Addis Ababa University

School of Pharmacy

Assessment of Ceftriaxone Utilization in Different Wards of Federal Police Referral Hospital: A Retrospective Study

Tariku Shimels (BPharm, BA)

Addis Ababa, Ethiopia

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Assessment of Ceftriaxone Utilization in Different Wards of Federal Police Referral Hospital; A Retrospective Study

Tariku Shimels (BPharm, BA)

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Advisor: Teferi Gedif (BPharm, MPH, PhD)

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This is to certify that the thesis prepared by Tariku Shimels, entitled: 'Assessment of Ceftriaxone Utilization in Different Wards of Federal Police Referral Hospital; A retrospective Study' and submitted in partial fulfillment of the requirements for the Degree of Master of Science in Pharmacoepidemilogy and Social Pharmacy complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

Signed by the Examining Committee:

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Advisor _____ Signature_____ Date_____

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Abstract

Assessment of Ceftriaxone Utilization in Different Wards of Federal Police Referral Hospital, Addis Ababa; A Retrospective Study

Tariku Shimels

June, 2014

The irrational use of antimicrobials such as ceftriaxone is one of the current public health issues. The problem becomes twofold when it happens in low income countries like Ethiopia. The objective of this study is to assess the utilization of ceftriaxone in different wards of FPRH, Addis Ababa. An institution based retrospective cross sectional study design was used to evaluate the use of ceftriaxone. The assessment was done by reviewing medication records of patients who received ceftriaxone during hospitalization in the different wards of Federal Police Referral Hospital from 1 May, 2013 to 30 April, 2014. A systematic random sampling technique was used to select the samples from all the inpatient prescriptions containing ceftriaxone. Patient medication records/ charts were located based on the medical record number on the prescription papers. Data was collected by using a structured format and evaluated against the Standard Treatment Guideline of Ethiopia as well as the IDSA and ASHP guidelines. Out of the 682 patient medication records sampled, 571 were found to be complete and subsequently evaluated against the guidelines. Ceftriaxone was prescribed for 2048 (44.3%) of the 4423 admissions in the respective wards. Overall evaluation of ceftriaxone therapy for indication, dose, frequency and duration revealed that 346 (60.6%) of the patient medication records were compliant to recommendations set in the guidelines. Frequently noted non-compliant uses included continued uses as pre & post-operative prophylaxis, unsupported indication in certain

diagnoses and deviated duration of therapy in medical cases. Among the co-prescribed medications checked for potential interaction with ceftriaxone, warfarin, heparin and doxycycline were found to have a significant drug-drug interaction. Days of hospital stay, type/payment scheme of medical service and type of ward patients had been admitted in were the factors associated with compliant ceftriaxone use in FPRH. The compliance of ceftriaxone utilization in FPRH, to the guidelines, is moderate. However, all concerned bodies and the hospital should be engaged for developing antimicrobial guideline, provide ongoing trainings, establishing a DIC and promote health professionals' adherence to the national STG to fill the remaining gap.

Key words: Drug use evaluation, Ceftriaxone, Federal police referral hospital**.**

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Acronyms and Abbreviations

3GCs	3rd Generation Cephalosporins
AA	Addis Ababa
ADEs	Adverse Drug Events
ADR	Adverse Drug Reaction
AFI	Acute Febrile Illness
AGE	Acute Gastro Enteritis
AMR	Anti-Microbial Resistance
AOR	Adjusted Odds Ratio
ASHP	American Society of Health-System Pharmacists
C&S	Culture and Sensitivity
CAP	Community Acquired Pneumonia
CBC	Complete Blood Count
CEFX	Ceftriaxone and Cefotaxime
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COR	Crude Odds Ratio
CT	Computed Tomography
DACA	Drug Administration and Control Authority
DDI	Drug-Drug Interaction
DIC	Drug Information Center
DTC	Drug and Therapeutics Committee

DUE	Drug Use Evaluation
DUR	Drug Use Review
E.coli	*Eschertia coli*
EBR	Ethiopian Birr
FMHACA	Food Medicine and Health Care Administration and Control Authority
FPCHSD	Federal Police Commission Health Services Directorate
FPRH	Federal Police Commission Referral Hospital
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society Of America
Kg	Kilo Gram
K. Pneumonia	*Klibesella pneumonia*
MG	Mili Gram
MRI	Magnetic Resonance Imaging
MSH	Management Sciences for Health
OPD	Out Patient Department
PI	Principal Investigator
PH	Police Hospital
PMRs	Patient Medical Records
SBP	Spontaneous Bacterial Peritonitis
SGOT	Serum Glutamic Oxalo acetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SHEA	Society of Healthcare Epidemiology of America

SIS	Surgical Infection Society
SPSS	Statistical Package for Social Sciences
STG	Standard Treatment Guideline
TASH	Tikur Anbessa Specialized Hospital
TB	Tuberculosis
UTI	Urinary Tract Infection
WADTC	West Australian Drug and Therapeutics Committee
WBC	White Blood Cells count
WHO	World Health Organization

1. Introduction

Antimicrobials have played a remarkable role in public health through decreasing of morbidity and mortality (Tulchinsky and Varavikova, 2010). The 19th and 20th centuries are peculiar in that health and longevity of populations progressed as the result of substantial achievements in controlling infectious diseases (Fielding et al., 2010; Schlipköter and Flahault, 2010). This, however, was not without any challenges (Hawkey, 2008).

Anti-microbial resistance (AMR) due to the over and incorrect use of antimicrobials is one of the threatening issues of public health (Shankar et al., 2005; Dagnew et al., 2013). Many patients suffer due to harms arising from AMR because the infections caused by viruses, bacteria, and protozoa are no longer susceptible to the commonly available antibiotics (Abdulghani, 2012; AMRSE, 2009; Asensio, 2011; Tapsall et al., 2009; WHO, 2010; WHO, 2011a; WHO, 2011b). As a result, several stakeholders at every corner of the globe are striving to stimulate policies and actions in the healthcare system.

As emphasized in a report by WHO, the possible consequences that may arise include loss of productivity (loss in income, diminished worker productivity, time spent by family) and increased cost of diagnostics and treatment (consultation, infrastructure, screening, cost of equipment and drugs). In the same instance, while both the health and economic consequences of AMR are sought to be considerable and costly, it is difficult to quantify precisely as the available data are usually incomplete in many countries. The

additional human burden associated with it (pain, change in daily activities, psychosocial costs) is also undeniably huge (WHO, 2012).

The responsibility of ensuring that drug products dispensed to patients will provide the necessary outcome and will not harm lies within the healthcare system of any government. Focusing on quality assurance, therefore, is an important concern that begins with licensing and monitoring of the healthcare providers at all levels. This is particularly important for the proper use of antimicrobials which are at high demand in countries with high burden of infectious disease like Ethiopia; where also, the practice is reported to be poor leading to dangerous AMR pathogens (Adrian et al., 2007; Dagnew et al., 2013; Tiruneh, 2009; Tizazu et al., 2011, Tsega and Mekonnen, 2012). The inability of regulatory authorities to control the distribution and utilization of medicines in such nations is also another contributing factor (Cameron et al., 2011; Holloway et al., 2013).

To understand about the extent and respond in a timely basis, drug use studies using aggregate data or health facility indicators that may illustrate the over- or under-consumption of medicines are important. Further detailed concerns in drug use evaluation may include incorrect medicine choices, incorrect dose, prescribing drugs that cause ADRs or drug interactions, and the use of expensive drugs when cheaper ones would be possible. In recognizing this, WHO recommended the alternative way of evaluating medicines utilization pattern in a more rigorous manner in health facilities to identify inappropriate uses and to promote rational utilization of medicines through drug and therapeutic committees (WHO, 2003).

A drug use evaluation (DUE) alternatively called as a drug use review (DUR), is, thus, defined as an ongoing, systematic and criteria-based program of medicine use evaluation that will help to ensure appropriate medicine use (ASHP, 1988). If therapy is determined to be inappropriate or noncomplying to certain agreed up on requirements (guidelines), interventions with providers or patients will be necessary to optimize pharmaceutical therapy. DUE which serves as a tool or a system of improving the quality of medicine use in hospitals and clinics, is structured so that it will assess the actual process of prescribing, dispensing or administering a medicine (i.e., appropriate indications, dose, frequency, medicine interactions) or assess the outcomes (i.e., cured infections, decreased lipid levels)(MSH and WHO, 2007).

2. Literature Review

The proportion of appropriate ceftriaxone uses differ across the globe. A smallest figure was reported in a pediatric hospital of Thailand as 10% (Tapaneeyakul et al., 2000) whereas a highest figure was found to be 65.5% using prospective evaluations in Korean hospitals (Lee et al., 2009). The commonest reasons of inappropriate uses in many of the findings were mentioned to be continued empiric uses for presumed infections, wrong indication and duration of therapy (Abebe et al., 2012; Gururaja et al., 2013; Mulugeta and Tarekegn, 2009; Lee et al., 2009; Tapaneeyakul et al., 2000).

In India, prospective cross sectional studies were conducted to evaluate the utilization of ceftriaxone. In the surgical and medical wards of a teaching hospital, it was found that ceftriaxone had been prescribed in majority of the cases the higher being in the medical ward for about 72% of the inpatients (Gururaja et al., 2013). In the same hospital, metronidazole was the most commonly co-prescribed drug, whilst culture and sensitivity was not done in most of the cases. In another study of a tertiary care hospital, however, 26% of patients received cephalosporin as specific treatment in which ceftriaxone was prescribed for 48.5% of the cases (Joyiti and Babu, 2012). The top group of co-prescribed drugs in this hospital included; nitroimidazoles (17.8%), quinolones (13.9%), followed by macrolides, aminoglycosides & beta lactam antibiotics.

