

Assessment of Drug related Problems in Pediatric ward of Zewditu Memorial Referral Hospital, Addis Ababa, Ethiopia



Mequanent kassa (Bpharm)

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This is to certify that the thesis prepared by Mequanent kassa, entitled: assessment of Drug Related Problems in pediatric ward of Zewditu Memorial Referral Hospital Ethiopia. Submitted in partial fulfillment of the requirements for the degree of Master of Pharmacy in Pharmacy Practice complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

Signed by the Examining Committee:

Internal Examiner: Dr Ephrem Engidawork (Phd) -----Date\_\_\_\_\_

External Examiner: Dr Muluwork Tefera (M D) -----Date\_\_\_\_\_

Advisor: Dr Workineh Shibeshi (Phd) -----Date\_\_\_\_\_

Advisor: Dr. Tigist Bacha (MD) -----Date\_\_\_\_\_

Chair of Department

## **Abstract**

Assessment of drug related problems in pediatric ward of Zewditu memorial referral hospital, Addis Ababa, Ethiopia

Mequanent kassa, 2015

Addis Ababa University

Although medications play a vital role in the cure, palliation and inhibition of disease they also expose patients to drug-related problems (DRPs), which are common in hospitalized patients. Pediatrics are risky population to be affected easily by DRPs, as dynamic and kinetic behaviors of drugs in this population are usually different than adults. The focus of this study was to assess DRPs in the pediatric ward of Zewditu memorial referral hospital (ZMRH). A retrospective study was conducted on 285 randomly selected patients. Data was obtained through review of physician medication orders and patients' files. The incidence and type of DRPs were studied and documented using the Pharmaceutical care network Europe foundation (PCNE) classification system. Out of the 1055 medication orders reviewed, a total of 106 DRPs were identified in 90 patients with an incidence of 31.57%. The most frequently identified DRPs were dosing problems of drugs (42.45%). This was followed by drug-drug interactions (38.67%), and adverse drug reactions (8.49%). The number of prescribed drugs (AOR=2.3, 95% CI: 1.3-4.3; P=0.007) and total number of disease conditions (AOR=4.8, 95% CI: 1.9, 12.1; P=0.001) were potential risk factors for occurrence of DRPs. Based on the results drug related problems were common in this study, the most frequent were dosing problems and drug-drug interactions. Poly pharmacy and total number of disease conditions were potential risk factors. **Key words:** Drug related problems, pediatrics, Ethiopia

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## List of Abbreviations

ADR	Adverse Drug Reaction
AOR	Adjusted Odds Ratio
COR	Crude Odds Ratio
DDI	Drug-Drug Interaction
DRPs	Drug Related Problems
HAART	Highly Active Anti-Retroviral Therapy
HIV	Human Immunodeficiency Virus
JUSH.	Jimma University Specialized Hospital
NICU	Neonatal Intensive Care Unit
PCNE	Pharmaceutical Care Network Europe
PICU	Pediatric Intensive Care Unit
TB	Tuberculosis
ZMRH	Zewditu Memorial Referral Hospital

## **1. Introduction**

### **1.1 Background**

Although medications play a vital role in the cure, palliation and inhibition of disease, they also expose patients to drug related problems (DRPs) (Baena et al., 2006). There are variety of definitions and classification of DRPs. According to Pharmaceutical care network in Europe (PCNE), DRPs, have been defined as ‘an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes’, and it classified as dosing problems, adverse drug reaction(ADR), needs additional drug therapy, drug-drug interactions, unnecessary drug therapy and non-adherence (PCNE,2006; Annex I).

Hospitalized patients are more likely to be exposed to poly-pharmacy. This in turn is a concern for potential DRPs (Fijn et al., 2002). A potential problem is not manifest, but if left unresolved, it may lead to drug-related harm to the patient. However, an actual problem has resulted in clinical manifestations like adverse drug reaction or therapy failure due to incorrect dosage (Viktil et al., 2008). Therefore, addressing DRPs has become a priority, due to the complexity of today’s drug therapy, which consequently makes appropriate drug prescribing increasingly challenging (Blix et al., 2006; Ibrahim et al., 2013; Rashed et al., 2012).

The pediatric group of population is a risky population to be affected easily by DRPs, as pharmacodynamics and pharmacokinetic behavior of drugs in this population usually is different than adults (Wood et al., 2003). Epidemiological studies, which investigate DRPs in children, are scarce. Fewer studies have assessed all components of DRPs.

However, many studies focused on one aspect of DRPs such as adverse drug reactions (ADRs), or dosing problems. Accordingly, the results of such studies are incomplete to represent the wider picture of DRPs. But the present study was covering all the components of DRPs.

### **1.1.Statement of the problem**

Majority of hospitalized patients had DRPs (Blix et al., 2004) and it is a major safety issue for them. Some of the DRPs existed at the time of admission to hospital, while others arose during hospital management.

Even if, epidemiological data of DRPs in the pediatric population are still limited, a total of sixty two DRPs were identified in Pediatric Ward of a single center study from North West part of Pakistan, and the most DRPs were: untreated conditions (25.80%), improper drug selection (19.35%), drug interactions (9.67%), therapeutic duplication (1.61%), and drugs without indication (11.29%), (Alia et al., 2013). On the other hand, a study done in the UK and the Kingdom of Saudi Arabia, in a prospective cohort study was found that a total of 478 DRPs in 333 patients with overall DRPs incidence of 45.2%. The most common DRPs were: dosing problems, e.g. too low or high dose, too short or long dosing interval; medicine choice problems, e.g. inappropriate dosage forms, untreated indications; improper administration techniques, mainly reported from pediatric intensive care units (PICUs); (Rashed et al., 2012). However, a study done in Hong Kong was found that a total of 82 DRPs were experienced by 69 patients with overall incidence was 21.0%, and the most common DRPs were: dosing problems, e.g. too low or high dose, too short or long dosing interval; followed by drug choice problems and adverse drug

reactions. Sixty-seven (81.7%) DRPs cases were assessed as preventable, 42 (51.2%) as minor and 40 (48.8%) as moderate (Rashed et al., 2013).

