

Drug use evaluation of cotrimoxazole prophylaxis in people living with human immunodeficiency virus/acquired immune deficiency syndrome at Jimma University Specialized Hospital, Jimma, South West of Ethiopia, 2013

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ABSTRACT

Background: Drug use evaluation is a performance improvement method that focuses on evaluation and improvement of drug use processes to advice optimal patient outcomes. *Pneumocystis carinii* pneumonia (PCP) is the most common acquired immune deficiency syndrome (AIDS) defining illness. Antibiotics being the most commonly prescribed group of drugs the problem of its overuse are a global phenomenon. Cotrimoxazole (CTX) preventive therapy (CPT) was shown effectively prevents PCP in patients with clinical evidence of immune suppression. CTX has been widely used as a treatment for common infections in many resource limited areas and as a result, CTX resistance among these pathogens has increased dramatically. In response to these problems, this study aims to evaluate the use CTX prophylaxis for opportunistic infections in human immunodeficiency virus (HIV) patients at Jimma University Specialized Hospital (JUSH).

Methods: The study was done with retrospective cross-sectional review of medical records of HIV patients who have been on CTX prophylaxis in the hospital during September 11, 2012-September 10, 2013. To maintain the validity of data, the whole 135 patient cards were included in the study within the specified period. Data were collected from January 16, 2013 to February 15, 2013 using structured data collection format.

Results: From the study subjects, 82 (60.74%) were females 85.93% of patients were used appropriate dose of CPT and 13.3% patients use CTX against contraindication. Regarding to adverse drug reactions (ADRs), 3.7% of patients were developed rash while 2.2% cases were developed nausea during the follow-up period of CPT. However, only 5.9% patients have documented information about ADR of CPT. On the top of this, CD4 count and hemoglobin test were done for 82.96%, 64.4% patients respectively during initiation of CPT. However, renal function tests were performed only for 2.96% of patients while initiating CPT.

Conclusion: The use of CPT for people living with HIV/AIDS was found to be good in JUSH with regard to initiation and dosage. However, the practice of discontinuation of CTX, documentation of ADRs and follow-up for adverse effects of CTX should be improved by proper implementation and adhering to the national guideline of CPT.

Keywords: Cotrimoxazole, HIV/AIDS, Jimma, Ethiopia, Prophylaxis

INTRODUCTION

One of the most pressing problems facing public health providers and administrators in many countries is ensuring rational drug use. The conference of experts on the rational use of drugs convened by the World Health Organization (WHO) in Nairobi in 1985, defined rational drug use as: "The rational use of drug 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 and their community". Rational drug use implies an individual approach to patient treatment. The presence of standard treatment guidelines and drug formularies for selected drugs in a health facility does not ensure that they are prescribed and used correctly. One mechanism to ensure correct prescribing and use is drug use evaluation (DUE).¹

DUE is an ongoing, systematic process designed to maintain the appropriate and effective use of medications. It involves a comprehensive review of a patient's medication and health history before, during, and after dispensing in order to attempt to achieve appropriate therapeutic decision-making and positive patient outcomes. Pharmacists participating in drug utilization review programs can directly improve the quality of care for patients, individually and as populations, by striving to prevent the use of unnecessary or inappropriate drug therapy, prevent adverse drug reactions (ADRs) and improve overall drug effectiveness.²

DUE is a performance improvement that focuses on evaluating and improving drug use processes to achieve optimal patient outcomes. DUE may be applied to a drug or therapeutic class, or diagnosis. Through its focus on the system of drug use, DUE help to identify actual and potential drug related problems, resolve actual drug related problems, and prevent potential drug related problems that could interfere with achieving optimum outcomes from drug therapy.²

Pharmaceuticals can constitute up to 40% of the health care budget in a developing country, yet large proportion of the population often lack essential medicines. Antibiotics represent approximately 30% of acute care hospitals drug expenditure and they are prescribed for 20-50% of patients. The development of bacterial resistance to antibiotics has become a major problem throughout the world. Resistance organisms may emerge as a result of many factors; including irrational use of drugs. Studies have shown that 22-65% of antibiotic prescriptions are inappropriate. In several situations, the rational use of antibiotics has been reported to reduce the emergence of resistance strains. DUE is one of the increasing used methods in combating the development of bacterial resistance to antimicrobial agent.³