In a retrospective study conducted in an educational hospital of Tehran, it had been reported that 266 cases out of 300 received ceftriaxone as surgical prophylaxis (Shohrati et al, 2010).

Of this proportion, 32% was according to protocol and 68% was not. Likely, among the 34% who received the drug for infection treatment, only 17.4% were reported to be appropriate.

A drug use evaluation in Australia has also showed that the overall concordance of CEFAX (ceftriaxone and cefotaxime) use to the indications recommended in antibiotic guideline of the country was 27% (Marion et al., 2002). The finding of fifty one hospitals in Victoria identified that out of the total 671 cases, treatment of respiratory tract infections accounted 352(52%) and surgical prophylaxis was used in 99(15%) while treatment of skin/ soft tissue, urinary tract and gastrointestinal tract infections accounted 7% of the admissions. On the other hand, different level of variance was noted from the guideline in the treatments of various episodes in Armande-Kelmscott Memorial Hospital. In the medical cases, most variance was noted in therapy of skin, muscle and bone infections (10 episodes), followed by respiratory tract infections (5 episodes) and urinary tract infections (3 episodes). Half of these episodes were associated with inappropriate uses of ceftriaxone. It was also mentioned that ceftriaxone use was in appropriate in the treatments of cellulitis, mild to moderate pneumonia and urinary tract infections (WADTC, 2000).

A retrospective cross sectional study was conducted in Bumrungrad hospital of Thailand between April and May 2000 to evaluate the rational use of Ceftriaxone. The results showed that the inappropriate drug use in pediatric patients was 18 cases (90%) and adult patients were 30 cases that account for 83.3% (Tapaneeyakul et al., 2000). Another retrospective study in a university hospital of the same country was conducted in 2011 to determine the factors associated with appropriate usage of ceftriaxone according to local guidelines. Whereas

Ceftriaxone usage was considered appropriate in 162 cases (58.3%), it was reported that male gender (OR 0.51, CI 0.27-0.97), fever (OR 3.12, 95% CI 1.3-6.11), signs and symptoms of infections (OR 2.92, 95% CI 1.37-6.28), suspicion of sepsis (OR 7.90, 95% CI 3.67-17.07), and diagnosis of gastrointestinal tract infection (OR 0.20, CI 0.05-0.77) were associated with appropriateness of ceftriaxone usage (Angsana et al., 2011).

A survey on anti-microbial use and resistance in all regions of Ethiopia showed that there was a considerable degree of resistance to commonly used antimicrobials (FMHACA, 2009). The presence of a wide spread practice of anti-bacteria drugs prescribing for medical inpatients was prevalent. More than 70% have had one or more anti-bacteria prescribed in a range of 1-6 (and with an average of 1.5). Rational prescribing as measured by the extent of adherence to the standard treatment guideline (STG) 2004 was strikingly low.

The drug(s) chosen and the duration of therapy comply with the STG for pneumonia in 19.6%, meningitis in 33.3%, typhoid in 24.7%, urinary tract infection in 22.6%, and relapsing fever 14.8% only. The report also mentions that although there was some awareness on nosocomial infections, only little is done by facilities to prevent and contain it accompanied with low availability and utilization for culture & sensitivity tests. On top of this availability of key antibacterial and infection prevention materials was less than the ideal standard of 100%.

Other institution based retrospective cross sectional studies were conducted in the country to evaluate appropriateness of ceftriaxone utilization. The findings in these studies showed a

significant range of compliance to the standard treatment guideline of Ethiopia. A smallest figure was noted in Ayder Referral Hospital as ceftriaxone was prescribed appropriately by 35.8% of the cases (Abebe et al., 2012) whereas the highest percentage of compliance was 73% in Police hospital (Mulugeta and Tarekegn, 2009). A nearly average figure was also reported in Dessie Referral Hospital as 55.8% of appropriate prescribing (Ayenalem et al., 2013).

The top co-administered drugs in all of the hospitals included maintenance fluids. Ceftriaxone was mostly used in the treatments of pneumonia and meningitis in Police and Black Lion Hospitals as well as Dessie Referral Hospital while it was used as preoperative prophylaxis in Ayder Referral Hospital. Also in these studies, most inappropriate uses were reported to be in terms of duration and frequency of treatment. Potential drug-drug interaction noted during the evaluations was the co-administration of maintenance fluids containing calcium like ringer's lactate solution (Abebe et al., 2012; Mulugeta and Tarekegn, 2009; Ayenalem et al., 2013).

3. Statement of the Problem

The widespread misuse, together with the emergence of antimicrobial resistance and escalating unwanted expenditures have resulted in antimicrobials being the drugs most frequently chosen for DUE projects (ECDC & EMA, 2009; John and McGowan, 2004; WHO, 2012).

Ceftriaxone, as the most frequently used drug among the third generation cephalosporin class with a reputable broad spectrum activity and utilization in many developing countries (Khaled et al., 2013 and Salah, 2011), is also highly prone to such problems. Evidence from a study supports that it is most often prescribed before culture & sensitivity tests are made in the diagnosis process (Kaliamoorthy et al., 2012). It is, therefore, apparent that the expected desired clinical outcome, both in the public and the private healthcare settings, will be compromised.

The proportion of inappropriate use, as compared to standard guidelines and AMR impact of the drug has been documented in both the developing and developed countries. For example, a report by WHO has shown that AMR gram negative bacteria across the European Union member states, the Iceland and the Norway accounted the highest figure against ceftriaxone resulting in extra number of cases of infection, deaths and hospital days (WHO, 2012).

Inappropriate indication, empiric or prophylactic therapy and multiple drug uses were also reported to be associated with misuse of the drug in Port of Spain (Pinto Pereira et al, 2004). Similarly, a survey of antibiotic use trend in the German ICUs indicated that there was a dramatic 10 fold increase in E. Coli resistance to 3rd generation cephalosporins from 2001 to 2008 (Meyer et al., 2010). The study by Salah (2011) in Sudanese general Hospital wards has

also shown that there is an 86.1% and 95.8% resistance to ceftriaxone against patient isolates of E. coli and K. pneumonia pathogens respectively.

In Ethiopia, though there are no comprehensive studies to demonstrate the magnitude and direction of the problem across all the public hospitals of the country, few fragmented studies have documented the threatening incidence of noncompliant ceftriaxone use to the national STG. For example, it is reported that there was an inappropriate use of ceftriaxone in terms of incorrect indication, presence of drug interaction, absence of lab diagnosis, inappropriate duration of treatment and incorrect dosage regimen (Mulugeta and Tarekegn, 2009; Abebe et al., 2012).

However, the reported levels of overall appropriate use in these studies could be amenable to a series of questions as the tool used in evaluation was merely based on an STG developed for general hospitals that doesn't have an extensive coverage of practices in referral hospitals. So, the use of a more rigorous evaluation tool and displaying the magnitude of the problem in a more reliable way, at least at a facility level, is substantial.

The gap in Ethiopia seeks more attention as the practice of culture & sensitivity test is poor, transmission of resistant pathogens from person to person is potential and the fact that most health facilities do not have their own guideline or adhere strictly to the national guideline.

Apart from selective pressure from health professionals as well as patients for overuse of the drug and failure of hospital infection control practices, the lack of appropriate feedbacks after evaluative studies are conducted is a setback for intervention. Though there had been a 'drug use evaluation study' in the present study setting (Mulugeta and Tarekegn, 2009), there was no interventional feedback given to the hospital as to the knowledge of the PI of this study.

For a DUE is a continuous process done by hospital DTCs and concerned bodies to ensure rational pharmaceutical use, this evaluation is deemed to show the changes happened in the past five years.

Particularity of the study to Federal police referral hospital makes it more valuable as the drug use pattern in the hospital is quite distinct from other public hospitals. These include; that majority of patients are treated free of charge, that most of the patients are military with respective rank hierarchy whose admission classification may potentially affect level of care and that there are a considerable number of injury/fracture admissions necessitating the use of the drug as a pre-operative prophylaxis in all of such procedures.

Therefore, the initiation of this study is important for understanding the possible gaps in ceftriaxone utilization of the hospital and addressing them aggressively. The study will also have an advantage to see the changes from the earlier evaluation in 2009, and take the benefit of using a more rigorous tool composed of the national and international treatment guidelines.

4. Objective

4.1 General Objective

To assess the utilization of ceftriaxone in the different wards of Federal Police Referral Hospital, Addis Ababa

4.2 Specific Objectives

- To describe utilization pattern of ceftriaxone in the different wards of the hospital
- To evaluate the compliance of ceftriaxone utilization against national and international guidelines
- To identify potential drug-drug interactions of ceftriaxone and co-prescribed drugs
- To identify potential factors associated with compliance of ceftriaxone use in the hospital

5. Methodology

5.1 Study Setting

Federal Police Referral Hospital is one of the two military hospitals found in the capital of the country, Addis Ababa. The hospital was established between 19 November 1961 and 22 July 1962 as 'Police Force Hospital' by the contribution of the police community (FPCHSD, 2011). Along with its counterpart in Harar (named as 'Federal Harar police hospital'), the Police Force Hospital was opened to provide medical services to the police community and their families with minimal monthly fee. Currently, the hospitals are administered under the Federal Police Commission, and are named as the 'Federal Police Referral Hospital and the 'Federal Harar Police Hospital'.

