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Ceftriaxone Prescribing and Resistance Pattern at a National Hospital in Tanzania

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Abstract
Background: Since their discovery, antibiotics have contributed to dramatic fall in morbidity and mortality from bacterial infections. However, the emergence and spread of antibiotic resistance, continues to threaten the effectiveness of these agents. Ceftriaxone is one of the most important medications needed in a basic health system. Yet high levels of inappropriate use have been reported increasing the likelihood of emergence and spread of resistance.
Methods: We conducted a descriptive study to characterize ceftriaxone prescription and resistance at a tertiary hospital.
Results: Three hundred and sixty prescriptions were observed and 194 (54 %) deviated from the National Treatment guidelines with regards to indication. For patients with conditions for which ceftriaxone is recommended, 93 % (154 out of 166) prescriptions deviated from the guideline with regard to dosing frequency and 67 % deviated with regards to duration of administration. *Coagulase Negative Staphylococcus (CoNS), Escherichia coli, Klebsiella spp and Pseudomonas aeruginosa* were the most common isolates and with the highest ceftriaxone resistance rate (up to 80%).
Conclusions: At MNH, ceftriaxone is commonly inappropriately prescribed and the risk of emergence and spread of ceftriaxone resistant isolates may be high. Majority of *CoNS and Klebsiella species* are resistant, thus cautious ceftriaxone prescription is needed.

Keywords: Antibiotics, bacterial infection, antibiotic resistance

Introduction

Antibiotics are powerful and effective drugs in the fight against infectious diseases caused by bacteria and have been frequently used for decades worldwide for effective treatment of a variety of such infections (Jayakar et al. 2011). As the result, they have contributed to a dramatic fall in morbidity and mortality from bacterial infections over the years (Drug Administration and Control Authority of Ethiopia in collaboration with Management Sciences for Health, August 2009). However, the emergence and spread of antimicrobial resistance among bacterial strains, has continued to threaten the effectiveness of treatments with antibiotics and to date, antimicrobial resistance is one of the most serious challenges we face in the effort to control infectious diseases.

The major mechanism which underlies the emergence and spread of antimicrobial resistance is the exposure of microbes to sub-therapeutic concentrations of anti-infective agents such as antibiotics. This usually follows inappropriate use of antimicrobials. Indeed, studies have shown the existence of misuse of antibiotics resulting from their inappropriate prescription among other causes (Zhang & Guo, 2012). Several inappropriate antibiotic prescribing practices have been highlighted in

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different studies which include irrational drug selection, improper indication of drug use, irrational combined medication, inappropriate drug dose, frequency and route of administration (Zhang & Guo, 2012; Haldeman et al. 2020; Nyongole et al. 2015; Sonda et al. 2019) with potentially serious effects on health (Harrison & Svec, 1998). Antibiotics are prescribed incorrectly (in terms of indication for use) or sub optimally (in terms of dosage regimen) for certain bacterial infections (Slama et al., 2005); (Larson, 2007). It has been appreciated that resistance develops when humans are either treated unnecessarily or given inappropriate regimens and either the resident flora or the invading pathogens or even both can subsequently develop or acquire resistance-coding DNA (Peterson & Dalhoff, 2004).

As a result of antibiotic overprescribing and overuse, certain bacteria have become resistant to some of the most powerful antibiotics available today (Goossens, Ferech, Vander Stichele, Elseviers, & Group, 2005). Studies performed among in-patients to identify patterns of use and appropriateness of prescribing have revealed that 22-65% antibiotic prescriptions are either not appropriate or not correct [(Drug Administration and Control Authority of Ethiopia in collaboration with Management Sciences for Health, August 2009). When putting this into consideration, focusing on antibiotics that are prescribed often times, evaluation would be important to prolong the useful life of these agents (Bell, 2001). High proportions of resistance to third-generation cephalosporin for *Escherichia coli* and *Klebsiella pneumoniae* have been reported (Moyo et al. 2010; Moyo at al. 2010). Also decreased susceptibility to third-generation cephalosporins, the treatment of last resort for gonorrhea, has been verified in 36 countries (WHO, 2014). Bacterial resistance is increasing to the extent that none of the available antibiotics work for some of the infections that medical practitioners are confronted with in health facilities around the globe (Shlaes, 2010). Over prescribing of antibiotics is one of the main reasons behind the high prevalence of antimicrobial resistance observed today (Ciofi et al., 2008; Rehm, Sekeres, & Neuner, 2009).

Ceftriaxone, a third generation cephalosporin, is among the most commonly prescribed and empirically used antibiotic (Elfaki, 2009; Ebrahimzadeh et al. 2008;Davoudi, Najafi, Soleymani, Asghari, & Ehsani, 2013) making it prone to bacterial resistance. Resistance to ceftriaxone develops in bacteria primarily due to the ability to produce β-lactamases which inactivate ceftriaxone's β-lactam ring. Extended Spectrum β- Lactamases (ESBLs) are encoded by transferable conjugative plasmids which also quite often code resistant determinants not only to other antibiotics such as aminoglycosides and tetracyclines but also among related and unrelated Gram-negative bacteria (Adeniyi et al. 2006; Butaye et al. 2003), thereby making infections caused by ESBL producing organisms difficult to control. *Salmonella* species resistant to ceftriaxone have been detected in Asia, Europe, South and North America and North Africa (Dunne et al., 2000). There are strains of *Neisseria gonorrhoeae* with high level resistance to ceftriaxone in France (Unemo et al., 2012). Studies done in Tanzania reported high levels of ceftriaxone resistance especially in *Escherichia coli* and *Klebsiella* species (Sabrina et al. 2010; Manyahi et al., 2014).

