftriaxone utilization versus protocol

The overall inappropriateness of ceftriaxone use (indication, duration, dose, frequency, drug interaction and culture and sensitivity test) was 85.6 %based on the protocol prepared regarding rational use of this drug. Higher proportion of inappropriate use was observed for inappropriate indication (56.30%) followed by drug-drug interaction (43.0%) (Figure 3).

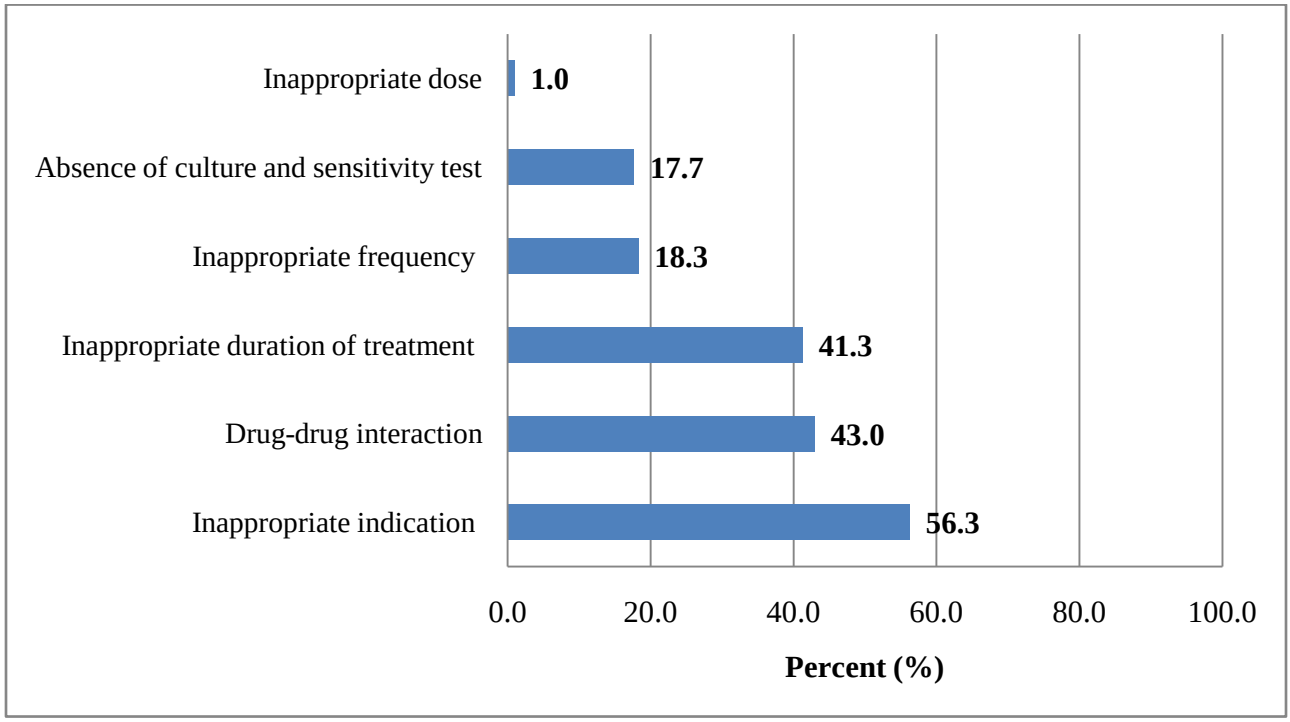

Figure 3: Criteria referenced inappropriate use of ceftriaxone at Armed Forces Referral and Teaching Hospital

4.9 Inappropriate use of ceftriaxone in different wards

The highest inappropriate use was observed in gynecology and obstetrics ward (93.3%) followed by orthopedics ward (90.7%) (Table 8).

