Research Paper:

Early Hospitalization Reduces the Length-of-Hospital Stay and Antibiotic Use in Children With Moderate Diarrhea: A Study in Bangladesh

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ABSTRACT

Background: Childhood diarrheal diseases are common with mild-to-severe mortality rate worldwide. Lower-Middle-Income Countries (LMICs), including Bangladesh in South Asia, are still unable to save their under-5 lives due to diarrheal conditions.

Objectives: The main aim of this study was to evaluate the duration of hospital stay and use of antibiotics in under-2 children with moderate diarrhea in Bangladesh.

Methods: This study was done on hospitalized 6 months to 2 years old pediatric patients (n=212) with an uncontrolled moderate type of diarrhea in 3 districts of Bangladesh. Based on the history of diarrhea onset, 133 and 79 patients were allocated in the Early Hospitalization (EH) and Delayed Hospitalization (DH) groups, respectively.

Results: To treat uncontrolled diarrhea at home, antibiotic therapy was initiated in 36.7% of patients in the DH group without any valid prescription, whereas only 7.5% of patients in the EH group received antibiotics (P<0.05). In the DH group, 67.1% of children received different antibiotic therapies for treating their diarrhea with or without other hospital-acquired infections during their extended hospital-stay period, resulting in Antibiotic-Associated Adverse Events (AAAEs) in 17.7% of the patients. At the same time, 21.1% of the patients in the EH group received antibiotics that caused AAAEs in 2.2% of them (P=0.001). The EH group, who received doctors' consultations and hospitalized within 2 days of the onset of diarrhea, stayed in the hospital for a maximum of 4 days. It was less than half a time that of the children in the DH group (P<0.05) (stayed for a maximum of 10 days), who visited doctors and admitted to hospitals at a later stage of diarrheal-onset.

Conclusions: Early doctor visits and hospitalization of under-2 children with uncontrolled moderate diarrhea may reduce the severity of the disease and risk of severe acute malnutrition, minimize the use of antibiotics with minimum chance of occurrence of adverse drug events, and cause early discharge from hospital.

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1. Background

Despite living in the second decade of the 21st century with luminous pharmaceutical advancements, such as oral rehydration saline and zinc therapy, diarrhea is still the second leading cause of death in under-5 children worldwide (1-3). In Low-Middle-Income Countries (LMICs), including most countries in South Asia and Sub-Saharan Africa, diarrheal diseases are mainly responsible for the mild-to-severe rate of mortality and morbidity in children. In 2013, among the 6.3 million deaths of children globally before reaching their fifth year of life, diarrhea was accounted for 500000 deaths (4). In 2017, diarrhea was a leading cause of child death and accounted for 8% of total death of children worldwide (5). Centers for Disease Control and Prevention of the United States pointed out that diarrhea takes 2195 children's lives every day, and 801000 children every year. Also, diarrhea diseases are accused of 1 in every 9 child death before celebrating their fifth birthday (3, 4). As per the comment in Disability-Adjusted Life Years (DALYs), diarrhea is liable for 3.6% of the total global disease burden (6). If this child death-trend persists, 4.4 million children under the age of 5 will die by 2030, and diarrhea will be a leading cause for tracing this death-figure (4).

According to the statement of the United Nations Children's Fund (UNICEF), diarrhea mostly occurs among South Asian children less than 2 years of age, resulting in possible death (5). Basically, diarrhea is not a disease, but it is a symptom of other illnesses. Diarrhea is better defined as the presence of loose or watery stool, generally with increased frequency. Clinically, diarrhea is of three types: acute watery diarrhea lasting several hours to one week; acute bloody diarrhea; and persistent or chronic diarrhea for 14 days or longer (7). The severity of diarrhea depends on the frequency of loose or watery stool. So, the frequencies of more than 10 times, below 10 times, and a couple of times are called severe diarrhea, moderate diarrhea, and mild diarrhea, respectively (8). Acute diarrhea is caused by bacterial, viral, or parasitic infections and is resolved shortly with available remedies such as Oral Rehydration Salt Solution (ORSS) and zinc supplements. The World Health Organization (WHO) and meta-analyses of several randomized controlled trials recommended that Oral Rehydration Therapy (ORT), including hypo-osmolar oral rehydrating salts solutions and zinc supplements, are the primary treatment management in acute diarrhea (7, 9-11). However, acute diarrhea may produce moderate to severe complications, especially in younger children (<5 years) (12). When acute diarrhea (less than 1 week) is not appropriately managed, it turns into Persistent Diarrhea (PD) (up to 14 days or more). At this stage, it becomes more complicated, requires hospitalization, and has a high rate of mortality, mostly in under-5 children (7).

