

# Prolonged acute diarrhea in adults: Decades of observation from epidemiological perspective in urban Bangladesh

Sumon Kumar Das<sup>1</sup>, Mohammad Jobayer Chisti<sup>1</sup>, Shah Nawaz Ahmed<sup>1</sup>, Mohammad Abdul Malek<sup>1</sup>, Fahmida Dil Farzana<sup>1</sup>, Farzana Ferdous<sup>1</sup>, Jonathan Latham<sup>2</sup>, Abu Syed Golam Faruque<sup>1\*</sup>

<sup>1</sup>Centre for Nutrition and Food Security (CNFS), International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh

<sup>2</sup>London School of Hygiene and Tropical Medicine, London, UK

Email: \*[gfaruque@icddr.org](mailto:gfaruque@icddr.org), [sumon@icddr.org](mailto:sumon@icddr.org), [chisti@icddr.org](mailto:chisti@icddr.org), [shahnawz@icddr.org](mailto:shahnawz@icddr.org), [mamalek@icddr.org](mailto:mamalek@icddr.org), [fahmidaf@icddr.org](mailto:fahmidaf@icddr.org), [farzanaf@icddr.org](mailto:farzanaf@icddr.org), [jonathan.r.latham@gmail.com](mailto:jonathan.r.latham@gmail.com)

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## ABSTRACT

The study aimed to determine the epidemiological, clinical characteristics, and etiology of adults aged  $\geq 20$  years presented with prolonged acute diarrhea ( $\geq 7$  days). A total of 18,210 adults aged  $\geq 20$  years were enrolled in the Diarrheal Disease Surveillance System of icddr,b between 1993-2012 and included into the analysis. Of these, 17,631 (97%) had duration of diarrhea  $\leq 6$  days, 418 (2%) diarrhea presented with a duration of 7 - 13 days and rest 161 (1%) had history of diarrhea  $\geq 14$  days. A higher proportion of adult individuals who had duration of diarrhea  $\geq 14$  days (70% vs. 56%;  $p < 0.001$ ) and 7 - 13 days (62% vs. 56%;  $p = 0.006$ ) compared to those  $\leq 6$  days were male. At least 73% of all patients used oral rehydration solution; but proportion was lower among prolonged acute diarrhea groups. Use of antimicrobials was higher among those with duration 7 - 13 days (81%) and  $\geq 14$  days (81%). Diarrhea lasting  $\geq 14$  days, 47% were suffering from chronic energy deficiency and 30% had history of smoking. Individuals with diarrhea  $\geq 7$  days less frequently presented with vomiting, watery stool, frequency of stool  $> 10$  times/24 hours, drowsy or lethargy, fast breathing, some or severe dehydration, received intravenous saline for initial corrections of dehydration and stayed for longer duration in hospital ( $\geq 24$  hours) but more often presented with abdominal pain. Stool microscopic examination showed less frequent presence of red blood cells (36% vs. 44%;  $p = 0.043$ ) and fecal leucocytes (50% vs. 59%;  $p = 0.029$ ) among individuals with diarrhea  $\geq 14$  days compared to those with  $\leq 6$  days. None was infected with *Vibrio cholerae* ( $\geq 14$  days) (3% for 7 - 13 days);

however, isolation rate of *Aeromonas* was higher among adults with duration for  $\geq 14$  days (11%). Only 15% with  $\geq 14$  days were positive for *Shigella* contrary to 19% (7 - 13 days) and 56% ( $\leq 6$  days). Differences in sociodemographic, clinical presentation and etiology varied with duration of diarrhea among adults.

**Keywords:** Adult; Bangladesh; Diarrhea; Prolonged Acute Diarrhea

## 1. INTRODUCTION

Gastroenteritis due to various enteropathogens is not only a global burden among children but also among adults [1-3]. A recent study estimated diarrheal disease morbidity rates among adults in the South East Asian region to be 29.9 episodes/100 person-years compared to 88.4 episodes/100 person-years in older children in the Eastern Mediterranean region [4]. Although, mortality decreased over the last few decades among children, it remains consistent for adults [4].