Table 8: Inappropriate use of ceftriaxone in different wards of Armed Forces Referral and Teaching Hospital

Type of ward	Ceftriaxone utilization		Total
	Inappropriate n (%)	Appropriate n (%)	
Medical	108(80)	27(20)	135
Surgical	59(89.4)	7(10.6)	66
Gynecology and obstetrics	56(93.3)	4(6.7)	60
Orthopedic	19(90.5)	2(9.5)	21
ICU	15(83.3)	3(16.7)	18

4.10 Factors associated with inappropriate ceftriaxone use

Analysis using binary logistic regression indicated that factors such as gender, ward and treatment types were significantly associated with inappropriate ceftriaxone use. However, age and diagnosis type failed to be significantly associated with inappropriate ceftriaxone utilization. The multivariable binary logistic regression analysis showed that there was no statistically significant association between gender and ward of the patient with inappropriate ceftriaxone utilization. However, the type of treatment had statistically significant association with inappropriate utilization of ceftriaxone. The odds of inappropriate use of ceftriaxone in empiric and prophylaxis treatment had increased by 93.1% (AOR=0.069, CI: 0.014, 0.35) and 99.8% (AOR=0.002, CI: 0.001, 0.024), respectively as compared to specific treatment (Table 9).

Table 9: Factors associated with inappropriate ceftriaxone use at Armed Forces Referral and Teaching Hospital

Variable	Utilization		COR (95% CI)	AOR (95% CI)
	Inappropriate n (%)	Appropriate n (%)		
Gender				
Female	122 (40.7)	11(3.6)	1.0	1.0
Male	135(45.0)	32(10.7)	2.63 (1.27, 5.442)	1.826 (0.725, 4.602)
Ward				
Medical	108(36.0)	27(9.0)	1.0	1.0
Surgical	59 (19.7)	7(2.3)	0.475 (0.195, 1.155)	1.534 (0.507, 4.637)
Gyn/Obs	56(18.7)	4(1.30	0.286 (0.095, 0.857)	4.03 (0.77, 21.087)
Ortho	19(6.3)	2(0.7)	0.421(0.092, 1.919)	0.608 (0.129, 2.857)
ICU	15(5.0)	3(1.0)	0.80 (0.216, 2.963)	0.943 (0.251, 3.546)
Treatment				
Specific	2(0.06)	8(2.7)	1.0	1.0
Empiric	154(51.3)	34(11.3)	0.055 (0.011, 0.272)	0.069(0.014, 0.35)*
Prophylaxis	101(33.7)	1(0.3)	0.002 (0.0 ,0.03)	0.002 (0.001, 0.024)

* Statistically Significant at P<0.05

4.11 Responses of key informants

Physicians were interviewed to assess the reasons behind high and inappropriate utilization of ceftriaxone in the final stage of data collection. More than half of the physicians thought that high utilization rate of ceftriaxone was due to its effectiveness in comparison with other available antibiotics. Moreover, half of the respondents considered its frequent use in empiric therapy were because of unavailability of other more appropriate drugs (Table 10).

Table 10: Responses of physicians regarding ceftriaxone use at Armed Forces Referral and Teaching Hospital (multiple responses were possible)

Interview questions	Responses	Percent (%)
Why was C&S test not sent for most of the patients?	Cost /Affordability issue	17.6
	Culture results are not reliable	5.9
	It takes long time to get results back	47.05
	Service not available	5.9
	Patients come after initiation of antibiotics	52.9
In the survey conducted, it was found out that ceftriaxone was administered on a twice-daily basis for almost all medical conditions. What do you think is the reason for this?	Just because of tradition of practice	17.6
	To ensure its effectiveness	17.6
	There are guidelines which promote this practice	82.4
It was found out that there is very high utilization rate of ceftriaxone in this hospital. In your opinion, what do you think is the reason for this?	Effectiveness	64.7
	Low rate of toxicity	29.4
	Availability	52.9
	Ease of administration	5.9
In your opinion, why is ceftriaxone being co-administered with drugs including ringers lactate, furosemide and heparin?	Less availability of other drugs	29.4
	Practice shows no problem up on concomitant administration	70.6
In your opinion, why is ceftriaxone used as an initial empiric therapy in such cases as pneumonia, wound treatment, meningitis, and urinary tract infection and as a prophylaxis in different type of surgery?	Local guidelines recommend such indication	29.4
	Unavailability of other more appropriate drugs	52.9
	Cost of other appropriate drugs	17.6
In the present survey, it was found out that ceftriaxone was used for prolonged duration without switching to PO antibiotics (eg. In CAP for > 14 days and in surgical prophylaxis for 5-7 days). In your opinion, what do you think is the reason for this?	Practically , it is possible to do so	23.5
	Unavailability of equivalent PO medicine	58.8
	Local guidelines recommend such practice	5.9

Response of microbiologists regarding culture and sensitivity test

The major reasons for most C&S results to be negative were attributed to sample collection after initiation of antibiotics, inappropriate sample collection and improper use of transporting medium. It was also noted that the bacteriology test results would require 3 days to be sent to the ordering physician.