Diarrhea (acute and persistent) is accountable for more than half of all children's deaths in the African and South-East Asian regions, including Bangladesh (an LMIC) (13, 14). Ninety percent and 60% of PD cases happen in children before their 6 months and below 1 year of age, respectively. This condition is a real threat to young children's lives in LMICs, mostly when it is not adequately managed at its acute stage (within the first 7 days of initiation) (15, 16). Children's death in Bangladesh is a national burning issue, and diarrhea is one of the leading causes of under-5 children's death. Multiple Non-Governmental Organizations (NGOs), WHO, United Nations (UN), UNICEF, and the International Center for Diarrheal Disease Research, Bangladesh (ICDDR, B) and different agencies of the local government are closely working in Bangladesh to reduce the child death from diarrheal diseases. The high incidence of under-5 children's death due to diarrhea mostly happen in rural areas of Bangladesh. The above-mentioned world's leading organizations, accompanied by the Bangladesh government, are trying to strengthen the system of diarrhea management from households without using too much of pharmaceutical products, including antibiotics (17).

Study objectives

The principal objective of this study was to evaluate the length-of-hospital stay and antibiotic use associated with the early versus delayed hospitalization of under-2 children with moderate diarrhea in Bangladesh.

2. Methods

Study design

This 3-month-long prospective, observational study was conducted from August 2019 to October 2019 in multiple non-government hospitals of Dhaka, Cumilla, and Noakhali districts of Bangladesh. The study samples were children admitted to hospitals with moderate diarrhea. To collect the study patients' data, we contacted the parents of all children (patients). All patients' previous diseases, medication, and birth history were collected directly from the parents, and time-to-time medical history was collected from the corresponding medical centers. The progression of the patient's health status was recorded daily, and a continuous follow-up chart was maintained.

Study Samples

The targeted samples of this study were 6 months to 2 years old patients (n=212) with an uncontrolled moderate type of diarrhea (frequency of loose or watery stool below 10 times over 24 h) (8) started at home 48 hours to 5 days ago. Following the age-range and study criteria, 133 patients were taken as the Early Hospitalization (EH) group because they were admitted to hospitals to treat their uncontrolled high frequency loose or watery diarrhea that originated at home within the last 2 days. Seventy-nine patients of the same age group admitted to hospitals with similar characteristics of diarrhea initiated within the previous 5 days were considered as samples in the Delayed Hospitalization (DH) group. The weight and height of all patients were measured by using a digital body weight/height measurement scale (BY 90 baby scale, Beurer GmbH, Germany) by a trained nurse during admission. Bodyweight was graded following the percentile range (underweight: <the 5th percentile; healthy weight: between the 5th and the 85th percentile; overweight: Between the 85th and the 95th percentile; and obese: ≥the 95th percentile) (18). From hospital admission to hospital discharge, data of all the treatment managements, clinical progression, and clinical interventions in all patients were collected, systematically, and analyzed. All the patients' (both EH and DH groups) clinical outcomes, nutritional therapies, and antibiotic use data were evaluated group-wise and compared to each other accordingly.