Ceftriaxone is on the World Health Organization's (WHO) List of Essential Medicines, the most important medications needed in primary health facilities. Yet there are very high levels of inappropriate ceftriaxone prescription and use in both developing and developed countries (Lee et al., 2009; Pereira et al. 2004; Ayinalem et al. 2013). There are a limited number of studies on ceftriaxone prescription and use in Tanzania. Compared to other medicines, ceftriaxone use is not extensively researched in Tanzania possibly because it is a relatively new drug and that prescribers have not faced problems with its efficacy in their clinical practice. However, ceftriaxone is among the most vulnerable drugs to be over prescribed because of its high anti-bacterial efficacy, wide spectrum of activity and low potential for toxicity (Lee et al. 2009). Therefore, our study was done to provide data on how this drug is used at Muhimbili National Hospital (MNH), in Tanzania.

There has been an increased use of ceftriaxone in Tanzania recently despite that the drug is reserved for treatment of relatively few infectious conditions. This increasing trend in its use may

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result into decreased efficacy and ultimately emergence of resistance. This study was designed to characterize ceftriaxone prescribing in medical wards (including its indications, dosage, frequency of administration; and duration of therapy) and comparing this to recommendations in the National Treatment Guidelines. During the same time period as this study was conducted, we looked at the ceftriaxone susceptibility pattern to bacterial isolates at MNH.

Materials and Methods

The reported study was a hospital-based cross-sectional study involving male and female patients admitted to the MNH's general medical wards (3, 4, 5, and 6). In addition, permission to conduct the study was obtained from the MNH's Head of Research and Consultancy Unit. There are five general medical wards in the MNH's Mwaisela block with bed occupancy of about 300 beds. These wards are divided in specialized units with total daily admissions of about 40- 60 patients.

Included in our study, were male and female patients aged 13 years and above; admitted to a general medical ward during the study period; received ceftriaxone prescription on admission and who had given written informed consent or assent to participate. Patients whose ceftriaxone prescriptions were missing one or more information on the indication, dose, and frequency of administration or duration of therapy were excluded.

Medical files of all previous day's admissions were checked for ceftriaxone prescription after the unit's post admission round. All patients with ceftriaxone prescription were invited to participate in the study; consenting or assenting patients were checked for eligibility and eligible patients were enrolled. Data were collected using a specially designed form, which was completed for each patient. Socio-demographic data were obtained directly from patients whereas additional clinical data including other drug prescriptions were extracted from the patients' medical files and treatment charts. For patients referred from peripheral health facilities, additional information on ceftriaxone prescription prior to admission but for the current illness was also extracted.

The Lemeshow formula was used to calculate the minimum sample size for the study. We assumed a 64 % rate for inappropriate ceftriaxone prescription (Shohrati et al. 2010) and set a statistical significance level of 5 %, and the minimum sample size for the study was calculated to be 353 patients. Patient ceftriaxone prescription data were checked against the Tanzania National Essential Medicine List and Standard Treatment Guideline's ceftriaxone prescription recommendation to evaluate appropriateness of study patients' ceftriaxone prescription. All ceftriaxone prescriptions were assessed for appropriateness with regards to indication whereas, only patient prescriptions with appropriate indications were further evaluated for appropriateness with regards to dosage, frequency, and duration of therapy. Data were analyzed using IBM SPSS Statistics for windows, version 23.0 (Armonk, NY: IBM Corp.).

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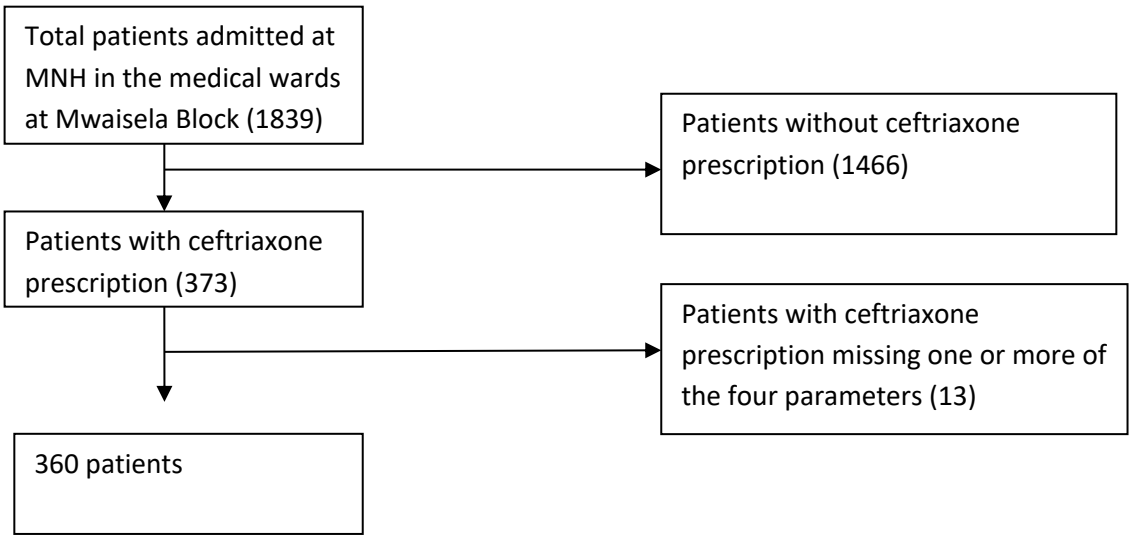