There are a number of consequences associated with DRPs which include hospitalizations, long-term care admissions, emergency department visits, additional physician office visits, and additional prescriptions. In addition to these, substantial costs are also associated with DRPs. For example, the economic burden arising from drug related morbidity and mortality in USA was \$177.4 billion annually (Ernst et al., 2001). Whereas, £100707 was reported in Australian study (Easton et al., 2004).

Drug related problems induced hospital admissions and emergency department visits have been significantly increased over the past few decades. Accordingly, 5-28% were reported in various studies (Al-Arifi et al., 2014; Malhotra et al.,2001, Pirmohamed et al.,2004). Drug related problem induced pediatric hospital admission is also a major public health issue. For example, studies from Australia investigated pediatric hospital admissions as a result of DRPs and found that 4.3% of pediatric admissions and 3.3% of emergency department visits were related to DRPs (Easton et al.,2004).In addition to this, other studies conducted in Lebanon, Israel, and Australia report the frequency of such admissions to range between 7.9% and 17.7% (Major et al.,1998, Easton.,1998;Yosselson-Superstine et al.,1982).A review states that incidence rates for ADRs causing pediatric hospital admission ranged from 0.4% to 10.3% of all children (Smyth et al.,2012).Therefore, DRPs are of major concern in view of their physical, psychological and economic burden to the patients and to society as a whole.

To our knowledge, such a study was not studied in this area in Ethiopia. Therefore, this study was designed to determine prevalence, common DRPs types, and factors associated with DRPs at the pediatric ward of ZMRH, Addis Ababa Ethiopia. The study findings would be used as a base line on epidemiology and potential associated risk factors for drug-related problems in hospitalized children in Ethiopia.

### **1.3. Literature review**

The purpose of this literature review is to provide an overview of the context where the drug related problems in pediatric pharmacotherapy arise and to examine those problems in detail.

### **1.4. Prevalence of ADR**

Children are thought to be at a higher risk of adverse drug events including medication errors and adverse drug reactions (ADRs) than adults due to their physiology and immature mechanism of drug metabolism (Ghaleb et al., 2010, Rashed et al., 2012). Different studies have reported different factors that predispose patients to ADRs. However, compared to adults fewer data are available regarding risk factors for ADRs (Gonzalez et al., 1998, Impicciatore et al., 2001), and prevalence of ADRs in children, Because children, especially the younger ones, are less articulate in describing symptoms, and their nonverbal communication is often misunderstood or ignored, even serious adverse reactions in children often go unreported to health practitioners or authorities (Yewale et al., 2012).

Literature shows that, the potential for adverse drug reactions within the pediatric inpatient population is about three times as high as among hospitalized adults (Kaushal et

al., 2001). For instance, a prospective cohort study was conducted on 1020 patients who were admitted to 2 academic medical centers during a 6-week period in USA reported that 18.7% of potential ADRs were developed during the study period (Fortescue et al., 2003).

However, different figures were reported by a variety of studies such as, 0.9% incidence rate in Italy (Gallo et al., 2012), 13.4% in Hong Kong (Rashed et al., 2013), 9.53% incidence rate in Nottingham university (Impicciatore et al., 2001), 17.7% in UK (Thiesen et al., 2013), 16.7% in five European and non-European hospitals (Rashed et al., 2012), 4.4% incidence rate in India (Verma et al., 2014), 30 ADRs identified by Priyadharsini et al., (2011), 8.2 % in Saudi Arabia (Khan et al., 2013), 14.1% in Mali (Oumar et al., 2012), and 7.9% United Kingdom (Bellis et al., 2013).

### **1.5. Dosing problems**

According to Foli et al., (1987), Pediatric patients especially aged 2 years and less and pediatric intensive care unit patients received the greatest proportion of errant orders. For example, a prospective cohort study was conducted in children who were admitted to a medical ward, pediatric intensive care unit or neonatal intensive care unit of seven Hong Kong hospitals, to determine the epidemiology and identify risk factors for DRPs in hospitalized children, during a 3 month period. The study results showed that, (42.7%) of dosing problems was reported (Rashed et al., 2013).

Different results were reported by a variety of studies, 54% in UK and the Kingdom of Saudi Arabia (Rashed et al., 2012), 22.1% dose errors and 5.4% of dosing frequency errors in King Abdulaziz medical City (Al-Jeraisy et al., 2011), 0.15 % to 34.8 % incidence rate of incorrect dose in middle eastern countries (Alsulami et al., 2013), 49.3

% in Spain (Fernández et al., 2013), 34% in USA (Condren et al., 2010), 28 % in USA (Fortescue et al., 2003), 34 % in USA (Kaushal et al., 2001), 11.1 % by (Lesar et al., 1997), 50 (8%) for inappropriate indication and 42 (7 %) for inadequate dose by Monica et al., (2011), 38.0% under dosage and 18.8% over dose in Nigeria (Oshikoya et al., 2007), 31.39% wrong dose and 4.48% wrong frequency in Ethiopia Zeleke et al., (2014) and 26.5 % of dose errors in Ethiopia (Girma and Feleke, 2010).

### **1.6. Drug-Drug interactions**

Drug interactions refer to the interference of a drug in the action of another drug or the interference of food or nutrient in the action of drugs. It is estimated that interactions occur in 3 to 5% of patients receiving few drugs, and when 10 to 20 drugs are used, this rate reaches 20%. Pediatric patients require special attention from health professionals in terms of drug interactions, as they react to drugs differently from adults. The body parts that are responsible for the excretion and elimination processes are not fully developed until 1 year of age, resulting in extended half-life of metabolized drugs and reduced excretion, which may result in toxicity problems (Martinbiancho et al., 2007).

An already designed proforma was used to enter the collected data regarding selected typical patients cases of pediatric infectious diseases, to evaluate effective clinical Pharmacy clerkship as an emerging programme on drug related problems in Pediatric Ward- a Single Centre Study from north west part of Pakistan, was reported that 9.67% of drug interactions (Alia et al., 2013).

