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Comparative analysis and evaluation of current antidiarrheal prescribing trends with representative brand in pediatric population of Pakistan

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ABSTRACT

Background: Inappropriate management of diarrhea is the main cause of morbidity and mortality in the pediatric population worldwide, more especially in developing countries including Pakistan.

Method: The sample size was calculated using World Health Organization (WHO) and Expanded *Program on Immunization (EPI)* info calculator. 240 prescriptions were collected from eight hospitals including four public hospitals (Pakistan Institute of Medical Sciences, Polyclinic Hospital, Holy family Hospital and Benazir Hospital) and four private hospitals (Hearts International Hospital, Maroof Hospital, Railway hospital, Bilal Hospital) of twin cities of Pakistan (Islamabad and Rawalpindi). **Objectives:** The purpose of this study was to analyze current prescribing trends of diarrheal management followed by comparative pharmaceutical evaluation of representative brands Parameters recorded from prescriptions were demographics (age and gender), presenting complaints and medications prescribed. Prescriptions were evaluated by their comparison with standard treatment guidelines. **Results:** Data were evaluated using a statistical package for social sciences (SPSS version 16.0) for descriptive statistics and cross-tabulations along with Chi square test. Diarrhea was presenting complaint in 106 (44%) of peads among age group 0-2 years. Out of 106 (44%) cases of diarrhea, 52 (20%) cases have prescribed an antibiotic in combination with other medications, which was not indicated according to standard guidelines. The use of oral rehydration solutions (ORS) was also limited. Zinc supplementation with ORS is indicated treatment for diarrhea and was prescribed to 21 (9%) cases. **Conclusion:** Hence, it has been concluded that standard treatment guidelines were not followed thoroughly which leads to increased morbidity, complications and cost.

Keywords: Antidiarrheal, Prescribing Trends, Pediatric Population, ORS, Diarrhea.

INTRODUCTION

Diarrheal diseases are considered as one of the leading causes of morbidity and mortality worldwide in the pediatric population because of their inappropriate treatment. Diarrhea accounts for 9.9% of 6.9 million deaths among children less than 5 years of age. According to a survey in Pakistan, about 2 million children die annually due to diarrhea [1, 2]. Irrational drug use is a matter of concern in current-day medical practices. Irrational use or misuse means that drugs are used in conditions where their efficacy is decreased or the desired effect is not achieved [3]. Irrational prescribing is a global problem, which leads to ineffective and unsafe treatment, antibiotic resistance, prolonged therapy, adverse effects, and increased cost of treatment. Irrational drug use is not only a major problem of developing countries but developed countries as well [4, 5].

Pakistan has no exception in this regard. Advancements in healthcare led to easy access to pharmaceutical agents and the absence of regulatory mechanisms. More than half of medicines prescribed or dispensed are sold improperly and around 50% of total patients are unable to take medicines correctly. Almost one-third of the world's population is unable to access essential drugs [6]. The WHO classified diarrhea as acute watery diarrhea (cholera), acute bloody diarrhea (dysentery) and persistent diarrhea. Acute watery diarrhea is also termed cholera and may last for days leading to dehydration. Acute bloody diarrhea is also known as dysentery and can lead to sepsis and damage the intestinal mucosa in severe conditions. Persistent diarrhea is the type of diarrhea that lasts for up to 14 days or longer. Persistent diarrhea leads to malnutrition and dehydration [7].

Causative agents for infectious diarrhea can be viruses, bacteria, or any other parasite. The most common strains include rotavirus, *shigella*, *salmonella*, *vibrio cholera* and *Escherichia coli* (*E. coli*). Rotavirus causes severe illness associated with fever and vomiting in children less than 5 years of age. 40% of all diarrhea-associated hospitalizations are caused by rotavirus. *Shigella* strains are transmitted through contact with the infected person. *Shigella* strains multiply and spread causing inflammation and ulceration leading to fever and dysentery. *Vibrio cholera* strains contaminate food or water and spread as outbreaks. Pathogenic *E. coli* strains are responsible for morbidity and mortality in children. *Salmonella spp.* of any particular species is responsible for Gastroenteritis along with fever and diarrhea. Antimicrobials are only indicated in case of diarrhea after stool microscopy and sensitivity tests [8].

Researchers have concluded that only 22% of diarrheal cases underwent medical treatment. Treatment of acute diarrhea is compulsory as it affects the quality of life. Standard treatment guidelines for gastroenteritis as suggested by the World Gastroenterology organization suggest a combination of oral rehydration therapy, dietary modifications, probiotics, multivitamin supplements, antimicrobials and supportive and symptomatic treatment [9].

Oral rehydration therapy plays a major role in treatment of diarrhea while other treatment options such as antidiarrheal, antimotility and antibacterial agents have specified and limited roles to play. Probiotics have emerged as an important treatment option for infectious diarrhea in infants and children [10]. This study involved evaluation of current prescribing trends of anti-diarrheal in the pediatric population of Islamabad and Rawalpindi followed by a comparative pharmaceutical evaluation to support the selection of most appropriate therapy.

MATERIALS AND METHODS

A clinical descriptive cross-sectional study from twin cities of Pakistan, the federal capital Islamabad and Rawalpindi was performed after analyzing the problem of irrational prescribing in diarrhea along with its adherence to standard treatment guidelines. Prescriptions were collected from four government and four private hospitals of twin cities (Islamabad and Rawalpindi) to analyze current prescribing trends of diarrheal management in the pediatric population. Three commonly used local brands of metronidazole (Anti-Amoebiasis) are compared with 1 multinational brand taken as standard.

Sampling

Prescriptions were collected from eight public and private sector hospitals of Islamabad and Rawalpindi (Polyclinic hospital, Pakistan Institute of Medical Sciences, Holy Family Hospital, and Benazir Bhutto Hospital, Railway Hospital, Bilal Hospital, Hearts International Hospital and Maroof Hospital). 240 prescriptions were collected from eight hospitals in the twin cities of Pakistan.