Whereas services to the community are allowed on a part time basis and charged schemes (named as 'private wing') since two years back, most of the regular work hour and duty service is rendered to the police community referred from all over the country. Though, both on job and retired members as well as their families (children & spouses) are eligible for free medical service with a monthly fee, relatives of members, injured members by a third body, third bodies injured by members and members in the Federal Prison who used medications (only drug costs are charged in this group) are subjected to payment. Payments for charged patients are settled by the responsible organ in the respective groups i.e. members for their relatives, members/third bodies for the injured and Federal Prison for the prisoners.

The hospital has a total of 310 beds and is engaged in providing diagnostic and medical treatment to in-patients along with other services, such as out-patient, laboratory services,

pharmacy services, cafeteria, emergency, delivery, family planning (FP), reproductive health services, voluntary counseling and testing (VCT) etc. It also provides training and apprentice-ship services for students from the Police health professional training institute.

There are a total of 629 employees in the hospital of whom 317 are health professionals. Among the health professional categories include, 7 specialists, 34 general practitioners, 7 pharmacists, 23 public health officers, 12 druggists, 140 nurses and others. Two hundred thirty of the health professionals are also military while the remaining 87 are civil.

5.2 Study Design

An institution based retrospective cross sectional study design was conducted from 10 to 30 June 2014 to assess the utilization of ceftriaxone in the different wards of the hospital.

5.3 Source Population

The source population of this study was all the medication records of the all patients who have been admitted to the emergency, pediatrics, surgical, medical as well as gynecological/ obstetrics wards of FPRH from 1 May2013 to 30 April 2014.

5.4 Study Population

The study population of this study was those patient medication records of all patients that have been admitted in different wards of the hospital and received any dose/course of ceftriaxone during the study period.

Inclusion Criteria

- Medication records(charts) of Patients that have been admitted to the emergency, gynecologic/ obstetrics, medical, pediatrics and surgical wards of FPRH from 1 May 2013 to 30 April 2014;
- Medication records (charts) of patients who had received any dose/ course of ceftriaxone within the twelve months period;
- Medication records containing adequate data on such variables as socio-demography (age, sex, membership and military status), drug related variables (dose, frequency, duration), and diagnosis.

Exclusion Criteria

- Medication records of patients that have been admitted before and after the period mentioned under the inclusion criteria;
- Medication records (charts) of patients admitted to the private wing;
- Medication records (charts) of patients who are from the outpatient department (OPD);
- Medication records (charts) that have not contained data on any of the following variables; age, sex, membership and military status of patients, dose, frequency and duration of ceftriaxone therapy, assessments for which the drug has been prescribed.

5.5 Sample Size and Sampling Method

5.5.1 Sample Size

Similar studies have employed different time periods (ranging from one to twelve months) and sample sizes for evaluating drug utilization from patients' records. WHO recommends that for a drug use evaluation including those involving cross sectional surveys, at least 600 patient encounters are required (WHO, 1993). The document also mentions that based on the number of health facilities in which a drug use evaluation is to be done, the number of encounters per facility may vary but must end up to reach the minimum number of 600. Therefore, this study had adapted the above recommendation and has made some adjustments as presented below.

Recommended number of Patient medication records (charts) required = **600**

Adjustments for incomplete and missing charts= 10% (i.e. 10%*600) =**60**[1]

Excess prescriptions because of rounding off fraction from the interval=**22**

Total samples required to be drawn (600+60+22) = **682** patient medication records

5.5.2 Sampling Method

A systematic random sampling technique was employed in this study. Initially, patient prescription papers from the emergency and inpatient pharmacy within the period to be evaluated were collected and coded chronologically. Next, prescription papers containing

[1] A 10% adjustment was taken based on an arbitrary inspection of 20 inpatient PMRs containing ceftriaxone from the inpatient pharmacy encounters of which 2 were found as incomplete to contain 'duration' and 'diagnosis' data.

ceftriaxone were selected and kept in the same chronologic order of days and months they had been prescribed. Prescription papers with repeated order for the same patient were excluded.

There had been a total of 2048 prescription papers obtained as the sampling frame. A sampling interval of 3 was taken by dividing the total number of prescriptions (2048) to the total number of patient medication records required in the study (660). Next, any of the numbers 1, 2 or 3 were chosen randomly (which in this case was 2) to begin the first sample. Then, the remaining samples were selected based on the interval of 3. In cases where there encountered prescription papers with no card numbers or name of patients during selection, those found immediate to the incomplete ones were considered. Because, the sampling interval taken was a rounded down from 3.1 to 3, it finally resulted to extra 22 prescriptions to be included in the study.

5.6 Data Collection Procedures

5.6.1 Data Collection Instrument

Data abstraction format was developed based on the Standard Treatment Guideline (STG) of Ethiopia (DACA, 2010), and the guidelines of the American Society of Health-System Pharmacists (ASHP) and Infectious Diseases Society of America (IDSA) (Annex II) and the patient characteristics of the study setting. For majority of the conditions, the STG was used to evaluate compliance of ceftriaxone use in terms of indication, dose, frequency and duration. For new indications and diagnoses not included in the STG, the ASHP and IDSA guidelines were used. Moreover, the manual for Drug and Therapeutics Committee training prepared by Management Sciences for Health and World Health Organization (MSH & WHO, 2007) was used on appropriate procedures and variables of a DUE.

5.6.2 Data Collectors

This study employed three pharmacists for data collection. They were trained on the purpose and the use of the data abstraction format. At the same time, they were oriented to ethical principles of confidentiality and data management prior to their involvement with data collection process.

5.6.3 Data Quality Control

Data quality control issues were ensured by conducting the pretest on inpatients' medication records and prescription papers obtained from Hayat and Zewditu Memorial Hospital. The consideration of patient characteristics and patient record formats in the study setting was an important step to explore potential variables that influence compliant ceftriaxone use. While training was given at the beginning to the data collectors, regular supervision and assistance was held during data collection period to ensure consistency and accuracy.

5.7 Variables

Dependent Variables

- Compliance of ceftriaxone prescription to national and international guidelines
- Presence of drug-drug interaction

Independent Variables

- Age
- Sex
- Number of drugs co-prescribed

- Reason for use (prophylactic or therapeutic)
- Type of therapy (empiric or specific)
- Presence of comorbidity (no or at least one)
- Days of hospital stay
- Source ward
- Type of service (charged or free)
- Military status (military, civil or others)
- Membership status(Federal police, Regional police or Federal prison)
- Residence/ working area (AA vs. Regions)
- Type of patient (on job member, retired member, member's family)

5.8 Operational Definitions

Course: Administration of at least one dose of ceftriaxone. If the course is repeated more than 24 hours after a previous dose (and the drug was re-prescribed), this will be taken as a new course.

Empiric therapy: ceftriaxone administration commenced before or without identification of any ceftriaxone-sensitive bacterial pathogen.

Specific therapy: ceftriaxone administration commenced after the identification of a ceftriaxone –sensitive bacterial pathogen.

Compliance of ceftriaxone use: is when the observed practice of ceftriaxone prescribing is equivalent to the Guidelines considered. Alternative terms to this could also be 'appropriate use'

Recommendations: are statements within the IDSA's accepted level of evidence quality and strength to assist practitioners and patients in making decisions about uses of ceftriaxone for specific clinical circumstances.

Step-down therapy; refers to converting ceftriaxone intravenous therapy to any oral agent in another class or to a different medication within the third generation cephalosporin class.

Pre-operative prophylaxis; in this study refers to the administration of ceftriaxone for the prevention of infection after surgery or operational procedures after injury or fracture.

Bone & soft tissue infections; the assessments collectively considered in this as bone and soft tissue infections encompass bone infections, soft tissue infections and diabetic foot ulcer.

Other diseases; the diseases collectively labeled in this study as "other diseases" are those rare cases accounting of less than 1% for consuming ceftriaxone individually. These include, brain abscess, bronchitis, COPD, dysentery, neurosyphilis, orbital cellulitis, otitis media and pelvic inflammatory disease.

Medication records; otherwise called as charts, patient medication records or cards are patient records with detailed personal, diagnostic and medication histories.

5.9 Ethical Consideration

The study was approved by the School of Pharmacy Research and Ethics Committee, College of Health Sciences, Addis Ababa University. After an application letter of permission was written to the health services directorate of Ethiopian Federal Police Commission, permission was obtained and a Cooperation letter was then written to the records office of the hospital. The confidentiality of the data collected was maintained. Whereas data was analyzed and

interpreted aggregately, all patient direct-identifiers (name, telephone number, medical record /card number and name of relative) were not considered.

5.10 Data Analysis

After coded and checked manually for completeness, data was filled in to Statistical package for social sciences (SPSS) version 20 and cleaned before analysis. Descriptive statistics was used for analyses in socio-demographic variables, duration of ceftriaxone therapy, daily dosage distribution, appropriateness, common diseases ceftriaxone was prescribed for, the frequently co-prescribed drugs in the different wards of the hospital and the extent of overall ceftriaxone use.

For determining presence of potential drug-drug interactions, different online databases namely; Medscape, epocrates, drugs.com and Micromedex were used. Technical assistance and recommendation on reliability of the databases was obtained from Tikur Anbessa Specialized Hospital Drug Information Center.

A binary logistic regression was used to determine the association between selected potential factors (age, sex, days of hospital stay, number of comorbidity, number of drugs co-prescribed, type of therapy, type of service, type of ward, membership of patients and military status of patients, and appropriate use of ceftriaxone. Three separate steps of the model were run to obtain significant determinants among the ten categorical variables and interacting 'comorbidity vs. number of drugs' variables.

