EVALUATION OF CEFTRIAXONE UTILIZATION IN MEDICAL AND EMERGENCY WARDS OF TIKUR ANBESSA SPECIALIZED HOSPITAL

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A thesis submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University in partial fulfillment of Master of Pharmacy degree in Pharmacy Practice

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School of Graduate Studies

This is to certify that the thesis prepared by Alemayehu Sileshi entitled "*Evaluation of ceftriaxone utilization in medical and emergency wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia"* and submitted in partial fulfillment of the requirements for the degree of Master of Pharmacy in Pharmacy Practice (M.Pharm) complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Abstract

Evaluation of ceftriaxone utilization in medical and emergency wards of Tikur Anbessa Specialized hospital

By: Alemayehu Sileshi

Addis Ababa University, 2015

Background: Ceftriaxone is one of the most commonly used antibiotics due to its high antibacterial potency, wide spectrum of activity and low potential for toxicity. The global trend shows misuse of this drug.

Objective: This study was conducted to evaluate the appropriateness of ceftriaxone use in medical and emergency wards of Tikur Anbessa Specialized Hospital (TASH).

Methods: A prospective cross-sectional study was conducted by reviewing medication records of 314 patients who received ceftriaxone during hospitalization at TASH between February 1 and June 30, 2014. Drug use evaluation (DUE) was conducted to determine whether ceftriaxone was being used appropriately based on six criteria namely indication for use, dose, frequency of administration, duration of treatment, drug-drug interaction (DDI) and culture and sensitivity (C&S) test. The evaluation was made as per the protocol currently developed. Additionally, areas which need intervention were identified and interventions were implemented.

Results: The prescribing rate of ceftriaxone was found to be very high (58% point prevalence). Ceftriaxone use was empiric in 274 cases (87.3%) and specific in 5 cases (1.6%). The most common indication for ceftriaxone use was pneumonia; observed in 110 cases (35.0%). The most common daily dosage, frequency of administration and duration of treatment with ceftriaxone were 2g (88.9%), twice-daily (98.4%) and 8-14 days (46.2%), respectively. Inappropriate use of ceftriaxone was observed in most cases

(87.9%), the greatest proportion of which was attributed to inappropriate frequency of administration (80.3%), followed by absence of C&S test (53.2%).

Conclusions: This study revealed that the inappropriate use of ceftriaxone was very high in the medical and emergency wards of TASH. This may lead to emergence of resistant pathogens which in turn lead to treatment failure and increased cost of therapy. Therefore, adherence to current evidence-based guidelines is recommended.

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

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List of Abbreviations

ARH	Ayder referral hospital
C&S	Culture and sensitivity test
CDC	Centers for disease control and prevention
CI	Confidence interval
DDD	Defined daily dose
DDI	Drug-drug interaction
DIC	Drug information center
DRH	Dessie referral hospital
DTC	Drug and therapeutic committee
DUE	Drug use evaluation
E. cloacae	Enterobacter cloacae
E. coli	Escherichia coli
ESC	Extended-spectrum cephalosporin
et al.	And other authors/colleagues
FHRH	Felege Hiwot referral hospital
FMHACA	Food, medicine and healthcare administration and control authority
GRASP	Gonococcal resistance to antimicrobials surveillance programme
ICU	Intensive care unit
INR	International normalized ratio
MDR	Multi-drug resistant
MIC	Minimum inhibitory concentration
No	Number
OR	Odds ratio

p	p – value
PBPs	Penicillin-binding proteins
PH	Police hospital
PO	Orally
POSGH	General Hospital, Port of Spain
r	Spearman correlation coefficient
RTI	Respiratory tract infection
SD	Standard deviation
Spp	Species
STG	Standard treatment guideline
TASH	Tikur Anbessa Specialized hospital
USA	United States of America
UTI	Urinary tract infection
vs	Versus
WHO	World health organization

1. INTRODUCTION

1.1 Background

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 it was developed for clinical use. It is commercially available as the disodium salt (Figure 1) (Diego *et al.*, 2010). Its bactericidal activity results from inhibition of bacterial cell wall synthesis. It does so by binding to cell wall synthesis enzymes known as penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested (Lullmann *et al.*, 2005; Katzung, 2006).

It 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 temperatures. Accordingly, ceftriaxone for injection reconstituted with water to a concentration of 100 mg/mL, was chemically stable for at least 4 days when stored at temperature 23 ± 2 °C under presence and 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 $C_{18}H_{16}N_8Na_2O_7S_3 \bullet 3.5H_2O$. It has a calculated molecular weight of 661.60 and the following structural formula (Yue & Shen, 2012).

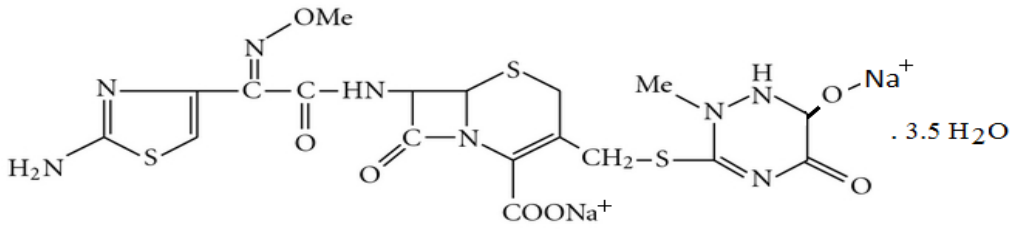

Figure 1: Chemical structure of ceftriaxone

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 (Yue & Shen, 2012).

Ceftriaxone is one of the cephalosporins, and this class of drugs is the most widely used antibiotics for treating common infections. The cephalosporins are a large group of related beta-lactam antimicrobial agents with broad-spectrum of activity, low rates of toxicity and ease of administration. Various cephalosporins are effective for treatment of many conditions, including urinary tract infections (UTI), pneumonia, skin, soft tissue, bone and joint infections, bacteraemia, sepsis, typhoid fever and meningitis (Babu & Jyothi, 2012). These class of antibiotics are classified by "generation"; first, second, third, fourth and fifth. In general, lower-generation cephalosporins have more gram-positive activity and higher-generation cephalosporins have more gram-negative activity (Harrison & Bratcher, 2008).

1.2 Statement of the problem

Antimicrobial agents are among the most commonly used and misused of all drugs (Meer & Gyssens, 2001; Pereira *et al.*, 2004). Despite strenuous efforts to control their use and promote optimal prescribing, practitioners still continue to prescribe excessively. But, 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 (Davey *et al.*, 2006; Mickael & Mulugeta, 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 (Gururaja *et al.*, 2013). In turn, antibiotic resistance is a major factor contributing to increased morbidity and mortality of patients as well as cost of medical care. It was indicated in the work of Lee *et al.* (2009) that antimicrobial drug resistance has been projected to add between $100 million and $30 billion annually to health-care costs. In line with this, it was cited in the work of Ayinalem *et al*. (2013) that the inappropriate use of ceftriaxone caused, worldwide, an annual cost of $4-5$ million pertaining to infection caused by antibiotic resistant bacteria. The other study conducted in Spain regarding the use of third generation cephalosporins, wherein ceftriaxone was the most frequently prescribed agent, found out that the cost of inappropriate antibiotic use was twice as much for patients who were treated appropriately (Pereira *et al.*, 2004).

Studies indicate that the problem of antibiotic resistance has noticeably worsened in Ethiopia during the past several years. In line with this, assessment conducted by Food, Medicine and Healthcare Administration and Control Authority of Ethiopia (FMHACA) (2009) has shown that there is not only higher utilization but also irrational use of antibiotics. This in turn is also associated with fueling an ever-increasing need for new drugs. Therefore, prudent prescribing of antimicrobial drugs is essential as it may reduce incidences of antimicrobial drug resistance (Ibrahim *et al*., 2012).

Ceftriaxone is one of the most commonly used antibiotics due to its high antibacterial potency, wide spectrum of activity and low potential for toxicity (Lee *et al*., 2009). 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 UTIs, 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). For example, the study done at General Hospital, Port of Spain (POSGH) from January to June 2000 indicated that higher percentage (58%) of ceftriaxone was prescribed for the treatment of RTI (Pereira *et al.,* 2004). This is comparable with the finding of the study done in 10 Victorian hospitals of Australia, where treatment of RTI with ceftriaxone accounted for 52% (Robertson *et al*., 2002). It is also comparable with the finding of the study done in the medical wards of TASH in which treatment of RTI with ceftriaxone accounted for

58.1% (Ayele, 2013) .The other suggested reason for its increased use is pertained to its low toxicity profile although it may occasionally result in injection site pain, hardness and other side effects such as headache, unusual bleeding, red pinpoint spots under the skin, pale or yellowed skin, dark colored urine, weakness, urinating less than usual, seizure, swelling of tongue, vaginal itching or discharge, hemolytic anemia (Bell *et al*., 2005), biliary pseudolithiasis (Ceran *et al.*, 2005), drug-induced toxic hepatitis (Peker *et al.*, 2009) and neurotoxicity (Kim *et al.*, 2012).

As far as our experience is concerned, there is no prospectively conducted and published study aimed at the evaluation of ceftriaxone utilization in Ethiopia. The retrospective studies conducted regarding this issue are only few. For example, one of such studies was conducted to comparatively evaluate the use of ceftriaxone in Police hospital (PH) and TASH (Mickael & Mulugeta, 2009). But, it was retrospectively done and hence lacks the advantage of making intervention during the course of treatment with this drug besides the possible lack of complete data while reviewing patient medical records. Additionally, this study involved only a small sample size of 63 cases and this therefore minimizes its representativeness to the target population. On the other hand, some of the other local retrospective studies done regarding ceftriaxone utilization did not consider duration of treatment and C&S test as criteria. Furthermore, they focused on a specific department, most notably the department of internal medicine. Therefore, the present study overcame these limitations of the previous studies by using improved study design (prospective cross-sectional study). The study design of the present study also enabled it not to suffer from incompleteness of data. Besides, relatively larger sample size was used compared to the previous study done at TASH (314 vs 63). Furthermore, all wards of the internal

medicine and emergency departments were included to enhance the generalizability of the study findings. The appropriate hospital that can indicate the practice of ceftriaxone utilization in Addis Ababa is TASH as it is the biggest and oldest teaching, tertiary, referral hospital where numerous infectious cases present. Thus, this study was designed to evaluate the utilization of ceftriaxone at TASH.

