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Monitoring Efficacy of Therapeutic for Rotavirus Diarrhea Hospitalizations in Yemen based on WHO Guideline

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ABSTRACT

To assess the efficacy of therapeutic on *Rotavirus* diarrheal hospitalizations among children ≤ 5 years of age based on world health organization (WHO) guideline. Based on a longitudinal observational study, 1027 fecal samples were collected from children (less than 5 years), suffering from diarrhea attended at the Yemeni Swedish hospital (YSH) in Taiz , Yemen from January 2009 to December 2012 . *Rotavirus* infection was detected by re – validated enzyme linkage immunosorbent assay (ELISA) on stool specimens of children. The treatment course consists of two methods, namely, intravenous rehydration fluid therapy (IV) for inpatient and oral rehydration fluid therapy (OR) for outpatient with treatment of the major symptoms, namely, fever and vomiting based on anti – pyretic and anti – emetic if necessary . The efficacy of therapy quality outcomes was assessed clinically and reported. Firstly, the results of re - validated ELISA method were precise to each analyte with percent relative standard deviation (RSD %) of intra-assay and inter – assay (< 5.0 %). Furthermore, the interval of accuracy for the method exhibited well recovery value of 93 - 100 % and the coefficient correlation (R^2) value was 0.99 as a good linear method for *Rotavirus* infection. Secondly , A total of 581 out of 1027 (56.57 %) patients were admitted as inpatients for IV fluid therapy , while 446 (43.43 %) were seen in the outpatient ward receiving OR fluid therapy . The recovery of patients was 98.10 % for IV and 98.43 % for OR, statistically, that was not significantly different (p> 0.05) . In conclusion , A successful *Rotavirus* treatment guidelines in Yemen will rely upon best sustained diagnosis by application Good Laboratory Practice (GLP) which is clear in specific – precise , reliable and accurate method to detect the virus and the best efficacy of therapy by Good Clinical Practice (GCP) which is clear in treatment of *Rotavirus* diarrhea which protects against dehydration by fluid therapy .

Keywords: *Rotavirus*, Monitor, Therapy, Diarrhea, Validation, ELISA

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INTRODUCTION

Rotaviruses are the leading cause of severe gastroenteritis in infants and young children < 5 years of age worldwide and they are the cause of approximately half a million deaths each year [1-3], leading to an enormous disease burden; every minute a child dies because of *Rotavirus* infection.

The prevention of *Rotavirus* can be classified into two lines . First line, the vaccine that has high impact to decline the percent of *Rotavirus* hospitalizations among < 5 years. However, this introduction will increase the immune pressure against wild-type *Rotavirus* strains circulating in the community, altering the forces and balances that drive *Rotavirus* evolution. There is concern that antigenically distinct novel or rare strains may be selected and spread, decreasing vaccine efficacy [4,5] . These were clear in some countries that found *Rotavirus* hospitalizations post-vaccination to be at 69 % – 80 % in El Salvador [6] and 65 % – 83 % in Belgium[7] . Also , while the lower decline of *Rotavirus* hospitalizations was recorded in developed countries namely Mexico (11% – 40%) 8 and Panama (22 % - 37%) [9] . In addition , the higher decline of *Rotavirus* hospitalizations was recorded by Australia in (89 % – 94 %) [10] . Although , there are now two new *Rotavirus* vaccines to prevent severe *Rotavirus* disease but the *Rotavirus* may infect the children due an immunization of children or development of the diverse and evolving *Rotavirus* strains [4,5]. Therefore, the fluid therapy is recommended [11] and we need the second line to prevent the *Rotavirus* diarrhea based on treatment guidelines such as World Health Organization (WHO) . WHO reported that there is no specific treatment for acute *Rotavirus* infection, and involves management of symptoms and, most importantly, maintenance of hydration[12] . If untreated, children can die from the resulting severe dehydration [13].

This study aims to monitor the efficacy of fluids therapy in the treatment of acute *Rotavirus* diarrhea detected by using Enzyme Linkage Immune – Sorbent Assay (ELISA) re - validated analytical method.

MATERIALS AND METHOD

Study area

Taiz, is one of the largest governorates in Yemen, with an area of 10.000 km2 and a population of about 2.5 million inhabitants, living in 23 districts. The total population of children < five years is 540,000 according to the last national census conducted in 2004 [14] .

Study design

A cross sectional study conducted by recruiting children hospitalized from diarrhea within the age group ≤ 5 years at the Yemeni-Swedish Hospital (YSH) in Taiz. The study was conducted from January 2009 until December 2012 at YSH; the only public hospital which admits children and provides maternal health care in Taiz city. The study was classified into two parts , the first part for detection of *Rotavirus* infection based on Good Laboratory Practice (GLP) namely re - validation of ELISA analytical method , the second part for treatment of *Rotavirus* diarrhea based on Good Clinical Practice (GCP), namely, the therapeutic impact monitoring and the outcome quality of the treatment response [15 -17] .

Ethical issue

Mothers or child's guardians received a simple explanation of the aim of the study and were asked to participate. If they agreed, the samples were collected and interviews were conducted. Confidentiality of the collected data was achieved by keeping data records in a locked room with limited access to the research team only.