Figure 1: Study Profile

At the same time during the study period, all bacteriology clinical samples from all departments at MNH sent to the Bacteriology unit of the Central Pathology Laboratory (CPL) for culture and sensitivity and, which yielded positive cultures with significant growth were subjected to ceftriaxone chemo-sensitivity testing. Sensitivity pattern of bacterial isolates were recorded in a specially designed form. Additional information on type of specimen and the department from which the sample came from was also recorded.

The samples received in the Laboratory were processed for culture and sensitivity testing as follows: Specimens were inoculated onto Blood and MacConkey agar plates and were incubated aerobically at 37°C overnight. The cultured plates were examined after 24 hours and organisms identified by their colonial morphology, Gram staining and appropriate biochemical tests using standard techniques(Koneman, Allen, Janda, Schreckenberger, & Winn, 1997). The results were interpreted according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI)(Wayne, 2007)**.** Ceftriaxone susceptibility of the isolates was determined by Modified Kirby – Bauer disc diffusion method, according to CLSI recommendations.

Ceftriaxone discs of 30 micrograms by Oxoid Ltd. Hampshire, England were used for the isolated micro- organisms. The zones of inhibition were measured and the organisms identified as sensitive or resistant based on standard criteria. Control strains were used for checking quality of discs and reagents.

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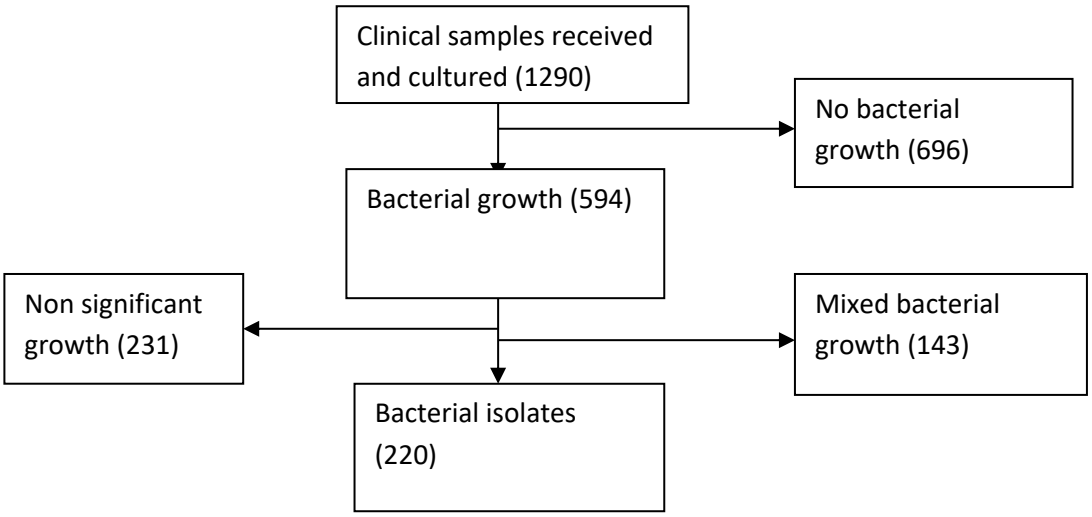

Figure 2: Selection flow chart for clinical samples

Results

A total of 1839 patients were admitted to the medical wards (3, 4, 5 and 6) at MNH during the study period and in 360 (20.8 %) of these patients, ceftriaxone was prescribed and were all included in the study. Most (75.6%) of these study participants were residing in the city of Dar es salaam and about thirty percent (29.7%) were self-referral. Of those referred from health facilities, 20.9% had ceftriaxone prescribed before being admitted to the medical wards at MNH suggesting that MNH prescribes ceftriaxone as often as the peripheral health facilities in Dar. The mean (±SD) age of study participants was 45± (19.2) years and males accounted for the majority (52.5 %) of the total study population. Most of the cases were from the infectious disease and pulmonology unit (32.2%) followed by the neurology unit (Table 1).