1.3 Literature review

1.3.1 Trend in ceftriaxone utilization practices

1.3.1.1 Global trend

Drug utilization studies are a pre-requisite for the formulation of drug policies. Irrational use of medicines is widespread throughout the world, particularly the antimicrobials including ceftriaxone (Sapna *et al.,* 2012). Evidences regarding prescribing rate and appropriateness of ceftriaxone utilization are presented as follows.

There are a number of studies which show an increased ceftriaxone use and hence potential for antibiotic resistance to occur. For example, a study conducted in Besancon hospital of France indicated that the utilization rate of ceftriaxone, expressed in defined daily dose (DDD)/1000 patient days, shows increment from 22.02 in 1999 to 32.03 in 2002 (Muller *et al.*, 2004). Another surveillance study conducted in four Singapore public hospitals from 2006 to 2008 also showed an increased prescription of ceftriaxone (Hsu *et al.,* 2010). A similar result was found from a prospective study conducted in the surgical post-operative wards of Ambedkar Medical College of Bangalore, from June to August, 2012. According to the finding of this study, cephalosporins were the most commonly prescribed antibiotics; observed in 67 cases (46.85%). Among the

cephalosporins, it was ceftriaxone that was the most frequently prescribed; observed in 34 cases (23.77%) (Sapna *et al.*, 2012), implying widespread use of this drug. Similarly, the study conducted at POSGH indicated that ceftriaxone was the most widely used agent among the other cephalosporins in which 66% of studied patients received it (Pereira *et al.*, 2004).

In a prospective interventional study conducted at one of a high complexity teaching hospitals of Brazil, it was found out that ceftriaxone was the antibiotic most prescribed in both pre-intervention and intervention periods; observed in 23.4% and 21.6% of cases, respectively (Rodrigues *et al.*, 2013). Similarly, in a cross-sectional study conducted at the University hospital of the West Indies it was found out that 45 patients (41.3%) received prophylactic antibiotics, wherein ceftriaxone was the most commonly prescribed agent (31.7%), followed by metronidazole (19.0%) (Chin *et al.*, 2010). Additionally, the European surveillance of antimicrobial consumption project which collected data on 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). Similarly, the study conducted at one of the rural hospitals in USA revealed that ceftriaxone was the second most frequently used antibiotic, in which it accounted for 19% of the total antibiotics used during the study period following quinolones (26%), antibiotics most commonly prescribed during the study period (Mylotte & Weislo, 2000).

Evaluation of ceftriaxone utilization can also be made possible by assessing the level of its appropriate usage. Among studies conducted this way was a prospective study done at 10 university hospitals in Korea from February 1 to June 30, 2006 among 400 patients

who received ceftriaxone. The finding from this study indicated that the inappropriate use of ceftriaxone was 34.5%, implying a potential for emergence of drug resistance. This study also indicated that inappropriate C&S tests prior to the initial ceftriaxone dose accounted for 33.5% and inappropriate duration of therapy with this drug accounted for 42.8% (Lee *et al.*, 2009). Likewise, the result from a study conducted in the emergency room of a University hospital in Thailand from April 1 to May 31, 2010 found out the inappropriate use of this drug to be 41.7% (Phuphuakrat *et al.*, 2013). But, the inappropriate use of ceftriaxone was found to be very high in the study done to evaluate the utilization trend of this drug in Iran. This study indicated that of the 300 patients enrolled, 34% received ceftriaxone for infection treatment wherein 85.3% were not according to the protocol prepared for DUE of this drug (Shohrati, 2010).

Previous studies also showed the utilization pattern of this drug in terms of the frequency of its prescribing by specialty. Among these studies, a retrospective drug utilization review conducted from April to June 2010 in North Bay regional health centre indicated that ceftriaxone was more frequently prescribed by specialists at the emergency department than those at the other (Mohamed, 2010). But, studies showed that irrational prescribing of drugs is more prevalent at the emergency department as compared to other wards (West *et al.*, 2012).

Appropriateness of antibiotic use can also be evaluated in terms of cost of the antibiotics used. Among others, cost reduction in treatment with antibiotics can be achieved by switching parentral antibiotics to either equivalent oral antibiotics or antibiotics of narrow-spectrum and low cost. In line with this, a study conducted in the inpatient pediatric division of Johns Hopkins hospital indicates that there was estimated annual

cost saving of $18,618 by changing ceftriaxone to cefotaxime (Lee & Glenn, 1995). In the setting of TASH although cefotaxime is less available, other equivalent switching should be made to achieve cost minimization. As far as treatment with ceftriaxone is concerned, cost minimization can also be achieved by practicing the once-daily administration of this drug for most of its indications. For example, an interventional study done in USA by Wade and McCall (1995) with the aim of assessing the pharmacoeconomic impact of inappropriate ceftriaxone use found out that a significant number of patients received a twice-daily dosing of ceftriaxone while they were supposed to receive a once-daily dosing regimen. This study indicated that the once-daily dosing of ceftriaxone instead of twice-daily dosing, where appropriate, resulted in cost savings in excess of $25,000. There are evidences which show the effectiveness of the once-daily administration of this drug. For instance, the study conducted in Japan among adults found out that the once-daily administration of ceftriaxone even at a dose of 0.5g is effective on various infecting organisms (Iida *et al.*, 2009). The finding of this study was consistent with the result obtained from the other study conducted in Japan among the pediatrics, in which the estimated pharmacokinetic/pharmacodynamic result confirmed the appropriateness of once-daily dose of 20 mg/kg (Iida *et al.*, 2011).

1.3.1.2 Local trend

In Ethiopia, studies show that the consistency of ceftriaxone prescription to the national standard treatment guideline was found to be low. One of the evidences in line with this statement is a comparative retrospective DUE of ceftriaxone conducted at PH and TASH in 2009. The finding from this evaluation reveals that ceftriaxone was correctly prescribed for 45 cases (71.4%) and 46 cases (73%) out of 63 cases in TASH and PH,

respectively. It was also indicated in this study that among the drugs co-administered with ceftriaxone, ringer lactate IV comprises 40.9% and 44.4% possible potential for interaction in TASH and PH, respectively (Mickael & Mulugeta, 2009). Although the study involved small sample size which may affect its representativeness, one can clearly see the presence of misuse of ceftriaxone at both hospitals.

Similarly, the retrospective study conducted among 296 patients at Ayder referral hospital (ARH), Mekelle, Ethiopia from July to September, 2011 found out the inappropriate use of this drug in 64.2% of cases (Abebe *et al.,* 2012). A close result was obtained from the other retrospective DUE of ceftriaxone conducted at Dessie referral hospital (DRH), Dessie, Ethiopia from December to January, 2013. Among the 316 cases included in this study, it was found out that 146 cases (46.2%) received inappropriate treatment with ceftriaxone. It was also indicated in this study that most inappropriate uses were seen in terms of duration of treatment (43.3%) in case of pneumonia followed by frequency (24%) for the treatment of meningitis (Ayinalem *et al.,* 2013). In both studies, the evaluation of ceftriaxone use was made as per the standard treatment guideline (STG) of Ethiopia. The results from these studies indicate the presence of a significant inappropriate use of the drug implying a potential for the emergence of drug resistance.

Other local studies also show that this drug is being used at an increasing rate compared to the other antibiotics. One of such studies was a retrospective antimicrobials use evaluation conducted in Arba Minch hospital, Arba Minch, Ethiopia from 20-28 May 2012 among patients admitted to the medical ward. This study indicated that ceftriaxone was the most commonly prescribed drug among the other antibiotics (19.3%) followed by

penicillin G (12.0%) (Chelkeba, 2013). But, there are bodies of evidences which show the increase in antibiotic resistance with increased use of antibiotics (Davey *et al.*, 2006).

1.3.2 Emergence of microbial resistance against ceftriaxone

Development of new antimicrobial drugs is an essential component in the effort to remain ahead of emerging microbial resistance. However, when new antibiotics are used with unrestrained enthusiasm, a predictable consequence is the further expansion of resistance. It is indicated in the work of various scholars that the emergence of resistance against third-generation cephalosporins and hence of ceftriaxone is of great concern, although neither the risk factors for resistance nor its real impact on mortality have been well defined (Dancer, 2001; Ariza *et al*., 2012). Resistance against ceftriaxone is increasingly emerging as a consequence of irrational use of the drug as can be evidenced by the following study results.

In the study done in the USA from 1996 - 1998, it was found out that the prevalence of ceftriaxone-resistant Salmonella was 0.1% (1 of 1326) in 1996, 0.4% (5 of 1301) in 1997, and 0.5% (7 of 1466) in 1998 *(*Dunne *et al.*, 2000). Thus, as it can obviously be seen from the statistical evidences of this study, the prevalence of ceftriaxone-resistant Salmonella increased with advance in time. The emergence of resistance to ceftriaxone was also studied among the clinical strains of E. cloacae. One of such studies is the one that was conducted in Besancon hospital of France from 1999 to 2002. The findings from this study indicate that the proportion of E. cloacae isolates resistant to extended spectrum cephalosporins (ESCs) increased from 24.3% to 29.6% ($p = 0.04$) during the study period. Within the subclass constituted by first-line ESCs, the proportion of

ceftriaxone increased from 64.3% to 77.6%. In this study, a moderate correlation was found between ceftriaxone use and frequency of resistance as the Spearman correlation coefficient (r) was found to be 0.46 ($p < 0.05$) (Muller *et al*., 2004).