Increasing age resulting in functional disorders of the gastrointestinal system often affects bowel habits including passage of loose stool and diarrhea [5,6]. Infection with enteropathogens, in addition to compromised immunity and physiological state of the intestine often results in prolonged acute diarrhea and also responsible for chronic sufferings [5,6]. Several studies have already documented different patho-physiological conditions regarding prolonged acute diarrhea as well as chronic diarrhea including hormonal imbalances as well as etiopathogens [5]. Prolonged acute diarrhea among adults is not only a chronic suffering for the patient but also a burden for the family and for the nation too [4,7]. However, there is limited information on prolonged acute diarrhea with regard

\*Corresponding author.

to socio-demographic characteristics, clinical features, and its etiology in developing countries like Bangladesh.

The International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) maintains around the clock Diarrheal Disease Surveillance System (DDSS) in urban Dhaka, the capital city which has been active since 1979 [8]. The analysis was undertaken to help address the knowledge gap, with the ultimate aim to determine the epidemiological and clinical characteristics and etiology of diarrhea among adults who presented with prolonged acute diarrhea.

## 2. MATERIALS AND METHODS

### 2.1. Study Site, Population, and Source of Data

Established in 1962, the Dhaka Hospital of icddr,b is located in Dhaka, the capital city of Bangladesh. The hospital provides care and treatment to people with diarrheal diseases, who mostly come from urban and peri-urban Dhaka. During the last 20 years, the hospital has provided cost free care and treatment to over 140,000 patients each year. The DDSS has been established in 1979, which systematically sampled patients—4% of all patients from 1979 through 1995, followed by 2% of all the patients since 1996. The DDSS currently collects information on clinical, epidemiological and demographic characteristics, feeding practices particularly of infants and young children, and fluid and drug therapy received at homes of every 50<sup>th</sup> patient, irrespective of age, sex, disease severity or socioeconomic status by administering a structured questionnaire.

### 2.2. Sample Frame

We categorized the adults aged 20 years and above into three groups according to the duration of their diarrhea before coming to the hospital. These classifications are:  $\leq 6$  days (acute diarrhea), 7 to 13 days (prolonged acute diarrhea) and  $\geq 14$  days (prolonged diarrhea). We followed their epidemiological identities such as sociodemographic and host characteristics, clinical course of the disease and etiology of diarrhea. Relevant information was extracted from the electronic database of the DDSS for the period 1993 to 2012.

### 2.3. Definition

Diarrhea was defined as passage of three or more number of abnormally loose or watery stools in the preceding 24 hours. An individual aged 20 years and above was considered as adult. Adults who had a history of diarrhea 7 days and above before coming to the hospital were defined as prolonged acute diarrhea [9,10]. Fever was defined as axillary temperature more than 37.8°C. Chronic energy deficiency was defined as individuals with BMI

less than 18.5 and individuals with BMI  $\geq 25.0$  was considered as overweight and obese.

### 2.4. Specimen Collection and Laboratory Procedures

A single, fresh, stool specimen (at least 3.0 ml or grams) was collected from each of the patients and immediately sent to the Clinical Laboratory for detection of *Shigella* [11], *Vibrio cholerae* [12,13], *Campylobacter* spp. [11], *Aeromonas* spp. [11], *Salmonella* [11], *Giardia lamblia* [14], *Entamoeba histolytica* [15], and rotavirus [16] following standard laboratory methodology. A stool microscopic examination was also performed in the same laboratory following standard procedure.

### 2.5. Data Analysis

Data analyses were done using Statistical Package for Social Sciences (SPSS) Windows (Version 15.2; Chicago, IL) and Epi Info (Version 6.0, USD, Stone Mountain, GA). For categorical variables, differences in the proportions were compared by Chi-square test and a probability of  $< 0.05$  was considered as statistically significant. Strength of association was determined by estimating odds ratio (OR) and its 95% confidence interval (CI). Wealth index was measured by using information on household assets by computing principal component analysis. A weight was attached to each item from the first principal component. The households were classified into socio economic status (SES) quintiles based on the wealth index: quintile 1 (poor), 2 (lower middle), 3 (middle), 4 (upper middle), and 5 (rich). In the analysis, duration of diarrhea was categorized into 3 stratum such as: 1)  $\leq 6$  days; 2) 7 - 13 days; and 3)  $\geq 14$  days.