In the first step, all variables including the interaction categories (number of comorbidity and co-prescribed drugs) were entered. As there was no contribution of the interaction, the group

of interacting categories was rejected from the model and the individual predictors were run separately to obtain the unadjusted odds ratio. Finally, all predictors used in the second phase were entered and run together to obtain the adjusted odds ratio for potential confounders. The odds ratio estimate was based on a 95% confidence interval for level of significance.

6. Results

6.1 Background and Socio-demographics of Patients

Of all the total 682 patient charts assessed in this study, 571 were found to contain the required data with a completeness ratio of 83.7% and considered for subsequent analysis. The mean age of patients was 33.4 Years ranging from 3 months to 89 years (with a standard deviation of ±17.7 Years). Four hundred seventy one (82.5%) of the patients were aged between 14-65 years. Three hundred eighteen (55.7%) were male whereas 253(44.3%) were female. Majorities were members of Regional police (50.4%) followed by Federal police (44.3%) and Federal prison (5.3%). As to of military status, 258(45.2%) were military, 186(32.6%) were others (families & relatives) and 127(22.2%) were civil. More than two third (71.1%) of the patients had also no comorbidities (**Table 1**).

Table 1; Background and Socio-demographic distribution of patients in Federal Police Referral Hospital; June, 2014, (n=571)

Variables		**Frequency**	**Percent**
Age* (years)	<14	61	10.7
	14-65	471	82.5
	>65	39	6.8
Sex	Male	318	55.7
	Female	253	44.3
Membership	Federal police	253	44.3
	Regional police	288	50.4
	Federal Prison	30	5.3
Military status	Military	258	45.2
	Civil	127	22.2
	Others**	186	32.6
Comorbid condition	Have no comorbidity	406	71.1
	At least single comorbidity	165	28.9

*** Others include families or relatives of either civil or military members of police.*

6.2 Extent and Pattern of Ceftriaxone Treatment

Out of the total 4423 patients admitted and treated in the respective wards, 2048 (44.3%) had ever prescribed with at least a single dose of ceftriaxone. The median days of hospital stay was 7 days (ranging from 1 to 240 days) whilst the mean duration of treatment was 5.2 days (ranging from stat to 50 days). Three hundred eighty nine (68.1%) patients were treated for 2-7 days followed by those who took the drug for 1 day, 83 (14.5%), 8-14 days, 53 (9.3%), stat, 29 (5.1%) and more than 14 days, 17 (3%) (**Table 2)**.

Table 2; Ceftriaxone therapy duration among patients in FPRH; June, 2014, (n=571)

Duration	Number of Patients	Percent
Stat	29	5.1
One day	83	14.5
2-7 days	389	68.1
8-14 days	53	9.3
>14 days	17	3
Total	571	100

In 449 (78.6%) patients, ceftriaxone was found to be dosed as 2g /day followed by <2g/day in 106 (18.6%) and 4g/day in 16(2.8%) of the admissions.

Three hundred sixty six (64.1%) of the patients were prescribed with ceftriaxone for therapeutic reasons and the rest 205(35.9%) took the drug for prophylactic purposes. A total of nine blood cultures had been found to be done and only three showed growth of a specific

microorganism (*E.coli*). The six patients whose culture didn't show any growth were found to continue the drug and were considered as treated empirically, making the total patients who were treated empirically 363 (99.2%). One culture incubated for seven days was reported to show no growth of any organism (**Table 3)**.

Table 3; Susceptibility pattern of *E.Coli* to Ceftriaxone in FPRH; June, 2014 (n=9)

Growth condition	**Organism was isolated and Susceptible to ceftriaxone**		**No organism was isolated**		**Total Cultures done**	
	N	**%**	**n**	**%**	**n**	**%**
In 7 days	-	-	1	11.11	1	11.11
In 48 hours	3	33.33	5	55.56	8	88.89
Overall					9	100

As shown in **Table 4**, out of a total of 571 patients who have had ceftriaxone prescribed, 552 (96.7%) had at least one type of routine investigation done before or during ceftriaxone therapy. In the rest 19 (3.3%), no test was done at all. Hematologic tests were the most frequently done tests accounting for 459(80.4%) of the cases and gram stain the least, done for 66(11.6%).

Table 4; Types of routine investigations done before/during ceftriaxone treatment in FPRH; June, 2014 (n=552)

Routine investigation	**Frequency**	**Percent**
Hematologic tests	459	80.3
Urine analysis tests	405	71.0
Liver function tests	402	70.4
Renal function tests	329	57.7
Imaging	250	43.7
Widal weil felix tests	161	28.2
Gram stain	66	11.6

***Percentages do not add to 100 as multiple responses are possible.*

Maintenance fluids, diclofenac and metronidazole were the top three co-medications prescribed in 275 (48.2%), 209 (36.6%) and 70 (12.3%) patients respectively (**Table 5**).

Table 5; Top ten drugs frequently co-prescribed with ceftriaxone in FPRH; June, 2014 (n=571)

Drugs	**Frequency**	**Percent**
Maintenance fluids	275	48.2
Diclofenac	209	36.6
Metronidazole	70	12.3
Tramadol	50	8.8
Cimetidine	44	7.7
Paracetamol	39	6.8
Gentamicin	36	6.3
Cloxacillin	35	6.1
Furosemide	34	6.0
Metoclopramide	26	4.6

** *Percentages do not add to 100 as multiple responses are possible*.

6.3 Compliance to National & International Guidelines

Among the 571 patient charts evaluated for compliance in the present study, 346 (60.6%) were found to agree with the recommendations set in the Ethiopian standard treatment guideline for general hospitals and the IDSA as well as ASHP guidelines. The rest 225(39.4%) were not according to the guidelines (**Figure 1**).

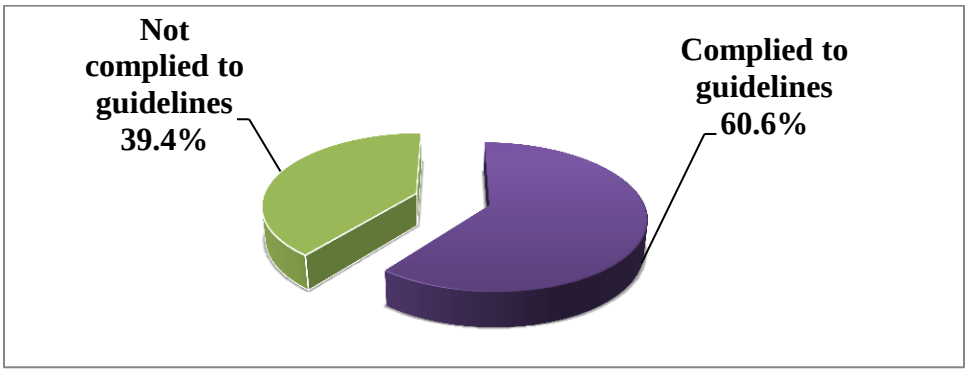

Figure 1; Overall compliance of ceftriaxone utilization against national and international guidelines in FPRH; June, 2014 (n=571)

The highest proportion of ceftriaxone use was observed in internal medicine ward accounting for 276 (48.3%) of the cases; followed by 144(25.2%) in surgical, 86 (15.1 %) in gynecologic/ obstetrics, 38(6.7%) in pediatrics and 27(4.7%) in emergency wards. The most frequent noncompliance was noted from emergency department in 18 of the 27 cases (66.7%) followed by surgical ward, 80(55.6%), gynecology/obstetrics, 35 (40.7%), pediatrics, 13 (34.2%) and internal medicine, 79 (28.6%) (**Figure2**).

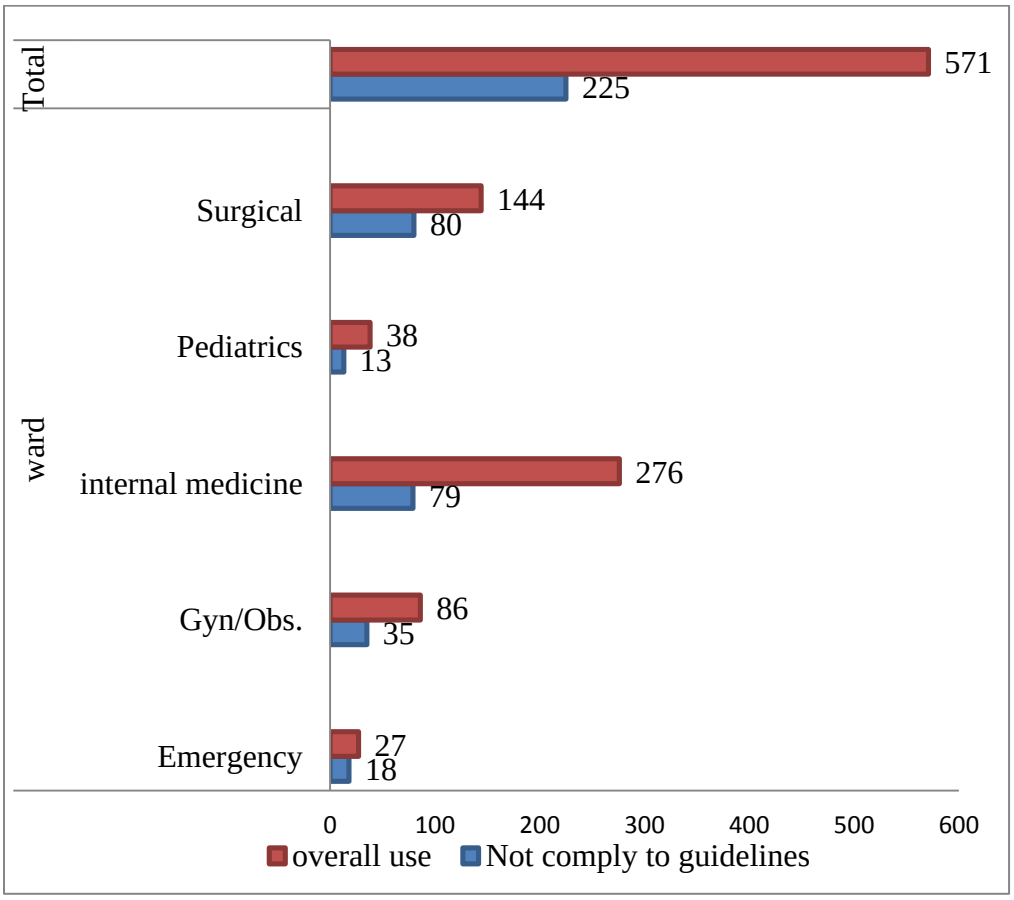

Figure 2; Inappropriate utilization of ceftriaxone in different wards of FPRH; June, 2014(n=571)