5. DISCUSSION

Ceftriaxone is a major drug that is used in the treatment of many important infections due to its high antibacterial potency, wide spectrum of activity, and low potential for toxicity (Abebe *et al*., 2012). The over use of broad-spectrum cephalosporins particularly ceftizoxime, cefuroxiume and ceftriaxone have been implicated in the emergence of multidrug resistance gram positive and gram negative bacteria (Kheder *et al*., 2011**).** It was found out that there was very high utilization rate of ceftriaxone in this hospital and the interviewed physicians agreed that there was high utilization rate of this drug and this was ascribed to the good availability, good effectiveness and low toxicity rates of the drug. However, this is being challenged by the increasing frequency of beta-lactamase-mediated resistance (Lee *et al*., 2009).

In many developing countries, the guidelines for antibacterial treatment are limited, thus increasing the inappropriate use of these agents. Antibiotics are often prescribed empirically for all types of infections, both for bacterial and viral infection, further encouraging indiscriminate use of them (Azhar *et al*., 2010). Common reasons for inappropriate use of ceftriaxone included continued empiric use for presumed infections, prophylactic preoperative injection, and empiric therapy for fever (Lee *et al*., 2009). In the present study, prophylactic use of ceftriaxone, use of ceftriaxone in the absence of compelling clinical or microbiological evidence of infection, incorrect use or indication of ceftriaxone were also the reasons for inappropriate utilization. All of these practices are associated with emergence of bacterial resistance (Salgado *et al*., 2014). Emergence of antimicrobial resistance is the result of the use, overuse and misuse of antibiotics. The increased prevalence of known resistant organisms and the emergence of newly resistant organisms have resulted in delays ineffective therapy and the length of hospitalization and have led to increased cost for patients (Ayinalem *et al.,* 2013). Hence, prudent and rational use of antibiotics has to be promoted to retard the development of resistance and extend the viability of the existing medicines, which is only possible if baseline data about antibiotic utilization is available (El-Ashmony *et al*., 2011)

The overall inappropriateness of ceftriaxone use (indications, dose, frequency, duration, drug – interaction and culture and sensitivity test considered) was 85.6%. The present result is in line with a study conducted at Tikur Anbesa Specalized hospital, Addis Ababa,Ethiopia (87.9%)(Sileshi *et al*., 2016) and Iran (85.3%) (Shohrati *et al*., 2010). But it was higher than from studies done in Dessie, Ethiopa (46.2%) (Ayinalem *et al.*, 2013), Bahidar ,Ethiopia (39%) (Bantie *et al.,* 2014), Mekelle, Ethiopia (64.2%) (Abebe *et al.*, 2012) and Korea (34.5%) (Lee *et al*., 2009). This difference might be

attributable to the nature of methodology employed in evaluating the use of the drug. The highest inappropriate utilization was observed in gynecology and obstetrics ward (93.3%) and orthopedics ward (90.5%).This is due to fact that ceftriaxone was mainly prescribed for surgical prophylaxis Empiric and prophylactic treatments were found to have significant association with inappropriate utilization of ceftriaxone. The multivariable logistic regression analysis showed that the odds of being inappropriate use increased by 0.069 and 0.002 times in empiric and prophylactic as compared to specific treatment. This might be due to inappropriate indication, drug, and drug interaction with ceftriaxone. Similar study was found at Tikur Anbesa Specalized Hospital,Addis Ababa, Ethiopia that showed positive association between empiric treatment and inappropriate utilization of ceftriaxone (Selshie *et al*., 2016).