A random collection of prescriptions fulfilling inclusion criteria were selected to overcome any chance of bias. The pediatric population fulfilling the specific criteria were included in the present study. The criteria was the inclusion of an age group ranging from 0 to 12 years, presenting complaints of diarrhea, while both sexes were also included in the study. On the other hand, those patients having age more than 12 years with no diarrheal complaints were excluded from the study. The present study was conducted over a time of 13 months starting from September 2016 to October 2017. Ethical approval in the form of letters/ NOC was collected from all public sector tertiary care hospitals after presenting the research project in ethical review board committees of each institution. The study was discussed with concerned physicians and data was collected.

Data collection tool and procedure

Prescriptions were collected as a tool for data collection. Data from prescriptions were filled in a form attached in Annexure 1 containing parameters to be studied. Data collection permission from hospitals was requested after discussing project details with a panel of concerned physicians in the ethical committee of each hospital. Respondents were informed about the project. Prescriptions containing relevant information were collected from each facility. From each public and private facility, 30 prescriptions were taken so 240 prescriptions were collected from eight facilities of Rawalpindi and Islamabad (four public and four private).

Data analysis

After data collection, data were coded and analyzed by using SPSS version 16.0. Descriptive statistics are used to determine the frequencies, percentage tables, graphs, prevalence and incidences of variables. Statistical analysis was done by using Chi-Square test to find out the differences and association among variables.

Assessment of Pharmaceutical parameters

The assessment included the evaluation of various pharmaceutical parameters such as pH as well as content assay as specified in British Pharmacopoeia (BP). Three local brands and one multinational brand of antidiarrheal (Metronidazole) were evaluated against a reference standard.

pH determination

pH values were determined using calibrated pH meter. Four brands of metronidazole suspension were analyzed for pH and were compared with the reference range given in British Pharmacopoeia.

High Performance Liquid Chromatography (HPLC) assay

Content Assay of different brands of metronidazole is performed by HPLC method as stated in the British Pharmacopoeia [11]. Solution (1) is prepared by adding enough metronidazole benzoate equivalent to 200 mg of metronidazole with 150ml of methanol. Added water with mixing and cooling to make up volume up to 250ml and centrifuged it. For solution (2), dissolved 20 mg of metronidazole (British Pharmacopoeia catalogue for reference standard) in 150ml methanol with water, mixing and cooling was performed to make up volume up to 250ml. Dilute 1 volume to 10 volumes with methanol (60%).

RESULTS

A sample of 240 prescriptions from paediatric wards of eight hospitals in Islamabad and Rawalpindi were collected to evaluate prescribing trends of diarrheal management. Prescriptions were evaluated for four parameters including age group, Gender, Type of complaints and Medications prescribed. These parameters were cross tabulated to evaluate the relationship between them and presented in figures.

Paediatrics ranging from 0-12 years were evaluated, which are further subdivided into 0 to 2, 3 to 6, 7 to 9 and 10 to 12y of age. 45% of paediatrics was among age group 0 to 2y of age. 30% of paediatrics were among 3 to 6y of age. 13% and 12 % belonged to 7 to 9 and 10 to 12y of age, respectively. The majority (45 %) of the population belonged to the age group 0 to 2 years of age (Figure 1).

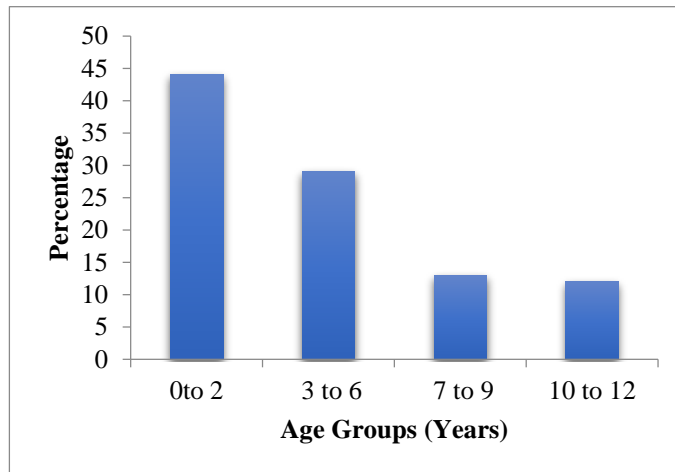


Figure 1: Bar plot of percentage of different age groups

The figure 2, illustrates the gender-based classification of data. Out of the total number of sampled prescriptions, 47% are males and 53% are females. This also illustrates that female (53 %) are more affected with diarrhoea in comparison to males.

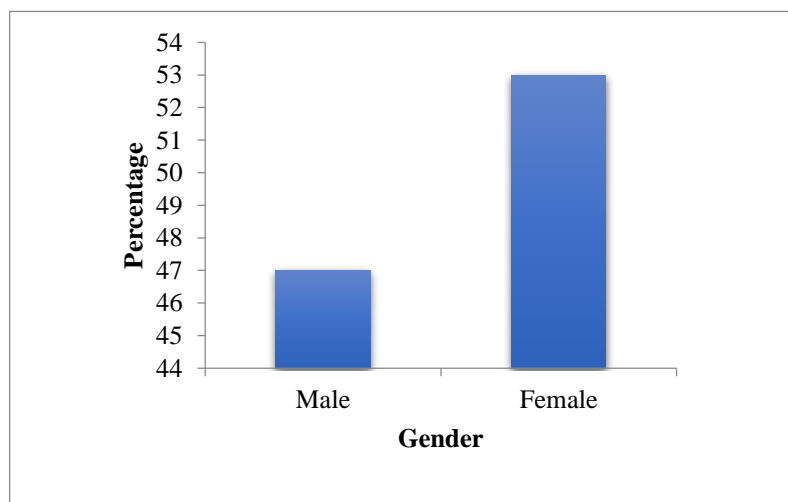


Figure 2: Bar plot of percentage of both genders

Figure 3 illustrates different age groups and their gender-based distribution. In the age group 0 to 2 years, 21% were males and 23% were females. In the age group 3 to 6 years, 14% were males and 16% were females. The age group 7 to 12 years comprised of 6 % males and 7 % females. Whereas, in the age group 10 to 12 years both males and females accounted equal percentage which is 6 %.