Among the top ten diagnoses for which ceftriaxone was prescribed, the highest proportion was in pre-operative prophylaxis which accounted about 225 (39.4%) patients. Next higher figures were for pneumonia in 140(24.5%), AFI in 31(5.4%), UTI in 28(4.9%), meningitis in 18(3.2%), AGE in 17(3%), sepsis in 15(2.6%), bone & soft tissue infections in 10(1.8%) and cellulitis in 10(1.8%) cases. All assessments recorded during the evaluation period are shown below (**Table 6**). Ceftriaxone was prescribed for AFI, AGE, wound, bronchial asthma, stroke and peptic ulcer disease which were not recommended by the guidelines as eligible indication.

Likely, noncompliance to guidelines was observed in 113(50.2%) of pre-operative uses, 3(20%) of sepsis and 2(20%) of cellulitis treatment.

Table 6; Common conditions for which ceftriaxone was prescribed and respective compliance of utilization against national & international guidelines in FPRH; June, 2014 (n=571)

	Overall use	**Comply to guidelines**	
Assessments	**n**	**n**	**%**
Pre-operative prophylaxis	225	112	49.8
Pneumonia	140	125	89.3
AFI	31	0	0
UTI	28	27	96.4
Meningitis	18	16	88.9
AGE	17	0	0
Sepsis	15	12	80
Bone & STIs	10	9	90
Cellulitis	10	8	80
UGIB/ascites/peritonitis	10	9	90
Wound	10	0	0
Endocarditis	8	7	87.5
Bronchial asthma	7	0	0
Stroke	7	0	0
Appendicular mass/abscess	6	6	100
Other diseases	23	15	65.2
Total	**571**	**346**	**60.6**

Table 7 below shows a list of the most common reasons for noncompliance. Nearly half (49.3%) of the deviations were from surgical and gynecologic/obstetrics wards which

practiced either a longer duration or wrong timing (including prolonged post-operative use, post-operative initiation of first dose or initiation of first dose long before surgery) of ceftriaxone usage in surgical prophylaxis. Similarly, wrong indications and overall duration of therapy in certain diagnoses composed the subsequent higher percentages in 83(36.9%) and 17(7.6%) of the noncompliant cases respectively. The least proportion of variation from guidelines was observed in wrong diagnosis prescribed with ceftriaxone (i.e. patients assessed as pneumonia while, in fact, it was not) in 4 (1.8%) patients.

Table 7; Common types of noncompliance of ceftriaxone utilization to national and international guidelines in FPRH; June, 2014 (n=225)

Reasons of noncompliance to guidelines	**Frequency**	**Percent**
Unaccepted use for prophylaxis	113	50.2
Wrongly indicated	83	36.9
Unsupported duration	19	8.5
Wrong dosage	5	2.2
Unsupported Step-down switch	5	2.2
Total	**225**	**100**

6.4 Potential Drug-Drug Interactions among Drugs Co-prescribed and Ceftriaxone

Among the total 46 drugs checked for potential drug-drug interactions, database processing result was obtained for 5 (10.9%) drugs accounting of 101(17.7%) patient encounters (**Table 9**). Among these, for three drugs namely, warfarin, doxycycline and heparin used by 31(5.4%) of the patients were commented to cause significant interaction by the Medscape database. However, a variation was seen as same drugs were classified differently in other databases (for warfarin vs. ceftriaxone; Epocrates, minor interaction; Micromedex, moderate interaction; for ceftriaxone vs. heparin; drugs.com, minor interaction).

Table 8; Result of different databases for potential drug-drug interaction between ceftriaxone and other co-prescribed drugs in FPRH; June 2014 (n=101)

Name of drugs co-prescribed	Number (%)	Tool used	Result obtained	Justification	Remark
Furosemide	34 (6)	Medscape	Minor or non-significant interaction	Ceftriaxone increases toxicity of furosemide by pharmacodynamics synergism. Increased risk of nephrotoxicity	
		Drugs.com	Causes occasional nephrotoxicity	Cephalosporin antibiotics like ceftriaxone can occasionally cause damage to the kidneys, and using it with furosemide may increase that risk. This interaction is more likely to	

				occur when the cephalosporin is given at high dosages by injection into the vein or when it is given to the elderly or individuals with preexisting kidney function impairment.	
Warfarin	4 (0.7)	Medscape	Significant interaction possible	Ceftriaxone increases effects of warfarin either by anticoagulation or by decreasing vitamin K-producing intestinal flora	Monitor closely
		Epocrates	Monitor /modify treatment	Mechanism not well known; but increases bleeding probably through ceftriaxone's action on vitamin k producing normal flora	
		Drugs.com	Causes bleeding easily	Using ceftriaxone together with warfarin can cause one to bleed more easily	Test for prothrombin time or INR and adjust doses
		Micromedex	Moderate interaction	Concurrent use of ceftriaxone and warfarin may result in an increased risk of bleeding	
Doxycycline	15(2.6)	Medscape	Significant interaction possible	Doxycycline decreases effects of ceftriaxone by pharmacodynamics antagonism. Bacteriostatic agents may	Monitor closely

				inhibit the effects of bactericidal agents	
Heparin	12(2.1)	Medscape	Possible serious or life-threatening interaction	Ceftriaxone will increase the level or effect of heparin by anticoagulation. Cephalosporins may decrease prothrombin activity	Monitor closely; use alternatives if available
		Drugs.com	Minor interaction	Consumer information on this interaction is not currently available; some minor interactions may not be clinically significant or harm all patients	Good to adjust medication/doses
Gentamycin	36(6.3)	Drugs.com	Occasional nephrotoxicity	Gentamicin can sometimes cause damage to the kidneys, and using it with a cephalosporin antibiotic like ceftriaxone may increase that risk	Adjust doses or monitor therapy

6.5 Factors Associated with Compliance of Ceftriaxone Use to National and International Guidelines

As presented in **Table 9** below, a two-step binary logistic regression was done to determine potential association of the variables; age, sex, presence of comorbidity, number of drugs co-prescribed, days of hospital stay, reason of use, type of wards, type of service, type of membership and military status to compliant use of ceftriaxone. Though similar outcomes were obtained in the variables; type of wards and type of service from both the unadjusted and adjusted odds ratios, there was a considerable variation in half of the variables. The adjusted logistic regression analysis finally retained that 2-7days of hospital stay (AOR; 0.582, 95%CI, 0.349-0.969) and free of charge medical service (AOR; 0.129 , 95% CI, 0.047-0.351) were associated with a decrease in the compliance of ceftriaxone use to guidelines.

On the other hand, being admitted to gynecology/obstetrics (AOR; 3.228, 95% CI, 1.59-6.555), medical ward (AOR; 3.085, 95% CI, 1.436-6.624) and pediatrics ward (AOR; 5.205, 95% CI, 1.52-17.822) as well as being a member of either a federal (AOR;8.521, 95% CI, 2.428-29.901) or a regional police (AOR; 7, 95% CI, 1.973-24.833) were associated with a more likelihood of compliant use to the guidelines.

Table 9; Factors associated with compliance of ceftriaxone use to National and International guidelines in FPRH; June, 2014 (n=571)

Factors		Crude		Adjusted	
		OR	**95% CI**	**OR**	**95% CI**
Age (Years)	<14	0.72	0.311-1.666	1.096	0.36-3.339
	14-65	0.759	0.381-1.515	1.304	0.597-2.848
	>65	1		1	
Sex	Male	0.98	0.699-1.374	0.833	0.523-1.327
	Female	1		1	
Comorbidity	No	0.574	0.39-0.844	0.867	0.554-1.359
	Yes	1		1	
Number of drugs co-prescribed	0	0.838	0.522-1.343	1.116	0.656-1.898
	1	0.636	0.395-1.023	0.715	0.419-1.221
	>=2	1		1	
Days of hospital stay	One day or less	0.396	0.199-0.786	0.683	0.26-1.794
	2-7 days	0.678	0.442-1.039	0.582	0.349-0.969*
	8-14 days	0.963	0.569-1.632	0.954	0.536-1.696
	15 days or more	1		1	
Wards	Emergency	0.625	0.263-1.484	0.703	0.187-2.637
	Gyn/obstetrics	1.821	1.06-3.13	3.228	1.59-6.555*
	Medical	3.117	2.049-4.743	3.085	1.436-6.624*
	Pediatrics	2.404	1.14-5.071	5.205	1.52-17.822*
	Surgical	1		1	
Reason for use	Therapeutic	2.085	1.469-2.958	1.443	0.698-2.985
	Prophylactic	1		1	
Type of the service	Free	0.45	0.257-0.788	0.129	0.047-0.351*
	Charged	1		1	
Membership	Federal police	1.338	0.622-2.879	8.521	2.428-29.901*
	Regional police	1.071	0.501-2.287	7	1.973-24.833*
	Federal prison	1		1	
Military status	Military	1.001	0.681-1.469	1.447	0.847-2.473
	Civil	1.19	0.747-1.895	1.683	0.951-2.977
	Others	1		1	

**Indicates presence a significant association*

7. Discussion

Less than 50% of the patients in the present study had taken at least a single dose of ceftriaxone (an overall prescribed proportion of 44.3%). A considerable difference is noted from studies conducted in other countries. A higher figure was reported by a prospective evaluation in a teaching hospital medicine ward of India (Gururaja et al., 2013) accounting for 72%. Despite the fact that this higher figure might, most likely, have been resulted from the shorter period that the study evaluated (5 months) and that it focused only to the medicine ward, the extent of utilization in the present study remains to be relatively better. Additional factors of variation could also be as; diseases pattern, knowledge of prescribers and pharmacists on rational use of antibiotics, the supply chain of the drug in the market, purchasing power and perception of patients towards injectable medications or antibiotics in the two countries.