A cross sectional study was conducted by Ismail et al.,(2013), to identify the frequency, levels and predictors of potential drug-drug interactions (pDDIs) in a pediatric ward of a teaching hospital in Pakistan on 400 pediatric patients found that, 25.8 % of drug-drug interactions and the most frequently implicated drugs were phenobarbital, diazepam ,dexamethasone, rifampin, and furosemide.

However, a higher prevalence of drug-drug interactions were reported in HIV-infected children on antiretroviral therapy in Nigeria study 67.1% and the most frequently involved drug combinations were, nevirapine and fluconazole, zidovudine and fluconazole ,zidovudine and rifampicin, and nevirapine and prednisolone (Oshikoya,et al.,2014).

### **1.7. Need additional drug and unnecessary drug**

Another aspect of DRPs is unnecessary drugs due to, duplicate prescription of drugs. The prevalence of duplicate prescription in a study done at general pediatric ward and (PICU) in Saudi Arabia showed that 1% (Al-Jeraisy et al., 2011). Comparable result was reported in Pakistan 1.61% (Alia et al., 2013) and in the pediatric wards of Dessie referral hospital 1.79% (Zelege et al., 2014).

Needs additional drug therapy due to untreated conditions reported, in North West part of Pakistan, was 25.80% (Alia et al., 2013).

### **1.8. Risk factors to Drug related problems**

Different variables are potential risk factors for the development of drug related problems in hospitalized children. Therefore, different variables were reported by different published literatures. For example, in a large prospective study in UK and Saudi was reported that, poly pharmacy and transferred admission (another hospital or ward) were

potential risk factors for the occurrence of drug related problems (Rashed et al., 2012)..However, a review article on drug-related problem in children with chronic kidney disease study showed that, prolonged hospitalization, number of medicines prescribed, and in children undergoing dialysis, were risk factors for the development of DRPs (Ibrahim et al., 2013). However, Hong Kong study reported that, the number of prescribed drugs and ‘certain infectious and parasitic diseases’, were potential risk factors for occurrence of DRPs (Rashed et al., 2013).

## **2. Objectives of the study**

### **2.1. General objective**

To assess drug related problems in the pediatric ward of Zewditu memorial, referral hospital, Ethiopia.

### **2.2. Specific objectives**

- To determine the incidence of DRPs
- To describe types and frequency of DRPs
- To identify, drugs that are frequently involved in DRPs
- To identify factors associated with DRPs

### **3. Methods**

#### **3.1. Study setting**

The study was conducted in the pediatric ward of Zewditu memorial, referral hospital (ZMRH). Zewditu memorial referral hospital is a 180 bed referral and it is one of the largest hospitals in Ethiopia. A total of 720 (460 medical and 260 non-medical) staff members are working in the hospital. The hospital is located in Addis Ababa; the capital city of Ethiopia and is run by Addis Ababa city health bureau. The hospital has different departments and clinics in it: internal medicine, pediatrics, gynecology/obstetrics, surgery, dentistry clinic, psychiatry clinic, HIV clinic, and dermatology. Pediatric ward has 65 beds, and it provides inpatient services for a total of 1200-1500 patients per year for admitted patients. On the average, about 1-3 children are admitted daily at the pediatric ward. A total of 9 doctors; comprising of 3 senior pediatricians, 6 general practitioners, and 16 nurses are working at the ward.

#### **3.2. Study Design and period**

This was a retrospective cross-sectional study, reviewed patient charts and physician medication order notes over a 12-month period, for Children who had been treated at pediatric ward of Zewditu memorial referral hospital (ZMRH) from June 5 2013 to June 5 2014.

#### **3.3. Sample Size and Sampling Methods**

The Sample size was calculated based on single population proportion formula (Pourhoseingholi et al., 2013). By using the following assumption:  $(1.96)^2$  were used for

$Z_{\frac{\alpha}{2}}$  and the proportion (P) of DRP in these groups was 50% because no research had been published on this topic in Ethiopia before June 2014. With 95% confidence interval (CI) and marginal error (d) of 5%, the sample size was found (n): 384

$$n = \frac{Z_{\frac{\alpha}{2}}^2 P (1 - P )}{d^2}$$

The number of source population (N) in the study period i.e the number of patients admitted in the ward from June 5 2013 to June 5 2014 was 1100.

The size of the population is less than 10,000. Therefore; the sample size should be corrected using the following correction formula.

$$\text{corrected sample size} = \frac{NXn}{N + n}$$

The calculated sample size; by using the above correction formula was 284.6~ 285.

Where: n- is the non-corrected sample size which is 384

N- is the size of the study population which is 1100

Simple random sampling method was used to take samples, for one year (June 5 2013 to June 5 2014), from the patient's admission registration book during data collection process. Card number of each patient was recorded in piece of paper then it was collected in box. Finally samples were drawn from this box for the study.

### **3.4. Source and study population**

All patients visiting to pediatric ward of ZMRH during the study period were considered to be the source population. On the other hand, the study population was all patients

admitted to pediatric ward of ZMRH during the study period and that fulfilled the inclusion criteria.

### **3.5. Inclusion and exclusion criteria**

#### **Inclusion criteria**

- Patients who were admitted to pediatric ward of ZMRH with in the study period.
- Patients whose age was less than 15 years of age
- Patients whose hospital stays were greater than 48 hour

#### **Exclusion criteria**

- Due to the differences of their metabolism and physiology of malnourished patients from other patients they were excluded from the study
- Excluded charts and notes for which background information was incomplete and charts which has no drug orders

### **3.6. Data Collection Procedure**

#### **3.6.1. Instruments**

Data was taken from patient medical charts and medical records. A standard data recording format, was used (Annex II), it was prepared by reviewing different literature for important variables to DRPs and it was tested in the same setting prior to the main data collection and the necessary adjustment was done. The following data was recorded for each Patient: age, Children were grouped in to six categories' by reviewing different literature, gender, principal diagnosis and concomitant disease states based on the

international classification of diseases,10th revision (ICD-10) codes (WHO-ICD10,2014), and the length of hospital stay computed as the number of days from admission to discharge. Length of hospital stay were categorizing in to three classes by reviewing different literature. Other data collected included biochemistry and hematology results, microbiological culture and sensitivity tests. For each medication chart, the data collected included generic and/or trade name of medications, dosage regimen including (dose, dosing frequency, and duration of therapy), start date and stop date of the medications.