Additionally, a number of studies conducted from 2006 to 2012 in different parts of the world reveal an increased emergence of resistance against ceftriaxone. One of such studies is the surveillance study which assessed the correlation of antibiotic prescription and resistance of gram-negative bacteria in Singaporean hospitals from 2006 to 2008. Accordingly, a significant resistance rate (21.7%) was seen among the E. coli isolates against this drug (Hsu *et al.*, 2010). Likewise, a significant drug resistance rate to ceftriaxone (64%) was found from a study conducted in Khartoum, Sudan among 214 MDR E. coli isolates (Ibrahim *et al*., 2012). The other study conducted in England and Wales, the gonococcal resistance to antimicrobials surveillance programme (GRASP) found out an increasing minimum inhibitory concentration (MIC) drift of the gonococcal population to ceftriaxone. The raise in MIC in turn indicates the emergence of a potentially therapeutically challenging phenotype (GRASP report, 2011). Similarly, an increase in MIC for ceftriaxone was reported by CDC, USA in August 2012. This report indicates that the percentage of samples of urethral Neisseria gonorrhoeae isolates exhibiting elevated MICs increased from 0% in 2006 to 0.4% in 2011 for ceftriaxone. The increase in MIC was observed throughout the study period. But, the elevation in MIC of the drug implies an increased resistance to it (CDC, 2012).

There are also studies conducted locally to assess microbial resistance against antibiotics including ceftriaxone. One of such studies assessed the drug resistance pattern of gram-negative bacteria isolated from nosocomial surgical site and blood stream infection

among operated patients at Felege Hiwot referral hospital (FHRH), Bahirdar, Ethiopia from October to January, 2010/2011. As per the result obtained from this study out of the 22 tested organisms, 18 (82%) were found to be resistant to ceftriaxone, which actually is a highly significant number (Mulu *et al.*, 2012).

From the evidences presented so far, it is clearly shown that there are both increased and inappropriate utilization of ceftriaxone. This may be one of the contributing factors for the increased emergence of ceftriaxone-resistant pathogens. This kind of practices may be associated with treatment failure and increased cost of therapy. It is, therefore, important to assess on the one hand, whether there is an increased utilization rate and on the other hand, whether there is a considerable inappropriate utilization of this drug in the setting of TASH and if so, in terms of which criteria and why.

2. OBJECTIVES

2.1 General objective

To evaluate the appropriateness of ceftriaxone use in medical and emergency wards of TASH, Ethiopia and thereby to compile baseline data outlining the appropriate use of this drug.

2.2 Specific objectives

- To assess the appropriateness of ceftriaxone use in terms of its indication for use, dosage of administration, frequency of administration, duration of treatment, interaction with other drugs (DDI) and the implementation of C&S test prior to the initiation of this drug.
- To assess the reasons behind the inappropriate utilization of ceftriaxone by making use of key informants.
- To identify key areas of intervention in relation to ceftriaxone use and thereby take action.

3. METHODS

3.1 Study setting

This study was conducted at the medical and emergency wards of TASH located in Addis Ababa, capital city of Ethiopia and Africa Union. TASH is one of the biggest tertiary referral government hospitals and it is administered under Addis Ababa University. This hospital offers diagnosis and treatment for approximately 370,000 - 400,000 patients a year. It is the biggest hospital in the city where resident, medical, clinical pharmacy and other health science students get their attachment for clinical practice. The hospital has 800 beds, 130 specialists and offers 24 hours service (Kaleab, 2014).

3.2 Study design and period

The criteria used for antibiotic selection in this study were antibiotic with a risk of abuse, one that is being used in high amounts in Ethiopian hospitals, and antibiotic that is likely causing resistance due to increased usage. Accordingly, ceftriaxone, a broad-spectrum parenteral cephalosporin was selected as it best fits the aforementioned criteria. A prospective cross-sectional study was conducted to carry out DUE by reviewing medical records for a total of 314 patients who received ceftriaxone between February 1 and June 30, 2014. The DUE was made as per the criteria of the currently developed protocol regarding the rationale use of this drug. The present study also involved making intervention regarding the inappropriate utilization of ceftriaxone.

3.3 Sample size and sampling method

Sample size was calculated using the single proportion formula at 95% confidence interval (CI) and P-value of 0.5.

$$n = [Z\ \alpha/2^2\ \mathrm{P}(1-\mathrm{P})]/d^2$$

$$n = [(1.96)^2\ (0.5)(1-0.5)]/(0.05)^2 = 384.16$$

When the above sample size was adjusted based on the total number of patients who were estimated to take ceftriaxone during the study period (N = 923; 430 from internal medicine department and 493 from the emergency department), the required minimum sample would be:

$$n_{final} = \frac{n}{1+\frac{n}{N}}$$

$$n_{final} = \frac{384.16}{1+\frac{384.16}{923}} = 271.3 \cong 272$$

Where

n is the minimum sample size required for very large population (≥10,000) (the non-corrected sample size)

N is the size of the source population

Z is the critical value for a given CI

P is expected proportion of correct ceftriaxone use (0.5 was considered as P = 0.5 gives a maximum sample for the desired CI)

d is margin of error

By adding 10% contingency, the final sample size would be 299. But, a relatively larger number of participants (314 patients) were included in the present study. This was obtained by enrolling all eligible patients who took ceftriaxone during the study period at the selected wards. A large sample size of 314 was considered to ensure its

representativeness. The issue of representativeness was well addressed as on the one hand, all units of the medical and emergency wards (both ICU and non-ICU) were included and on the other hand, all eligible patients were included in the study.

3.4 Population

3.4.1 Source population

All patients admitted to medical and emergency wards of TASH constituted the source population.

3.4.2 Study population

All in-patients in the medical and emergency wards of TASH admitted between February 1 and June 30, 2014 were taken as the study population.

3.4.3 Sample population

All in-patients admitted to medical and emergency wards of TASH between February 1 and June 30, 2014 and who satisfied the inclusion criteria constituted the sample population.

3.5 Inclusion and exclusion criteria

In-patients whose age are greater than or equal to 18 years were eligible provided that they took ceftriaxone during the study period at each of the selected wards.

On the other hand, patients who refused to participate in the study and patients with medical records of insufficient or illegible information were excluded.

3.6 Study variables

3.6.1 Independent variables

In this study, the independent variables include age, sex, department type, treatment type, diagnosis type, C&S test, indication for use, dose, frequency of administration, duration of treatment and DDI with ceftriaxone.

3.6.2 Dependent variable

The main dependant variable of this study is the appropriateness of ceftriaxone utilization.

3.7 Data collection and analysis

3.7.1 Instruments

Data abstraction format: 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 I) which was prepared for the purpose of this study. The content of the data collection format was designed to record department type, patient demographics, patient chart number, admission and discharge dates, working diagnosis, past medical history, physical examination, sign and symptoms, abnormal laboratory tests, abnormal diagnostic results, C&S results, information regarding administration of ceftriaxone including its indication, dose, frequency of administration, duration of therapy, reasons why it was inappropriately prescribed, any DDI with ceftriaxone and information regarding the other co-administered medications.

Key informant interview: data were also collected by interviewing 10 physicians practicing in the infectious disease unit of TASH. Additionally, 6 microbiologists practicing in the microbiology laboratory unit of this hospital were interviewed. They were selected based on their long time professional experience in the study area. Accordingly, consultant physicians, senior residents and MSc holder microbiologists were selected. The interview was made through self-administered questionnaire supplemented with clarification by the principal investigator (Annex III). The interview revolved around issues that stood out during chart review and patient follow-up, including among others, the reasons behind: why was C&S test not sent for investigation in most cases, why was ceftriaxone administered on a twice-daily basis in almost all cases, why was ceftriaxone being used at a very high utilization rate, why was ceftriaxone co-administered with drugs including ringers lactate, warfarin, and heparin and why was ceftriaxone used for prolonged duration of treatment without switching to oral antibiotics. These questions had also been addressed with most physicians during the data collection phase provided that the issue occurred in a given patient case. This in turn enabled the identification of possible range of responses and hence the final interview instrument was designed in to a semi-closed questionnaire. Similarly, the experiences of microbiologists 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

Three clinical pharmacists were employed for the purpose of data collection. Half-day training was given for the data collectors to familiarize them with the data abstraction format and thereby to facilitate the data collection process.

3.7.3 Data quality control

To assure the quality of data the following measures were undertaken. The data collection format was pretested on 16 patients (5% of the sample size). This was conducted on the medical records of patients other than those included in the study. Additionally, data collectors were trained on how to use such formats and how to approach other health care workers. Furthermore, the data collection process was checked continuously by the principal investigator on daily basis for its completeness and accuracy before the patient gets discharged.

3.7.4 Data analysis and interpretation

DUE was conducted to determine whether ceftriaxone was being used appropriately based on the protocol currently prepared regarding the rationale use of this drug. To do so, six criteria namely indication for use, dose, frequency of administration, duration of treatment, DDI with ceftriaxone and C&S test were used to evaluate its use. As the study was conducted prospectively, information regarding all of these criteria was obtained for each patient enrolled in the study. Accordingly, the data outcomes from those evaluations were entered into Statistical Package for Social Sciences (SPSS) version-16.0 software. It was then analyzed using the same software. Finally, the results obtained were summarized and compared with the findings of studies conducted somewhere else.

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. It was also possible to compute the overall appropriateness using scientific calculator. 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 (314 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 (314 cases). The responses of key informants were also analyzed using content thematic analysis. Accordingly, the collected dataset (key informants' response) was first made well familiarized and then significant themes (patterns) were identified. Finally, analysis of the themes were made and contextualized in relation to the existing literature.

Analysis using binary logistic regression and multivariate logistic regression was made to observe whether there was association between factors such as gender, age groups, department types, units where patients were admitted, diagnosis type, treatment types and inappropriate ceftriaxone use. Significance of the associations was determined at the 0.05 level.

[*] AND condition: the use of ceftriaxone in a given patient was considered to be appropriate if all the outcomes of evaluation with respect to the six criteria were found to be appropriate.