However, a lower result of cephalosporin usage (30.02%) was reported by a prospective cross sectional study in the tertiary care hospital of the same country (Jyothi and Babu, 2012). Though the study documented relatively higher figure (48.5%) ceftriaxone consumption in the medicine ward that was compared among other cephalosporin drugs, the results would definitely change had both studies involved similar wards and denominators (all admission vs. those who received only cephalosporin). The availability and use of generic cephalosporin class substitutes in India might be the major reason for the low proportion of cephalosporin (ceftriaxone) utilization whereas ceftriaxone is usually prescribed only with few substitutes from the class in our study setting.

The mean duration of treatment in the hospital was 5.2 days (ranging from stat to 50 days). In fact, more than two third (68.1%) of the patients were treated for 2-7 days. This duration was

lower than the figure obtained in Ayder referral hospital (Abebe et al., 2012) and Korean hospitals (Lee et al., 2009) which reported 7.2 and 10.3 days respectively. The low figure in this study is a justification for a more frequent step-down switch of ceftriaxone (intravenous) to other (oral) antimicrobials as well as prevalence of cases that could be treated and recovered within seven days of overall duration. The median days of treatment duration by a study in Victorian hospitals was also found to be 3.0 days (Marion et al., 2002), further, lower than ours (median of 5.0 days). Generally, whereas a shorter duration of intravenous therapy would be desirable in most cases to reduce hospital stay and cost (Timothy et al., 2007), such factors as; severity and site of infection, types and number of comorbidities, and patients' response to alternative oral regimens are important before making this decision.

Four hundred forty nine (78.6%) of the patients in this study were dosed 2g/day. This figure is close to the proportion of patients (79.4 %) who received the same daily dosage in Ayder referral hospital (Abebe et al., 2012). Nevertheless, a lower proportion (63.6%) was also reported by the study in Dessie referral hospital (Ayinalem et al., 2013) whereas a higher figure (85.3%) was reported in Korean hospitals (Lee et al., 2009) for the same daily dosage. The fact that most of the patients were prescribed with a 2g/day regimen and that it agreed with other studies, may imply for most of the assessments were recommended under this daily dosage with few exceptions (i.e. meningitis, brain abscess, and infective endocarditis) and that most were adults.

In our study, only 9 patients were found with their culture and sensitivity done and of which 3 showed growth and sensitivity within 48hours (0.8%). This is a very small proportion compared to the practice in other countries such as; in India 25.4% (Jyothi and Babu, 2012), Korean hospitals 66.5% (Lee et al., 2009), and Victorian Hospitals 2.7% (Marion et al., 2002). This, in

turn, implies that there is a low practice of culture and sensitivity prescription in this study setting given the fact that there is no unit to do culture and sensitivity.

More than half (60.6%) of the patient medication records in this study were found with an overall compliance of ceftriaxone use to national and international guidelines. The figure is lower than that obtained by a comparative retrospective study in Black lion and the same hospital which reported 71.4% and 73% appropriate use respectively. The difference could be explained by the smaller number of charts evaluated (63 charts from each hospital) and possibility of a narrow evaluation period covered in the earlier study. Though, decline of appropriate practices in the past five years would be of a concern that poses a question, the use of a less comprehensive tool in the past study might also, most likely, have resulted for tolerance of deviations against the STG considered, thus making up the figure higher. Yet, in Korean hospitals, a higher proportion of appropriate ceftriaxone utilization was reported (65.5%). This might be accounted for appropriate medical practice in korea and better methodology used (prospective study design) (Hyuck et al., 2009).

On the other hand, smaller figures of compliant ceftriaxone use were obtained by studies in Ayder referral hospital (Abebe et al., 2012) and Dessie referral hospital (Ayinalem et al., 2013) in Ethiopia, Victoria hospitals of Australia (Marion et al., 2002), an educational hospital in Iran (Shohrati et al., 2010) and Bumrungrad hospital of Thailand (Tapaneeyaku et al.,2000). The fact that the reports in Ayider and Dessie referral hospitals showed lower figure than the present evaluation might likely be due to the presence of experienced professionals as a permanent and contracted basis and access to various training packages in the study setting. In victoria hospitals, compliant use was lower probably because the study involved large number of (51) hospitals that might have different level of practice. The results from studies in Iran and

Thailand were lower possibly related to the small number of patients as well as wards involved in the studies in addition to outcome measures by the study in Thailand.

Highest proportion of ceftriaxone use was found in the medical ward accounting for 276(48.3%) patients followed by surgical ward (25.2%). The least percentage of admission (attendance) was to the emergency unit (4.7%). This shows that ceftriaxone is most utilized for therapeutic purposes (in various infections) and surgical cases (most of which were fractures and injuries to the bone and soft tissues) in adults. In contrary, most frequent noncompliant uses were noted in the emergency (66.7%) whilst the least was obtained in the medical ward (28.6%). Most of the deviation in the emergency was due to the overuse of the drug for diagnoses; AFI, wound, AGE, and bronchial asthma unparalleled to the guidelines' indication.

The use of ceftriaxone was most remarkable in pre-operative prophylaxis that composed of 225 (39.4%) patients. Of these, again, more than half (50.2%) were non-compliant to the guidelines taking of the top rank. Noncompliance to the same indication was also reported as a topmost by the study in Ayder referral hospital (Abebe et al., 2013). However, the proportion was lower (29.6%) when compared to our finding. The higher proportion of noncompliance use in pre-operative prophylaxis in our study setting might be ascribed for the reason that evaluation was based on both timing of initiation and duration. Accordingly, initiation of the first dose after surgery and continued use of the drug (more than a single additional dose) after a procedure were considered as unacceptable.

Nonetheless, the utilization of the drug long before procedures, additional single dose after procedures, or amount of dosage in the right timing were exempted as the guidelines allow flexibility and no consensus to a fixed cut point was found in the literature. Indeed, ceftriaxone

had also been prescribed in AFI, AGE, wound, bronchial asthma, bronchitis, stroke, and peptic ulcer disease for which it was not indicated in the guidelines. The lack of strong drug and therapeutics committee (DTC) and drug information center (DIC) in the hospital is also a factor for the observed noncompliance.

This study had used alternative means of drug interaction checker databases for detecting possible drugs that need caution while used along with ceftriaxone. Though all were similar in the format they present results, the level of significance of the interaction was commented quite differently across the databases. Warfarin, heparin and doxycycline were the drugs sought for more attention. The Medscape database recommended either to monitor patients or use alternatives during concurrent use of ceftriaxone and either of warfarin or heparin.

Other study has also documented that concomitant use of ceftriaxone with warfarin had elevated the international normalization ratio (Clark and Burns, 2011). This is likely because, ceftriaxone is supposed to act directly as anticoagulant or indirectly through eradication of intestinal/gut floras responsible for vitamin K production, a known endogenous blood coagulator. Maintenance fluids containing ringer's lactate were the top co-prescribed drugs which necessitate attention of possible calcium-ceftriaxone precipitation.

From the results of the binary logistic regression, it was found that the likelihood of compliant ceftriaxone use to the guidelines decreased among the patients stayed for 2-7days as well as those treated for free of charge (AOR; 0.582, 95%CI, 0.349-0.969 and AOR; 0.129, 95% CI, 0.047-0.351 respectively). The fact that nearly half of all the patients (48.2%) and most of the cases in emergency, surgical and gynecologic/obstetrics wards, where frequent deviation was noted, were admitted for 2-7 days justifies this association. Equally important, to this, is the

unlimited free access of police members and their families to get medical service at any time that queues weekends and off hours. For this reason probably, most of the patients admitted to/treated in the emergency are less likely to get prescribed with full duration of treatment and appropriate indication. On top of that, patients' preference for injectable drugs and not satisfied with painkillers/ analgesics, repeated emergency load in the weekends and prescribers' and dispensers' negligence to rational antibiotic uses are possible factors contributing for the less compliance in that scheme. Most of the patients (87%) in the present study were also treated as a free scheme which can have an effect for the observed negative association.