### 2.6. Ethical Consideration

The DDSS was approved by the RRC (Research Review Committee) and ERC (Ethical Review Committee) of icddr,b. Patients were enrolled and their stool specimens were collected for various laboratory tests only after they/their parents (in case of minors) provided a verbal consent.

## 3. RESULTS

A total of 18,210 adults aged 20 years and above were enrolled in the DDSS. Of them, 17,631 (97%) had a duration of diarrhea  $\leq 6$  days (mean age; 37 years), 418 (2%) had diarrhea lasting for 7 to 13 days (mean age; 41 years), and the remainder 161 (1%) had history of diarrhea for  $\geq 14$  days (mean age; 42 years).

A higher proportion of individuals with duration of diarrhea 7 - 13 days and  $\geq 14$  days were male compared to those adults with history of diarrhea  $\leq 6$  days. At least 73% of all adults used oral rehydration solution before

coming to the hospital and proportion was lower among prolonged acute diarrhea group (**Table 1**). However, individuals with duration of diarrhea 7 days and above received more antimicrobials prior to hospital visit compared to adults with acute onset ( $\leq 6$  days). A significantly higher proportion of adults with diarrhea  $\geq 14$  days suffered from chronic energy deficiency and had history of smoking compared to adults with diarrhea with duration of  $\leq 6$  days. Other indicators like use of unboiled drinking water, sanitary toilet, family size, and proportion of overweight and obesity were not associated with duration of diarrhea (**Table 1**).

Adult individuals with prolonged acute diarrhea ( $\geq 7$  days) presented with less vomiting, watery stool, less often had frequency of stool  $>10$  times/day, not drowsy or lethargic or had fast breathing, had less often some or severe dehydration, less frequently received intravenous saline for initial correction of dehydration and did not stay longer in the hospital ( $\geq 24$  hours) compared to adults with acute diarrhea ( $\leq 6$  days). However, abdominal pain was more frequently reported by the adult patients with prolonged acute diarrhea (**Table 2**). Microscopic stool examination showed presence of red blood cells (RBC)

and fecal leucocytes less commonly among prolonged acute diarrhea ( $\geq 14$  days) compared to acute diarrhea patients ( $\leq 6$  days) (**Table 2**).

Individuals with shorter duration of diarrhea ( $\leq 6$  days) were significantly more frequently infected with *Vibrio cholerae* and *Shigella* compared to adults with prolonged acute diarrhea. However, the isolation rate of *Aeromonas* was greater among adults with history of diarrhea  $\geq 14$  days (**Table 3**). Other pathogens causing gastroenteritis such as *Salmonella*, *Campylobacter*, *Aeromonas*, *Entamoeba histolytica*, *Giardia* and rotavirus were equally distributed irrespective of duration of diarrhea (**Table 3**).

#### 4. DISCUSSION

None of the adults with prolonged acute diarrhea attending the hospital triage with history of diarrhea for 14 days and more was infected with *Vibrio cholerae*. Clinical characteristics revealed that adult individuals with shorter duration of diarrhea presented with acute manifestations compared to those with prolonged duration which were detected to have often presence of this bacteria [17,18]. It is well documented that *Vibrio cholerae* infection is not only considered an acute illness but is