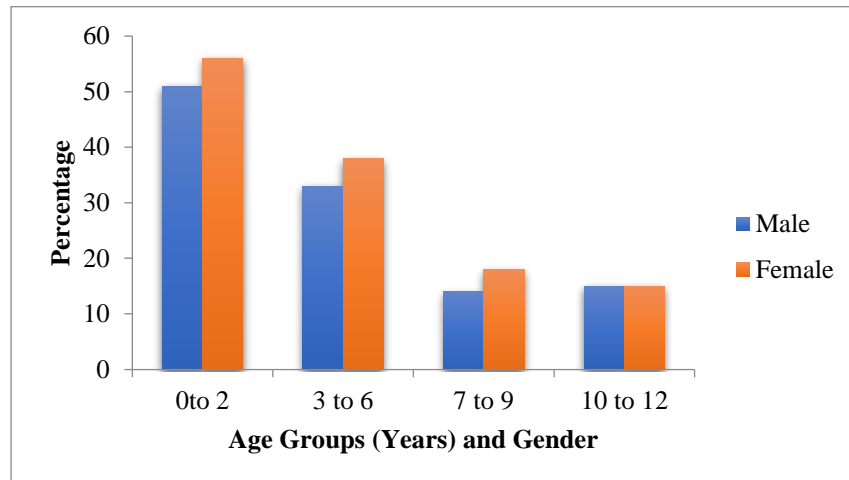


Figure 3: Bar plot of percentage of gender versus age groups

Figure 4 shows different age groups and complaints. The most common presenting complaint was diarrhoea followed by fever with diarrhoea. 44% of children suffered from diarrhoea and 42% of children suffered from fever with diarrhoea. Diarrhoea along with abdominal pain was observed in 10% of cases. Acute Gastroenteritis was observed in 4% of cases amongst all age groups.

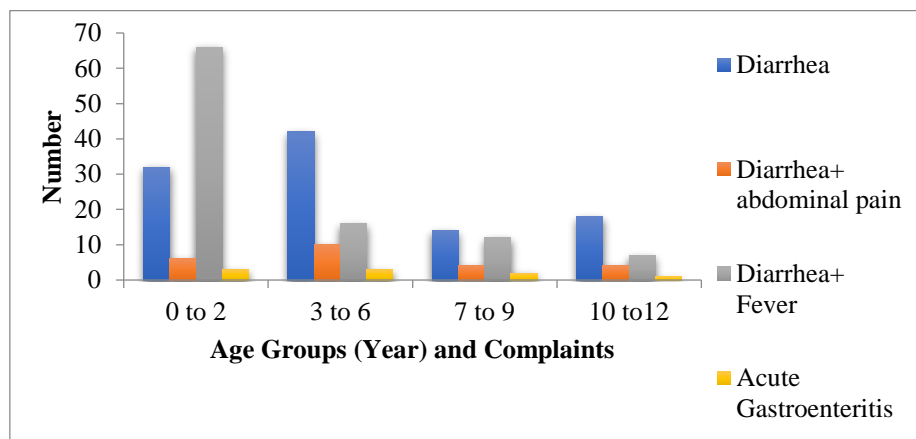


Figure 4: Bar plot of frequency distribution for complaint versus age group

Figure 5 shows prescribed combinations of drugs to different age groups. Prescribed medication records show that the most prescribed combination of medicines was an antibiotic plus syrup Panadol or Brufen along with syrup zincate. The second most prescribed combination was syrup antibiotic plus suspension Flagyl along with Panadol and ORS.

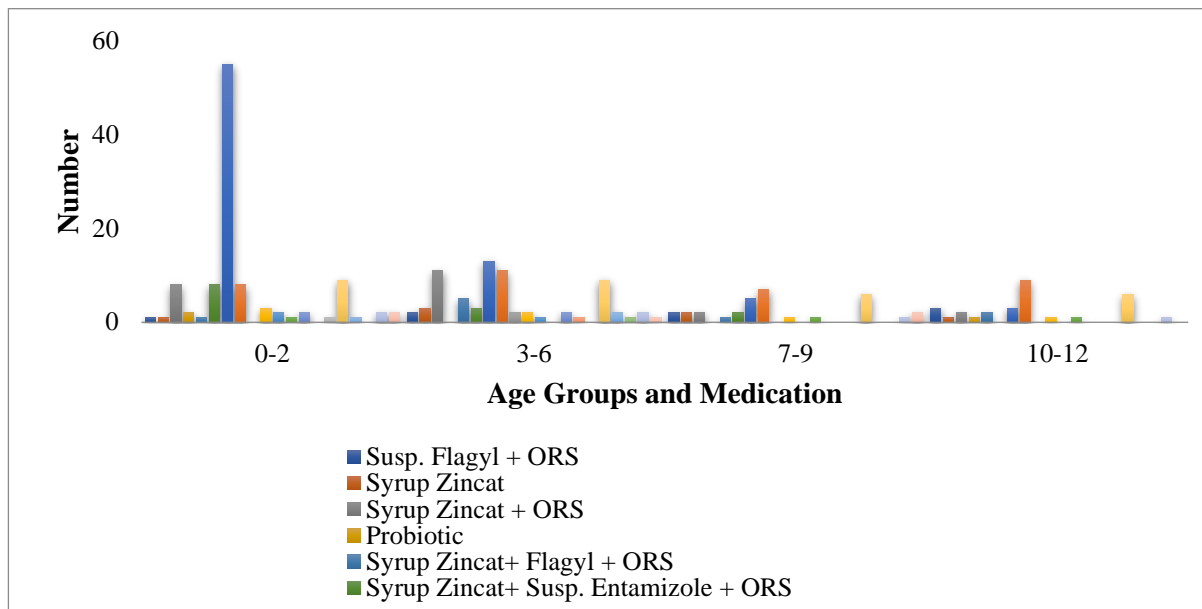


Figure 5: Graph of the combination of medications prescribed versus different age groups.