Inclusion and exclusion criteria

The inclusion criteria of this study were patients (6 months to 2 years old) with a moderate type of diarrhea initiated 2 to 5 days before hospitalization; no hospitalization history for any disease over the last 1 month; no record of renal impairment, moderate to severe hepatic impairment and any gastrointestinal disorder; and full level of consciousness. Severe malnourished patients; those with known congenital disabilities; a history of chronic diarrhea; and patients with comorbidities, including cardiac anomalies, convulsion, and pneumonia, were excluded from this study.

Statistical analysis and approval

The obtained data were analyzed using IBM SPSS statistics v. 22 software. The results are expressed as Mean±SD and percentages. The Pearson Chi-square test and the independent t test were used for categorical and numerical variables, respectively. The Confidence Level (CI) was 95%. The statistical significance level was set at P<0.05. Informed consent was obtained from the legal guardians (father/mother) of each patient (younger children) included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval (1907SH-OR014) by the Human Research Ethics Committee of Square Hospital, Dhaka, Bangladesh, on July 15, 2019.

3. Results

All patients of this study were of South Asian origin with a mean age of 12.3±5.3 months and 12.3±5.5 months in the early and delayed hospitalization group, respectively (P=0.54) (Table 1). The number of male patients in both EH (88, n=133) and DH (51, n=79) groups was higher than female patients (EH: 45; DH: 28) (statistically not significant) (Table 1). With low-birth-weight, 29.1% (23, n=133) patients in the EH group and 40.4% (17, n=79) patients in the DH group born (P<0.05) (Table 1). Among all children, 8.2% (11, n=133) and 7.5% (6, n=79) children in the EH and DH groups, respectively, stopped getting their mother's breast-milk (P>0.05) before finishing their 2 years of age (Table 1). Ninety-one and 67 patients were with healthy body weight in the EH and DH groups, respectively; 36 and 8 patients were underweight in the EH and DH groups, respectively; and 6 and 4 children were found overweight during their hospital admission in the EH and DH groups, respectively (Table 1). No obese patient was found in the EH or DH group during hospitalization.

Previous medical histories, disease condition, past and current medication history, and birth history was taken by pediatric doctors from the parents of every patient in this study. A complete individual patient-wise evaluation note was generated before admitting the patient to the hospital. Before admitting to the hospital, the mean±SD number of 8-hourly stool frequency of the study patients was 1.85±0.8 times and 3.2±0.4 times in the EH and DH groups, respectively, and that was statistically significant. Thirty-nine percent of patients (n=133) in the EH group were reported with electrolyte imbalance during their hospital admission, whereas 78.4% (n=79) of patients in the DH group had electrolyte imbalance, including hypokalemia (P<0.05) (Table 1). The degree of dehydration (severe dehydration, some dehydration, and no dehydration) (9) was estimated in all study patients (assessed based on the presence of dry mouth symptoms, less frequent urination, lack of tear in crying, and body immobility) (7, 9) of both the groups during hospital admission with moderate diarrhea. Some dehydration (fluid deficit 50-100 mL/kg of body weight) (11) was found at a higher rate (45.5%) in the patients of the DH group than that

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Table 1. Baseline characteristics of the participants, clinical conditions, and adverse drug events

Characteristics		No. (%)/ Mean±SD		P
		The EH Group (n=133)	The DH Group (n=79)	
Ethnicity	South asian	133 (100)	79 (100)	-
Age (months)	Mean±SD	12.3±5.3	12.3±5.5	0.549
	Range (min-max)	6-24	6-24	
Gender	Male, No.	88	51	0.412
	Female, No.	45	28	
History of low-birth-weight		23 (29.1)	17 (40.4)	0.006
Not feeding breast-milk		11 (8.2)	6 (7.5)	0.861
Bodyweight status	Underweight	36	8	0.003
	Healthy weight	91	67	
	Overweight	6	4	
During admission	Eight-hourly stool frequency	1.85±0.8 times	3.2±0.4 times	0.001
	Electrolyte imbalance	52 (39.0)	62 (78.4)	0.001
	Some dehydration	55 (41.3)	36 (45.5)	0.549
	Fever (>100.4º F)	20 (15.0)	23 (29.1)	0.005
	Sign of malnutrition	8 (6.0)	54 (68.3)	0.001
	Initiated AT before hospitalization	10 (7.5)	29 (36.7)	0.001
AAAE during hospital-stay		3 (2.2)	14 (17.7)	0.001

SD: Standard Deviation; AT: Antibiotic Therapy; AAADE: Antibiotic-Associated Adverse Event.