### **3.6.2 Data Collectors Recruitment and Training**

Data was collected by two final year pharmacists, and the data collectors were trained by the principal investigator about the aim of the study, the strict use of the data abstraction format and what and how to collect the data from the patient medical chart.

### **3.6.3 Data Quality Control**

In order to assure the quality of data, the data abstraction format was pretested prior to the main data collection on a sample equivalent to 14 (5%) of the total sample size in randomly selected patient medical charts, which were not included in the study and appropriate adjustment was done on the data abstraction format. In addition to this, the principal investigator had supervised the data collectors during data collection. The collected data was checked for completeness and consistency on daily basis.

### **3.6.4 Data Analysis and Interpretation**

Drug related problems were realized by reviewing and analyzing all medication orders, administration sheets, laboratory and diagnostic test results, then DRPs were identified by

evaluating the appropriateness, of prescriptions in terms of indication, dosage, duration of therapy, appropriateness of drug choice, with ministry of health Ethiopia and WHO: Pocket book of pediatric hospital care: Ethiopia. Guidelines for the management of common illnesses in hospitals; 2010, and Nelson text book of pediatrics 19<sup>th</sup> edition. Potential DDIs were identified using Medscape online drug interaction checker, up-to-date version 21.2 and Micromedex, a freely available online medical decision support tool that provides current and clinically relevant information concerning drug interactions and pharmacotherapy a pathophysiologic approach. The classification of DRPs was developed by considering the classification system of specified by PCNE (version5.01). Accordingly, the DRPs classification had six categories namely; dosing problems, drug-drug interaction, adverse drug reaction, unnecessary drug, need additional drug therapy and non-adherence.

The collected data were entered into Epi Info version 7 and exported to statistical Package for the social sciences (SPSS) version 20 for stastical analysis. In order to summarize the result, descriptive statistics including: frequency, mean and standard deviation was used. The number of DRPs per patient was determined to estimate the incidence of DRPs. The incidence was calculated by dividing the number of patients who experienced DRPs by the total number of study population.

Both univariate and multivariate analysis was run. Based on the univariable analysis; the variables that were significant ( $P \leq 0.05$ ) included in the multivariate analysis to control confounders and to identify factors independently associated with the occurrence of DRPs. The Results of, univariate and multivariate analysis was reported as crude(COR)

and adjusted odds ratio (AOR) at 95% confidence intervals (95% CI) respectively. P-value  $\leq 0.05$  was considered as statistical significance.

### **3.7. Study variables**

#### **3.7.1 Dependent variable**

- Drug related problems

#### **3.7.2. Independent variables**

- Sex
- Age
- Number of disease conditions
- Number of drugs used
- Duration of Hospital stay

### **3.8. Ethical Consideration**

Letter of ethical clearance was obtained from ethics committee of the School of Pharmacy, Addis Ababa University, Addis Ababa city health bureau as well as pediatric Department of ZMRH. Privacy and confidentiality was ensured during review of patients' chart by data collectors. Thus, name and address of patients were not recorded in the data abstraction format.

### 3.9. Operational Definitions

An ADR is ‘an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dose regimen, or withdrawal of the product’ (Edwards et al.,2000).

**Dosing problems:** Dose of the drug ordered is  $\pm 10\%$  of the recommended dose and Wrong frequency (frequency that deviates from the recommended practices)

## 4. Results

### 4.1. Socio-Demographic and Clinical Data of Patients

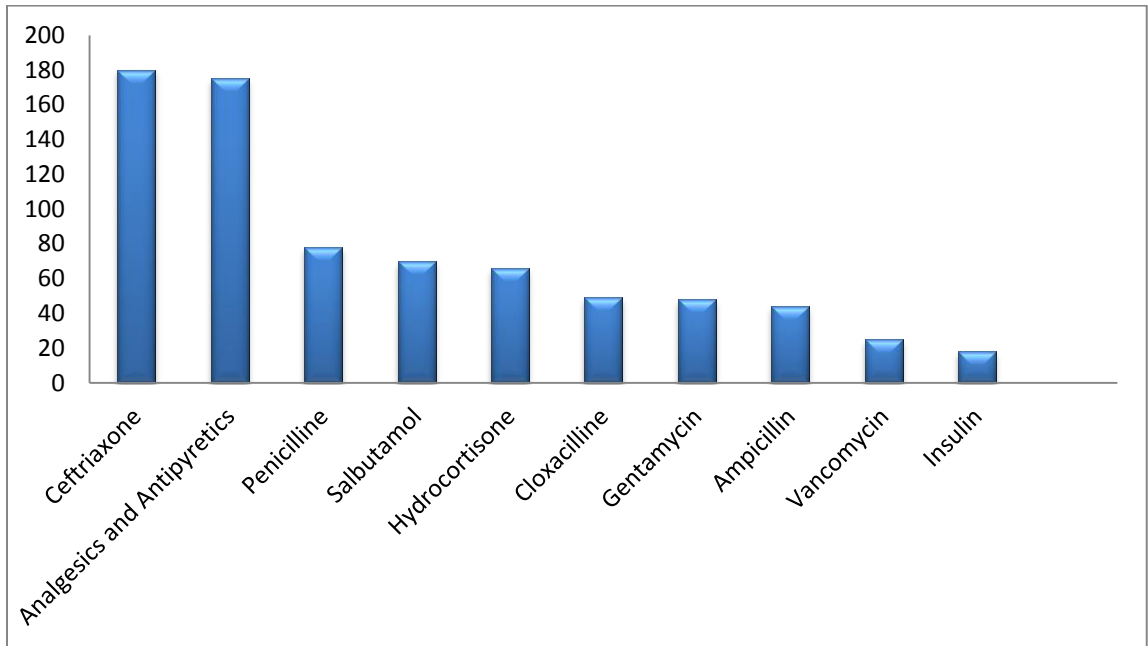
A total of 285 pediatric patients fulfilled the inclusion criteria were included in the study. Of 285 pediatrics, 151 (53%) were female. The mean age of the studied population was 2.8 (SD=1.2) years (range 10 days to 14 years and 6 month). The highest age group was (29 days to  $\leq 1$  years), which accounted for 31.2%. Majority of the patients had single disease condition, which accounted for 47.4%. The mean duration of hospital stay was 3.7 (SD=1.6) days. Most of the patients had  $\leq 3$  days of hospital stays, which accounted 57.2%. The details of socio-demographic characteristics and clinical data of the patients are summarized in **Table 1**.