Data collection

Within two days after hospitalization, at least 4-8 mg of stool was directly collected and stored in a sterile plastic container. Samples were kept at 2 - 8 °C, for a maximum of 8 days until they were transported to the laboratory where they were stored at −20 °C prior to analysis. Clinical information was obtained from the child's mother or guardian. Information included the child's sex, age at admission, symptoms, hydration status, height, weight, and length of hospital stay.

***Rotavirus* Analysis by ELISA**

The ELISA method (IDEIA Kit - Dako Ltd., Cambridgeshire, UK) validated assessment of linearity, accuracy, precision , limit of quantification and limit of detection of *Rotavirus* antigen is stool sample and used for samples analysis [18,19] . ELISA – based *Rotavirus* analysis and using a polyclonal antibody prepared against the common antigen presented on *Rotavirus* VP6 (a major group specific protein). These antibodies were used in a solid phase sandwich type ELISA using a micro plate containing 96 weels [20].

Guideline Fluid Therapy

Two therapies fluid protocols have been used . The first protocol namely oral rehydration (OR) solution was used for outpatient to prevent the mild and weak diarrhea. The OR is used for 24 hours that contains the WHO/UNICEF's formula namely 2.6 grams sodium chloride , 2.9 grams trisodium citrate dihydrate , 1.5 grams potassium chloride , 13.5 grams anhydrous glucose per liter of water . This equates to 84 mEq sodium, 65 mEq chloride, and 20 mEq potassium per liter of fluid. The second line is the intravenous rehydration solution (IV), it was administered to

infants in two – doses a day , the first dose given at the morning and the second dose at the evening . IV formula is one liter of Ringer's lactate solution contains: 130 mEq of sodium ion = 130 mmol/L ; 109 mEq of chloride ion = 109 mmol/L; 28 mEq of lactate = 28 mmol/L; 4 mEq of potassium ion = 4 mmol/L; 3 mEq of calcium ion = 1.5 mmol/L. The severe dehydration was treated by IV rehydration fluid namely 30 cc / kg within 30 minutes , then 70 cc/kg within 4 hours until the dehydration was removed . OR solution was used after dehydration namely 70 cc/kg for 4 hours until the dehydration was removed [21 -23] . Also , treatment of the major symptoms, namely, fever and vomiting based on anti – pyretic and anti – emetic if necessary .

Statistical methods

Demographic, laboratory, and clinical results data were entered and analyzed using Excel Software 2010. Descriptive analysis and Chi-square test were used to make comparisons among categorical variables. For all statistical analyses, a *p* -value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Subject characteristics

A total of 1027 children less than or equal to 5 years were diagnosed with *Rotavirus* diarrhea and admitted at the hospital from January 2009 to December 2012. Of those, 446 were treated by OR fluid therapy and 581 were treated by IV fluid therapy . The age range of patients was from 1-59 months. More males than females were admitted (60 % vs 40%) respectively.

Re - validation of ELISA method

Specificity

The absence of matrix interferences with Rotavirus antigen. On the other mean , no significant cross-reactivity or interference was observed

Linearity

Linearity was performed for ELISA method to detect the *Rotavirus* antigen and the coefficient correlation (R^2) value to be 0.990 **.**

Precision

The CV (%) for precision of the re – validated method was presented in Table 1 . The maximum CV (%) was 4.5 % in intra – assay , and the minimum CV (%) in intra – assay to be 4.9 % .

Accuracy

The accuracy (represented by recovery) of ELISA method was determined at the concentrated targeted levels used to detect the *Rotavirus* antigen in Table 1 . All recoveries were within acceptable limits (93 % – 100 %) , indicating that the method was suited for the analysis of *Rotavirus* antigen in children in Taiz , Yemen .

Table 1: Re - validation of ELISA method

Parameters	**Linearity**		**Precision (CV %)**		**Accuracy**
	Linearity (R^2)	**Sensitivity**	**Intra – assay**	**Inter–assay**	**(%)**
Rotavirus **Ag**	0.99	98.7 %	4.8	4.9	3
Interval Confidences (%)	96 – 100	95 – 101	95 – 101	95 – 101	95 – 101

***Rotavirus* diarrhea treated by IV fluid therapy**

Fecal samples were collected from 581 children less than or equal to 5 years of age diagnosed with diarrhea during the period from January 2009 to December 2012 . All children had diarrhea for a period of 1-2 days before hospitalization. 56.57 % of children infected with *Rotavirus* diarrhea was treated by IV fluid therapy. The ratio of recovery was 98.10 % compared to the unimproved states that was 1.80 % (Table 2) . The mortality of patients was 0.68 % among 3 – 5 months due to sever diarrhea .