Table 1: Baseline characteristics of patients prescribed with ceftriaxone in medical wards of MNH from February to May, 2015 (N=360)

Characteristic	*n (%)*
Age in years	
<18	15(4.2)
18-65	285(79.2)
>65	60(16.6)
Mean (±SD) age	**45(±19.2)**

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Characteristic	*n (%)*
Sex	
Male	189(52.5)
Female	171(47.5)
Unit of admission in the medical wards	
Nephrology	51(14.2)
Infectious disease and Pulmonology	116(32.2)
Endocrinology	24(6.7)
Neurology	73(20.3)
Gastroenterology	65(18)
Dermatology	2(0.6)
Hematology	29(8)
Area of Residence	
Ilala district	104(28.9)
Temeke district	51(14.2)
Kinondoni district	117(32.5)
Out of Dar es Salaam	88(24.4)
Referral status	
Referred from a health facility	253(70.3)
Self-referral	107(29.7)
Ceftriaxone prescribed in patients referred from health facilities	**N=253**
Yes	53(20.95)
No	200(79.05)

Overall, pneumonia was the commonest condition for which ceftriaxone was prescribed. However, in 194 (54 %) of the patients, ceftriaxone was prescribed for conditions not in the list of conditions for which ceftriaxone is recommended according to National treatment guidelines. In addition, ceftriaxone was commonly prescribed (73 %) at a dose of 1g once a day. This is below the minimum recommended for any condition except for dental abscess, Ludwing's angina and caesarian section prophylaxis (table 2).

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Table 2: Ceftriaxone prescription at MNH for conditions in which ceftriaxone is recommended (daily dose/frequency)

Condition	1g once (%)	1g twice (%)	2g once (%)	2g twice (%)	1g thrice (%)	Total
Pneumonia	84(79.2)	5(4.7)	15(14.2)	1(0.9)	1(0.9)	106
Meningitis	12(44.4)	1(3.7)	11(40.7)	3(11.1)	0(0)	27
Upper gastrointestinal bleeding	18(69.2)	4(15.4)	2(7.7)	2(7.7)	0(0)	26
Acute chest syndrome	2(100)	0(0)	0(0)	0(0)	0(0)	2
Infective endocarditis	1(100)	0(0)	0(0)	0(0)	0(0)	1
Pelvic inflammatory disease	3(100)	0(0)	0(0)	0(0)	0(0)	3
Pancreatitis	1(100)	0(0)	0(0)	0(0)	0(0)	1
Total	121(72.9)	10(6.0)	28(16.9)	6(3.6)	1(0.6)	166

For patients with conditions for which ceftriaxone is recommended, the dose and frequency of administration prescribed were not according to the treatment guidelines in 93 % of them. In addition, the duration of ceftriaxone administration was not according to treatment guidelines in 67 % of these patients (Table 3). However, overall, majority (29.4 %) of all Ceftriaxone prescriptions were for pneumonia (an appropriate indication). Even so, only 5 % of these prescriptions were according to National guideline in terms of dose and frequency of administration and only 23 % in terms of duration of treatment (Table 3).

Of the 360 prescriptions 152 (42 %) were co-prescriptions of Ceftriaxone and at least one other drug or intravenous fluid with potential for interaction. Furosemide and Ringer's lactate were the commonly co-prescribed medications.

One thousand two hundred and ninety different clinical samples (excluding stool and high vaginal swabs) collected from patients during the study period were received in the laboratory. These clinical samples were cultured to isolate the organisms and two hundred and twenty (17 %) of these samples yielded positive cultures with significant growth.

Table 3: Prescriber's Compliance to the National Treatment Guideline

Condition	Number of Prescription n=166	%Prescription complying with guideline	
		Daily dose/frequency	Duration of therapy
Pneumonia	106	4.7	23
Meningitis	27	11.1	6
Upper gastrointestinal bleeding	26	15.4	25

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Condition	Number of Prescription	%Prescription complying with guideline	
	n=166	Daily dose/frequency	Duration of therapy
Acute chest syndrome	2	0	0
Infective endocarditis	1	0	0
Pelvic inflammatory disease	3	0	0
Pancreatitis	1	0	1

Most of the isolates were from blood, pus and urine. *Staphylococcus albus* was the commonest isolate from blood whereas *Pseudomonas aerugenosa*, and *Escherichia coli* were the common isolates from pus and urine respectively (table 4). Most of the ceftriaxone resistant isolates were from blood and urine. Seventy-eight percent of *Staphylococcus albus* isolated from blood were resistant to ceftriaxone; 61 % of *Escherichia coli* isolated from urine were resistant whereas 53 % of *Pseudomonas aerugenosa* isolated from pus were resistant to ceftriaxone. All the six *Escherichia coli* isolates from blood were resistant to ceftriaxone; whereas 61 % (43 out of 70) and 50 % (4 out of 8) *Escherichia coli* isolates from urine and pus respectively were resistant to ceftriaxone. Likewise, all three Klebsiella spp isolates from blood were resistant to ceftriaxone, 84 % (16 out of 19) isolates from urine and 73 % (8 out of 11) isolates from pus were resistant to ceftriaxone. All the four isolates from sputum were sensitive to ceftriaxone.