**Table: 1** Socio-demographic and clinical data of the patient in pediatric ward of ZMRH, June 5 2013 to June 5 2014.

<b>Patient characteristics</b>		<b>Frequency</b>	<b>Percentage</b>
<b>Sex</b>	Male	134	47
	Female	151	53
<b>Age</b>	Neonate (birth to 28 days)	21	7.4
	Infant (29 days to $\leq$ 1years)	89	31.2
	Toddler ( $>$ 1yearsto $\leq$ 3years)	69	24.2
	Preschool ( $>$ 3yearsto $\leq$ 5years)	16	5.6
	School age ( $>$ 5yearsto $\leq$ 10years)	37	13.0
	Adolescent ( $>$ 10yearsto $<$ 15years)	53	18.6
	Mean 2.8, SD 1.2		
<b>No of disease conditions</b>	1	135	47.4
	2	110	38.6
	3	30	10.5
	4	10	3.5
	Mean 2.8, SD 1.2		
<b>No of drugs used</b>	$<$ 5 Drugs	207	72.6
	$\geq$ 5 Drugs	78	27.4
	Mean 3.7, S D 1.8		
<b>Duration of hospital stays</b>	$\geq$ 2 to $\leq$ 3 Days	163	57.2
	4 – 6 Days	103	36.1
	$\geq$ 7 Days	19	6.7
	Mean 3.7 S D 1.6		
<b>Type of disease diagnosed</b>	Infectious and parasitic diseases	156	39.7
	Disease of the respiratory system	117	29.8
	Nervous system	45	11.4
	Disease of genitourinary	23	5.8
	Disease of the blood and blood forming organs	18	4.5
	Endocrine and metabolic disease	17	4.3
	Cardio vascular system	5	1.3

#### 4.2. Profile of Prescribed Medications

A total of 1055 drugs were prescribed for 285 patients. The mean, number of drugs prescribed in the study population with a standard deviation was,  $3.7 \pm 1.8$  (range 1-11). The most commonly prescribed drugs were ceftriaxone 180(63.2%), followed by analgesic and antipyretic 175 (61.4%), and crystalline penicilline 78 (27.4%). The details are summarized in **Figure 1**.



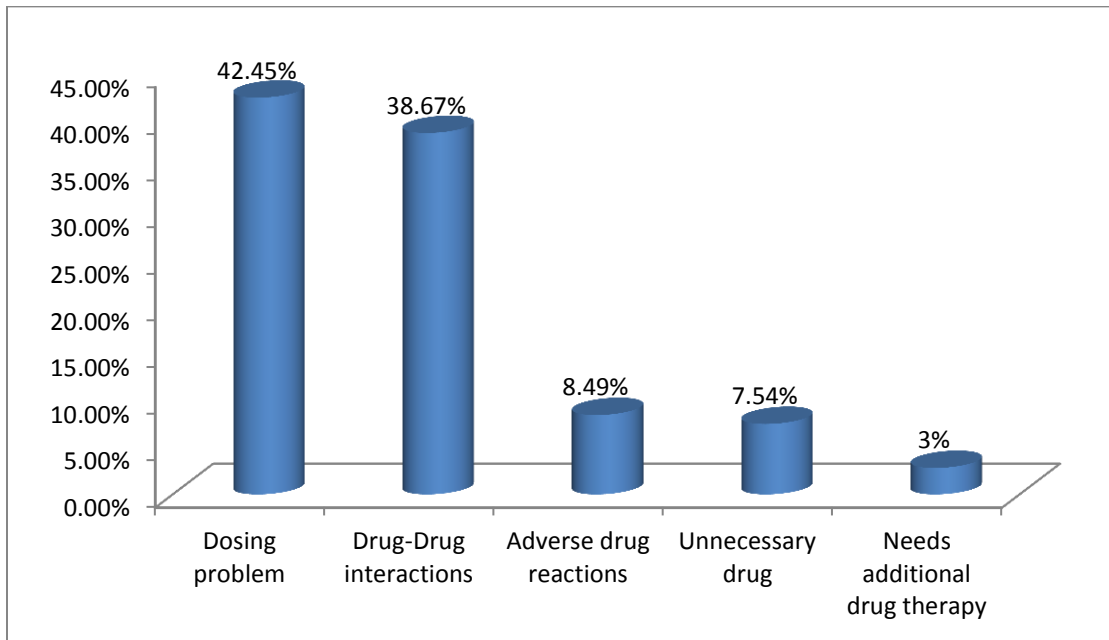
**Figure 1:** Most prescribed drugs among patients admitted in pediatric ward of Zewditu memorial referral hospital, June 5 2013 to June 5 2014.

#### 4.3. Type and percentage of Drug related Problems

A total of 106 DRPs were identified in 90 patients. The overall incidence was 31.57%. Among 285 patients, 49(54.4%) males and 41(45.6%) female patients were exposed to drug related problems. From the total DRPs identified a total of 74 (69.8%) patients had one drug related problems, while 16 (15.09%) patients had two DRPs in the total DRPs.