**Table 1.** Socio-demographic characteristics among adults according to duration of diarrhea.

Indicators	$\geq 14$ days n = 161 (%)	7 - 13 days n = 418 (%)	$\leq 6$ days n = 17,631 (%)	OR (95% CI) p value <sup>a</sup>	OR (95% CI) p value <sup>b</sup>
Age (mean $\pm$ SD)	42 $\pm$ 17	41 $\pm$ 15	36 $\pm$ 14	-4.64 (-6.13, -3.15) <0.001	-5.51 (-7.76, -3.36) <0.001
Male sex	113 (70)	261 (62)	9815 (56)	1.87 (1.32, 2.67) <0.001	1.32 (1.08, 1.63) 0.006
Use ORS prior to hospital	117 (73)	334 (80)	15722 (89)	0.32 (0.22, 0.47) <0.001	0.48 (0.38, 0.62) <0.001
Use antimicrobials prior to hospital	131 (81)	339 (81)	276 (57)	3.34 (2.21, 5.07) <0.001	3.22 (2.35, 4.41) <0.001
Use sanitary toilet	4 (3)	14 (3)	454 (3)	0.96 (0.30, 2.71) 0.859	1.31 (0.73, 2.30) 0.407
Use un-boiled drinking water	133 (83)	320 (77)	13578 (77)	1.42 (0.93, 2.18) 0.113	0.97 (0.77, 1.23) 0.865
Family size ( $>5$ )	58 (36)	177 (42)	6808 (39)	0.90 (0.64, 1.25) 0.554	1.17 (0.95, 1.43) 0.135
Wealth Index					
Poorest	43 (28)	110 (28)	3339 (21)	1.47 (1.02, 2.12) 0.039	1.48 (1.18, 1.86) <0.001
Lower middle	32 (21)	63 (16)	3090 (19)	1.10 (0.73, 1.65) 0.706	0.80 (0.60, 1.06) 0.126
Middle	25 (16)	75 (19)	3970 (24)	0.59 (0.38, 0.92) 0.019	0.72 (0.55, 0.93) 0.012
Upper middle	20 (13)	69 (17)	3122 (19)	0.62 (0.38, 1.01) 0.056	0.88 (0.67, 1.16) 0.386
Richest	36 (23)	81 (20)	2743 (17)	1.48 (1.00, 2.18) 0.051	1.26 (0.98, 1.62) 0.078
Smoking habit	49 (30)	98 (23)	3910 (22)	1.54 (1.08, 2.18) 0.016	1.07 (0.85, 1.36) 0.577
Chronic Energy Deficiency (BMI $< 18.5$ )	70 (47)	155 (40)	6151 (38)	1.46 (1.05, 2.05) 0.025	1.09 (0.88, 1.34) 0.445
Overweight and obese (BMI $\geq 25.0$ )	16 (11)	44 (11)	1428 (9)	1.25 (0.72, 2.16) 0.480	1.33 (0.95, 1.84) 0.099

<sup>a</sup>Comparison between individuals with duration of diarrhea  $\leq 6$  days and  $\geq 14$  days; <sup>b</sup>Comparison between individuals with duration of diarrhea  $\leq 6$  days and 7 - 13 days.

**Table 2.** Clinical characteristics and stool microscopic examination among adults according to duration of diarrhea.

Indicators	≥14 days n = 161 (%)	7 - 13 days n = 418 (%)	≤6 days n = 17,631 (%)	OR (95% CI) p value <sup>a</sup>	OR (95% CI) p value <sup>b</sup>
Vomiting	25 (16)	129 (31)	13806 (78)	0.05 (0.03, 0.08) <0.001	0.12 (0.10, 0.15) <0.001
Watery stool	49 (30)	255 (61)	16720 (95)	0.02 (0.02, 0.03) <0.001	0.09 (0.07, 0.11) <0.001
Purging >10 times 24 hours	42 (26)	175 (42)	9850 (56)	0.28 (0.19, 0.40) <0.001	0.57 (0.47, 0.70) <0.001
Drowsy or Lethargic	30 (19)	150 (36)	13943 (79)	0.06 (0.04, 0.09) <0.001	0.15 (0.12, 0.18) <0.001
Fast breathing	6 (4)	37 (9)	7948 (45)	0.05 (0.02, 0.11) <0.001	0.12 (0.08, 0.16) <0.001
Some or severe dehydration	28 (17)	154 (37)	14280 (81)	0.05 (0.03, 0.08) <0.001	0.14 (0.11, 0.17) <0.001
Received Intravenous saline	8 (5)	51 (12)	9731 (56)	0.04 (0.02, 0.09) <0.001	0.11 (0.08, 0.15) <0.001
Fever (>37.8°C)	5 (3)	13 (3)	580 (3)	0.94 (0.34, 2.39) 0.927	0.94 (0.52, 1.69) 0.948
Abdominal pain	115 (71)	321 (77)	10956 (62)	1.52 (1.07, 2.18) 0.019	2.02 (1.59, 2.55) <0.001
Duration of stay in the hospital (≥24 hours)	25 (16)	60 (15)	3926 (23)	0.62 (0.40, 0.97) 0.037	0.58 (0.44, 0.77) <0.001
Red blood cells (1 - >50)	54 (36)	171 (43)	7515 (44)	0.70 (0.49, 0.99) 0.043	0.96 (0.78, 1.18) 0.742
Fecal leucocytes (11 - >50)	76 (50)	215 (54)	10084 (59)	0.69 (0.50, 0.97) 0.029	0.82 (0.67, 1.01) 0.062
Macrophage (1 - 10)	47 (31)	143 (36)	5810 (34)	0.87 (0.60, 1.24) 0.469	1.10 (0.89, 1.35) 0.421