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in the EH group (41.3%) (Table 1). Higher than normal body temperature (fever) was detected more in the DH group (29.1%) than the patients of the EH group (15%) (P<0.05). Children in the EH group had more than 10-time fewer signs of malnutrition (6%) (including lack of appetite, tiredness, lack of concentration, and mental depression) than the DH group (68.3%), and this was statistically significant (Table 1). Interestingly, 36.7% of patients in the DH group started antibiotic therapy to treat uncontrolled diarrhea without consulting with any doctor or having any valid prescription. However, when diarrhea was not controlled properly, they turned back to the hospital, finally. On the contrary, a significantly lower percentage of patients (7.5%, n=133) in the EH group came under any antibiotic therapy before admitting to the hospital (Table 1). The use of antibiotics for the treatment of complicated diarrhea with or without other hospital-acquired infections in the children of the DH group resulting in a higher rate of Antibiotic-Associ-

ated Adverse Events (AAAEs) (including hives, skin rash, itchy skin and eyes, angioneurotic edema, and mild respiratory distress) (17.7%) during their extended duration of hospital-stay while the children of the EH group were less experienced with AAAEs (2.2%) during their comparatively shorter period of hospital-stay (P=0.001) (Table 1). The most common AAAEs were hives, itching, and restlessness (mild reactions), and no moderate or severe adverse event was recorded with antibiotics among the children of both groups taken antibiotics.

Most of the Under-2 children admitted in hospital with an uncontrolled moderate type of diarrhea with altered physical conditions received antibiotic therapy to treat diarrhea. Patients in the EH group came to the hospital and were hospitalized within 48 hours of the onset of diarrhea at home. During their stay in the hospital, 21.1% of the patients required different antibiotic therapies for their diarrhea treatment, whereas 67.1% of patients
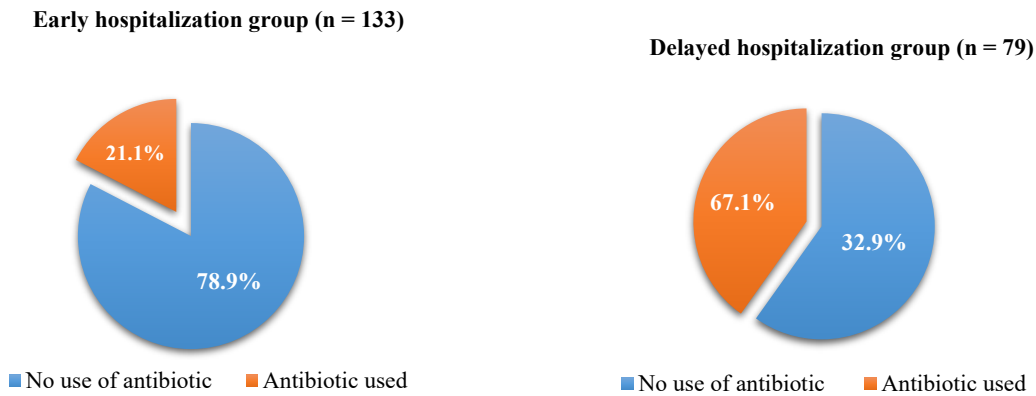
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Early hospitalization group (n = 133)

21.1%

78.9%

■ No use of antibiotic ■ Antibiotic used

Delayed hospitalization group (n = 79)

67.1%

32.9%

■ No use of antibiotic ■ Antibiotic used

Figure 1. Use of antibiotics during hospitalization in the patients

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in the DH group were undergone antibiotic therapies during their hospital stay (P=0.001). The main reasons behind this higher percentage of antibiotic use in the DH group were their deteriorated physical condition, the severity of diarrhea, and increased risk of comorbidities during their admission (Figure 1).