The overall percentage ceftriaxone resistance was highest with *Coagulase Negative Staphylococcus (CoNS)* (79.5) followed by *Klebsiella spp,* (77.1), *Escherichia coli* (63.5) *and Pseudomonas aeruginosa* (57.1); P = 0.003.

Table 4: Isolated Bacteria and their Sensitivity to Ceftriaxone

Types of Specimen	Isolated bacteria	Sensitivity to Ceftriaxone		
		Sensitive	Resistant	Total
Blood	*Escherichia coli*	0 (0%)	6 (100%)	6 (100%)
	Klebsiella spp	0 (0%)	3 (100%)	3 (100%)
	Pseudomonas aeruginosa	1(100%)	0 (0%)	1 (100%)
	Staphylococcus albus	8 (21.6%)	29 (78.4%)	37 (100%)
	Staphylococcus aureus	3 (100%)	0 (0%)	3 (100%)
	Streptococcus pyogenes	0 (0%)	2 (100%)	2 (100%)
Total		12 (23.1%)	40 (76.9%)	52 (100%)
Pus	*Escherichia coli*	4 (50%)	4 (50%)	8 (100%)
	Klebsiella spp	3 (27.3%)	8 (72.7%)	11 (100%)
	Proteus mirabilis	5 (100%)	0 (0%)	5 (100%)
	Pseudomonas aeruginosa	8 (47.1%)	9 (52.9%)	17 (100%)
	Staphylococcus aureus	10 (66.7%)	5 (33.3%)	15 (100%)
	Streptococcus pyogenes	2 (66.7%)	1 (33.3%)	3 (100%)
Total		32 (54.2%)	27 (45.8%)	59 (100%)
Urine	*Enterococci*	0 (0%)	1 (100%)	1 (100%)
	Escherichia coli	27 (38.6%)	43 (61.4%)	70 (100%)
	Klebsiella spp	3 (15.8%)	16 (84.2%)	19 (100%)
	Proteus mirabilis	0(0%)	1(100%)	1 (100%)
	Pseudomonas aeruginosa	0 (0%)	3 (100%)	3 (100%)
	Staphylococcus albus	0 (0%)	2 (100%)	2 (100%)
	Staphylococcus aureus	2 (33.3%)	4 (66.7%)	6 (100%)
Total		32 (31.4%)	70 (68.6%)	102 (100%)

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Discussion

Our data show that ceftriaxone prescription at MNH, in all aspects (indication, dose, and frequency and duration of administration) is far from what is recommended suggesting that by and large, Ceftriaxone is incorrectly prescribed at MNH. As the result, the risk of development of Ceftriaxone resistant bacteria isolate may be high. Our findings further suggest that ceftriaxone is more prescribed at MNH than the peripheral health facilities in Dar es Salaam. MNH is a teaching hospital for the Muhimbili University of Health and Allied Sciences and other health sciences universities in and around Dar es Salaam city and most of the clinicians at MNH are highly qualified and experienced and as such, these results are surprising. However, for reasons that we cannot speculate here, there could be a valid, evidence based, reason for this deviation from the National Treatment Guideline. This study was not designed to explore reasons for National Guideline deviations and therefore, future studies to determine the reasons for deviation may be necessary.

Likewise, our observation that Ceftriaxone is more prescribed at MNH than in peripheral health facilities can be partly explained by a different understanding of ceftriaxone indications among clinician at MNH. However, this observation can also be due to the more varied medical conditions seen in patients admitted to the medical wards at MNH.

Overall, our findings argue for a review of the National Treatment Guideline with regards to ceftriaxone prescription that should involve all stakeholders with a view of identifying technical and operational gaps in the existing national treatment guideline with subsequent design and implementation of strategies to improve and promote prescriber guideline adherence such as establishment of antibiotic stewardship programs. This may also apply for other commonly prescribed antibiotics. As a long-term strategy however, it is important to the MNH to consider including measures to improve adherence to national guidelines such as improvement in diagnostics, staff training and re-training, as part of its comprehensive antibiotic stewardship program.

We have observed that ceftriaxone is commonly prescribed to patients without indication, a finding in keeping with a study done in Mbeya zonal referral hospital (Haldeman et al., 2020; Nyongole et al., 2015). Our finding that Ceftriaxone was prescribed for conditions not in the National Treatment Guideline recommendation in more than 50 % of patients is in keeping with those reported in a study done in Ayder Hospital, Ethiopia (Abebe et al. 2012). However, similar studies in four other different hospitals in Ethiopia one in Korea, and one in Tanzania found values lower than in the present study (Lee et al. 2009; Ayinalem et al. 2013; Michael & Mulugeta, 2009; Bantie, 2014; Sonda et al., 2019). Even so, these findings suggest that inappropriate Ceftriaxone prescription is a widespread problem not limited to Tanzania. Yet use of an antibiotic including Ceftriaxone without indication is an excellent reason for high rate of bacterial resistance, risk for toxicity and allergic reactions (Zhang & Guo, 2012). Therefore, unless there is sound reason for deviation, it is important that prescribers stick to the treatment guidelines.