Although advances in the management of human immunodeficiency virus (HIV) have dramatically reduced the incidence of opportunistic infections, *pneumocystis carinii* pneumonia (PCP) remains an important respiratory infection, particularly when it is the presenting feature of previously undiagnosed HIV infection.⁴

PCP is the most common acquired immune deficiency syndrome (AIDS) defining illness cotrimoxazole (CTX) prophylaxis was shown to effectively prevent PCP in patients with clinical evidence of immune suppression. WHO and the Joint United Nations program on HIV/AIDS have recommended CTX preventive therapy (CPT) for people living with HIV/AIDS (PLWHA) in Africa with symptomatic HIV diseases (WHO stage 2.3 or 4) and asymptomatic individuals who have a CD4 count of less than or equal to 500 cells/mm³. Wide scale use of prophylactic CTX may increase the spread of antimicrobial resistance in communities to other pathogens. It would therefore be prudent to confine the use of CPT only to those patients who will benefit from it.⁴

DUE criteria with threshold were set based on the 2005 national guidelines. The criteria included were indication to start and discontinue CTX dose and frequency of administration, contraindications, ADR and some laboratory tests conducted for monitoring patient conditions. For each criterion, a threshold limit was set to measure the extent of practitioner's adherence to the national CPT guidelines.⁵

DUE is an authorized, structured, ongoing review of physician's prescribing, pharmacists dispensing and patient use of medications. It involves and comprehensive and thoroughly review of patients history cased and medication data before (prospective DUE), during (concurrent DUE) and after (retrospective DUE) the medications are dispensed to ensure if medications are being used statically as per the guidelines set for each health care unit. It is an important subset of the general health care management process which plays a key role in managed health care system in identifying, interpreting problems and makes possible improvement in the proper use of medication.⁶

Antibiotics being the most commonly prescribed group of drugs the problem of its overuse are a global phenomenon. In India, the prevalence of use of antimicrobial agents varies from 24% to 67% and in Duke University Medical Center, the value is 34.2%. As per Kunin's criteria, it was observed that 64% of total antibiotics prescribed were either not indicated or inappropriate in terms of drug or dosage. In many prescribing pattern cases, antibiotics are used without bacteriological investigations.⁷

Antibiotics as a group contribute significantly to the cost of drugs and are claimed worldwide to account for 15-30% of total health budget. It is estimated that in India, they account for over 50% of the value of drugs sold. The increasing overuse is associated with the development of antimicrobial resistance by an organism as well as ADRs. In several situations, the rational use of antibiotics has been reported to have reduced the emergence of resistant strains.⁸

CTX has been widely used as a treatment for common infections in many resource limited areas and as a result, CTX resistance among these pathogens has increased dramatically. Resistance of non-typhoid salmonella and pneumocystis isolates to CTX has been reported to the 44% and 52%, respectively in Uganda and approximately 80% and 90 %, respectively in Miami.⁹

In response to the above mentioned problems, our study proposes to investigate information that open ways to provide feedback for a prescriber and dispenser on their performance in implementing treatment protocols and their compliance with preset approved guidelines for use of each and every medication.

Objectives of the study

General objective

- To evaluate the use CTX prophylaxis for opportunistic infections in HIV patients at Jimma University Specialized Hospital (JUSH).

Specific objectives

- To assess CTX is indicated as per the guideline
- To assess CTX is used in the right prophylactic dosage
- To evaluate the extent of drug-drug interaction and contraindication with CTX
- To assess how and when CTX is discontinued.

METHODS

Study area and study period

The study was conducted in the antiretroviral therapy (ART) clinic of JUSH, Jimma Zone, Oromia Region, South West of Ethiopia which was located 346 km from Addis Ababa. The study was conducted from January 16, 2013 to February 15, 2013.

Study design

A retrospective cross-sectional DUE was conducted based on patient medical cards. DUE criteria with threshold value for each variable was developed based on the guidelines for CPT in Ethiopia. The criteria include the major aspects of CPT therapeutic indication, contraindications, management of ADRs, drug interaction monitoring of CPT. Relevant data was collected from patient cards using data collection format, analyzed using SPSS version 16 software and evaluated against the developed criteria.