Based on the interviewed physicians, ceftriaxone was used as an initial empiric therapy in cases such as pneumonia, wound treatment, meningitis, and urinary tract infection and as a prophylaxis in different type of surgery due to unavailability of other more appropriate drugs. It was also found that 62.7% of patients received ceftriaxone for empirical therapy. This is lower than from a study done at Tikur Anbesa Specalized Hospital,Addis Ababa, Ethiopia (87.3%) (Selishi *et al.,* 2016). This could be due to the fact that 36 % of ceftriaxone was indicated for surgical prophylaxis. And, this is lower than from the a study done about the empiric use of third generation cephalosporin in Spain (68.2%) (Pereira *et al*., 2004). The difference may be the latter study included other additional antibiotics. The present study identified that 64 % of ceftriaxone prescription was according to its therapeutic indication compared to its prophylactic use. This is lower than from a study done at Tikur Anbesa Specalized Hospital, Addis Ababa, Ethiopia (88.9 %) (Selishi *et al.,* 2016). This difference may be attributed to the exclusion of surgery departments in the latter study.

Surgical site infection represent a major cause of morbidity in surgical patients, affecting only around 2% of patients with clean cases, but 15-20% contaminated cases (Mulwafu *et al*.,2010). Nearly 30-50% of antimicrobials used in hospitals are prescribed for surgical prophylaxis (Mistry et al.,2013). However, the local and international guidelines do not recommend ceftriaxone for surgical prophylaxis. The use of third or fourth-generation cephalosporins is not recommended for routine antimicrobial prophylaxis as use may lead to development of resistant organisms (Bratzler et al., 2013). But the result of this study showed that one most frequent indication for ceftriaxone use was surgical prophylaxis (36.0%). However, this is higher than from the studies done at Tikur Anbesa Specalized Hospital, Addis Ababa, Ethiopia (11.1%) (Selishi *et al.,* 2016) and Victoria (15 %) (Robertson *et al*., 2002). This difference may be due to the fact that there were more surgical cases.

Culture and susceptibility testing are absolutely essen-tial to ensuring confirmation of the appropriateness of empirical therapy or redirecting therapy in a safe and effective manner so that it actually targets the causative agent of the infection (Salgado *et al*., 2014). Furthermore, microbiological testing provides a picture of the local microbiota and its susceptibility profile—aspects that can assist in and guide better prescribing of empiric antibiotic therapy (Karnikowski *et al*., 2014; Baron *et al*., 2014**)**. When ceftriaxone used empirically, should be reevaluated within 72 h of initiating therapy and when C&S data are reported. Therapy should be discontinued if the C&S report demonstrates that the organisms are sensitive to equally efficacious, less costly antibiotics (Lee *et al*., 2009). In the present study, it was observed that C&S test was not done in (96.7 %) cases who received ceftriaxone for any reason. However, some of the accepted reasons why C&S test was not sent were prior initiation of therapeutic antibiotic regimen cases (45.0%) and the use of ceftriaxone for prophylactic indications (34.0%**).** Only 3.3% cases were sent for culture and sensitivity testing from the (21.0%) cases that had acceptable reason for culture and sensitivity tests. The interviewed physicians agreed that C&S tests were not done in significant proportion of cases and this was ascribed to be due to prior initiation of therapeutic antibiotic regimen and delayed culture result. On the other hand, the interviewed microbiologist agreed that the reason why the bacteriology results were unconvincing could be due to sample collection after initiation of antibiotics, inappropriate sample collection, improper use of transporting medium, and failure to request appropriate laboratory test. Besides, they agreed that it takes, on average, 3 days for culture results to become available. From those C&S test was done, growth was observed in two of the samples. This result is different with similar studies conducted elsewhere including Pakistan (31.4%) (Iqbal *et al.*, 2008), Nepal (47.4%) (Bajimaya *et al*., 2010), Bangladesh (77%) (Furqan & Paracha, 2014) and at Tikur Anbesa Specalized Hospital, Addis Abeba, Ethiopia (24.2%) (Selishi *et al.*,2016) . The difference may be attributed to the small number of samples sent in the present study. Microbial resistance to antimicrobial agents seriously undermines efforts to control infectious diseases. Ethiopia, like other developing countries, is affected by high infectious diseases burden. Emergence and spread of antimicrobial resistance further poses hindrance on the fight to alleviate this burden (FMHACA, 2009). In the present study, out of cases for which sensitivity was done, resistance was seen in all of the cases (two) to ceftriaxone.