In our study, pneumonia and meningitis were the common appropriate indications for Ceftriaxone according to the National Guideline. This finding is similar to those reported in three hospitals in Ethiopia (Abebe et al., 2012; Michael & Mulugeta, 2009). This may mean that many clinicians are aware of the National Treatment Guideline for the treatment of pneumonia and meningitis. But what is surprising is that only about 5 % of all pneumonia prescriptions were according to guideline in terms of dose and frequency of administration, and only 23 % in terms of duration of

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treatment. This highlights the need for review of Ceftriaxone prescription guideline including clinician awareness status.

Dose, frequency of administration, and duration of therapy are equally important (WHO, 2012). In the present study, dose and frequency of administration was correct in only 7 % of Ceftriaxone prescriptions in patients with indication according to National guideline. Correct Ceftriaxone dosing, as it is with other medicines, is central to therapeutic success (WHO 2012)]. By contrast, incorrect dosing can results in poor patients outcomes such as treatment failure, toxicity, adverse effects, and development of drug resistance that may have significant cost to the health care system (WHO, 2012). We have observed incorrect duration of therapy with Ceftriaxone occurring at a frequency four times higher than previously reported (Bantie, 2014). This implies that the Ministry of Health may save significant cost of health care by implementing interventions that aim at improving and promoting appropriate antibiotic prescribing.

Commonly co-prescribed medicines

Up to 97% had one or more drugs and/or intravenous fluids prescribed with Ceftriaxone. The same observation was reported in several studies done in Ethiopia [(Abebe et al., 2012; Ayinalem et al., 2013; Michael & Mulugeta, 2009; Bantie, 2014). By and large this practice may be explained by co-morbidities for which Ceftriaxone is indicated and those in which the co-prescribed drugs and/or intravenous fluids are used especially in the setting of a tertiary care hospital like MNH. This practice carries risks when the co-prescribed drug has potential interaction with ceftriaxone. Interactions may increase or decrease the effects of the drugs concerned and may cause unexpected toxicity or sub optimal effect. Our data show that the co-prescription of drugs or intravenous fluid with interaction potential is common at MNH and Furosemide and Ringer's Lactate are the commonly co-prescribed medications. Other studies have also shown that co- prescription of ceftriaxone and potentially interacting drugs is common (Abebe et al. 2012; Ayinalem et al. 2013; Michael & Mulugeta, 2009; Bantie, 2014). However, the clinical significance of these interactions is not well established. Furosemide increases the risk of renal impairment associated with ceftriaxone use especially when high intravenous doses of ceftriaxone are used or when the patient has pre-existing renal disease. More work is needed to assess the risk of such co-prescription.

Resistance pattern of isolates

In the current study, *Coagulase Negative Staphylococcus (CoNS), Escherichia coli, Klebsiella spp and Pseudomonas aeruginosa* were the most common isolates. These isolates had the highest resistance rate to ceftriaxone of up to about 80% with statistically significant differences. High resistance of these isolates in the current study is similar to other studies (Panta et al. 2013; Javeed et al. 2011)] though values in the current study are higher. This may imply that resistance is increasing with time. But also the difference can be attributed to regional differences.

CoNS are potential pathogens especially of the blood stream. However, often times they are just contaminants. For *CoNS* to be considered a possible pathogen, it is usually a requirement that they are isolated from two different blood cultures. In this study *CoNS* were the most resistant organisms, all of them were from neonates and nearly 95% of them were recovered from blood cultures. The second most resistant organisms were the *Klebsiella species* with the majority isolated from urine. Clinicians therefore need to be cautious in prescribing ceftriaxone for infections caused by *Klebsiella species* as the majority of them are resistant.

The rising resistance of bacteria to antibiotics including ceftriaxone has been linked to irrational prescription and use of these antibiotics (Moyo et al. 2010; Blomberg et al.,2004); Dunne et al. 2000; Unemo et al. 2012). This rising resistance has negatively affected effective therapy, prolonged hospital stay and increased cost for patients and health care system at large.

Our data show that the current ceftriaxone prescribing practice at MNH may be associated with increased risk of emergence and spread of resistance. Indeed, the data also show high ceftriaxone resistance among isolates. However, no direct link can be drawn because the observed resistance is a result of previous ceftriaxone exposure among patients who provided clinical samples tested in this study. In addition, our study was conducted at one center and the findings may not be representative of the other health facilities in the country. Therefore, future studies are needed in the area of prescriber adherence to national treatment guidelines and antibiotic stewardship so as to design evidence-based interventions that will ensure improved prescribing practices.

Declarations

Ethics: The study proposal was reviewed and approved by the MUHAS scientific and Ethics Review Committee (IRB approval letter reference number MU/PGS/SAEC/Vol.XII/.

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Conflicts of interest: The authors declare that no competing financial conflicts of interest exist.

Author contributions: PS and JM – study design, data analysis and interpretation and manuscript preparation. TM – study design, data collection, data analysis and interpretation and manuscript preparation. PK,– data analysis and manuscript preparation. SM and GR – data interpretation and manuscript review.