Population

Source population

All patient cards of PLWHA in the ART clinic of JUSH.

Study population

All patients cards of PLWHA in the ART clinic of JUSH who were on CPT from September 11, 2012 to September 10, 2013.

Sampling techniques and sample size

All the study population was included in the study within the specified period. Hence, sampling technique was not used and the whole 135 patients (who were on CPT during

September 11, 2012-September 10, 2013) were included in the study.

Variables

Independent variables

- Patient characteristics (age, sex, pregnancy, and breast feeding)
- Patient's clinical condition
- Laboratory profiles of the patients.

Dependent variables

- Indication
- Contra indication
- Drug-drug interaction
- Dosage/dose, frequency and duration
- Monitoring of CPT
- Discontinuation of CPT.

Data processing and analysis

The collected data were filtered, categorized and the result was analyzed with SPSS version 16 software and presented using tables and graphs.

Data quality control

To maintain the quality of data, the data collection format was tested by a pilot study and necessary adjustment was made on the data collection format. On the top of this, training of data collectors was done during data collection and supervision of data collectors were done during the data collection period to maintain the completeness of the data.

Ethical consideration

Formal ethical clearance was obtained from the Ethical Review Board of College of Medicine and Health Sciences of Jimma University and presented to the medical director of JUSH for the sake of permission to conduct the study.

Inclusion and exclusion criteria

Patient medical cards within complete socio-demographic data and dosage regimen of CPT were included in the study.

Limitation of the study

The scarcity of literature on DUE, poor documentation of ADRs and lack of laboratory set up for determination of renal function test were the major limitations for the completeness of the study.

RESULTS

A total of 135 patient records were evaluated for CPT appropriateness. Among these, 113 (83.7%) patients were in the age group of 15-49 years where as 17 (12.6%) and 5 (3.7%) patients were under 15 and above 50 years of age respectively. From the study subjects, 82 (60.74%) patients were females, whereas 53 (39.26%) patients were males who were under CPT (Table 1-3).

Appropriate dose of CPT versus inappropriate dose of CPT

From 135 cases, 116 (85.93%) uses appropriate dose of CPT while 19 (14.07%) inappropriate dose of CPT (Table 4 & Figure 1).

CPT use against contraindication

From 135 patients, 18 (13.3%) patients were used CTX against contraindication. However, there was not documented evidence about the consequence of contra use of CPT (Table 5).

Drug interaction

Zidovudine based regimen were used in for 16 (11.85%) cases with CPT which might have double blood toxicity in advanced HIV patients; however, there was not documented consequences of blood toxicity (anemia) due to the combined use of zidovudine and CPT.

ADRs monitoring and documentation

Regarding to ADR_s, 5 (3.7%) patients were developed rash, while 3 (2.2%) patients were developed nausea during the follow-up period of CPT. For 3.7% of the patients, CPT was discontinued and desensitized for the recommended period of time which was in line with the national guideline of CPT. Furthermore, 8 (5.9%) patient cases had documented information about the occurrence of ADRs while 127 (94.1%) patient cases did not have documented information about ADRs of CPT. Hence, this study showed that there was poor monitoring and documentation of ADRs.

Indication of CPT

From the study population, 123 (91.1%) patients were appropriately initiated CPT according to the national guideline while in 12 (8.89%) patients CPT was inappropriately indicated.

According to the national guideline, it is recommended to measure the laboratory profile of the patient before commencing CPT. from the study population, CD4 count and hemoglobin level were determined for 112 (82.96%) and 87 (64.4%) of cases, respectively. However, renal function tests were performed only in 4 (2.96%) cases (Table 6).

Table 1: Age sex distribution of PLWHA on CPT in JUSH from September 11, 2012 to September 9, 2013.

Age	Characteristics		Total (%)
	Sex		
	Male frequency (%)	Female frequency (%)	
<15 years	5 (3.7)	12 (8.89)	17 (12.6)
15-49 years	44 (32.6)	69 (51.1)	113 (83.7)
50 years and above	4 (2.96)	1 (0.74)	5 (3.7)
Total	53 (39.26)	82 (60.74)	135 (100)

Table 2: Marital status, religious status and level of education of PLWHA on CPT in JUSH from September 11, 2012 to September 9, 2013.