***Rotavirus* diarrhea treated by OR fluid therapy**

On the other hand , fecal samples were collected from 446 children less than or equal to 5 years of age diagnosed with diarrhea during the period from January 2009 to December 2012 . Overall *Rotavirus* infections were treated to 98.43 % post treatment compared to the unimproved states that was 1.50 % . The mortality of patients was not recorded in mild and weak diarrhea . In brief , the recovery of patients with IV and OR, statistically, that was not significantly different ($p > 0.05$)

Table 2: *Rotavirus* Diarrhea Post – Treatment based on Fluid Therapy N : 1027

	IV Fluid Therapy n : 581							**OR Fluid Therapy n :** 446						
Age	***Rotavirus* Infection**			**Outcomes**				***Rotaviru* Infection**			**Outcomes**			
(months)	**Male**	**Female**	**Total**	**Improved**	**Died**	**Transferred**	**Unknown**	**Male**	**Female**	**Total**	**Improved**	**Died**	**Transferred**	**Unknown**
0 – 2	11	10	21	21	-	-	-	11	15	26	26	-	-	-
3 – 5	50	30	80	76	4	-	-	22	32	54	53	-	1	-
6 – 8	84	41	125	122	-	-	3	69	48	117	116	-	-	1
9 – 12	108	65	173	171	-	2	-	70	61	131	129	-	2	1
13 – 17	40	29	69	68	-	1	-	33	21	54	53	-	-	1
18 – 23	38	17	55	55	-	-	-	25	3	28	28	-	-	-
24 – 59	39	19	58	57	-	-	1	22	14	36	35	-	-	1
Total	370	211	581	570	4	3	4	252	194	446	439	0	3	4
number (n)	63.68	36.31	100	98.10	0.68	0.51	0.68	56.50	43.50	100	98.43	0	0.67	0.89
Percent **(%)**														

DISCUSSION

Rotaviruses are a leading cause of severe diarrhoeal disease and dehydration in infants and young children throughout the world. Most symptomatic episodes occur in young children between the ages of 3 months and 2 years [24] . The virus spreads rapidly, presumably through person-to-person contact, airborne droplets, or possibly contact with contaminated toys. Symptoms usually appear approximately two to three days after infection, and include projectile vomiting and very watery diarrhoea, often with fever and abdominal pain [25] . *Rotavirus* is the most common cause of severe diarrhea in children worldwide and diarrhea deaths in children in developing countries. Recent previous study was recorded by Yemeni – Swedish hospital in Taiz , Yemen that the most common cause of diarrhea (40.0%) in infants and young children less than or equal to five years [26,27] . Therefore , the monitoring of *Rotavirus* therapy impact depends on two parts in our study , the first part is GLP and the second part is GLP 15 , 16,17 Firstly, m GLP approach gives enough guarantees for the future results that will be generated by this method during samples analysis . Calibration and validation of ELISA method for *Rotavirus* analysis were carried out . The big problem in Yemen in treatment of diarrhea depended on clinical symptoms and general stool examination based on microscopic method to see the a parasites and bacteria and virus can not detected by this method. This diagnosis is not robust and specific to detect the bacteria. The microscope may play a role to diagnose the parasites that cause diarrhea such as *Entamoeba histolytica* and *Giardia lamblia* only [28]. Knowledge of the causative agents of diarrhea is important as a guide for the clinical management and also to carry out preventive measures in reducing the risk of the prevalence and recurrence of diarrhea .

Secondly , GCP in treatment of *Rotavirus* diarrhea was carried out based on the best laboratory diagnosis . Two therapies fluid protocols, namely, OR and IV have been used in Taiz, Yemen .The IV has proven highly effective in preventing severe *Rotavirus* diarrhea in children and safe from the possible complication of intussusceptions , that are admitted in hospital (in patient) administered to infants in a two – dose course in a day , with the first dose given at the morning and the second dose at the evening . The therapy fluid are the best prevention strategy employed in Yemen during our study period to control diarrhea by *Rotavirus* disease and the OR therapy that is used for outpatient to prevent the mild and weak diarrhea . Therefore, we believe that the improvement of patients we observed is due to the GCP approach .

The most important aspect of the treatment of acute diarrhea is the maintenance of fluid and electrolyte balance, particularly in children and in the elderly. On the other hand , in non-

pathogenic diarrhea or viral gastroenteritis, the antibiotics and antidiarrhoeal drugs are best avoided. Initial therapy should be with OR or IV preparations , which contain electrolytes and glucose . For sever *Rotavirus* diarrhea , medical care by physicians and nurses experienced with the effect and progression of the disease can save lives – decreasing mortality rates . Maintenance of the patient's body fluid volume is critical to sever *Rotavirus* care [11 , 23] . In Taiz, the therapy fluid program for treatment of the *Rotavirus* diarrhea improved the child's health . The results showed that 100 % of the specimens were *Rotavirus* - positive in pre – treatment period and treated up to 98 % post - treatment period.

CONCLUSION

In conclusion , A successful *Rotavirus* treatment guideline in Yemen will rely upon the best sustained diagnosis by application GLP which is clear in specific – precise , reliable and accurate method to detect the virus and the best efficacy of therapy by GCP which is clear in treatment of *Rotavirus* diarrhea that protects against dehydration by fluid therapy . OR solutions that are most helpful for mild dehydration. Severe dehydration may require hospitalization for treatment with IV fluids therapy , which are given to patients directly through their veins

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