Furthermore, the point prevalence regarding the utilization rate of ceftriaxone was determined. To do so, among patients admitted to medical and emergence wards of TASH, those who were receiving ceftriaxone were counted. The survey was made at the same point in time for all wards to avoid any double counting because of transfer of patients from one ward to the other. This procedure was performed three times at three different times and the average was taken to obtain the most likely utilization rate of ceftriaxone.

3.8 Interventions implemented

3.8.1 Overview

One of the major challenges in healthcare is ensuring that medicines are used rationally. This requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them. However, rational use of medicines remains the exception rather than the rule. Studies indicated that for those people who receive medicines, more than half of all prescriptions are incorrect and more than half of the people involved fail to take them correctly (Wiedenmayer *et al.*, 2006).

In addition, there is growing concern at the increase in the global spread of antimicrobial resistance. As it is cited in the work of Wiedenmayer *et al.* (2006), a report by WHO reveals findings of up to 90% resistance to original fist-line antibiotics such as ampicillin and cotrimoxazole for shigellosis, up to 70% resistance to penicillin for pneumonia and bacterial meningitis, up to 98% resistance to penicillin for gonorrhoea, and up to 70% resistance to both penicillins and cephalosporins for hospital-acquired Staphylococcus aureus infections. More specifically, misuses as well as resistance to ceftriaxone are

prevalent both locally and globally as it was addressed in the literature review part of this study. Likewise, it was found out in the present study that both the utilization rate and inappropriate utilization of this drug at medical and emergency wards of TASH were very high. It was, therefore, important to implement some interventional strategies.

3.8.2 Approaches of intervention

In this study, various interventional approaches were used, the most notable ones being preparing protocol regarding the rationale use of ceftriaxone and conducting seminar regarding the appropriate use of this drug.

3.8.2.1 The protocol

A protocol entitled "*Antibiotic Selection of Common Infections: Rational Use of Ceftriaxone*" was currently developed as part of the interventions in this study. It was prepared by the joint effort of professionals from School of Pharmacy (Department of Pharmacology and Clinical Pharmacy) and School of Medicine (Department of Internal Medicine). It was prepared by compiling current evidence-based recommendations regarding the use of this drug from WHO guideline 2013, STG of Ethiopia 2010, and other sources of information such as Harrison's Principles of Internal Medicine 2012, The Sanford Guide to Antimicrobial Therapy 2012, UpToDate, Medscape, and other peer-reviewed journals. More focus was given to "The Sanford Guide to Antimicrobial Therapy" as this guide is among the most widely accepted guidelines in many parts of the world.

The protocol covered such topics as introductory information on ceftriaxone, pharmacology of ceftriaxone, antibiotic selection of common infections and literature

review on the utilization of ceftriaxone. Among others, the section entitled "*Antibiotic selection of some infections*" is the most important and core part of the material. It is important to note that those infectious diseases addressed in this section are diseases where the use of ceftriaxone is recommended either primarily or alternatively. Although the main focus of this material is compiling baseline data on the appropriate use of ceftriaxone, it also addressed the appropriate antibiotic selection of common infections. That is, the primary as well as alternative antibiotic treatment of common infectious diseases where ceftriaxone is being used was addressed. This was made to ensure the usefulness of the protocol. Additionally, the usual etiologies of the respective diseases are presented in an attempt to enhance the strength of the evidences compiled for each disease.

The protocol is designed for use by medical professionals involved in the curative as well as preventive care at the hospital level as far as appropriate use of ceftriaxone is concerned. To this end, an attempt was made to prepare the protocol in the simplest and most practical way possible to address the questions and problems faced by the medical staff. Accordingly, the infectious diseases are arranged based on their alphabetical order. It is also planned to publish the protocol in the form of pocket-sized hand book so that it will be easily portable. The key components of the protocol were also prepared on a single sheet of broacher so that portability will be no more an issue. Prior the use of this protocol it is supposed to be approved by drug and therapeutic committee (DTC) of TASH.

3.8.2.2 The seminar

The other intervention made in optimizing the use of ceftriaxone was a seminar arranged on 26 June 2014. It was entitled "*Appropriate use of ceftriaxone*". On the seminar, a total of 43 participants were availed, majority of which were Residents as they are the main target group (Annex V). The e-mail addresses of the participants were obtained to send them the soft copy of the protocol post approval.

Discussion was also made with the participants as part of the seminar. Accordingly, the following were the main suggestions raised:

- The need for budget allocation re-arrangement to enhance the laboratory service of TASH was also raised.
- The need to build a team composed of multi-disciplines that control the use of antibiotics. The composition of the suggested team is depicted in Figure 2.

Figure 2: The suggested team in promoting appropriate use of antibiotics at TASH

3.8.2.3 Miscellaneous interventions

Immediate interventions (regarding the utilization of ceftriaxone) were made during data collection in cases of very important issues including concomitant use of this drug with ringer lactate, prolonged use of this drug for surgical prophylaxis, the use this drug as an initial empiric treatment in clinical conditions like neutropenic fever, lymphadenitis, etc. This was made possible through the communication held among the principal investigator, data collectors and the physicians in charge of attending the patients.

3.9 Ethical considerations

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. Ethical approval was also obtained from the Ethical Review Board of School of Pharmacy and respective departments of School of Medicine, College of Health Sciences, Addis Ababa University.

3.10 Operational definitions

- ***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.

- ***Confirmed diagnosis****:* Diagnosis made by the judgment of clinicians' team based on adequate evidences such as imaging and/or laboratory findings and clinical manifestations.
- ***Suspected diagnosis****:* Diagnosis made by the judgment of clinicians' team without adequate evidences such as imaging results, laboratory findings or clinical manifestations.
- ***Empirical treatment****:* Antibiotic administration initiated before or without identification of ceftriaxone-sensitive bacterial pathogens.
- ***Specific treatment****:* Antibiotic administration initiated after identification of ceftriaxone-sensitive bacterial pathogens.
- ***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.
- ***Abnormal lab test***: The results of laboratory tests such as CBC, liver function tests, kidney function tests, etc are not within the normal range.
- ***Abnormal diagnostic results:*** The results of imaging studies such as X-ray, CT-scan, etc show the presence of disease.

4. RESULTS

4.1 Socio-demographic characteristics

A total of 314 patients (169 males) with a mean age of 37.7 ± 17.2 (SD), (ranging from 18 to 86 years) were included in the present study. More proportion of the study participants were in the age group of 18-65. Most cases involved the department of internal medicine (73.6%); the remainders were in emergency department (26.4%). Additionally, analysis of the specific units of admission revealed that patients who took ceftriaxone during the study period were mostly non-ICU (93.6% vs 6.4%) (Table 1).

Table 1: Socio-demographic characteristics of patients included in the study

Characteristics	**Category**	**No (%)**
Sex	Male	169 (53.8)
	Female	145 (46.2)
Age	18-65	285 (90.8)
	≥65	29 (9.2)
Department	Internal medicine	231 (73.6)
	Emergency	83 (26.4)
Unit of admission	Non-ICU	294 (93.6)
	ICU	20 (6.4)

4.2 Prescription pattern

The utilization rate of ceftriaxone was found to be very high (58% point prevalence) at the medical and emergency wards of TASH during the study period. Analysis of the practice also indicated that almost all prescriptions of ceftriaxone were issued for empirical therapy. Only very few of them were used for specific treatment. It was also found out that 55.1% of cases received ceftriaxone for diseases where it is indicated as primary (first-line) therapy according to current evidence-based guidelines. On the other hand, it was used for diseases other than its primary indications in 44.9% of cases (Table 2).

Table 2: Types of treatment with ceftriaxone received by the study participants

Characteristics	Category		No (%)	Total
Indication of ceftriaxone	Primary		173(55.1)	314
	Alternative		83(26.4)	
	Not indicated		58(18.5)	
Type of treatment with ceftriaxone	Therapeutic	Empiric	274(87.3)	314
		Specific	5(1.6)	
	Prophylactic	-	35(11.1)	

4.3 Indications

The top three most common indications for ceftriaxone were respiratory tract infections (35.4%), prophylactic indications (11.1%) and skin, soft tissue and bone infections (10.8%). More specifically, this drug was indicated mostly for pneumonia (35.0%),

followed by prophylaxis for trauma/injury (6.1%) and pyogenic meningitis (5.4%). It was not justified to use ceftriaxone in 18.5% of patients based on current evidences from guidelines. The detail information is shown in Table 3.

Table 3: Indications for which ceftriaxone was prescribed

Indication by system	**No (%)**
Respiratory tract infection (RTI)	111 (35.4)
Prophylactic indication (PI)	35 (11.1)
Skin, soft tissue and bone infection (SSBI)	34 (10.8)
Central nervous system infection (CNSI)	28 (8.9)
Sepsis and septic shock (SSI)	15 (4.8)
Cardiovascular infection (CVI)	11 (3.5)
Urinary tract infection (UTI)	10 (3.2)
Gastro-intestinal infection (GII)	6 (1.9)
Non-indications (NI)	58 (18.5)
Total	314 (100)

RTI: community acquired pneumonia, hospital acquired pneumonia, aspiration pneumonia, otitis media; NI: neutropenic fever, tonsilopharyngitis, lymphadenitis, CHF, periodontal abscess, etc; PI: trauma, surgical prophylaxis, upper GI bleeding; SSBI: diabetic foot ulcer, cellulitis, wet gangrene, osteomyelitis, pyomyositis; CNSI: pyogenic meningitis, brain abscess; SSI: sepsis and septic shock; CVI: sub-acute bacterial endocarditis, pericarditis; UTI: pyelonephritis, other UTI; GII: acute bacterial gastroenteritis, cholangitis, RVI with chronic diarrhea; IAI: spontaneous bacterial peritonitis, primary bacterial peritonitis.

Analysis of the practice also indicated that ceftriaxone was more prescribed for suspected infections compared to those confirmed (52.5% vs 47.5%).