Bar graph of combination of medications prescribed versus different age groups. The most commonly prescribed combination among 0-2 years age group was syrup antibiotic plus syrup Zincate plus Panadol/Brufen whereas A.B syrup plus Suspension Flagyl plus Panadol and ORS were prescribed to all age groups from 0-12 years.

Chi square test (table 1) has a value 0.01 less than p -value 0.05 indicating that complaints and age groups are related significantly.

Table 1: Chi-square Test

Chi Square Test	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	33.749	9	0.00
Likelihood Ratio	34.587	9	0
Linear-by-Linear Association	11.641	1	0.001
N of Valid Cases	240		

p -value less than 0.05 was considered significant

Table 2: Chi-square Test

Chi-Square Tests	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	84.210	57	0.011
Likelihood Ratio	89.036	57	0.004
Linear-by-Linear Association	0.488	1	0.485
N of Valid Cases	240		

p -value less than 0.05 was considered significant

Table 3: Chi-Square Test

Chi-Square Test	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	5.340 ^a	3	.149
Likelihood Ratio	5.366	3	.147
Linear-by-Linear Association	2.736	1	.098
N of Valid Cases	240		

p value less than 0.05 will be considered significant

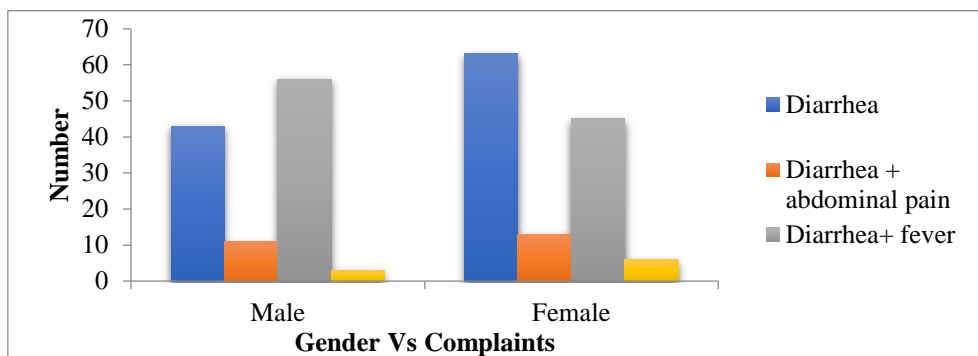


Figure 6: Gender v/s Complaint

Gender v/s complaints bar graph shows males were mostly encountered with diarrhea plus fever whereas presenting complaint in most females was diarrhea.

Table 4: Chi-Square Test

Chi-Square Tests	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	19.457 ^a	19	0.428
Likelihood Ratio	25.277	19	0.152
Linear-by-Linear Association	0.855	1	0.355
N of Valid Cases	240		

p value less than 0.05 was considered significant

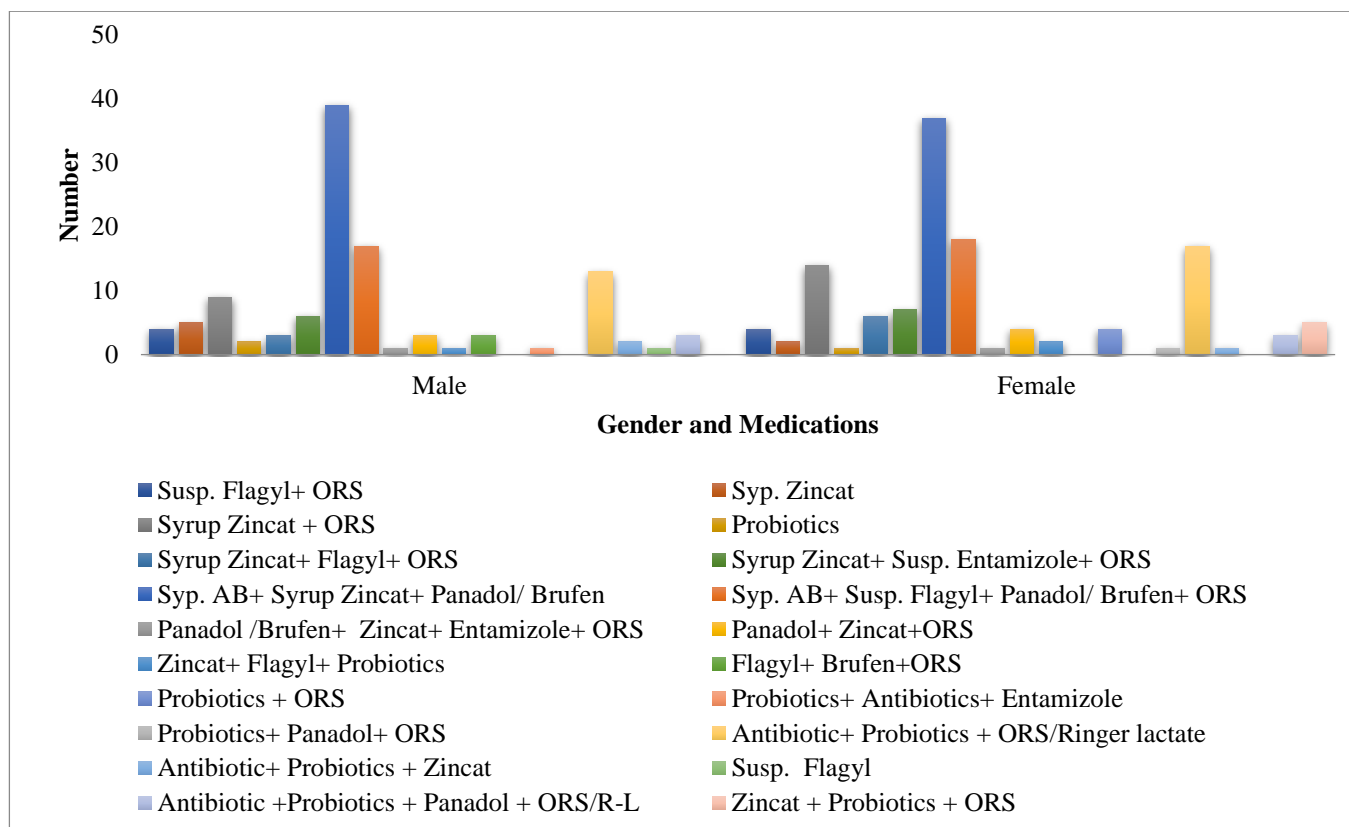


Figure 7: Gender v/s Medication. Graph explains that both genders were commonly prescribed syrup. A.B plus syrup. Zincat plus Brufen/Panadol combination.