Of these DRPs identified, dosing problems 45(42.45%) was found to be the most frequent followed by drug-drug interactions (DDI) 41 (38.67%) and adverse drug reactions 9(8.49%). The details of each type of DRPs identified are summarized in

**Figure 2.**



**Figure: 2** Types of Drug related problems at pediatric ward of Zewditu memorial referral hospital, June 5 2013 to June 5 2014.

#### 4.4. Drugs and Diseases Implicated in Drug Related Problems

The most prevalent specific diseases implicated in DRPs were pneumonia, asthma; HIV, seizure and TB. Drugs involved in DRPs were categorized into different therapeutic classes and anti-infectives, analgesics or antipyretics and anti-epileptics were the most prevalent categories. As individual drug, ampicillin (14.1%) followed by phenobarbital and diazepam was the most frequently associated with DRPs. **Table 2** summarizes top 10 drugs involved in drug related problems.






**Table: 2** Top ten specific drugs associated with drug related problems in the pediatric ward of Zewditu memorial referral hospital, June 5 2013 to June 5 2014.

Drug name	DDI	ADR	Dosing problems	Untreated conditions	Unnecessary drug	Total %
Ampicillin	0	0	15	0	0	14.1
Phenobarbital	13	0	0	0	0	12.2
Diazepam	11	0	0	0	0	10.3
Diclofenac	4	0	0	0	5	8.4
Hydrocortisone	9	0	0	0	0	8.4
Salbutamol	7	0	0	0	0	6.6
Phenytoin	6	0	0	0	0	5.6
Vancomycin	0	0	6	0	0	5.6
Gentamycin	0	0	6	0	0	5.6
Zidovudine	0	5	0	0	0	4.7

In this study around 42.45% of DRPs were identified as dosing problems followed by drug-drug interactions and others, the details of each of the identified DRPs with their examples are summarized in **Table 3**.

**Table: 3** Examples of drug related problems identified in pediatric ward of Zewditu memorial referral hospital, June 5 2013 to June 5 2014.

Dose too low	<p>A 4 month old patient weight 3.7 kg was prescribed crystalline penicillin 125000 IU IV QID instead of the correct dose 225000 IU IV QID in the treatment of severe pneumonia.</p> <p>A 4 month old patient weight 3. Kg was prescribed ceftriaxone 75 mg IV BID instead of the correct dose 150 mg IV BID in the treatment of bacterial meningitis.</p>
Wrong frequency	<p>Ampicillin 200 mg intravenous was prescribed twice a day instead of the correct frequency of four times a day for a twelve years old male Patient.</p> <p>Ceftriaxone 600 mg intravenous was prescribed three times a day instead of the correct frequency of two times a day for a six years old male patient.</p> <p>Azithromycin 500 mg PO was prescribed three times a day instead of the correct frequency of one time a day for a thirteen years old male patient.</p>
Adverse drug reactions	<p>A patient was on griseofulvin 350 mg PO daily developed facial edema due to the drug.</p> <p>A fourteen years old male patient who was on HAART medications developed severe anemia due to zidovudine (AZT).</p>

<p>Unnecessary drug Due to duplicate drugs</p>	<p>Both diclofenac 12.5 mg IM and paracetamol 125 mg were prescribed concomitantly.</p> <p>A patient was disseminated TB was simultaneously given hydrocortisone 50 mg IV BID and prednisolone 10 mg PO TID.</p>
<p>Drug-drug interaction</p>	<p>Ketoconazole + phenytoin  ketoconazole will increase the level or effect of phenytoin by affecting hepatic enzyme CYP2C9/10 metabolism.</p> <p>Theophylline + ciprofloxacin  ciprofloxacin will increase the level or effect of theophylline by affecting hepatic enzyme CYP1A2 metabolism. Possible serious or life-threatening interaction. Monitor closely. Use alternatives if available.</p> <p>Cimetidine + dexamethasone  cimetidine will increase the level or effect of dexamethasone by affecting hepatic/intestinal enzyme CYP3A4 metabolism.</p> <p>Metronidazole + dexamethasone  metronidazole will increase the level or effect of dexamethasone by affecting hepatic/intestinal enzyme CYP3A4 metabolism.</p> <p>Diclofenac + prednisolone  Either increases toxicity of the other by pharmacodynamics synergism.</p>

#### 4.5. Factors associated with Drug related Problems

The result of univariate binary logistic regression analysis on the association between different types of independent variables and drug related problems showed that patients who had three number of disease conditions had a significant association with drug related problems and were about seven (COR= 7, 95% CI: 2.94-16.22) times more likely to have drug related Problems compared with patients who had one disease condition. Similarly, patients who took five and above drugs were about four (COR=.3.6, 95% CI: 2.07-6.18) times more likely to have drug related problems compared to those patients who took less than five drugs **Table 4**.

**Table: 4** Univariate logistic regression result of factors associated with DRPs in pediatric ward of Zewditu memorial referral hospital, June 5 2013 to June 5 2014.

		DRPs		COR	P value
		Yes	No		
Sex	Male	49(54.4%)	85(43.6%)	1.00	0.089
	Female	41(45.6%)	110(56.4%)	1.5(0.94,2.56)	
Age	Neonates	6(6.7%)	15(7.7%)	1.00	0.634
	Infant	21(23.3%)	68(34.9%)	0.8(0.27,2.24)	
	toddler	20(22.2%)	49(25.1%)	1.0(0.35,3.01)	
	Preschool	8(8.9%)	8(4.1%)	2.5(0.64,9.77)	
	School age	16(17.8%)	21(10.8%)	1.9(0.60,6.01)	
	Adolescent	19(21.1%)	34(17.4%)	1.4(0.47,4.20)	
number of disease	1	27(30.0%)	108(55.4%)	1.00	0.000
	2	36(40.0%)	74(37.9%)	1.9(1.08,3.47)	0.024
	3	19(21.1%)	11(5.6%)	7(2.94,16.22)	0.000
	4	8(8.9%)	2(1.0%)	16(3.21,79.71)	0.001
number of drugs used	< 5 drugs	49(54.4%)	158(81.0%)	1.00	0.000
	≥ 5 drugs	41(45.6%)	37(19.0%)	3.6(2.07,6.18)	
duration of hospital stays	≤ 3 days	49(54.4%)	114(58.5%)	1.00	0.613
	4-6 days	34(37.8%)	69(35.4%)	1.1(0.68, 1.95)	
	≥ 7 days	7(7.8%)	12(6.2%)	1.4(0.50, 3.65)	