4.4 Culture and sensitivity test

Of the total 314 cases, C&S test was not done in most of the cases; observed in 281 cases (89.5%). Some of the accepted reasons why C&S test was not sent for investigation were prior initiation of therapeutic antibiotic regimen in 81 cases (25.8%) and the use of ceftriaxone for its prophylactic indications in 33 cases (10.5%). But the rest, 167 cases (53.2%) were considered to be unacceptable. Of the 33 cases in which C&S test was done, growth was observed in 8 cases (24.2%). The organisms were found to be resistant in nearly two third of cases (62.5%) to ceftriaxone (Table 4).

Table 4: Culture and sensitivity tests in patients prescribed with ceftriaxone

	C&S		**Growth**		**Sensitivity to ceftriaxone**	
	Done	**Not done**	**Yes**	**No**	**Sensitive**	**Resistant**
No (%)	33 (10.5)	281 (89.5)	8 (24.2)	25 (75.8)	3 (37.5)	5 (62.5)
Total	314 (100)		33 (100)		8 (100)	

The microorganisms isolated included citrobacter, E. coli, gram-negative and gram-positive bacteria in cluster, Klebsiella spp, Staphylococcus aureus and Staphylococcus saprophyticus (Table 5).

Table 5: Sensitivity test results of the isolated microorganisms to ceftriaxone

Bacteria	**Sensitive**	**Resistant**	**Total**
Citrobacter	1	0	1
E. coli	1	1	2
G (-) and G (+) bacteria in cluster	0	1	1
Klebsiella spp	0	1	1
Staphylococcus aureus	1	1	2
Staphylococcus saprophyticus	0	1	1
Total	3	5	8

G (-): gram-negative; G (+): gram-positive

4.5 Dosage and frequency of administration

The most commonly prescribed amount of ceftriaxone per administration (dose) was found to be 1g. It accounted for 87.9% of all cases. This was followed by the 2g dose of administration which constituted 11.8% of cases. The most common daily dosage of this drug was 2g accounting for 88.9% of cases. The most common frequency of administration was found to be the twice-daily administration accounting for 98.4% of cases. The details of dosage and frequency of administration with ceftriaxone are shown in Table 6.

Table 6: Distribution of ceftriaxone dosing and frequency of administration

Dose (amount given once)	**1g**	**1.5g**	**2g**	**Total**
No (%)	276 (87.9)	1 (0.3)	37 (11.8)	314 (100)
Dosage/day	**1g**	**2g**	**3g**	**4g**
No (%)	1 (0.3)	279 (88.9)	1 (0.3)	33 (10.5)	314 (100)
Frequency of administration		**Once-daily**	**Twice-daily**	
No (%)		5 (1.6)	309 (98.4)	314 (100)

4.6 Duration of treatment

The mean duration of treatment with ceftriaxone was found to be 10.4 days (ranging from 1 to 56 days). In most cases, duration of treatments with this drug fall in the range 8-14 days; observed in 46.2% of cases (Table 7*)*. Analysis of the specific duration of treatment with ceftriaxone revealed that it was most commonly given for 14 days (19.1%), followed by 10 days (13.5%) and 7 days (12.4%).

Table 7: Distribution of duration of treatment with ceftriaxone

Duration (days)	**Frequency**	**%**
1	9	2.9
2-7	117	37.3
8-14	145	46.2
15-21	33	10.5
> 21	10	3.2
Total	314	100

4.7 Concomitant administration of drugs

Among drugs co-administered with ceftriaxone during hospital stay, metronidazole took the first place. This was followed by tramadol, azithromycin and cimetidine (Figure 3). The percentage for co-administration of drugs was computed by dividing the frequency of co-administration to the total number of cases (314). Analysis of the present study also showed that the probability of intravenous incompatibility was observed between ceftriaxone and ringer lactate in 21 cases (6.7%), and this was identified as major DDI. The most common type of potential DDI identified in the present study was moderate DDI. This was mainly attributed to heparin (22.6%), followed by warfarin (6.7%). The potential DDI identified as minor was due to concurrent use of ceftriaxone with either furosemide or gentamycin or both (Table 8).

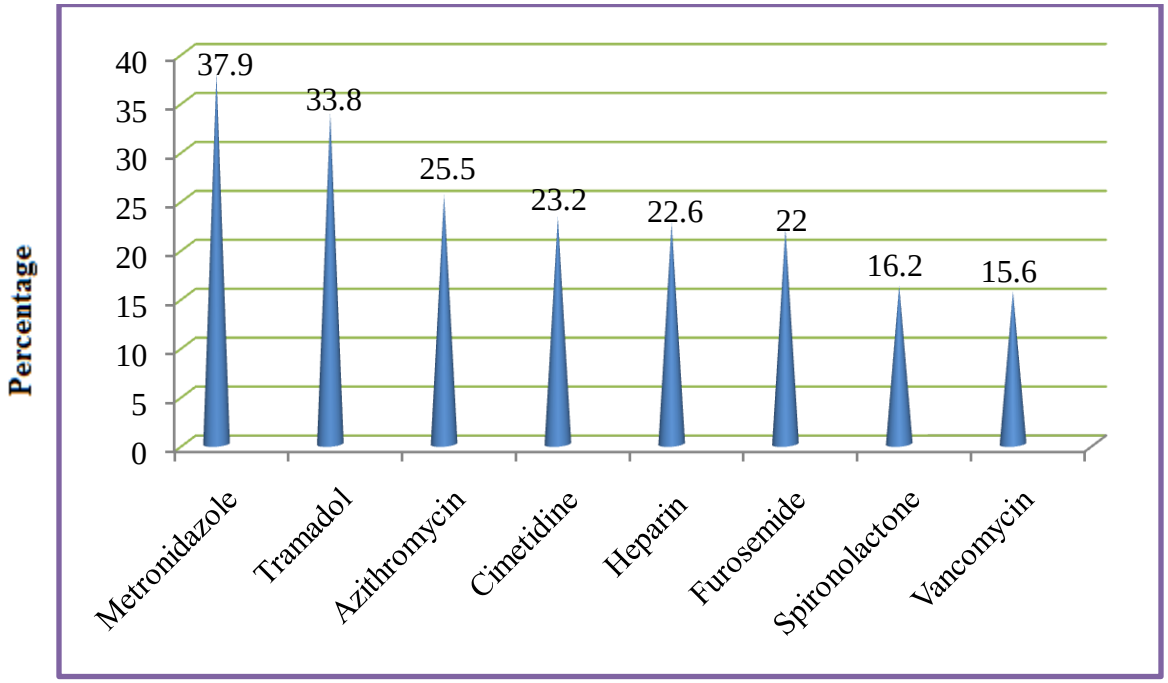

Figure 3: The top frequently co-administered drugs with ceftriaxone

Table 8: Co-administered drugs with potential drug - drug interaction

Co-administered drug	Severity of DDI	Frequency (n = 314)	%
Ringer lactate	Major	21	6.7%
Warfarin	Moderate	21	6.7%
Heparin	Moderate	71	22.6%
Furosemide	Minor	69	22%
Gentamycin	Minor	18	5.7%

4.8 Practice of ceftriaxone utilization versus protocol

As can be seen from Figure 4, most of the ceftriaxone prescriptions (utilizations) were found to be inappropriate as per the protocol prepared regarding the rationale use of this drug; observed in 87.9% of cases. Appropriate use was observed only in 12.1% of the cases. The greatest proportion of inappropriate use was attributed to inappropriate frequency of administration (80.3%), followed by absence of C&S test (53.2%) and inappropriate duration of treatment (50%). The remaining inappropriate use was attributed to inappropriateness in dose, indication and DDI (Figure 5). By excluding frequency of administration, the inappropriate use of this drug was found to be 77.1%, still remained high. The mechanisms as to computing these percentages were addressed in the methodology part.

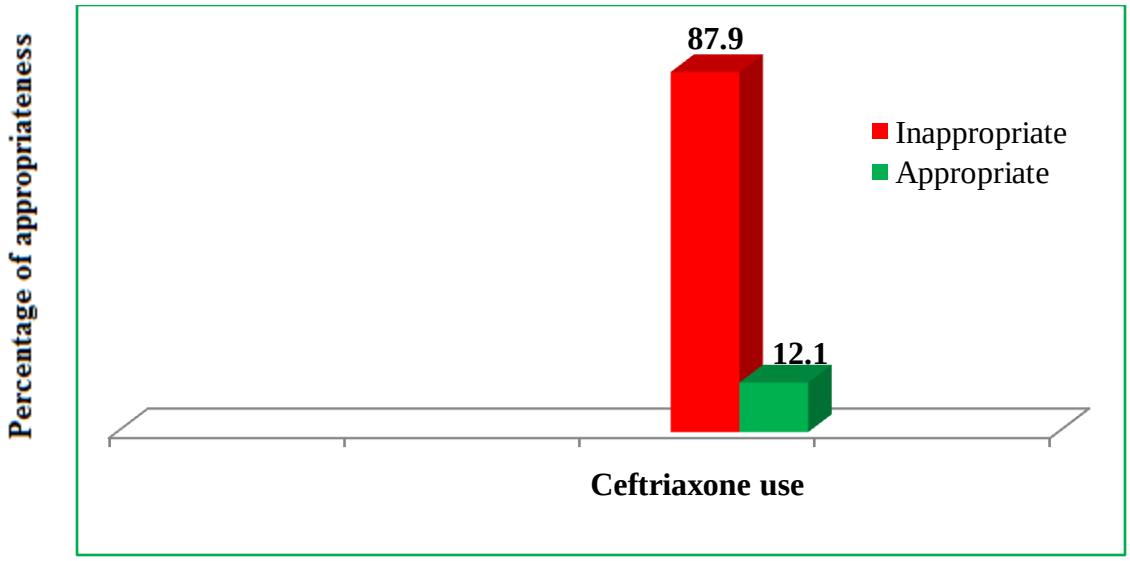

Figure 4: Appropriateness of ceftriaxone use in medical and emergency wards of TASH