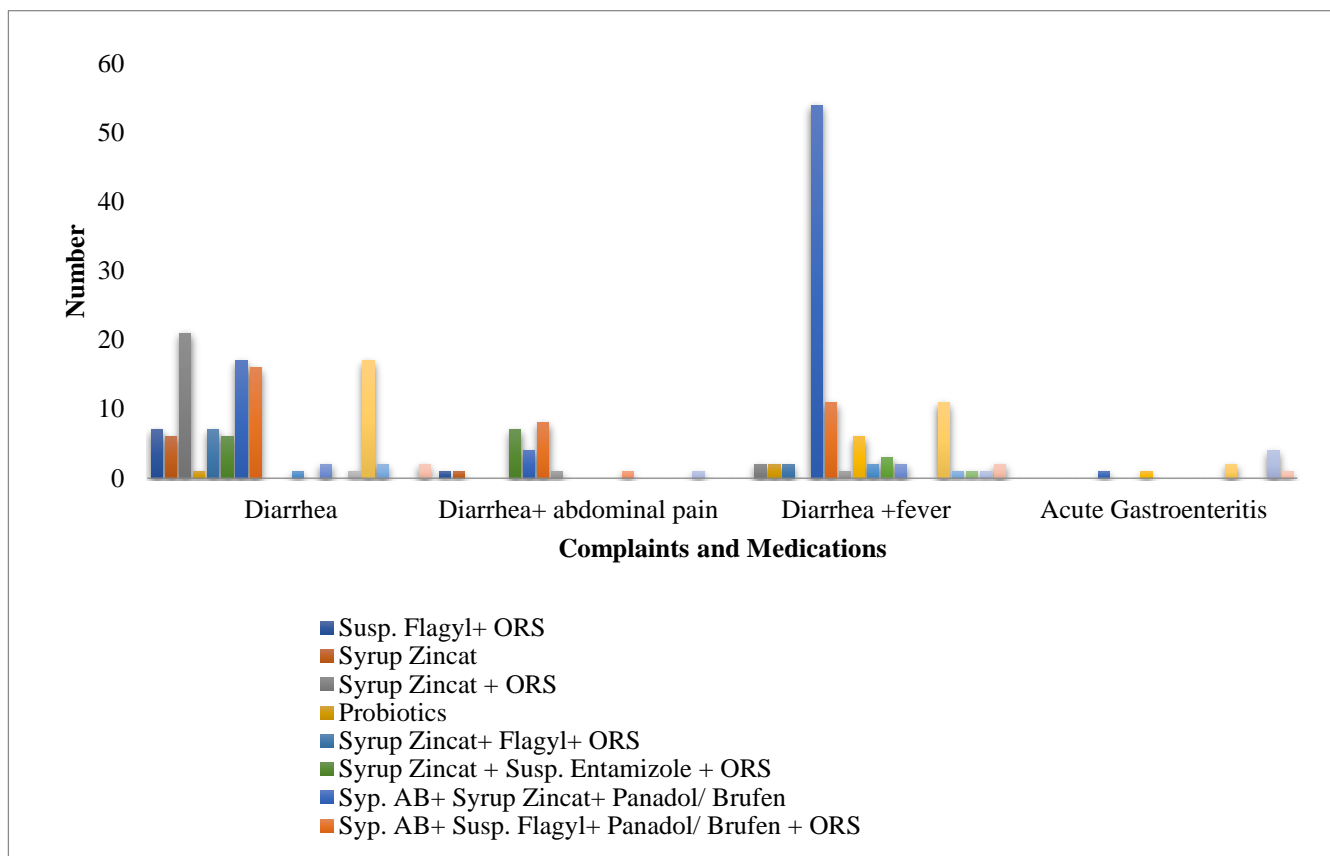


Figure 8: Complaint v/s Medication

Table 5: Chi-Square Test

Chi-Square Test	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	212.117 ^a	57	0.000
Likelihood Ratio	172.006	57	0.000
Linear-by-Linear Association	15.375	1	0.000
N of Valid Cases	240		

p value less than 0.05 will be considered significant.

Comparative Pharmaceutical Evaluation of Metronidazole

After analyzing current prescribing trends of antidiarrheals, it was observed that the most commonly prescribed combination of medications for all age groups was syrup A.B plus suspension metronidazole plus Panadol / Brufen and ORS. Therefore, from this combination Metronidazole suspension was selected and further evaluated for comparative pharmaceutical evaluation.

Four commonly prescribed brands of Metronidazole were selected including one multinational and three national brands. Selected brands were compared against the standard Metronidazole sample. HPLC and pH tests were performed according to B.P. HPLC reports are attached, and pH results are elaborated in table 6.

pH value

pH values of one multinational and three local brands of Metronidazole suspension are given in table number. Normal pH range for Metronidazole suspension is 5-6.5. All four brands comply with pH requirements.

Table 6: Brand names and pH values of various Brands used in the study.

Brands	Codes	Batch no.	Mfg. Date	Exp. Date	Mfg License No.	Reg. no.	pH
Flagyl	M1	WP096	05-2017	04-2019	000007	001214	6.0
Metrozine	M2	0770	08-2017	08-2019	000647	010933	6.2
Klint	M3	0120	06-2017	05-2019	000072	014423	6.1
Menidazole	M4	MZ-267	10-2015	10-2017	000340	029569	6.1

Content Assay

HPLC method reveals content assay results in the figures below. The normal range for content assay of Metronidazole lies within 95-105 % range.