References

Abebe, F. A., Berhe, D. F., Berhe, A. H., Hishe, H. Z., & Akaleweld, M. A. (2012). Drug use evaluation of ceftriaxone: The case of ayder referral hospital, Mekelle, Ethiopia. *International Journal of Pharmaceutical Sciences and Research, 3*(7), 2191.

Adeniyi, B., Amajoyi, C., & Smith, S. (2006). Plasmid profiles of multidrug resistant local uropathogenic Escherichia coli, Klebsiella spp., Proteus spp., and Pseudomonas spp. isolates. *J Biol Sci, 6*, 527-531.

Ayinalem, G. A., Gelaw, B. K., Belay, A. Z., & Linjesa, J. L. (2013). Drug use evaluation of ceftriaxone in medical ward of Dessie Referral Hospital, North East Ethiopia.

Bantie, L. (2014). Drug use evaluation (DUE) of Ceftriaxone injection in the in-patient wards of Felege Hiwot Referral Hospital (FHRH), Bahir Dar, North Ethiopia. *Int J Pharma Sci, 4*(4), 671-676.

Bell, D. M. (2001). Promoting appropriate antimicrobial drug use: perspective from the Centers for Disease Control and Prevention. *Clinical Infectious Diseases, 33*(Supplement 3), S245-S250.

Blomberg, B., Mwakagile, D. S., Urassa, W. K., Maselle, S. Y., Mashurano, M., Digranes, A., . . . Langeland, N. (2004). Surveillance of antimicrobial resistance at a tertiary hospital in Tanzania. *BMC public health, 4*(1), 45.

Butaye, P., Cloeckaert, A., & Schwarz, S. (2003). Mobile genes coding for efflux-mediated antimicrobial resistance in Gram-positive and Gram-negative bacteria. *Int J Antimicrob Agents, 22*(3), 205-210.

Ciofi, D. A. M., Raponi, M., Tozzi, A., Ciliento, G., Ceradini, J., & Langiano, T. (2008). Point prevalence study of antibiotic use in a paediatric hospital in Italy. *Euro surveillance: bulletin Europeen sur les maladies transmissibles= European communicable disease bulletin, 13*(41), 541-544.

Davoudi, A., Najafi, N., Soleymani, A., Asghari, H., & Ehsani, R. (2013). Evaluation of antibiotic prescription pattern in Fatimah Zahra heart hospital of Sari, at north of Iran; one year survey. *International Journal of Medical Investigation, 2*(3), 0-0.

Drug Administration and Control Authority of Ethiopia in collaboration with Management Sciences for Health, S. P. S. M. S. (August 2009). *Antimicrobial use, resistance and containment baseline survey syntheses of findings*. Retrieved from Addis Ababa Ethiopia:

Dunne, E. F., Fey, P. D., Kludt, P., Reporter, R., Mostashari, F., Shillam, P., . . . Stamey, K. (2000). Emergence of domestically acquired ceftriaxone-resistant Salmonella infections associated with AmpC β-lactamase. *Jama, 284*(24), 3151-3156.

Ebrahimzadeh, M. A., Shokrzadeh, M., & Ramezani, A. (2008). Utilization pattern of antibiotics in different wards of specialized Sari Emam University Hospital in Iran. *Pak J Biol Sci, 11*(2), 275-279.

Elfaki, A. (2009). Assessment of Antibiotics prescription in Hospitalized Patients at Elobeid Hospital, Sudan. *Sudan journal of medical science, 3*(4), 191-204.

Goossens, H., Ferech, M., Vander Stichele, R., Elseviers, M., & Group, E. P. (2005). Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *The Lancet, 365*(9459), 579-587.

Haldeman, M. S., Kishimbo, P., Seddon, M., Sangare, A., Mwasomola, D., Hall, J., . . . Nsojo, A. (2020). Evaluation of Antimicrobial Utilization and Concordance with National Guidelines at a Tertiary Hospital in the Southern Highlands Zone of Tanzania. *Am J Trop Med Hyg, 102*(2), 370-376. doi:10.4269/ajtmh.19-0231

Harrison, J. W., & Svec, T. A. (1998). The beginning of the end of the antibiotic era? Part II. Proposed solutions to antibiotic abuse. *Quintessence Int, 29*(4), 223-229.

Javeed, I., Hafeez, R., & Anwar, M. S. (2011). Antibiotic susceptibility pattern of bacterial isolates from patients admitted to a tertiary care hospital in Lahore. *Biomedica, 27*, 19-23.

Jayakar, B., Aleykutty, N., & Mathews, S. M. (2011). Changes in daily defined doses (DDD) of antibiotics after restricted use in medical inpatients. *Journal of Applied Pharmaceutical Science, 1*(6), 22.

Koneman, E. W., Allen, S. D., Janda, W., Schreckenberger, P., & Winn, W. (1997). *Diagnostic microbiology*.