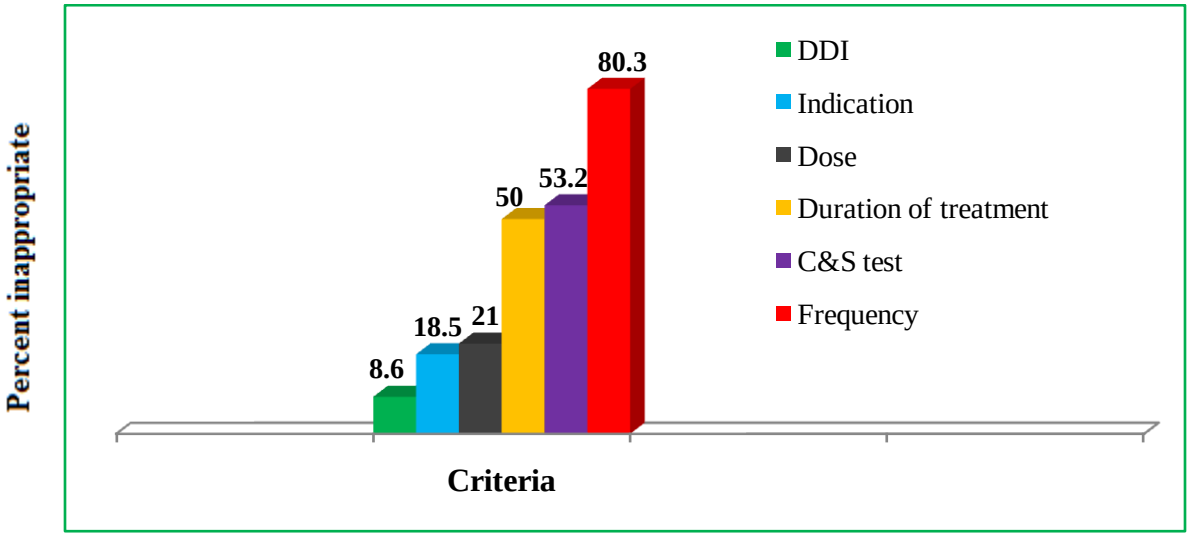

Figure 5: Criteria referenced inappropriate use of ceftriaxone in medical and emergency wards of TASH

Analysis of the practice also indicated that the proportion of inappropriate use was slightly more in the emergency ward compared to the medical wards (90.4% vs 87%).

In terms of the first few top indications, the analysis of practice indicated that the inappropriate use of ceftriaxone was by far greater than the appropriate use in pneumonia, trauma/injury and wet gangrene (Table 9).

Table 9: Appropriateness of ceftriaxone use among the top few indications

Indication		**Appropriate (No, %)**	**Inappropriate (No, %)**	**Total**
Pneumonia	CAP	0 (0)	75 (100)	75 (100)
	AP	0 (0)	30 (100)	30 (100)
	HAP	0 (0)	5 (100)	5 (100)
Trauma/injury		2 (10.5)	17 (89.5)	19 (100)
Pyogenic meningitis		9 (52.9)	8 (47.1)	17 (100)
Sepsis		9 (69.2)	4 (30.8)	13 (100)
Cellulitis		6 (46.2)	7 (53.8)	13 (100)
Wet gangrene		0 (0)	12 (100)	12 (100)
Brain abscess		7 (63.6)	4 (36.4)	11 (100)

CAP: community acquired pneumonia; AP: aspiration pneumonia; HAP: hospital acquired pneumonia

4.9 Factors associated with inappropriate ceftriaxone use

Analysis using binary logistic regression indicated that factors such as gender, age groups, department types, units where the patients were admitted and diagnosis types failed to be significantly associated with inappropriate ceftriaxone use. By contrast, the type of therapy with ceftriaxone was found to have a significant association with utilization of this drug. Accordingly, ceftriaxone use was significantly inappropriate (not justified) when used as empiric than specific therapy. Multivariate logistic regression

analysis was performed to control the effect of any confounder and ensured the presence of such association (Table 10).

Table 10: Factors associated with inappropriate ceftriaxone use

Variable	Appropria-teness		COR (95% CI)	AOR (95% CI)	p-value
	No	Yes			
Gender					
Male	147	22	0.829(0.417-1.646)	0.771(0.358-1.658)	0.505
Female	129	16	1.00	1.00	
Age					
18-65	250	35	0.824 (0.237-2.866)	0.669(0.164-2.721)	0.574
> 65	26	3	1.00	1.00	
Department					
Emergency	75	8	1.399 (0.614-3.189)	1.557(0.549-4.422)	0.405
Internal med.	201	30	1.00	1.00	
Unit					
Non-ICU	260	34	1.912 (0.604-6.053)	2.535(0.730-8.804)	0.143
ICU	16	4	1.00	1.00	
Treatment type					
Empiric	243	31	31.355(3.395-289.55)	36.98(3.884-352.072)	0.002
Specific	1	4	1.00	1.00	
Diagnosis type					
Suspected	146	19	1.123 (0.570-2.213)	1.379(0.648-2.931)	0.404
Confirmed	130	19	1.00	1.00	

Internal med.: Internal medicine; COR: crude odds ratio; AOR: adjusted odds ratio; p-value: the value obtained using multivariate logistic regression.

4.10 Responses of key informants

The following are the responses of the key informants.

Table 11: Responses of the interviewed physicians regarding ceftriaxone use

Interview questions	Responses	Number of Respondents
Why was C&S test not sent for most of the patients?	Service is not available	8
	Patients come after initiation of antibiotics	5
	Culture results are not reliable	5
	It takes long time to get results back	2
Why was ceftriaxone administered on a twice-daily basis for most cases?	Just because of tradition of practice	5
	There are guidelines which promote it	4
	To ensure its effectiveness	2
Why is the utilization rate of ceftriaxone very high in TASH?	Good availability	8
	Good effectiveness	5
	Low rates of toxicity	4
	Ease of administration	4
Why is ceftriaxone being co-administered with ringers lactate, warfarin and heparin?	Less availability of other drugs	5
	No problem up on such administration	4
	Absence of checking for interaction	2
Why is ceftriaxone used in neutropenic fever, periodontal abscess, etc?	Cost of other more appropriate drugs	4
	Unavailability of other appropriate drugs	4
Why was ceftriaxone used for prolonged duration as in surgical prophylaxis?	Unavailability of equivalent PO medicines	3
	Lack of guidelines	2
	It should not have been used this way	1

Table 12: Responses of the interviewed microbiologists regarding C&S test

Interview questions	Responses	Number of respondents
What can you say about the quality of microbiology laboratory?	Poor quality due to the use of expired reagents or antibiotic discs	4
	Currently, its quality is improved	2
Why is most C&S tests end up with negative result?	Sample collection after initiation of antibiotics	4
	Use of expired reagents or antibiotic discs	3
	Inappropriate sample collection	2
	Failure to request appropriate laboratory test	1
	Improper use of transporting medium	1
Who will take the bacteriology test result after it is done?	Physicians	5
	Patients	3
	Attendants	1
On average, how long does it take for C&S result to come back (in day)?	Mostly 3 days	5
	Some cultures (eg. blood culture requires 7-14 days)	3

5. DISCUSSION

The present study was mainly aimed at evaluating the utilization of ceftriaxone by making use of six criteria. Accordingly, the findings obtained were compared with the findings of studies conducted somewhere else as follows.

The present study showed a very high utilization rate of ceftriaxone (58% point prevalence). This is similar with the results obtained in General Hospital, Port of Spain (POSGH), in which most of the studied patients (66%) received ceftriaxone (Pereira *et al.*, 2004). It is also similar with the results of a study conducted by Babu and Jyothi (2012), Sapna *et al.* (2012), Babu *et al.* (2012) and Chelkeba (2013), where ceftriaxone was the most widely prescribed cephalosporin. But it is quite different from the results of a study conducted by Kaliamoorthy *et al. (*2012) in tertiary care teaching Hospital, India, in which ceftriaxone took the third place in terms of utilization rate (19.5%), following cefixime (32.7%) and cefotaxime (31.3%). This difference may be attributed to the less availability of these drugs in the setting of TASH. In the present study, the interviewed physicians agreed that there is high utilization rate of this drug and this was ascribed by the good availability of the drug, good effectiveness and low toxicity rates of this drug. But, increased antibiotic usage is associated with increase in microbial drug resistance (Davey *et al.*, 2006; Lee *et al.*, 2009).

The result of this study also shows that most prescriptions of ceftriaxone was accounted by its therapeutic indication (88.9%) compared to its prophylactic use. Among its therapeutic uses, almost all were empirically prescribed based on physicians' clinical judgment (87.3% of all cases). This is higher than the value obtained from the empiric

use of antibiotics in the study conducted at the University hospital of the West Indies, where ceftriaxone was the most commonly prescribed antibiotics; two-thirds of patients (67.9%) were treated with empiric antibiotics (Chin *et al.*, 2010). The difference may be attributed to the fact that the latter study included other additional antibiotics in determining the rate of empiric antibiotic use. Although the use of ceftriaxone for its primary indication was found to be fair (55.1%), its use for cases other than its primary indications was found to be high (44.9%). Nearly half of such indications (18.5%) were due to the use of the drug for those cases where its empiric use is not recommended and this needs further attention.

In this study, pneumonia was found to be the most common indication for ceftriaxone, in which it accounted for 35% of all indications. This is similar with the case of study done at Dessie referral hospital (DRH), wherein the most common indication (36.4%) of this drug was pneumonia (Ayinalem *et al.,* 2013). It was also found out in the present study that, ceftriaxone was mainly indicated for RTIs (35.4%), followed by its use in prophylactic indications (11.1%) in terms of indication by system. This is comparable with the study done in 10 Victorian hospitals, where treatment of RTI with ceftriaxone accounted for 52% (Robertson *et al*., 2002). But in the study conducted at Ayder referral hospital (ARH), ceftriaxone was most commonly prescribed for preoperative prophylaxis followed by pneumonia (Abebe *et al*., 2012). This difference may be attributed to the inclusion of surgery department in the latter study. Analysis of the practice also indicated that more proportion of ceftriaxone (52.5%) was indicated for suspected diseases. But such type of practice may contribute to the emergence of drug resistance.