Table 7: Content Assay of Metronidazole Suspension

Brands	Codes	Retention time	AUC of sample	AUC of standard	Drug content (mg)	Drug content (%)	Limit
Flagyl	M1	8.293	5007746	5076561		100%	95-105%
Metrozine	M2	8.281	5262226			99.9%	
Klint	M3	8.28	5137853			99.9%	
Menidazole	M4	8.282	5234368			99%	
Metronidazole Standard	M	8.283					

The above table shows the content uniformity results of four brands of metronidazole. The reference range of metronidazole assay content lies within 95-105% [11].

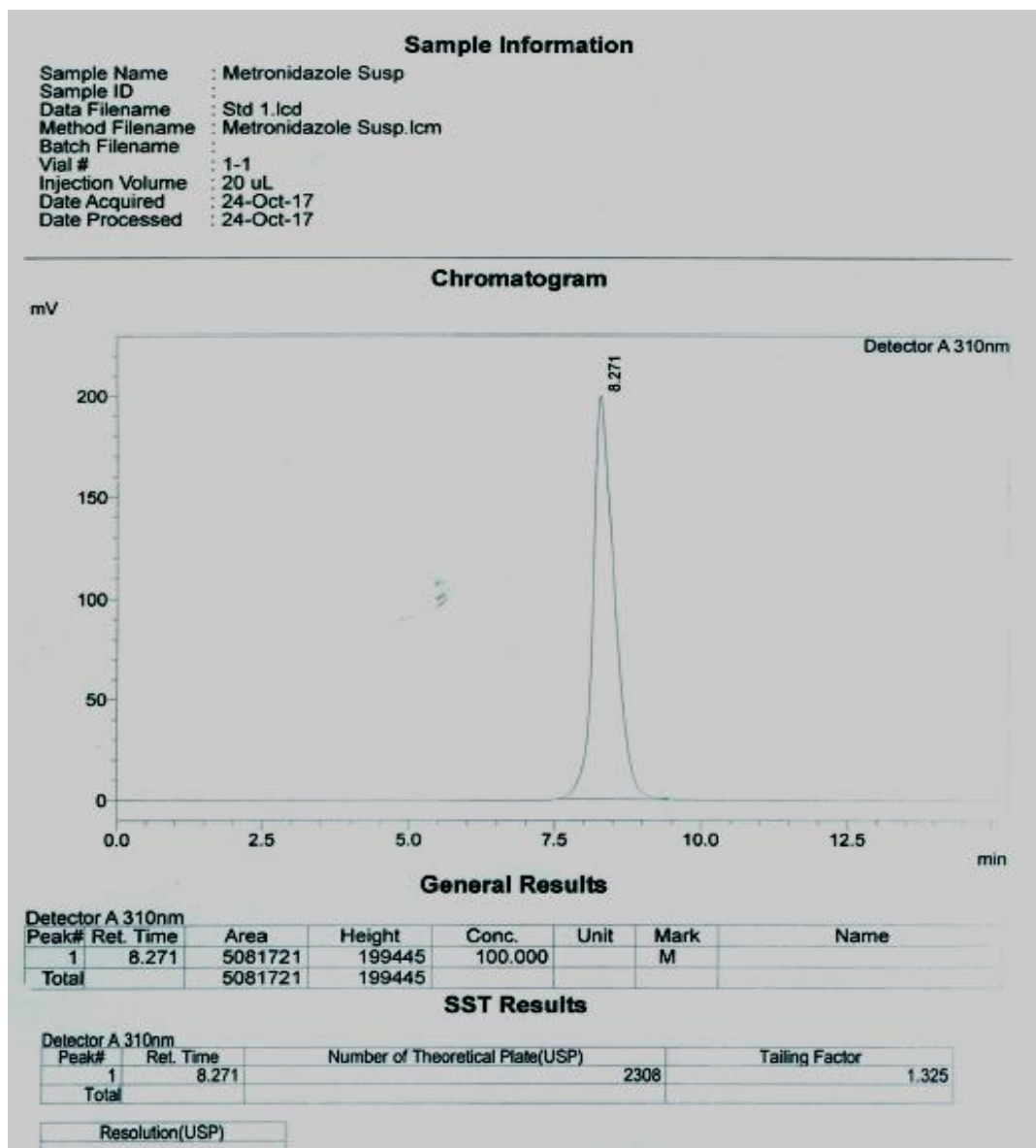


Figure 9: HPLC peak of Metronidazole reference standard I

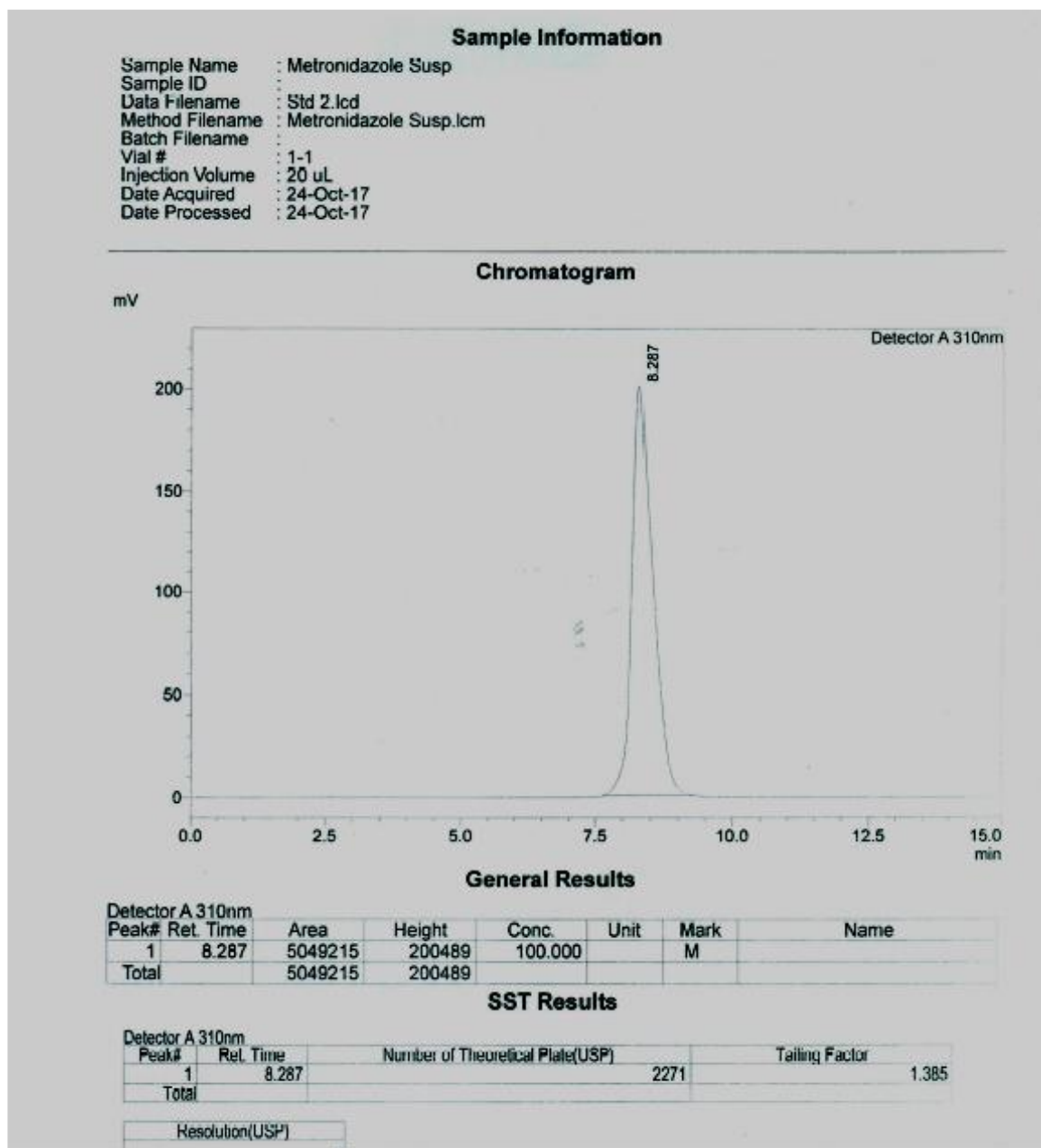