All patients of the EH group who were admitted early to hospital after the diarrheal event had a short period of hospital-stay. After getting admission to the hospital, they came under the anti-diarrheal treatment with or without the right antibiotic therapy, and the management of other symptoms started immediately. All patients of both groups received commercially available ORSS (ORSaline-N, Social Marketing Company, Bangladesh) and zinc supplement (Baby Zinc 20 mg dispersible tablet, ACME, Bangladesh). Within a maximum of 4 days (average length-of-hospital stay was 1.5 days), diarrheal diseases of all patients of the EH group were treated successfully. They were discharged from hospitals,

whereas the DH group patients stayed at a maximum of 10 days (average length of hospital stay was 3.7 days) in hospitals to cure their complications completely. Then they were discharged to home (P<0.05) (Figure 2).

4. Discussion

In this study, we compared the children who developed a moderate type of diarrhea at home and visited the nearest hospital within 48 hours of its initiation before deterioration of their physical condition (due to dehydration, electrolyte imbalance, and generalized weakness) with the children who came to the hospital with a lower health condition, one or more comorbidities, and life-risk associated with an uncontrolled moderate type of diarrhea. Here we found that the children of the EH group came to take doctors' consultation in the hospital during the early stage of moderate-diarrhea ultimately hospitalized for a shorter time (on average 1.5 days) compared to the children (the DH group) who were de-
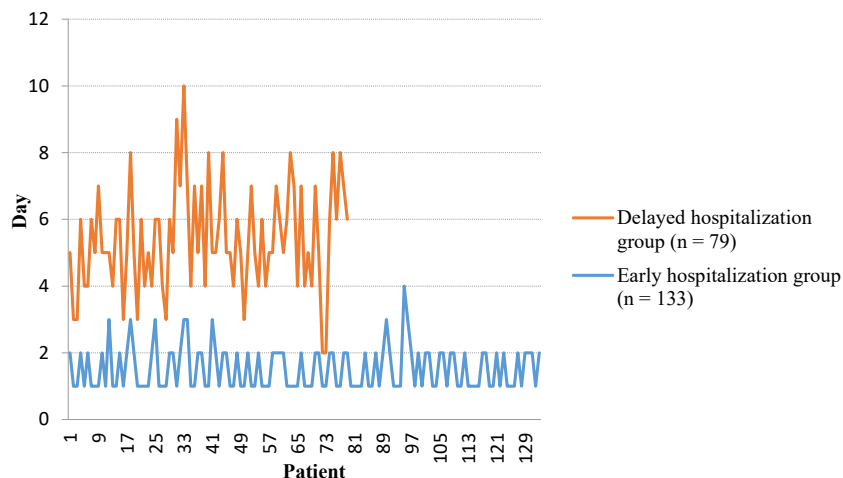

Figure 2. Length-of-hospital stay of the patients

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layed to come in hospital after a long-period (average hospitalization time was 3.7 days) of detecting diarrhea. By this time, they were treated with traditional home-remedies. The acute type of diarrhea that generally lasts for less than 7 days are prevalent in children under-5 in LMICs, including Bangladesh. When the acute phase of diarrhea is not appropriately managed or turned into persistent diarrhea, it becomes more deadly for young children, so hospital admission is required (19). In Bangladesh, from 1989 to 2014, the child mortality rate has been reduced to 65%, and the child death rate has been declined from 133 to 46 deaths per 1000 live births (20). With this improvement in the child death rate in Bangladesh, diarrhea is still a leading cause of under-5 children's death. So the proper control of diarrheal diseases in this age-group may improve the under-5 child survival rate (19). A study demonstrated that 25% of children (aged between 1 to 4 years) deaths was accounted for PD, which was initiated as acute diarrhea and not appropriately managed at the early disease stage (16). This study found that early hospitalization of 6 months to 2 years old children, who were struggling with moderate diarrhea (at an early stage) at home, improved their disease condition shortly and significantly shortened their hospital stay duration.