Larson, E. (2007). Community factors in the development of antibiotic resistance. *Annu Rev Public Health, 28*, 435-447. doi:10.1146/annurev.publhealth.28.021406.144020

Lee, H., Jung, D., Yeom, J. S., Son, J. S., Jung, S.-I., Kim, Y.-S., . . . Ki, H. K. (2009). Evaluation of ceftriaxone utilization at multicenter study. *The Korean journal of internal medicine, 24*(4), 374-380.

Manyahi, J., Matee, M. I., Majigo, M., Moyo, S., Mshana, S. E., & Lyamuya, E. F. (2014). Predominance of multi-drug resistant bacterial pathogens causing surgical site infections in Muhimbili National Hospital, Tanzania. *BMC research notes, 7*(1), 500.

Michael, M., & Mulugeta, T. (2009). Comparative retrospective drug use evaluation of ceftriaxone injection in Police and Black lion Hospitals. In: EPA.

Moyo, S. J., Aboud, S., Kasubi, M., Lyamuya, E. F., & Maselle, S. Y. (2010). Antimicrobial resistance among producers and non-producers of extended spectrum beta-lactamases in urinary isolates at a tertiary Hospital in Tanzania. *BMC Res Notes, 3*, 348. doi:10.1186/1756-0500-3-348

Moyo, S. J., Aboud, S., Kasubi, M., Lyamuya, E. F., & Maselle, S. Y. (2010). Antimicrobial resistance among producers and non-producers of extended spectrum beta-lactamases in urinary isolates at a tertiary Hospital in Tanzania. *BMC research notes, 3*(1), 348.

Moyo, S. J., Aboud, S., Kasubi, M., & Maselle, S. Y. (2010). Bacterial isolates and drug susceptibility patterns of urinary tract infection among pregnant women at Muhimbili National Hospital in Tanzania. *Tanzan J Health Res, 12*(4), 236-240. doi:10.4314/thrb.v12i4.52997

Nyongole, O., Akoko, L., Mwanga, A., McHembe, M., Kamala, B., & Mbembati, N. (2015). Antibiotic use in urological surgeries: a six years review at Muhimbili National Hospital, Dar es salaam-Tanzania. *Pan Afr Med J, 22*, 226. doi:10.11604/pamj.2015.22.226.6253

Panta, K., Ghimire, P., Rai, S. K., Mukhiya, R. K., Singh, R., & Rai, G. (2013). Antibiogram typing of gram negative isolates in different clinical samples of a tertiary hospital. *Asian J of Pharmaeutical and Clinical Research, 6*, 153-156.

Pereira, L. M. P., Phillips, M., Ramlal, H., Teemul, K., & Prabhakar, P. (2004). Third generation cephalosporin use in a tertiary hospital in Port of Spain, Trinidad: need for an antibiotic policy. *BMC infectious diseases, 4*(1), 59.

Peterson, L. R., & Dalhoff, A. (2004). Towards targeted prescribing: will the cure for antimicrobial resistance be specific, directed therapy through improved diagnostic testing? *Journal of Antimicrobial Chemotherapy, 53*(6), 902-905.

Rehm, S. J., Sekeres, J. K., & Neuner, E. (2009). Guidelines for Antimicrobial Usage. *Cleveland clinic*.

Shlaes, D. M. (2010). *Antibiotics: the perfect storm*: Springer Science & Business Media.

Shohrati, M., Hosseini, S., & Rahimian, S. (2010). Assessment of reasonable use of ceftriaxone in internal and surgical wards. *Trauma Monthly, 2010*(3, Autumn), 171-176.

Slama, T. G., Amin, A., Brunton, S. A., File, T. M., Jr., Milkovich, G., Rodvold, K. A., . . . Weiland, D., Jr. (2005). A clinician's guide to the appropriate and accurate use of antibiotics: the Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria. *Am J Med, 118 Suppl 7A*, 1s-6s. doi:10.1016/j.amjmed.2005.05.007

Sonda, T. B., Horumpende, P. G., Kumburu, H. H., van Zwetselaar, M., Mshana, S. E., Alifrangis, M., . . . Kibiki, G. S. (2019). Ceftriaxone use in a tertiary care hospital in Kilimanjaro, Tanzania: A need for a hospital antibiotic stewardship programme. *PLoS One, 14*(8), e0220261. doi:10.1371/journal.pone.0220261

Unemo, M., Golparian, D., Nicholas, R., Ohnishi, M., Gallay, A., & Sednaoui, P. (2012). High-level cefixime-and ceftriaxone-resistant Neisseria gonorrhoeae in France: novel penA mosaic allele in a successful international clone causes treatment failure. *Antimicrobial agents and chemotherapy, 56*(3), 1273-1280.

Wayne, P. (2007). Clinical and laboratory standards institute. *Performance standards for antimicrobial susceptibility testing, 17*.

World Health Organization. (2012). The pursuit of responsible use of medicines: sharing and learning from country experiences.

World Health Organization. (2014). *Antimicrobial resistance: global report on surveillance*: World Health Organization.

Zhang, Y., & Guo, B. (2012). Hospital antibiotic abuse and analysis of its adverse reactions. *African Journal of Pharmacy and Pharmacology, 6*(43), 3027-3031.