In order to control confounder's, multivariate logistic regression analysis was used to analyze variables, which were, significantly associated to DRPs in univariate analysis. These variables were number of disease conditions and number of drugs used. The analysis showed that both number of disease condition and number of drugs taken had significant association with DRPs. Based on this, patients who had three diseases condition were about five (AOR=4.8, 95% CI: 1.9,12.1) times more likely to have DRPs compared to those patients who had one disease condition. On the other hand, Patients who took five or more drugs were about two (AOR=2.3, 95% CI: 1.3- 4.3) times more likely to have DRPs compared to those patients who took less than five drugs **Table 5**.

**Table: 5** Multivariate logistic regression analysis result of factors associated with DRPs in pediatric ward of Zewditu memorial referral hospital, June 5 2013 to June 5 2014.

variables	DRPs		AOR	P value	
	Yes	No			
Number of disease	1	27(30.0%)	108(55.4%)	1.00	
	2	36(40.0%)	74(37.9%)	1.7(0.9,3.1)	0.098
	3	19(21.1%)	11(5.6%)	4.8(1.9,12.1)	0.001
	4	8(8.9%)	2(1.0%)	10.7(1.9,58.2)	0.006
Number of drugs used	< 5 drugs	49(54.4%)	158(81.0%)	1.00	
	≥ 5 drugs	41(45.6%)	37(19.0%)	2.3(1.3,4.3)	0.007

## 5. Discussion

The most frequently identified drug related problems in this study were, dosing problems, drug-drug interactions, and adverse drug reactions.

The incidence of DRPs in this study was (31.57%). However, a lower incidence of DRPs was reported in Hong Kong study 21.0 % (Rashed et al., 2013). This difference may be due to the differences in the hospital settings such as differences in training levels of prescribers, availability of support system and composition of health care team and difference in the definition of drug related problems. On the other hand, a higher incidence was reported in UK and the kingdom of Saudi Arabia study 45.2% (Rashed et al., 2012).

From this total incidence identified, the percentage of male patients with DRPs was higher than for female patients (54.4% vs. 45.6%), although the difference was not significant (COR=1.5, 95% CI: 0.94, 2.56,  $P = 0.089$ ), this finding is in agreement with other study (Rashed et al., 2013).

In this study, the most frequently identified DRPs was dosing problem of drugs, with a percentage of 42.45%. This value is lower than in UK and kingdom of Saudi Arabia 54% (Rashed et al., 2012). However; it is comparable with Hong Kong study 42.7% (Rashed et al., 2013).

The most frequently identified drug implicated in dosing problems in this study was ampicillin; this may be due to the higher prevalence of infectious disease, and prescription of this drug.

Dosing errors in pediatrics might result in ineffective treatment, due to sub therapeutic concentration, or toxicity due to over dose that may lead to mortality. Therefore, greater focus on improvement of safety of drugs used in children is necessary.

Generally inappropriate doses are more common in pediatrics than adults because of weight-based dosing calculations, fractional dosing (e.g., mg vs. Gm), and the need for decimal and incorrect recording of patients' weights (Lesar et al., 1997). The high prevalence of dosing problems in this study would make this an important area requiring further investigation.

The present study analysis on DRPs showed that potential drug–drug interactions were the second identified DRPs (38.67%). However, this percentage is higher than the percentage of 9.67% in Pakistan study (Alia et al., 2013). The drugs, most implicated to DDIs in the current study were phenobarbital, diazepam, and hydrocortisone. The high percentage of potential DDIs in this ward probably related to the prevalent of infectious diseases particularly HIV/AIDS and opportunistic infections that are managed with complex drug regimens, with a higher potential for interactions. In addition patients may also had a higher number of co-morbid conditions and take more drugs.

The patient needs to be closely monitored for manifestations such as lack of therapeutic efficacy or toxicity, especially for drugs whose therapeutic effects may be diminished or augmented when used in those combinations. Drug interaction is a major factor that might cause ADR, therapeutic failure and drug related harm to patients (Moura et al., 2009). As drug interactions can affect patient's clinical outcome, quality of life, as well as contribute to unnecessary healthcare cost.

In the present study, nearly, 8.49 % were found to be an ADR; this percentage is lower than the percentage of 13.4% found in Hong Kong study (Rashed et al., 2013). Most of the ADR occurred in the current study were due to HAART medication induced anemia due to zidovudine and the patients were switched to other drugs. On the other hand, corticosteroid and griseofulvin drugs were stopped to taken by the patients following blood sugar increment and facial swelling due to corticosteroid and griseofulvin drugs respectively.

The high number of ADR occurrence in this ward probably attributed to the use of multiple medications, which increases the risk of ADRs.

Patients with five or more drugs prescribed during their hospital stay had the highest risk of developing an ADR- three times higher compared to patients receiving between one and four drugs. One possible explanation might be that poly-pharmacy may increase the chances of drug-drug interaction, which leads to increased possibilities for an ADR to occur (Rashed et al., 2012, Vandembemt et al., 2000).

In this study, 7.54 % of total DRPs were identified as unnecessary drug due to duplicate prescription, these finding were comparatively higher in contrast with finding of Pakistan study 1.61% (Alia et al., 2013). Examples of some duplicate prescription, identified in this study, were noted especially with analgesic or antipyretic and gluco corticosteroids group of drugs. Administration of paracetamol and diclofenac, dexamethasone and

prednisolone, concurrently was seen in few cases leading to duplication because both of these drugs belong to the same class.