<sup>a</sup>Comparison between individuals with duration of diarrhea ≤6 days and ≥14 days; <sup>b</sup>Comparison between individuals with duration of diarrhea ≤6 days and 7 - 13 days.

**Table 3.** Distribution of pathogens among adults according to duration of diarrhea.

Pathogens	≥14 days n = 161 (%)	7 - 13 days n = 418 (%)	≤6 days n = 17,631 (%)	OR (95% CI) p value <sup>a</sup>	OR (95% CI) p value <sup>b</sup>
<i>Vibrio cholerae</i>	0 (0)	13 (3)	4344 (25)	0.00 (0.00, 0.09) <0.001	0.10 (0.05, 0.17) <0.001
<i>Shigella</i>	25 (15)	81 (19)	986 (56)	3.10 (1.97, 4.86) <0.001	4.06 (3.13, 5.25) <0.001
<i>Salmonella</i>	4 (3)	14 (3)	363 (2)	1.21 (0.38, 3.41) 0.920	1.65 (0.92, 0.92) 0.099
Rotavirus	3 (2)	3 (1)	667 (4)	0.49 (0.13, 1.59) 0.302	0.18 (0.05, 0.59) 0.002
<i>Campylobacter</i>	4 (3)	20 (5)	812 (5)	0.53 (0.17, 1.48) 0.275	1.04 (0.64, 1.67) 0.956
<i>Aeromonas</i>	17 (11)	42 (10)	1181 (7)	1.64 (0.96, 2.79) 0.073	1.56 (1.11, 2.17) 0.009
<i>Entamoeba histolytica</i>	5 (3)	14 (4)	292 (2)	1.95 (0.70, 4.97) 0.242	2.10 (1.17, 3.71) 0.011
<i>Giardia</i>	2 (1)	2 (1)	373(3)	0.60 (0.10, 2.46) 0.657	0.23 (0.04, 0.92) 0.034
Mixed infection	15 (9)	44 (11)	2055 (12)	0.78 (0.44, 1.36) 0.425	0.89 (0.64, 1.24) 0.526
No pathogen detected	50 (31)	156 (37)	8044 (46)	0.54 (0.38, 0.76) <0.001	0.71 (0.58, 0.87) <0.001

<sup>a</sup>Comparison between individuals with duration of diarrhea ≤6 days and ≥14 days; <sup>b</sup>Comparison between individuals with duration of diarrhea ≤6 days and 7 - 13 days.

also widely responsible for epidemics [19]. *Vibrio cholerae* infection is characterized with acute onset with profuse loss of water and electrolytes often resulting in severe dehydration, which requires intravenous saline for correction. If untreated, cholera has a high mortality rate [20]. On the other hand, *Shigella* which causes dysentery is less frequently reported among adults with history of diarrhea for 7 to 13 days and 14 days and more. Only 15% adults with diarrhea for 14 days or more were found to be infected with *Shigella*. Due to the invasive nature

of the pathogen, it disrupts intestinal epithelium and often presents with acute features of bloody mucoid stools with abdominal cramp, fever, and straining [21,22]. Comparatively, non-frequent presence of red blood cells and fecal leucocytes in stool microscopic examination among prolonged acute diarrhea groups were also found compared to acute onset.