Acute dehydration associated with frequent loose motion is a life-threatening event, especially in young children (7, 10, 11). More than 40% of patients in both groups (EH and DH) of this study developed some dehydration following moderate diarrhea. For more than the last 30 years, oral rehydration salt solution (a blended clean watery solution of measured salt and sugar) has saved more than 50 million lives. That included children worldwide, especially from severe dehydration in diarrhea, and that is why The Lancet journal declared ORSS as the most important medical innovation of the 20th century (21). In the late 1960s, the United States and Bengali scientists of the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR, B) developed ORSS. In the 1970s, the renowned Bangladeshi NGO, Bangladesh Rural Advancement Committee (BRAC), implemented a strategic plan to teach mothers to make ORSS at home by mixing Labon (salt) and Gur (sugar) in drinking water (22). However, due to the wrong measurement of ingredients and lack of understanding, the Ministry of Health and Family Welfare of Bangladesh is now discouraging the use of homemade ORSS and emphasizing the use of readymade packetized ORSS with zinc supplements available in most of the pharmacy shops, chain shops, and departmental stores at a lower price. In the absence of appropriate manage-

ment of acute diarrhea, mostly with conventional home remedies, including ORSS during the early stage, children get weaker, the risk of further diarrhea-associated complications is increased, and when admitted to hospital at a later stage (with moderate diarrhea), the total length-of-hospital stay is extended (23). Despite feeding mothers' breast milk, under-2 children with recurring episodes of loose or watery diarrhea are at high risk of developing malabsorption with or without vomiting. Malnutrition is a vital cause for developing uncontrolled moderate diarrhea in younger children group, and this may subsequently lead to severe malnutrition, which may exacerbate the disease state (24). A recent study on LMICs' young children group demonstrated that persistent diarrhea was responsible for 32% to 62% of young children's death, which was initiated as acute diarrhea at home, where the treatment and attention to the disease progression were inadequate (16).

In low-middle-income countries, including Bangladesh, every under-3 child has experienced three episodes of diarrhea every year, and inadequate immunization, unsafe drinking water, improper sanitation system, and lack of hand-hygiene are the potential factors for developing frequent diarrheal diseases. Recent data from WHO showed that 780 million people are in a crisis of fresh drinking water, and 2.5 billion individuals have no proper sanitation facility worldwide. Sixty percent death from diarrhea is due to unsafe drinking water, and 40% risk of diarrheal diseases can be reduced with appropriate hand hygiene using soap (5). Children are very vulnerable to this unviable environment, and as a result, globally, around 1.7 billion diarrheal cases in under-5 children are reported every year (7). Bacteria, viruses, or parasites initially generate acute diarrhea and then spread rapidly from person-to-person through contaminated foods and water in an unhygienic environment. A rapid fluid loss in the form of frequent diarrhea in children may result in severe dehydration and electrolyte imbalance. Even during severe acute diarrhea, the total fluid loss (through diarrhea and vomiting) can be 3 times higher than the total circulating blood volume (80–125–250 mL/kg of body weight/day) in a child (12).

At the time of moderate diarrhea, a treatment algorithm is highly needed to follow strictly. One of the oldest and very useful treatment algorithms is using an enormous amount of ORSS, vitamins, adequate mineral supplements (20 mg of elemental zinc), and appropriate use of antibiotics (25). In an under-2 child with moderate diarrhea, when this essential treatment algorithm is not appropriately performed at home, fluid loss increases excessively through diarrhea and vomiting, and

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malnutrition progresses rapidly. The clinical condition of the patient gets complicated, and it takes a long time to cure after hospitalization at this stage (12, 19, 25). In our study, the delayed hospitalization group of children were admitted to hospitals with complicated health conditions and different comorbidities such as severe acute malnutrition and electrolyte imbalance. As a result, they required longer hospitalization time and more pharmacotherapies, including antibiotics, for their complete treatment in the hospital than the children of the early hospitalization group.