Ceftriaxone was co-administered with drugs including ringers lactate, furosemide and heparin. Among drugs with potential for interaction, concomitant administration with ringer lactate constituted major DDI (Gin *et al*., 2009) and was prescribed in 36% case. This is higher than from

the studies done at Tikur Anbesa Specalized Hospital, Addis Ababa ,Ethiopia (6.7%)(Sileshi *et al*., 2016) and in Mekelle ,Ethiopia (33.1%)(Abebe *et a*l., 2012) . However, this is lower than from study done at Tikur Anbesa Specialized Hospital and Police Hospitals, Addis Ababa, Ethiopia (44.4%) (Mulugeta *et al.*, 2009). Physicians admitted during the interview that they had no idea whether there would be interaction with these two agents. Thus, physicians awareness should be increased so that practice could be improved in the future.

Suboptimal treatment, meaning not taking a full dose, often promotes an increased risk for development of resistance in bacteria, thus making emergence of antibiotic resistance inevitable (Azhar *et al*., 2010). In the present study, the most common prescribed dosage per day of ceftriaxone was 2g (75.7%). The mean duration of ceftriaxone therapy was found to be 5.17 days (range, 1to 18 days).). This is lower than from the study conducted in Korea 10.3 days (range, 1 to 61)(Lee *et al.*, 2009) and studies conducted in other areas of Ethiopia, including Mekelle 7.2 days, range 1 day to 32 days) (Abebe *et al.*, 2012) and Tikur Anbesa Specialized Hospital, Addis Ababa 10.9 days, range 1 to 56 (Sileshi *et al*., 2016). This difference could be attributed to differences in the indication of ceftriaxone in which, ceftriaxone was more indicated for surgical prophylaxis in this study and most of the patients admitted at AFRTH were not terminally ill.

AFRTH is the only referral and teaching military hospital of the country and organized under Health Main Directorate, Ministry of Defense. It provides free medical services to all Ethiopian military and their relatives. The hospital does not have its own guideline on how to use antibiotics. As a result, inconsistent prescribing practice was very common for similar cases and does not have functional pharmacy and therapeutic committee and drug information center for cost effective medication selection and use, medication decision policy. The high utilization rate of ceftriaxone for surgical prophylaxis and other cases as first line in the hospital was due to unavailability and shortage of other alternative drugs and most of prescribers believe that it is more superior in terms of its converge against gram negative and gram positive as compared to other antibiotics. However, increased antibiotic usage is associated with increase in microbial drug resistance (Davey *et al* 2006). The practice of ordering C and S test is low that help for increasing appropriateness of empirical therapy or redirecting therapy in a safe and effective manner so that it actually targets the causative agent of the infection (Anagaw *et al*., 2013).

6. LIMITATIONS OF THE STUDY

- The hospital has no guideline on how to use antibiotics. As a result, the rational use of ceftriaxone was evaluated by using other institution guideline.
- A cross sectional study design was used which does not allow temporal relationship to be established.
- The study was not multi-centered caution should be applied in extrapolating the results of this study.
- The present study focused on medical, surgical, GYN and obs, orthopedic and ICU wards. However, a more representative result would be obtained if pediatric ward was included.

7. CONCLUSION

The findings from the present study indicated that the inappropriate utilization of ceftriaxone was high, which could facilitate the emergence of bacterial strains that are resistant to the available antimicrobial agents, ultimately increasing cost of therapy and treatment failure. Empiric and prophylactic treatment were found to have a significant association with inappropriate utilization of ceftriaxone. Majority of inappropriateness was seen with indication of ceftriaxone, duration of therapy, drug-drug interaction and failure to request microbiological testing. Most of the doses and frequency were almost appropriate as per the set criteria of this study.

8. RECOMMENDATION

Based on the data generated, the following recommendations are made,

- To avoid this inappropriate utilization of ceftriaxone, prescribers must adhere to the standard treatment guideline while prescribing drugs to patients to ensure treatment uniformity and promote rational drug use
- Improve availability of key antibacterial to promote rational use of ceftriaxone
- The practice of ordering C and S test should be improved to bring better out come in the treatment.
- There is a need of continuous and ongoing drug use evaluation; improve the suitability of antibiotics use through the intensification of educational programs, establish an antimicrobial stewardship program, strengthen the DTC unit and capacitate clinical pharmacists in monitoring issues related to drug therapy.