Although the isolation rate of *Shigella* was relatively low among adults with prolonged acute diarrhea, a higher proportion complained of abdominal pain [20]. It



might contradict the disease process, but those who presented with prolonged acute diarrhea might have other chronic gastrointestinal disorders such as inflammatory bowel disease (IBD) presented either as Crohn's disease or as ulcerative colitis [23]. Both might have chronic history of diarrhea with abdominal pain and weight loss [23]. This might be explained by higher proportion of males presenting with prolonged acute diarrhea; moreover, dietary practices (high protein, sodium and sugar consumption) and behavioral factors (smoking) with socio-cultural norms would be the other factors for such over reporting. Moreover, mean age of individuals with prolonged acute diarrhea ( $42 \pm 17$  years) also favor with having chronic sufferings [24].

Significantly higher proportions of adults with prolonged acute diarrhea were smokers, the vast majority of which were males. This could also explain preponderance of the problem among males. Cigarettes contain nicotine that weakens protective factors such as gastric mucosal blood flow, mucosal restitution, epidermal growth factor, prostaglandin, glutathione and aggravated gastric acid secretion, increased infection with *Helicobacter pylori*, higher pepsinogen and vasopressin secretion all together alter gastrointestinal function resulting in nausea, anorexia and diarrhea [25-27]. This observation was supported by low BMI or higher rate of chronic energy deficiency among individuals with diarrhea lasting for 14 days and more. Chronic loss of water and electrolytes with loss of appetite resulting in reduced intake and impaired absorption would be the underlying predictors of current observation.

Most interestingly however was the presence of *Aeromonas* infection among adults with prolonged acute diarrhea ( $\geq 14$  days). *Aeromonas* is usually considered to be a self-limiting pathogen [28]. It is difficult to explain the higher isolation rate of *Aeromonas* among adults. Hypothetical explanations could be, individuals might have infected with pathogens that cause acute infection but once the disease progressed different enteropathogens might have sequentially predominated to worsen the duration of the illness as reported by Baqui A.H. *et al.* (1992) among under-5 children who developed persistent diarrhea [29].

Use of antimicrobials at home would be another challenge. Adult individuals with duration of diarrhea for 7 days and more might attempt to manage illness at home with oral rehydration solution and/or antimicrobials. On the other hand, use of antimicrobials might cause disease due to *Clostridium difficile*, responsible for chronic diarrhea among adults and elderly [30]. However, in the present study we did not target to isolate this pathogen.

## 5. LIMITATION

There are several limitations of the observations. Firstly, lack of information about repeated onset of prolonged

acute diarrhea. Either it was an episode of prolonged acute diarrhea or it might be a recurrent episode of prolonged acute diarrhea as part of chronic sufferings such as, irritable bowel syndrome or ulcerative colitis or Crohn's disease. Secondly, isolation of limited number of common pathogens those are causing gastroenteritis. There are other pathogens such as *Clostridium difficile*, *E. coli*, norovirus or *Cryptosporidium* responsible for prolonged acute or chronic diarrhea [31]. Thirdly, lack of information on immune status that often gets compromised with increasing age. Other than that, dietary habits and other endocrine disorders like hyperthyroidism or Addison disease or diabetic mellitus might have significant role in chronic sufferings. However, unbiased systematic enrollment with large sample size and high quality laboratory performance were the strengths of the study.

## 6. CONCLUSION

Increases in life expectancy as a result of modernization of care seeking facilities might invite chronic health problems like prolonged acute diarrhea among adults. Differences in socio-demographic, clinical presentation and etiology signify its public health importance. There is a lack of a national monitoring system regarding the epidemiological investigations with documentation of chronic illnesses like chronic diarrhea. At the same time, in-depth exploration or research should be implemented to address the knowledge gaps and continue the surveillance system to understand the changes in adult disease profiles of general population over the period.

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