The use of antibiotics in under-2 children with acute diarrhea without being adequately prescribed by a licensed physician is a controversial issue. Only bloody diarrhea is judiciously required antibiotics, but the high use of different antibiotics in diarrheal diseases in children is unclear (17). The study showed that in rural areas of Bangladesh, the rate of antibiotic use in male and female children was 31% and 36%, respectively, which was very close to the national antibiotic consumption (23). In this study, 36.7% of children in the DH group received antibiotic therapies at home for their diarrheal management with other treatment algorithms. The basis and rationality of antibiotic usages were not known.

On the other hand, the EH group children received less antibiotic therapy (7.5%) but reported to the hospital doctor at an earlier diarrhea stage. Multiple studies in Bangladesh found that in both rural and urban areas, antibiotics were used predominantly in acute diarrhea in under-5 children irrationally. In many cases, antibiotics are taken in diarrhea at home without having any prescription from a licensed physician. As a result, the risk of antibiotic resistance has increased among the children, and complete cure of diseases takes a longer time resulting in elevated hospital stay with increased treatment cost (26-29). The persisted diarrheal cases with late hospitalization results in more antibiotic use in children. A study found that in above 6 months old children, the use of antibiotics increased up to 79.38% for diarrheal treatment (19).

Moreover, overuse of antibiotics results in unwanted adverse drug events among children with diarrhea (30). A recent study showed that 42% of hospitalized pediatric patients developed antibiotic-associated adverse events, and these unwanted events complicated their overall treatment process during their hospital stay (31). In our study, children (the DH group) who came to the hospital at a later stage of uncontrolled moderate diarrhea received a higher percentage of antibiotic therapies (67.1%) for treating their uncontrolled diarrhea

and other nosocomial infections (during hospital stay), which corresponded to an increased rate of antibiotic-associated adverse events (17.7%). Whereas children in the EH group, who were reported to doctors of hospitals during the early stage of their moderate diarrhea, were managed with less antibiotic therapies (21.1%) for the same purpose, which let them less experienced to antibiotic-induced unwanted events (2.2%) during their hospital stay. Therefore, early hospitalization of children with moderate-to-severe diarrheal diseases (though staying on conventional home-remedies such as ORSS and zinc supplements) may result in short hospital-stay, less chance of acute diarrhea-associated rapid physical dilapidation, less chance of severe malnourishment, limited use of antibiotics for complete cure, and less possibility of experiencing adverse drug events during the period of hospitalization.

The significant limitations of this study were the small sample size of both groups, short duration of the study, lack of information about the etiology of diarrheal diseases, and limited information about the home-antibiotic use.

5. Conclusions

Acute diarrhea is a leading cause of child death worldwide. Children of LMICs are mostly living at a high risk of recurrent mild-to-severe diarrhea because of unsafe drinking water, improper sanitation, and lack of hand hygiene culture. Conventional home-remedies, including oral rehydration salt solution and zinc supplements, are primarily used to manage acute diarrhea at home. Still, this method sometimes fails to address diarrheal complications without having proper care and pharmacotherapies that are mostly available in hospital setups. This study found that in uncontrolled acute moderate diarrhea persisting over 48 hours in children (6 months to 2 years old), early hospitalization may be a practical solution. It results in a short hospital stay with less chance of further diarrhea-related complications, less risk of severe acute malnutrition, less requirement of antibiotic use for complication management, less scope of intending irrational antibiotic use at home, the limited possibility of antibiotic resistance, and minimum risk of antibiotic-associated adverse events during the hospital stay.

Ethical Considerations

Compliance with ethical guidelines

This study was conducted with the study-approval of the corresponding hospital authorities. Informed consent was obtained from the legal guardians (father/

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mother) of each patient (younger children) included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval (1907SH-OR014) by the Human Research Ethics Committee of Square Hospital, Dhaka, Bangladesh, on July 15, 2019.

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