Antibiotic treatment of infectious diseases guided by microbiology test result plays a crucial role in the provision of appropriate therapy. In the present study, it was observed that C&S test was not done in most of the cases (89.5%) who received ceftriaxone for any reason. Of these cases, the acceptable level was observed in 36.3% of cases and this was attributed to antibiotic initiation before admission to TASH and the use of ceftriaxone for its prophylactic indications after admission. On the other hand, the practice could not be justified by an acceptable reason in 53.2% of cases. This is higher than the result obtained from the study conducted in Korea, in which unacceptable level of C&S tests prior to the initial ceftriaxone dose accounted for 33.5% (Lee *et al*., 2009). This difference may be due to either the multi-center nature of the latter study or the presence of well-equipped and good quality microbiology laboratory in the Korean hospitals. In the present study, the interviewed physicians agreed that C&S tests were not done in significant proportion of cases and this was ascribed by unavailability of service, unreliable culture result, prior initiation of therapeutic antibiotic regimen and delayed culture result. As they said, service is not available during night and weekend and they added that culture results usually end up with no growth.

On the other hand, the interviewed microbiologists agreed that the reason why the bacteriology results were unconvincing could7 be due to sample collection after initiation of antibiotics, use of expired reagents or antibiotic discs, inappropriate sample collection, improper use of transporting medium, and failure to request appropriate laboratory test. Otherwise, they agreed that the quality of the current microbiology laboratory is poor due mainly to poor quality reagents. Besides, they agreed that it takes, on average, 3 days for culture results to become available. This is similar with the finding from the study

conducted at the University hospital of the West Indies, where culture reports took a mean of 3.7 days to become available (Chin *et al.*, 2010). It is unquestionable that sample should be collected prior to administration of antibiotics as far as it is aimed at identifying the causative agent. Once antibiotics have been initiated, the flora changes, leading to potentially misleading culture results (Baron *et al.*, 2013). Additionally, the use of expired laboratory reagents should be avoided as it compromises the quality of microbiology test results.

Consistent with the responses of interviewed physicians, growth was observed only in a quarter of samples sent for investigation (24.2%). This is lower than the values obtained from studies done at Pakistan (in 105 cases), Nepal (in 19 cases) and Bangladesh (in 100 cases) in which growth was observed in 33 cases (31.4%), 9 cases (47.4%) and 77 cases (77%), respectively (Iqbal *et al.*, 2008; Bajimaya *et al*., 2010; Furqan & Paracha, 2014). The difference may be attributed to the low sample sizes taken and the improved quality of microbiology laboratory in these studies. In the present study, out of cases for which sensitivity was done, resistance was seen in nearly two-third of cases (62.5%) to ceftriaxone. This is similar with the finding from study conducted in Khartoum, in which resistance to ceftriaxone was observed in 64% of cases (Ibrahim *et al*., 2012). But it is lower than the finding from study conducted in Bahirdar, wherein resistance to ceftriaxone was observed in 82% of cases (Mulu *et al.*, 2012). This difference could be attributed to differences in the number of tested microorganisms and the prescribing practice of the drug. In all of these settings, the increased utilization rate of this drug could be one factor contributing to the increased rate of resistance. But the development of antibiotic resistance has huge impact on the individual patient and the society at large.

At the individual level, the impact could be increased likelihood of treatment failure, prolonged illness, increased financial burden and greater risk of mortality. At societal level, the impact could be in terms of increased mortality, loss of productivity and spread of antibiotic resistant pathogens. It was pointed out by Dellit *et al.* (2007) that interventions including switching to narrow-spectrum antibiotics and/or reducing the use of broad-spectrum antibiotics should be implemented in combating antibiotic resistance.

In the present study, it was found out that the most common prescribed dose of ceftriaxone was 1g, observed in 87.9% cases, whereas, the most common daily dosage was found to be 2g, observed in 88.9% cases. This is similar with the result obtained from the study conducted in Korea, wherein the most common daily dosage of this drug was 2g (observed in 85.3% cases) (Lee *et al.*, 2009). But it is somewhat higher than the findings from the studies done at DRH and ARH, wherein the most common daily dosage of the drug was 2g in 63.6% and 79.4% cases, respectively (Abebe *et al.*, 2012; Ayinalem *et al.*, 2013). One of the possible reasons for the difference could be the inclusion of patients of all age group in the case of ARH, in which case pediatrics received lower daily doses of ceftriaxone.

The other staggering finding in the present study was regarding the frequency of administration with ceftriaxone, wherein the twice-daily administration accounted for almost all cases (98.4%); the rest being administered once-daily. Among the other criteria, frequency of administration took the first place in contributing to the inappropriate use of ceftriaxone; the inappropriate use of ceftriaxone with this criterion was observed in 80.3% of cases. This is similar with the result obtained in an interventional study done at USA, in which a significant number of patients received a

twice-daily dosing of ceftriaxone while they were supposed to receive a once-daily dosing regimen (Wade & McCall, 1995). But, it was different from the finding of the study conducted at DRH, where the frequency of administration with ceftriaxone took the second place in contributing to the inappropriate use of the drug (Ayinalem *et al.*, 2013). This difference could be attributed to differences in the two study settings in terms of tradition of practice. This reason was proposed as the physicians interviewed in the present study agreed that the administration of ceftriaxone on a twice-daily basis in most cases was just because of tradition of practice. But, antibiotic prescribing practices of this kind may result in considerable expense to the health care system. For instance, the study conducted in USA shows cost savings in excess of $25,000 after intervention was implemented in reducing the twice-daily prescribing of this drug (Wade & McCall, 1995). There is body of evidences which support the once-daily administration of ceftriaxone in most of its indications. For example, it has a large volume of distribution (7-12 L) and has shown excellent tissue and body fluid penetration after a dose of 1-2g; concentrations well above the MICs of most pathogens responsible for infection are detectable for more than 24 hours in over 60 tissues or body fluids including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone as well as cerebrospinal, pleural, prostatic and synovial fluids. Besides, the elimination half-life of this drug in adults is about 8 hours and this in turn enables the once-daily administration of the drug in most cases (Finkel *et al.*, 2009).

It was also found out in the present study that the mean duration of treatment with ceftriaxone (10.39 days, range: 1 to 56) is very similar with the findings from the studies conducted at 10 University hospitals of Korea and TASH, where it was found to be 10.3

days (range, 1 to 61) and 9.2 days, respectively (Lee *et al*., 2009; Michael & Mulugeta, 2009). But, it is different from the values observed in studies conducted at ARH and DRH, where it was found to be 7.2 days and 6.8 days, respectively. Such difference occurred as most duration of treatments with ceftriaxone were in the range 8-14 days (observed in 46.2% cases) as opposed to the cases of ARH and DRH, where the range with most frequent duration of treatments was 2-7 days (51.69%) and 2-7days (76.6%), respectively (Abebe *et al.*, 2012; Ayinalem *et al.*, 2013). This difference could be attributed to differences in patient condition. That is, patients who admit to TASH may be those who are, in most cases, terminally-ill requiring longer hospital stay and this in turn may cause physicians' to opt long duration of treatment with antibiotics.

However, it was found out in the present study that inappropriate duration of treatment with ceftriaxone took the third place in contributing to the overall inappropriate utilization of this drug; observed in 50% of cases. This was comparable with the finding from the Korean study, where inappropriate duration of therapy with this drug accounted for 42.8% (Lee *et al.,* 2009). In line with this, it was found out in the present study that treatment with ceftriaxone was continued without switching to oral medication in two-third of patients (66.2%) who deserved switching. Analysis of the practice also indicated that ceftriaxone was used for prolonged duration (4-7 days) in its use for prophylactic purpose as in surgery and trauma. But in these conditions a one-day prophylaxis with the drug is the usual recommendation although up to 3 days may be recommended based on the grade of the wound (Luchette *et al.*, 2000; Gilbert *et al*., 2012). The interviewed physicians agreed that such practices were due to lack of guideline and unavailability of

equivalent oral medications. As they said, this kind of practices constitutes mismanagement and should not be practiced.

Analysis of the practice indicated that metronidazole took the first place among drugs co-administered with ceftriaxone; observed in 37.9% of cases. This is different from the case of studies conducted at ARH and DRH, in which maintenance fluid was the most frequently co-administered agent with ceftriaxone (Abebe *et al.*, 2012; Ayinalem *et al.*, 2013). Among drugs with potential for interaction, concomitant administration with ringer lactate constituted major DDI (Hawboldt, 2009) and was prescribed in a considerable proportion of cases (6.7%). This is lower than the values obtained from retrospective studies conducted at ARH, TASH and PH, where co-administration was observed in 33.1%, 40.9%, and 44.4%, respectively (Michael & Mulugeta, 2009; Abebe *et al*., 2012). This may increase the probability of IV incompatibility between the two drugs as a result of binding of ceftriaxone to the calcium contained in ringer lactate. The possible management for this may be either thoroughly flushing between infusions with physiological salt-solution or using infusion lines at different sites, or replacing the infusion lines (Aschenbrenner & Diane, 2009; Bradley & Bocchini, 2009). The most common type of potential DDI identified as moderate was due to co-administration with heparin (22.6%) and warfarin (6.7%). This type of co-administration may result in increased risk of bleeding (Baxter, 2010). In line with this, 6 patients (1.9%) with this type of co-administration experienced either bleeding or increased INR, among which death due to excessive bleeding occurred in one patient. The interviewed physicians agreed that such practice was due to the less availability of other drugs and absence of checking for possible interaction before prescribing. In order to prevent these DDIs,

health care providers should have adequate information about DDIs. This can be achieved through encouraging clinical pharmacists so that they can provide evidence-based information in an attempt to deliver optimal health care to patients.