In this era of inflation, drug therapy costs are on the rise. This is cumbersome for developing nations particularly Ethiopia. Prevention of duplicate drug therapy will contribute in cost saving among hospitalized patients.

With regard to drugs to implicate DRPs in this study, anti-infective, analgesics or antipyretics and anti-epileptics are the three most common drug classes involved in DRPs. Similarly, anti-infective were the most common classes of drugs involved in DRPs in other studies from Hong Kong (Rashed et al., 2013) and UK (Rashed et al., 2012).

Anti-infective are used in very high number of prescriptions in pediatric ward of Zewditu memorial referral hospital due to most of the admitted patients were diagnosed with infectious diseases, as presented in (Figure 1), so this may be one reason for this class of drugs to appear as major class responsible for causing DRPs apart from others.

There is a higher prevalence of infectious disease in children. As a result, higher number of anti-infective drugs usage than any other group of drugs (Melander et al., 2003).

On the other hand, specific drugs like Ampicillin, phenobarbital and diazepam were the three most common drugs involved in drug related problems in this study. It was observed that most of medication orders from phenobarbital and diazepam were involved in drug-drug interaction with themselves and other drugs which explains why these drugs

are top on this list. However, most of the orders from ampicillin were incorrect frequency, which deviates from the recommended practices.

In the attempt to identify risk factors for the occurrence of DRPs in this study, poly pharmacy, and number of disease conditions were significantly associated to DRPs (Table 4), while sex, age and duration of hospital stays were not significantly associated to DRPs in univariate analysis. However, in multivariate logistic regression both poly pharmacy and number of disease conditions were found to be independent predictors of drug related problems in pediatric ward of Zewditu memorial referral hospital. Other published findings also support on the number of drugs ( $\geq 5$ ) taken by a patient is an important risk factor for the occurrence of DRPs (Ibrahim et al., 2013, Rashed et al., 2012, Rashed et al., 2013). The more complex drug therapy is the higher the risk of experiencing DRPs such as adverse effects, drug-drug interactions, medication errors and non-adherence may follow.

On the other hand, as the number of disease conditions are increased then number of drugs taken will be increase, this may result in ADR, drug-drug interactions, medication errors and non-adherence (Rashed et al., 2012).

Due to most of the study participants had shorter duration in the hospital. Patients will take less number of drugs. Consequently, the occurrence of DRPs in these patients will be decreased because the occurrence of drug-drug interactions, ADR and non adherence decreased.

## **6. Limitation of the study**

The primary limitation was it did not attempt to classify DRPs in severity level i.e, mild, moderate and severe due to the complexity of the study. Secondly the study did not attempt to assess adherence.

## **7. Conclusion**

The present study demonstrated that, drug-related problems were common at pediatric ward of Zewditu memorial referral hospital that needs great attention. The most frequently identified DRPs were dosing problems of drugs, followed by drug-drug interactions and adverse drug reaction. Poly pharmacy and number of disease conditions have been identified as important risk factors for occurrence of DRPs.

## 8. Recommendations

The following recommendations are forwarded based on the result of the study

- In order to develop appropriate prevention strategies, other prospective interventional studies should be done on the epidemiology and risk factors of DRPs in children at ZMRH.
- Pharmacists should routinely review medications and avoid dispensing combinations of drugs that may have serious DDIs
- The hospital should implement drug information center and utilization of different software to detect drug interactions.

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## **Annex I**

### **DRP registration format**

#### **TYPE OF PROBLEM**

##### **Drug therapy problem 1: Unnecessary drug therapy**

- There is no valid medical indication for the drug therapy at this time
- Multiple drug products are being used for a condition that requires single drug therapy
- The medical condition is more appropriately treated with nondrug therapy
- Drug therapy is being taken to treat an avoidable adverse reaction associated with another medication
- Drug abuse, alcohol use, or smoking is causing the problem

##### **Drug Therapy Problem 2: Needs Additional Drug Therapy**

- A medical condition requires the initiation of drug therapy.
- Preventive drug therapy is required to reduce the risk of developing a new condition
- A medical condition requires additional pharmacotherapy to attain synergistic or additive effects

##### **Drug Therapy Problem 3: Ineffective Drug**

- The drug product is not the most effective for the indication being treated
- The medical condition is refractory to the drug product
- The dosage form of the drug product is inappropriate
- The drug is not effective for the medical problem

#### **Drug Therapy Problem 4: Dosage Too Low**

- The dose is too low to produce the desired response.
- The dosage interval is too infrequent to produce the desired response.
- A drug interaction reduces the amount of active drug available
- The duration of drug therapy is too short to produce the desired response

#### **Drug Therapy Problem 5: Adverse Drug Reaction**

- The drug product causes an undesirable reaction that is not dose-related
- A safer drug product is required due to risk factors
- A drug interaction causes an undesirable reaction that is not dose-related
- The dosage regimen was administered or changed too rapidly
- The drug product causes an allergic reaction
- The drug product is contraindicated due to risk factors

#### **Drug Therapy Problem 6: Dosage Too High**

- Dose is too high
- The dosing frequency is too short
- The duration of drug therapy is too long
- A drug interaction occurs resulting in a toxic reaction to the drug product
- The dose of the drug was administered too rapidly.

### **Drug Therapy Problem 7: Noncompliance**

- The patient does not understand the instructions.
- The patient prefers not to take the medication
- The patient forgets to take the medication
- The drug product is too expensive for the patient
- The patient cannot swallow or self-administer the drug product appropriately
- The drug product is not available for the patient

11. ANNEX II

Data abstraction format

Patient Name (initials) \_\_\_\_\_ card no. \_\_\_\_\_ Age (yrs) \_\_\_\_\_ Sex \_\_\_\_\_

Wt. (kg) \_\_\_\_\_ Date of admission \_\_\_\_\_ Date of discharge \_\_\_\_\_

s. no.	Type of disease condition	treatment	Dosage regimen	Length of therapy	comment
1					
2					
3					
4					
5					
6					
7					
8					
9					

10					
11					
12					
13					

Pertinent lab values and investigations