Figure 10: HPLC peak of Metronidazole reference standard II

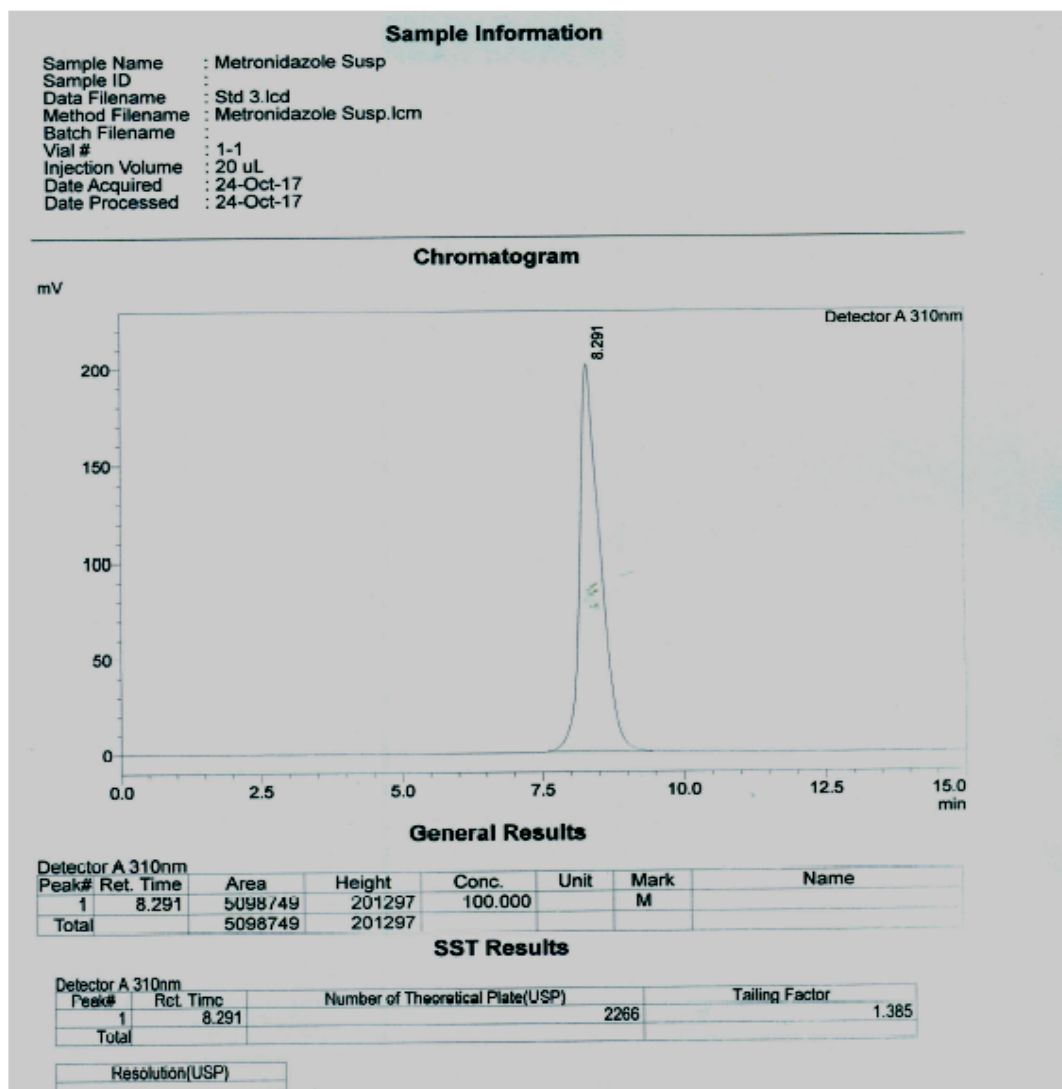


Figure 11: HPLC peak of Metronidazole reference standard III

Standard Treatment Guidelines

Dehydration is considered as a main cause of death due to diarrheal diseases due to insufficient rehydration therapies. Oral rehydration salts include a mixture of different salts and glucose mixed with water. Bloody diarrhea, persistent diarrhea and malnourishment also worsen diarrhea. Provision of oral rehydration therapy, continuous feeding, use of antimicrobials in case of bloody diarrhea, cholera and serious non-intestinal infections.