The major question in the present study was to answer whether there was a considerable inappropriate utilization of ceftriaxone in the study area. Accordingly, one among the other staggering findings was the answer to this question, wherein inappropriate use of this drug was found to be as high as 87.9%. This finding is similar with the result obtained from the study done at Iran, where the utilization of ceftriaxone was not according to protocol in 85.3% cases (Shohrati *et al*., 2010). But, it is higher than the values obtained from studies conducted at ARH and DRH, in which inappropriate use of this drug was observed in 64.2% and 46.2% cases, respectively (Abebe *et al.*, 2012; Ayinalem *et al.*, 2013). It is once again much higher than the values obtained from studies conducted at TASH and PH, in which inappropriate use of this drug was observed in 28.6% and 27.0% cases, respectively (Michael & Mulugeta, 2009). These differences may be attributed to the retrospective nature of the studies causing them to consider less number of criteria in evaluating the use of the drug. The other major possible reason for the discrepancy may be attributed to the guidelines used in making the DUE; the retrospective studies used Ethiopian STG and the present study used a protocol prepared regarding rational use of ceftriaxone. Similarly, it is higher than the finding from study done at Korea, where the inappropriate use of ceftriaxone was observed in 34.5% cases. Once again, the difference may be attributed to the number and type of criteria used. Besides, the Korean study was conducted in relatively many settings (10 hospitals) which could be another possible justification for the difference.

Analysis using binary logistic regression and multivariate logistic regression indicated that gender, age groups, department types, units of admission and diagnosis types were failed to be associated with inappropriate ceftriaxone usage. This was different from the study done at Thailand, in which female gender [OR: 1.96, 95% CI: 1.03-3.70] was associated with appropriateness of ceftriaxone usage (Phuphuakrat *et al*., 2013). This difference may be due to the enrollment of more proportion of females in the latter study (60.8%) compared to the present study (46.2%). By contrast, multivariate logistic regression showed a significant positive association between empiric treatment and inappropriate ceftriaxone usage in the present study [OR: 36.98; 95% CI: 3.884-352.072; p-value: 0.002]. This implies that empiric treatment with ceftriaxone was significantly associated with its inappropriate use.

6. LIMITATIONS OF THE STUDY

The present study focused only on internal medicine and emergency departments. But, a more representative result would be obtained if other departments (for example, surgical and orthopedic) were included. Additionally, local prospective studies done on drug utilization of ceftriaxone are limited. Hence, it was not possible to make comparison as the reader wanted to see. The study did not also show the period prevalence of ceftriaxone utilization rather it showed the point prevalence alone.

Furthermore, the number of physicians availed themselves on the seminar that was conducted as part of intervention was small. But, more effective seminar could be implemented if large number of the target groups were participated.

7. CONCLUSIONS

This study revealed that both utilization rate and inappropriate use of ceftriaxone were very high in the medical and emergency wards of TASH. This may lead to emergence of resistant pathogens which in turn compromises its effectiveness leading to treatment failure and increased cost of therapy.

The inappropriate utilization of ceftriaxone may also compromise patient safety.

8. RECOMMENDATIONS

Prescribers should limit the use of ceftriaxone only for infections that are proven or strongly suspected to be caused by bacteria. For example, the empiric use of this drug for cases other than its primary indications as in neutopenic fever, lymphadenitis, etc should be avoided. As part of this, adherence to the protocol currently prepared regarding the rationale use of this drug and other evidence-based guidelines is recommended. Prescribers should also direct therapy with C&S test result whenever it is possible.

The hospital (TASH) should make budget allocation re-arrangement to improve the quality of microbiology laboratory. It should also realize 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.

Researchers should conduct this study prospectively in other departments of TASH. This study should also be repeated to see if the interventions made will bring about changes in the utilization of ceftriaxone.

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Annexes

Annex I: Data collection form

<table>
<tr><td colspan="3">Tikur Anbessa Specialized Hospital, _____ Department (Internal Medicine, Emergency)</td></tr>
<tr><td>No.</td><td colspan="2">Patient information</td></tr>
<tr><td>1.</td><td>Patient demographic information</td><td>Pt card No._____ Sex: _____ Age: _____
Admission date: _____ Discharge date: _____</td></tr>
<tr><td rowspan="4">2.</td><td rowspan="4">Patient Medical Condition and Diagnosis</td><td>Working diagnosis</td></tr>
<tr><td>Past medical history</td></tr>
<tr><td>Physical examination</td></tr>
<tr><td>Sign and symptoms</td></tr>
</table>

		Abnormal Lab tests
		Abnormal Diagnostic Results
		C&S test (tick as appropriate): **a) Performed** ☐ If performed, tick as appropriate: i) Growth: Yes growth ☐ No growth ☐ ii) If growth: ⇒ What were the MOs isolated: _____ ⇒ What was its sensitivity? Sensitive to ceftriaxone ☐ Resistant to ceftriaxone ☐ **b) Not performed** ☐

3.	**Medication therapy**							
	Prescribed Medications	Dose	Dosage form	Route	Frequency	Duration	Indication	DI with ceftriaxone
i.	Ceftriaxone		Inj.					
ii								
iii								
iv								
v								

vi								
vii								
viii								

Other relevant information (for example, reasons for inappropriate prescribing or justification of the physician for the inappropriate prescribing, if any):

Date: _____ Data collector's name: _____

Annex II: Consent form

Addis Ababa University, College of Health Sciences, School of Pharmacy, Department of Pharmacology and Clinical pharmacy, Study on '*Evaluation of ceftriaxone utilization in medical and emergency wards of Tikur Anbessa Specialized Hospital'*.

Greeting: Hello, my name is_____. I am here today to collect data on the evaluation of ceftriaxone utilization at medical and emergency wards of TASH. The study is being conducted by Mr. Alemayehu Sileshi from Addis Ababa University, College of Health Sciences, School of Pharmacy, Department of Pharmacology and Clinical pharmacy, Post graduate program. The purpose of this study is to evaluate the appropriateness of ceftriaxone use in medical and emergency wards of TASH. 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: Alemayehu Sileshi, Tell: +251- 911560114, e-mail: alemayehusileshi45@yahoo.com

Are you willing to participate in this study?

1. Yes ……..….. Include in the participant list

2. No ……..…… Skip to the next participant

የስምምነት ቅጽ

በአ.አ.ዩ ጤ/ሳ/ኮሌጅ ፋርማሲ ት/ቤት ፋርማኮሎጂ እና ክሊኒካል ፋርማሲ ት/ት ክፍል በጥቁር አንበሳ ስፔሻያላይዝድ ሆስፒታል የሴፍትሪያክሶን መዲሃኒት አጠቃቀምን በተመለከተ በሜዲካል እና ኢመርጀንሲ የሆስፒታሉ የመታከሚያ ክፍሎች ስለሚደረግ የግምገማ ጥናት

ሠላምታ፡- ሄሎ፣ ስሜ ---------- ይባላል፡፡ ዛሬ እዚህ የተገኘሁ ሴፍትሪያክሶን ስለተባለዉ መዲሃኒት አጠቃቀምን በተመለከተ ከላይ በተገለጹት የሆስፒታሉ የመታከሚያ ክፍሎች ለሚደረግ የግምገማ ጥናት መረጃዎችን ለመሰብሰብ ነዉ፡፡ ጥናቱ እየተካሄደ ያለዉ በአ.አ.ዩ ጤ/ሳ/ኮሌጅ ፋርማሲ ት/ቤት ፋርማኮሎጂ እና ክሊኒካል ፋርማሲት/ት ክፍል ከድኅረ-ምረቃ ፕሮግራም አቶ ዓለማየሁ ስለሺ በተባሉ ግለሰብ ነዉ፡፡ የዚህ ጥናት ዓላማ በሆስፒታሉ 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 እንዲፈቅዱልኝ እጠይቀዉታለሁኝ፡፡ በመሆኑም የእርስዎን ማንነት የሚገልጽ (ለምሳሌ ስም) በመረጃ መሰብሰቢያ ቅጹ ላይ የማይካተቱ ሲሆን ሌሎችም መረጃዎች ምሥጢራዊነታቸዉ በጥብቅ የሚጠበቅ ይሆናል፡፡ የእርስዎ መረጃ በጥናቱ ዉስጥ እንዲካተት ፈቃጅም ከልካይም እርስዎ ብቻ ነዉ፡፡ በማንኛዉም ጊዜ ስለጥናቱ ጥያቄ ከተፈጠረብዎት ዋናዉን ተመራማሪ ለመጠየቅ/ለማግኘት ነጻነት እንዲሰማዎት ለመግለጽ እወዳለሁኝ፡፡**

የዋናዉ ተመራማሪ አድራሻ፡- አቶ ዓለማየሁ ስለሺ፤ ስ.ቁ: +251- 911560114፤ ኢ-ሜይል: alemayehusileshi45@yahoo.com

በጥናቱ ላይ ለመሳተፍ ፍቃደኛ ነዎት? ፍቃደኛ መሆንዎን በፊርማዎ ቢያረጋግጡልን?

1. **አዎ (ፊርማ……..) ወደ ተሳታፊዎች ዝርዝር ይጠቃለሉ**
2. **አይደለም …. ወደ ቀጣይ ተሳታፊ ተሻገር**

Annex III: Key informant interview for physicians

The following questions are based on the results obtained from drug use evaluation of ceftriaxone conducted in the medical and emergency wards of Tikur Anbessa Specialized hospital. 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 TASH.

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
    f. If other, describe_____
    _____

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
    d. If other, describe_____
    _____

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
e. If other, describe_____

_____

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
    c. If other, describe_____

    _____

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
    d. If other, describe_____

    _____

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 $\geq$ 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
    d. If other, describe_____

    _____

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 in medical and emergency wards of Tikur Anbessa Specialized 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: Sample pictures from a seminar held regarding "*Appropriate use of ceftriaxone*"