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ANEXES

Annex I: Consent Form (English Format)

Code No: - _____

Hello, my name is _____. I am here today to collect data on the evaluation of ceftriaxone utilization at different wards wards of AFRTH. Mr. Kelali Mehari from Addis Ababa University, College of Health Sciences, School of Pharmacy, Department of Pharmacology and Clinical pharmacy, Postgraduate program, is conducting the study. The purpose of this study is to evaluate the appropriateness of ceftriaxone use in medical and emergency wards of AFRTH. This is observational and prospective type of study so I request you to take part in this study by allowing your medical data to be included in the study. Your name will not be written in the data collection form and will never be used in connection with any information you tell us. There is no risk associated with participating in this study. All information regarding your medical condition will be kept strictly confidential. Your participation is voluntary and you are not obligated to participate in the study. If you feel discomfort with study, it is your right to drop it any time you want. If you have questions regarding this study, please feel free to contact the principal investigator via his address: Kelali Mehari, Tell: +251- 0913410700 or meharikelali@gmail.com

Are you willing to participate? Yes ☐ No ☐

Annex II: Data collection form

	1.Socio demographic characteristics
1.1	Age (Years)_____
1.2	Sex: ☐ Male ☐ Female
1.3	Admission date: _____ Discharge date: _____
	2. Diagnosis and treatment
2.1	Ward_____
2.2	Indication of ceftriaxone (working diagnosis)_____
2.3	Type of treatment : ☐ Prophylactic ☐ Therapeutic
2.4	Therapeutic : ☐ Empiric ☐ specific
2.5	Prophylactic : ☐ Per-operative prophylaxis ☐ Post-opertive prophylaxis ☐ Intera-operative prophylaxis ☐ Pre and post operative prophylaxis
	3.Culture and sensitivity test
3.1	Was C and S obtained after empiric therapy? ☐ Yes ☐ No
3.2	If the above question is yes when was the C and S test done ? A. Before initiating the first dose of ceftriaxone B. Within 24 hours C. Within 48 hours D. After 48 hours E. Other, specify _____
3.3	If question number 8 is yes what was the result ? ☐ Growth ☐ Not growth
3.4	If the result was growth what was the isolated microorganism? 1._____ 2._____ 3._____
3.5	Was the microorganism sensitive to ceftriaxone? ☐ Yes ☐ No
3.6	If question number 12 is no, did they continue the drug? ☐ Yes ☐ No

4. Medication therapy

4.1	Prescribed medication	Dose	Route	Frequency	duration	Drugs given concomitantly	Time gap between RL and ceftriaxone
	Ceftriaxone Inj						

Annex III: Key informant interview for physicians

The following questions are based on the results obtained from drug use evaluation of ceftriaxone conducted in different wards of AFRTH. Please respond by encircling the most appropriate alternative/s or by describing your additional opinion (if any). Your response on these questions will make possible the identification of the reasons behind some of the inappropriate use of this drug in AFRTH.

1) In your opinion, why is C&S test not sent for most of the patients in this hospital?

a. Cost/Affordability issue

b. Culture results are not reliable

c. It takes long time to get results back

d. Service not available

e. Patients come after initiation of antibiotics

2) In the survey conducted, it was found out that ceftriaxone was administered on a twice-daily basis for almost all medical conditions. What do you think is the reason for this?

a. Just because of tradition of practice

b. To ensure its effectiveness

c. There are guidelines, which promote this practice

3) It was found out that there is very high utilization rate of ceftriaxone in this hospital. In your opinion, what do you think is the reason for this?

a. Effectiveness

b. Low rates of toxicity

c. Availability

d. Ease of administration

4) In your opinion, why is ceftriaxone being co-administered with drugs including ringers lactate, warfarin and heparin?

a. Less availability of other drugs

b. Practice shows no problem up on concomitant administration

5) In your opinion, why is ceftriaxone used as an initial empiric therapy in such cases as neutropenic fever, periodontal abscess, poststreptococcal glomerulonephritis and suppurative lymphadenitis?

a. Local guidelines recommend such indications

b. Unavailability of other more appropriate drugs

c. Cost of other more appropriate drugs

6) In the present survey, it was found out that ceftriaxone was used for prolonged duration without switching to PO antibiotics (eg. In CAP for > 14 days and in surgical prophylaxis for 5-7 days). In your opinion, what do you think is the reason for this?

a. Practically, it is possible to do so

b. Unavailability of equivalent PO medicines

c. Local guidelines recommend such practice

Respondent's sig: _____ Date: _____

THANK YOU!!!