	Frequency (%)
1. Marital status	
Married	52 (38.5)
Single	35 (25.9)
Widowed	26 (19.3)
Divorced	22 (16.3)
Total	135 (100)
2. Religious status	
Orthodox	75 (55.6)
Muslim	48 (35.6)
Protestant	9 (6.67)
Other	3 (2.2)
Total	135 (100)
3. Educational level	
Illiterate	25 (18.6)
Grade 1-8	47 (34.8)
Grade 9-12	50 (37)
Above 12	13 (9.6)
Total	135 (100)

Table 3: Initial patient condition at the start of CPT among PLWHA on CPT in JUSH from September 11, 2012 to September 9, 2013.

Variables	Frequency (%)
Asymptomatic (CD4 count<350 cells/mm ³)	31 (22.96)
Stage II	48 (35.56)
Stage III	44 (32.59)
Stage IV	12 (8.89)
Tuberculosis	23 (17)
<i>Pneumocystis carinii</i> pneumonia	2 (1.48)
Oral candidiasis	9 (6.67)
Other	1 (0.74)

Table 4: Distribution of appropriate and inappropriate dose of CPT by age for PLWHA in JUSH ART clinic from September 11, 2012 to September 9, 2013.

	Age	Frequency (%)
Appropriate dose of CPT	<6 months	1 (0.74)
	6 months-5 years	9 (6.67)
	6-14 years	4 (2.96)
	>14 years	102 (75.56)
	Total	116 (85.93)
Inappropriate dose of CPT	<6 months	2 (1.48)
	6 months-5 years	1 (0.74)
	6-14 years	1 (0.74)
	>14 years	15 (11.1)
	Total	19 (14.07)

Table 5: CPT uses against contraindication for PLWHA in JUSH ART clinic from September 11, 2012 to September 9, 2013.

Evidence for contra use	Frequency (%)
Severe neutropenia	8 (5.9)
Severe thrombocytopenia	5 (3.7)
Severe anemia	3 (2.2)
Hepatic diseases	1 (0.74)
First trimester of pregnancy	1 (0.74)
Total	18 (13.3)

Table 6: Laboratory measurement of PLWHA during the initiation of CPT for PLWHA in JUSH ART clinic from September 11, 2012 to September 9, 2013.

Laboratory profile	Frequency (%)
CD4 count	112 (82.96)
Hemoglobin level	87 (64.4)
Liver function test	85 (62.96)
Complete blood count	78 (57.78)
Renal function test	4 (2.96)

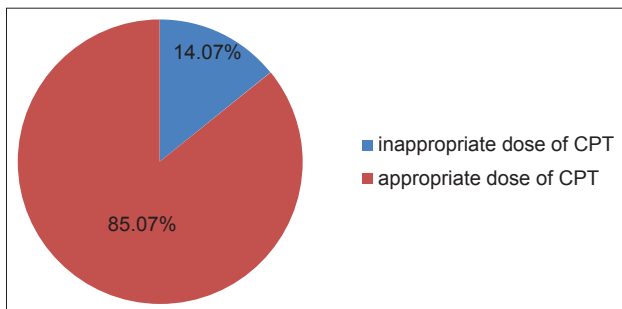


Figure 1: Appropriate and inappropriate dose of CPT for PLWHA in JUSH ART clinic from September 11, 2012 to September 9, 2013.

Laboratory monitoring at the regular interval according to the national guideline

From the study population, for 110 (81.5%) patients CD4 count was measured every 6 months which was consistent to the national guideline. When compared to other laboratory profile monitoring, there was better measurement of CD4 count at the regular interval of time (Figure 2).

DISCUSSION

This study has attempted to evaluate the pattern of rational use of CPT among PLWHA in JUSH ART clinic. Retrospective DUE is one of the ways to ensure medicines are used appropriately. If therapy was deemed inappropriately, intervention with providers or patients were necessary to optimize drug therapy.

The indication of CTX prophylaxis in JUSH was consistent with the criteria set by the national guideline of the country. Therefore, the indication to initiate CTX prophylaxis was encouraging in this hospital.