Among the wards, gynecologic/obstetrics (AOR; 3.228, 95% CI, 1.59-6.555), medical (AOR; 3.085, 95% CI, 1.436-6.624) and pediatrics (AOR; 5.205, 95% CI, 1.52-17.822) were found to predict a positive association of compliant ceftriaxone use to guidelines. This might be because; more number of professionals is involved in the respective wards making up of a multidisciplinary team in the patient care practice. Likely, the use of ceftriaxone among members of the federal (AOR; 8.521, 95% CI, 2.428-29.901) and regional police (AOR; 7, 95% CI, 1.973-24.833) was found to show a positive association compared to the members in the federal prison. This could, most likely, be attributed for the fact that majority of the patients were from the two commissions (44.3% Federal Police and 50.4% Regional police) compared against a few proportion (5.3% from Federal Prison).

In a similar study in Thailand, such factors as male gender (OR 0.51, CI 0.27-0.97), fever (OR 3.12, 95% CI 1.3-6.11), signs and symptoms of infections (OR 2.92, 95% CI 1.37-6.28), suspicion of sepsis (OR 7.90, 95% CI 3.67-17.07), and diagnosis of gastrointestinal tract infection (OR 0.20, CI 0.05-0.77) were reported to be associated with appropriateness of ceftriaxone usage (Angsana et al., 2011).

8. Limitations of the Study

Despite the more strength it adds to previous studies, this assessment was done based on a retrospective and cross sectional design. Furthermore, while outcome measures were totally ignored, potential factors as income level of patients, weight (except that used in pediatrics dose calculations), and cost of drugs that could possibly affect utilization of ceftriaxone in the hospital were not considered despite that service was free of charge for majority of the patients. The evaluation was relied, merely, on the medication records of patients/charts for which practices might have, actually, been different.

9. Conclusion

This study has shown that less than half proportion (44.3%) of patients admitted to Federal police referral hospital has been prescribed with ceftriaxone. An overall evaluation of its utilization in terms of indication, frequency, dosage and duration has revealed that there was a lower compliance to national and international guidelines as compared to the finding in 2009. Prescribing practices in pre-operative prophylaxis, ceftriaxone indication in certain diagnoses and duration of therapy in medical cases were the top areas that demand improvement. The study has, also, identified few drugs with potential drug-drug interaction. Close monitoring of patients who concomitantly use ceftriaxone with either warfarin or heparin and avoiding of co-administering ceftriaxone with ringer's lactate solution must be practiced. Compliant ceftriaxone use to national and international guidelines in FPRH was associated with days of hospital stay, type/payment scheme of medical service and type of ward patients were admitted to.

10. Recommendations

Based on the findings obtained in this study, we like to forward the following recommendations.

1) Follow up and strengthening of the DTC as well as establishing of a DIC in the hospital must be a concern of the Federal Police Commission Health Service Directorate. The EFMHACA and the Federal Ministry of Health (FMOH) must also take the lead to ensure narrowing of this gap.
2) Selective and Ongoing educational trainings and seminars especially that focus on rational drug use, AMR, ADEs and DDI must be given to the health professionals of the hospital. While this could, primarily, be initiated and coordinated by the pharmacy department as well as the medical logistics office, supervision and support is immensely important from higher stakeholders (FPCHSD, FMOH & EFMHACA).
3) Our result showed that there was a considerable inconsistency and variation of ceftriaxone use in pre-operative prophylaxis, certain cases in the emergency and overall duration of therapy to guidelines. One reason could be that the Ethiopian STG (for general hospitals) was limited to provide adequate information about all cases and all antimicrobials. The hospital is better to prepare its own treatment guideline and standard operational procedures for some cases.
4) EFMHACA should prepare a standard treatment guideline for referral hospitals. It has also to revise the 2010 STG for general hospitals as it was limited only to certain indications unlike other guidelines and it doesn't mention ceftriaxone as an alternative in surgical prophylaxis.
5) Continuous and periodic drug use evaluations that involve other selective drugs, especially, by the hospital DTC must be enhanced. To know more about the magnitude

and direction of the problem, future prospective evaluations considering all aspects that lacked in this study are also important.

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Annex I; International Guidelines and Recommendations

Prophylactic Use of Ceftriaxone

Prophylaxis refers to the prevention of an infection and can be characterized as primary prophylaxis, secondary prophylaxis, or eradication. Primary prophylaxis refers to the prevention of an initial infection. Secondary prophylaxis refers to the prevention of recurrence or reactivation of a preexisting infection. Eradication refers to the elimination of a colonized organism to prevent the development of an infection (ASHP, 2013). For the purpose of this study, only primary prevention will be assumed while considering compliance of the hospital's practice to recommendations.

Ceftriaxone is recommended as a preoperative prophylaxis at a dose of 2g with metronidazole for adults with age of 19 years and above and 50-75mg/kg for pediatrics aged 1-18 years. The updated American guidelines do not address its use in newborns (premature and full term) infants. Moreover, dose adjustment in renal and hepatic dysfunction is not necessary according to the guidelines when the drug is given as a single dose before surgery (ASHP, 2013).

The overall administration of first dose of most prophylactic antimicrobials is recommended to begin within 60 minutes before surgery as many controlled studies support (Bratzler and Houck, 2004; Steinberg et al., 2009; Weber et al., 2008). Consideration is given for medications that have extended times of infusion (e.g. fluoroquinolones and vancomycin) and it is recommended that these agents be started within 120 minutes before surgical incision. Likely, duration of antimicrobials in surgical prophylaxis should be less than 24 hours though the shortest effective time is not well known.

The postoperative administration of antimicrobials is not recommended by any of the four professional society guidelines of America (American Society of Health-System pharmacists (ASHP), Infectious Diseases Society of America (IDSA), Surgical Infection Society (SIS), and Society of Healthcare Epidemiology of America (SHEA)). The guidelines also use many literature evidences to support this argument (Bratzler and Houck, 2004; Dipiro et al., 1986; Fonseca et al., 2006; McDonald, 1998). An exception to this is cardiothoracic procedures for which prophylaxis duration of up to 48 hours has been accepted without evidence and merely based on expert panel consensus (Fred et al., 2006).

Therapeutic Use

Ceftriaxone is mentioned to be used in many specific diagnoses of suspected bacterial infections which are not explicitly defined in the standard treatment guidelines (STG) of Ethiopia. The therapeutic recommendations reviewed to this part are those diagnoses often encountered in Ethiopian hospitals but not addressed in the guideline to be treated by ceftriaxone. At the last paragraph of this section, however, a summary of the Ethiopian STG is presented.

Ceftriaxone, in combination with other antibacterial agents, can be used in empiric treatment of bacterial brain abscesses and other CNS infections (e.g., subdural empyema, intracranial epidural abscesses) caused by gram-positive aerobic cocci, Enterobacteriaceae (e.g., *E. coli*, *Klebsiella*), and/or anaerobic bacteria (e.g., *Bacteroides*, *Fusobacterium*). The dose for adults with meningitis, brain abscess and other CNS infections is 2g every 12 hours. While 7 days may be adequate for uncomplicated cases caused by susceptible *H. influenzae* or *N. meningitis*, 10–14 days is suggested for complicated cases or cases caused by *S. pneumoniae* and >21 days is suggested for meningitis caused by susceptible Enterobacteriaceae (e.g., *E. coli*, *Klebsiella*).

The general recommended dosage for pediatrics and children aged above one month is 80-100mg/kg every 12 to 24 hours (Tunkel et al., 2004; AHFS, 2008).

Similarly, intra-abdominal bacterial infections, like spontaneous bacterial peritonitis (SBP) are reported as major problems in patients with cirrhosis and acute gastrointestinal hemorrhage, occurring in between 25% and 65% of patients with gastrointestinal bleeding (Rimola et al., 1985; Hou et al., 2004). Studies show that the incidence is high particularly among patients with advanced cirrhosis and/or severe hemorrhage (Deschenes and Willeneuve, 1999; Bernard et al., 1999). While antibiotic prophylaxis is implied in such situations, ceftriaxone has been recommended to be a drug of choice in patients with gastrointestinal bleeding for preventing infection (Rimola et al., 2000; Wong et al., 2005; Garcia-Tsao, 2001) and decrease the rate of re-bleeding (Soares-Weiser et al., 2002) compared to other options like Norfloxacin (Fernandez et al., 2006).

However, in case of recurrent SBP, since it is uncertain whether prophylaxis should be continued without interruption until liver transplantation or death in all patients, the administration of Norfloxacin (400 mg/day, orally) is suggested as a prophylactic antibiotic (EASL, 2010). Nonetheless, Ceftriaxone is also indicated in upper gastro intestinal bleeding to reduce development of infections associated with esophageal variceal hemorrhage as a major complication of chronic liver disease (Garcia-Tsao et al., 2007).

Acute pyelonephritis is an infection of the upper urinary tract; specifically the renal parenchyma as well as renal pelvis occurring secondary to bacterial ascent through the urethra and urinary bladder. The causative agent for more than 80% of the cases reported was *E. coli* (Stam and Hooton, 1993). The IDSA guidelines recommend the use of extended spectrum cephalosporin

as alternative treatments (Waren et al., 1999). Accordingly, ceftriaxone 1-2 g is administered with or without an aminoglycoside for adult patients. For patients with mild pyelonephritis and have dramatic response to therapy, five to seven days of treatment is comparable to 14 days (Waren et al., 1999; Bailey, 1994). However, adults younger than 60 years without obstruction, renal abnormality or prostatitis respond well to 14 days of therapy relative to those with such conditions that require a longer duration of treatment (Bergeron, 1995).