Assessment of Child with Diarrhea

A child suffering from diarrhea should be assessed for signs like number of watery stools per day, presence of blood in stool, duration of diarrhea, presence of fever and cough. Other important information like immunization history and history of drugs used should also be assessed.

Physical examination

Physical examination involves following signs and symptoms to evaluate degree of dehydration. Following (Table 8) shows an assessment of child for dehydration.

Table 8: Assessment of child for dehydration

Assessment	No signs of dehydration	Some Dehydration	Severe Dehydration
Condition	Well, Alert	Restless, irritable	Lethargic or unconscious
Eyes	Normal	Sunken	Sunken
Thirst	Not thirsty, drinks normally	Thirsty, drinks eagerly	Drinks poorly or not able to drink
Feel: skin pinch	Goes back quickly	Goes back slowly	Goes back v slowly
Conclusion	Patient has no sign of dehydration	Patient has one or more signs, some dehydration	Patient has one or two signs, Severe Dehydration

Fluid deficit is calculated according to the degree of dehydration and percent weight loss. Following (Table 9) shows the degree of fluid loss.

Table 9: Assessment of fluid deficit

Assessment	Fluid deficit as %age body weight	Fluid deficit as ml/kg body weight
No signs of dehydration	<5%	<50ml/kg
Some dehydration	5-10%	50-100ml/kg
Severe Dehydration	>10%	>100ml/kg

Comparative Pharmaceutical Evaluation of Metronidazole

Comparative Pharmaceutical Evaluation of Metronidazole suspension was done by tests given in British Pharmacopoeia [11]. pH test is performed for determining the acidity of the formulation. pH test and Content assay test of four commonly used brands of metronidazole were done. Table 6 shows pH values of different brands of metronidazole and indicates that all four brands lie within the prescribed range of 4 to 5.1.

Content assay test was done by HPLC method according to British Pharmacopoeia (B.P, 2016). Content Assay results (Table 7) conclude that all four brands of metronidazole comply with prescribed range of British Pharmacopoeia [11].

DISCUSSION

In the present study for the first time, we evaluated the current antidiarrheal prescribing trends with the representative brand in the pediatric population of Pakistan. This treatment therapy shows that antibiotic prescription was very high as compared to complaints of fever along with diarrhoea. 31% of cases reported prescribing antibiotics prescribed to the age group 0 to 2 years. As most of the antibiotics itself are responsible for diarrhoea which can lead to worsening of diarrheal condition [12]. Secondly antibiotics were prescribed without culture sensitivity test (CST). According to standard treatment guidelines of WHO and CDC, antibiotics should be prescribed only after CST. Rehydration therapy and nutritious diet plays an important role in management of diarrhoea[13]. The use of ORS was limited. Chi square tests (Table 2) has value p value 0.00 less than 0.05 showing significant results suggesting that medications and age groups are related significantly.

Figure 8 shows gender versus presenting complaint concluding that 18% males and 26% females from the sampled population were affected from diarrhoea. Fever with diarrhoea affected 23% males and 9% females. Diarrhoea with abdominal pain affected 4% males and 5% females. Acute Gastroenteritis was the least observed complaint affecting 2% males and 3% females.

In the Table 3 of Chi-square test, has value 0.149 greater than p value 0.05 indicating that there is no significant relationship between presenting complaints and gender of paediatrics. This depicts those complaints are not gender specific.

Figure10 shows relationship between gender and medication showing that 16% males and 15% of females have treated with syrup antibiotic along with Panadol plus and zincate, whereas 7% males and 7.5% females were prescribed syrup antibiotics in combination with Flagyl suspension, Panadol plus and ORS.

Table 4 shows Chi-Square test value 0.428 greater than p value 0.05 indicating that there is no significant relationship between gender and medication prescribed. This also assumes that medications were prescribed independent of gender.

Complaint versus medication (Figure 12) shows that 7% peads were prescribed syrup antibiotic, syrup zinca and Panadol or brufen. While 6% peads were prescribed syrup antibiotic plus suspension Flagyl plus Panadol or brufen plus ORS. 7% prescriptions included an antibiotic plus probiotic plus syrup zincate plus ORS for complaint of simple diarrhoea. This irrational use of antibiotics in paediatric population is an alarming situation [14]. . Zincate plus ORS is preferred combination for treatment of diarrhoea and was prescribed to 9% peads. Second common presenting complaint was fever with diarrhoea. 22% cases were prescribed an antibiotic, zincate and Panadol or brufen. 4.5% of cases were prescribed an antibiotic plus suspension Flagyl plus Panadol plus ORS. 4.5% of cases were prescribed an antibiotic plus probiotic plus zincate. Combination therapy of an antibiotic and probiotic is still controversial and a matter of concern [15].

CONCLUSION

It has been concluded from the present study that there is a significant difference between prescribing patterns of antidiarrheal and standard treatment guidelines which in turn leads to increased morbidity and mortality in the pediatric population. Comparative pharmaceutical evaluation tests such as pH and HPLC were in line with reference ranges indicating that there is no problem in formulation development. It was seen that the age group 0-6 years were most affected with a complaint of diarrhea, which is a warning sign for the health department of Pakistan. It is the need of the time to improve prescribing practices according to standard guidelines to the improve health status of the pediatric population.

[1, 2]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

All the authors equally contributed in planning and collecting data, drafting manuscript and analyzing data to be qualified for authorships

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