Inappropriate use and overuse of medicines waste resources and results in significant patient harm in terms of poor patient outcomes and ADRs. As indicated in Figure 1, 85.93% of the patients were used appropriate dose of CPT. similarly, a retrospective study in Hawassa Referral Hospital showed that 87% of patients were used appropriate dose of CPT.¹⁰ Even though, the use of appropriate dose of CPT was encouraging, the prescribers should be more adhered to the national guideline to ensure rational drug use and enhance the quality of life of the patients.

From the study population, 13.3% of patients used CTX against contraindications. Among these 5.5% patients were developed severe neutropenia, 3.7% and 2.2% patients have severe thrombocytopenia and anemia respectively (Table 5). A study done in Zambia involving 540 HIV positive children (1-14 years) revealed that 5.7% and 3% of patients used CPT have anemia and neutropenia respectively.¹¹ When compared

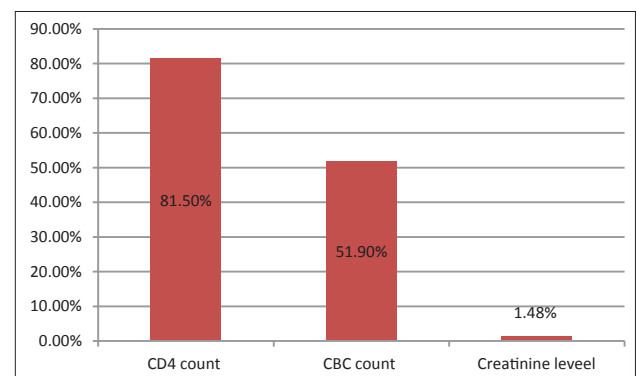


Figure 2: Laboratory monitoring of PLWHA at the regular interval according to the national guideline in JUSH ART clinic from September 11, 2012 to September 9, 2013.

to this study, there was a problem of taking attention about contraindication which was inconsistent to the national guideline. Hence, that the health care providers should be more adhered to the guideline for better treatment outcomes.

Regarding to ADRs, 3.7% patients were developed rash while 2.2% patients were developed nausea during the follow up period of CPT. Similarly, a study done on CPT use in 540 HIV positive children (1-14 years) in Zambia revealed that 0.3% of the study participants were developed skin rash.¹¹ As compared to the study done in Zambia, there was an occurrence of higher adverse effect in JUSH ART clinic. This might be due to poor attention of about the adverse effect of CTX. Furthermore, even though the national guideline recommends having appropriate documentation of ADR, there was poor monitoring and documentation of ADR information in the hospital.

Practitioners fully adhered to the national CPT guideline with regard to indication to start CPT though there was a problem in discontinuing the drug. Even though the guideline recommend discontinuation of CTX when CD4 count is greater than 500 cells/mm³, only in 2.2% of patients were discontinued. This helps to reduce the pill burden of patients on ART thereby improve their adherence and treatment outcomes.

According to the national guideline, it is recommended to measure the laboratory profile of the patient before initiating CTX. From the study population, CD4 count and hemoglobin level was determined for 82.96% and 87% cases respectively. However, renal function test was performed only in 2.96% cases (Table 6). This was due to lack of laboratory setup to conduct renal function test hence most of the patients were used CPT without assessing their renal function level which might cause crystalluria for patients with renal insufficiency. In another study, conducted in Hawassa Referral Hospital, the study had not address laboratory monitoring of hemoglobin results due to the lack of data on these profile.¹⁰ Hence, that as compared with this hospital, measurement of hematological profile was good in JUSH ART clinic.

CONCLUSION

The over use of CPT in PLWHA in JUSH was in line with the national guideline. However, discontinuation of CPT for those patients showing improvements in CD4 count wasn't according to the guideline. Besides, monitoring for ADR during the follow-up visit was not consistently done for all patients.

Recommendations

In order to improve the rational use of CPT and also to prevent the development of resistance the following recommendations was forwarded.

- The prescribers should adhere more the guideline concerning contraindication and drug interactions
- There should be proper monitoring and documentation of ADR during the follow up period for better treatment outcomes
- The responsible bodies should establish laboratory set up to determine renal function test for proper monitoring of laboratory profile during the follow up period
- There should be proper discontinuation of CTX according to the national guideline for those patients showing improvement in CD4 counts.

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