Other therapeutic indications of ceftriaxone for hospitalized patients include; in cases of chronic obstructive pulmonary disease (COPD) (Fein, 2000; Melissa and Dana, 2001), complicated and uncomplicated extra-biliary intra-abdominal infections (Joseph et al., 2010), infective endocarditis (Fauci et al. 2008) as well as bone and soft tissue infections (Catherine et al., 2011; AHFS, 2008).

In cases when excellent bioavailability is obtained and patients' conditions allow, the conversion of a parenteral antimicrobial therapy to oral form reduces length of hospital stay and cost of care (Timothy et al., 2007). As a step down therapy for patients who have been on ceftriaxone, the usual recommended oral forms are cefpodoxime and cefuroxime axetil. Though oral therapy can be used in treating variety of infections, there are occasions that require only parenteral administration due to severity or site of infection. These include endocarditis, meningitis, brain abscess, orbital cellulitis, other central nervous system infections, osteomyelitis, and endophthalmitis (AHFS, 2008).

The Ethiopian standard treatment guidelines for primary and general hospitals have also mentioned the therapeutic use of ceftriaxone in the following cases; bacillary dysentery, meningitis due to known/ unknown etiology, pneumonia due to known/ unknown etiology,

typhoid fever, diabetic foot ulcer, neonatal meningitis, acute epididymitis, chancroid, neurosyphilis, gonorrhea, orbital cellulitis, neonatal conjunctivitis, cellulitis, acute pelvic inflammatory disease, post aborted/ puerperal sepsis, sepsis and sexual assault (DACA, 2010). The specific doses, frequency of administration, and duration of therapy for each of the above diagnosis is contained within the data collection format.

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Annex II; Data Abstraction Format

Data Collector Initials; …….Drug……

In Gram	Daily dose	
In Days	Duration	
Mention here	Basic Lab Tests	
In Years /Months	Age	
	Sex	
Write any of 'P' for prophylactic; or 'T' for therapeutic	Reason for use	
Mention here	Other drugs	
Mention here	comorbidities	
	Days hos. stay	
Mention here	Source ward	
Write "S" for specific; "E" for empiric (Result & pathogen if specific)	Therapy type	
Write either as ''Free'' for members and their families and "paid" for relatives, prisoners	Service type	
Write either as "on job members", "retired members" , " family" or "relative" for eligibility	Eligibility	
Write either as "FP" , "RP" or "FPr" for members, their family or relative***	Membership	
Write "military", "civil'' or "other "for members, families or relatives ****	Military status	

Indicators	Criteria		**Patient n**
Indication	1. Stool Culture documented bacillary dysentery	1.	y/n
	2. Meningitis due to unknown etiology	2.	y/n
	3. Meningitis due to specific organism *(N.meningitis, S.pneumonia* resistant to B.pencillin and *H.influenza* resistant to Chloramphenicol, *P. aeruginosa & Enterobacteriaceae)*	3.	y/n
	4. Pneumonia due to common organism (Gram stained sputum)	4.	y/n
	5. Pneumonia due to specific organism (*P. aeruginosa, Enterobacteriaceae)*	5.	y/n
	6. Typhoid fever	6.	y/n

	7. Diabetic foot ulcer	7.	y/n
	8. Neonatal meningitis resistant to other antibiotics	8.	y/n
	9. Acute epididymitis	9.	y/n
	10. C &S confirmed Chancroid	10.	y/n
	11. Neurosyphilis	11.	y/n
	12. Gonorrhea	12.	y/n
	13. Neonatal conjunctivitis	13.	y/n
	14. Orbital cellulitis	14.	y/n
	15. Moderate to severe preseptal cellulitis	15.	y/n
	16. Acute Pelvic inflammatory disease	16.	y/n
	17. Post abortal /puerperal sepsis	17.	y/n
	18. Sexual assault	18.	y/n
	19. Child abuse	19.	y/n
	20. Sepsis	20.	y/n
	21. UTIs (pyelonephritis, cystis…)	21.	y/n
	22. Upper gastrointestinal bleeding in patients with cirrhosis and liver abscess	22.	y/n
	23. Preoperative prophylaxis	23.	y/n
	24. Brain abscess and other CNS infections	24.	y/n
	25. Infective endocarditis due to different pathogens	25.	y/n
	26. Acute otitis media	26.	y/n
	27. Bone and joint infections	27.	y/n

Dose	1. Adult ;1-2g , children;20-50 mg/kg/day	1.	y/n
	2. Adult 4g/day; children 80-100 mg/kg	2.	y/n
	3. Adult 4g/day; children 80-100 mg/kg	3.	y/n
	4. Adults 2g/day;	4.	y/n
	5. Adults 2-4g/day	5.	y/n
	6. Adult; 1g/day, children; 20-50mg/kg/day	6.	y/n
	7. Adults 1-2g/day	7.	y/n
	8. Pediatrics Max. 4g/day	8.	y/n
	9. Adults 250mg	9.	y/n
	10. Adults 250 mg	10.	y/n
	11. Adults 2g/day	11.	y/n
	12. Adults 250mg; pediatrics 125 mg	12.	y/n
	13. Pediatrics Max. 125mg/kg	13.	y/n
	14. Adults;1-2 g/day, children; 40mg/kg/day	14.	y/n
	15. Adults;1-2 g/day, children; 40mg/kg/day	15.	y/n
	16. 1g/day	16.	y/n
	17. Only adults 1g/day	17.	y/n
	18. Both adults and pediatrics 125 mg	18.	y/n
	19. Children 125-250mg	19.	y/n
	20. Adult;1-2g/day, children; 20-50mg/kg/day	20.	y/n
	21. Adult; 1-2g in single or equally divided doses	21.	y/n
	22. Adults ;1-2g in single or equally divided doses	22.	y/n
	23. Adults; 1-2g; pediatrics 50-75mg/kg 1hr before surgery	23.	y/n
	24. Adults; 2g	24.	y/n
	25. Adults; 2g	25.	y/n
	26. Pediatrics; 50mg/kg	26.	y/n
	27. Adults; 2g; pediatrics; 50-100mg/kg	27.	y/n

Frequency	1. Single or 2 divided doses im /slow iv,	1.	y/n
	2. Two divided dose iv	2.	y/n
	3. Two divided doses iv	3.	y/n
	4. Single/two divided doses iv/im	4.	y/n
	5. Two divided doses	5.	y/n
	6. Both adults &children ; single/two divided doses im/iv,	6.	y/n
	7. Two divided doses iv/im	7.	y/n
	8. Two divided doses	8.	y/n
	9. Single dose im	9.	y/n
	10. Single dose im	10.	y/n
	11. Single dose iv/im	11.	y/n
	12. Adults and pediatrics; Single dose im;	12.	y/n
	13. Single dose im	13.	y/n
	14. Two divided doses iv	14.	y/n
	15. Two divided doses iv	15.	y/n
	16. Single dose iv	16.	y/n
	17. Single dose iv	17.	y/n
	18. Single dose im	18.	y/n
	19. Single dose im	19.	y/n
	20. Single dose or two divided doses im/ slow iv	20.	y/n
	21. Single or two equally divided doses	21.	y/n
	22. Single or two equally divided doses	22.	y/n
	23. Single dose	23.	y/n
	24. Single or two equally divided doses	24.	y/n
	25. Single or two equally divided doses	25.	y/n
	26. Single dose	26.	y/n
	27. Single or two divided doses	27.	y/n

Duration	1. Stat	1.	y/n
	2. 7-10 days*	2.	y/n
	3. 7-21days*	3.	y/n
	4. 7 days	4.	y/n
	5. 7-10 days*	5.	y/n
	6. Adult; 5-7 days*, children; one day	6.	y/n
	7. 7-10 days*	7.	y/n
	8. 14-21 days*	8.	y/n
	9. 10 days	9.	y/n
	10. Stat	10.	y/n
	11. 10-14 days*	11.	y/n
	12. Stat (both)	12.	y/n
	13. Stat	13.	y/n
	14. 14 days	14.	y/n
	15. 10-14 days*	15.	y/n
	16. 10-14 days*	16.	y/n
	17. 7-10 days*	17.	y/n
	18. Stat	18.	y/n
	19. Stat (both)	19.	y/n
	20. 7-10 days*	20.	y/n
	21. 5-14 days*	21.	y/n
	22. 5-14 days*	22.	y/n
	23. Stat**	23.	y/n
	24. 7-21 days or more*	24.	y/n
	25. 21-28 days*	25.	y/n
	26. Stat	26.	y/n
	27. 14-28 days*	27.	y/n

If Noncompliance occurs in any of the above cases, possible reasons could be due to;		
1. Ceftriaxone was used for diagnoses other than it is recommended (Name Asst.)	**1**	
2. Wrong dosage used without justification of both renal & liver function tests	**2**	

3. Dosage in pediatrics was not based on Weight/ guidelines' recommendation	**3**	
4. Wrong frequency was used without justification	**4**	
5. Step down switch of ceftriaxone treatment was made to wrong drugs	**5**	
6. Step down switch of ceftriaxone was made in cases not recommended by the guidelines(*endocarditis, meningitis, brain abscess, orbital cellulitis, other central nervous system infections, osteomyelitis, and endophthalmitis)*	**6**	
7. Overall therapeutic duration of ceftriaxone treatment was not based on the guidelines	**7**	
8. Therapy continued while C&S result showed resistance	**8**	
9. Any else……..…….	**9**	

* Duration may vary depending on severity of infection and immune system (response to therapy) of the patient. **additional doses might be used in longer procedures or special reasons. ***Family or relative classification is based on members' attribute to FP, Federal Police; RP, Regional Police; FPr, Federal Prison.****Military status classification is based on employment to police.