Annex IV: Key informant interview for microbiologists

The following questions are based on the results obtained from drug use evaluation of ceftriaxone conducted at different wards of Armed Forces Referral and Teaching Hospital. Please respond by briefly stating your opinion.

1) What can you say about the quality of microbiology laboratory?

_____

_____

2) According to the finding of the present study, most C&S results were found to be negative. What do you think about the cause of these negative culture results?

_____

_____

3) Who will take the bacteriology test result after it is done?

_____

_____

4) On average, how long does it take for C&S result to come back (in day)?

_____

_____ Respondent‟s sig: _____ Date: _____ THANK YOU!!!

Annex V: Consent Form, Amharic format (የስምምነት ቅጽ)

የስምምነት ቅጽ በአ.አ.ዩ ጤ/ሳ/ኮላጅ ፋርማሲ ት/ቤት ፋርማኮልጂ እና ክሉኒካሌ ፋርማሲ ት/ት ክፍሌ በጦር ሀይሎች ሪፈራል እና ማስተማርያ ሆስፒታል የሴፍትሪያክሶን መዲሃኒት አጠቃቀምን በተመለከተ በተለያዩ ዋርዶች ተኝተው ታካሚዎች ስለሚደረግ የግምገማ ጥናት ሲሆን፡- ይህ ጥናት ስሜ ---------- ይባላል፡፡ ዛሬ እዚህ የተገኘሁ ሴፍትሪያክሶን ስለተባለዉ መዲሃኒት አጠቃቀምን በተመለከተ ከላይ በተገለጹት የሆስፒታል የመታከሚያ ክፍልች የሚደረግ የግምገማ ጥናት መረጃዎችን ለመሰብሰብ ነዉ፡፡ ጥናቱ እየተካሄደ ያለዉ በአ.አ.ዩ ጤ/ሳ/ኮላጅ ፋርማሲ ት/ቤት ፋርማኮልጂ እና ክሉኒካል ፋርማሲት/ት ክፍሌ ከድኅረ-ምረቃ ፕሮግራም አቶ ከላሊ መሀሪ በተባለ ግለሰብ ነዉ፡፡ የዚህ ጥናት ዓላማ በሆስፒታል ስላለዉ የሴፍትሪያክሶን መዲሃኒት አጠቃቀም ጥናታዊ ግምገማ ለማድረግ ብሎም ስለመዲሃኒቱ ትክክለኛ አጠቃቀም መሠረታዊ መረጃን ለማጠናቀር ነዉ፡፡ ስለሆነም እርስዎም መዲሃኒቱን በተመለከተ የሚደረግሎትን የህክምና መረጃ በጥናቱ ዉስጥ እንዲካተት እንዲፈቅዱሉኝ እጠይቀዎታለሁ፡፡ በመሆኑም የእርስዎን ማንነት የሚገለጽ (ለምሳሌ ስም) በመረጃ መሰብሰቢያ ቅጹ ሊይ የማይካተቱ ሲሆን ሌሎችም መረጃዎች ምሥጢራዊነታቸዉ በጥብቅ የሚጠበቅ ይሆናል፡፡ የእርስዎ መረጃ በጥናቱ ዉስጥ እንዲካተት ፈቃደኛ ካልሆኑ መተው ይችላሉ፡፡ በማንኛዉም ጊዜ ስለጥናቱ ጥያቄ ከተፈጠረብዎት ዋናዉን ተመራማሪ ለመጠየቅ/ለማግኘት ነጻነት እንዲሰማዎት ለመግለጽ እወዳለሁኝ፡፡ የዋናዉ ተመራማሪ አድራሻ፡- አቶ ከላሊ መሀሪ ፤ ስ.ቁ: +251- 0913410700፤ ኢ-ሜይሌ: meharikelali@gmail.comበ ጥናቱ ሊይ ሇመሳተፍ ፍቃደኛ ነዎት? ፍቃደኛ መሆንዎን በፊርማዎ ቢያረጋግጡሉኝ?

1. አዎ (ፊርማ……..

2. አይደለም ….