1   *Different features of cholera in malnourished and non-malnourised children: analysis of 10-*

2   *year surveillance data from a large diarrheal disease hospital in urban Bangladesh*

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Abstract

Background: Malnourished children are more prone to infectious diseases including severe diarrhea compared to non-malnourished children. Understanding of the differences in the presentation of severe diarrhea such as cholera in children with varying nutritional status may help in the early identification and management these children. However, data are scarce on differences in the presentation in such children. Thus, we aimed to identify the clinical differentials among children with cholera with or without malnutrition.

Methods: Data were extracted from diarrheal disease surveillance system (DDSS) of the Dhaka Hospital of icddr,b for the period, January 2008 to December 2017. Among under-five children, cholera positive (culture confirmed) and malnourished children (weight-for-age, weight-for-length or height-for-age Z score (WAZ, WHZ or HAZ) <-2) were considered as the cases (n=305) and children with cholera but non-malnourished (WAZ, HAZ, and WHZ $\geq$-2.00 to $\leq$+2.00) were the controls (n=276).

Results: A total of 14,403 under-five children were enrolled in the surveillance system during the study period. After adjusting for potential covariates such as maternal illiteracy and slum dwelling, it was revealed that under-five malnourished children with cholera significantly more often presented to the hospital during evening hours (6 pm to 12 mid-night) (OR=1.64, 95% CI=1.16-2.31, P<0.05), had fathers who were illiterate (OR=1.70, 95% CI=1.11-2.62, P<0.05), presented with history of cough within last 7 days (OR=1.64, 95% CI=1.10-2.43, P<0.05), dehydrating diarrhea (OR=1.70, 95% CI=1.15-2.53, P<0.05), and had longer hospitalization (OR=1.50, 95% CI=1.05-2.14, P<0.05).

41   **Conclusions:** The study results underscore the importance of understanding of the basic

42   differences in the presentation of severe cholera in malnourished children for prompt

43   identification and the subsequent management of these children. These observations may help

44   policy makers in formulating better case management strategy.

45   **Key words:** Cholera, Malnutrition, Dehydration, under-five children

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Author Summary:

48   Malnourished children are more vulnerable to infectious diseases including cholera in

49   comparison to the non-malnourished children. They often have suboptimal immune function,

50   though there is no precise information on whether there is any difference in associated factor(s)

51   or clinical course of cholera in under-five children with varying nutritional status. Therefore, this

52   study was conducted to elucidate these insights by using the surveillance data of the Dhaka

53   hospital of icddr,b. Among all the under-five children with cholera, 305 malnourished (WAZ or

54   WLZ or HAZ <-2) children constituted as the cases (malnourished), and another 276 non-

55   malnourished (WAZ, HAZ, and WHZ $\geq$-2.00 to $\leq$+2.00) cholera children formed the comparison

56   group.

57   In this study we revealed that care seeking at evening time was more common in the

58   malnourished children with cholera compared to those without malnutrition. Dehydrating

59   diarrhea was about two folds higher and prolonged hospitalization was frequent in malnourished

60   children with cholera than their counterparts. These key findings may help policy makers in

61   formulating better case management strategy in the near future.

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Introduction

Cholera is a leading public health concern globally, with an estimated 1.3-4.0 million cases occurring each year, worldwide [1]. Moreover, a significant disease burden of cholera has been reported in young children [2]. Higher rates of malnutrition among pre-school children have been observed in Bangladesh [3]. Malnourished children are at a higher risk of severity of diarrhea and death, moreover, the disease severity has been found to be associated with nutritional status, body size, and etiologic agents of diarrheal episodes [4]. A study in Brazil reported that the clinical presentations of early childhood severe diarrhea may vary because of diverse etiologies. Understanding of the differences in the presenting features of severe diarrhea especially in cholera, that are associated with varying nutritional status of the young children is thus critically important for early identification and management these children. Hence, with an attempt to address the existing knowledge gap as well as to share research findings with policy makers for formulating better case management strategy we undertook this study to examine the clinical feature differentials among children infected with *Vibrio cholerae* who presented with or without malnutrition.

Methods

Ethical statement

For this study, data were extracted from the electronic database of hospital-based diarrheal disease surveillance system (DDSS) of Dhaka Hospital of icddr,b. The DDSS has the approval from institutional review board of icddr,b (Research Review Committee and Ethical Review

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83   Committee) for data analysis. ERC was also pleased with the voluntary participation,

84   maitainance of rights of the participants and confidential handling of personal information by the

85   hospital doctors and accepted this consenting procedure. At the time of enrolment into DDSS,

86   verbal consent was obtained from the parents or the attending caregivers of each child following

87   hospital policy. The verbal consent was recorded by keeping a check mark in the questionnaire

88   that was again assured by showing the mark to parents or caregiver. DDSS is a routine ongoing

89   surveillance in hospitals of icddr,b located in Dhaka, Bangladesh. At the time of consenting,

90   parents or caregivers were assured of 'any risk being no more than minimal risk', 'their

91   participation is voluntary', 'their rights to withdraw from the study, and 'the maintenance of

92   strict confidentiality of disclosed information. They were also informed about the use of

93   collected data for analysis and using the results for improving patient care, conducting researches

94   and also publication without disclosing the name or identity of their children.

95   **Study population and study site**

96   Dhaka Hospital of icddr,b provides care and free treatment to around 150,000 diarrheal disease

97   patients each year and about 62% of them are children less than 5 years of age. The DDSS

98   systematically (from every 50th patient according to their hospital ID number) collects

99   information including age, sex, socio-demographic characteristics, clinical features, and etiology

100   of diarrhea. Parents or caregivers are interviewed by research assistants who collect

101   demographic, socioeconomic and clinical data. A physician documents the clinical findings

102   including dehydration status. A fresh stool sample is collected and submitted to laboratory for

103   microbiological evaluation. All relevant information is recorded into the electronic database as

104   soon as possible. For the present study, analysis was limited to under-five children who were

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105   cholera positive and enrolled into the DDSS from January 2008 to December 2017. Nutritional

106   status of these children was assessed at the time of discharge from the hospital. Weight was

107   measured nearest to 100 g using a digital scale and length/height was estimated using a locally

108   manufactured length board with a precision of 0.1 cm. Nutritional status was assessed by Z-

109   scores following WHO 2006 growth standards.

110   **Study design**

111   A case control study design was followed. The study group (cases) comprised of malnourished

112   diarrheal children with associated *Vibrio cholerae* infections and those presented at the same

113   time without malnutrition constituted the concurrent comparison group (controls).

114   **Definition**

115   Malnutrition was defined in children 0-59 months of age with any of the indices of malnutrition

116   such as: weight for age z-score (WAZ) or height for age z-score (HAZ) or weight for height z-

117   score (WAH) < -2. Non-malnourished children had WAZ, HAZ, and WHZ $\geq$-2.00 to $\leq$+2.00. A

118   child with cholera had growth of *V. cholerae* in the fecal specimen.

119   **Data Analysis**

120   Data were analyzed using SPSS for windows (version 20; SPSS Inc, Chicago, IL) and Epi Info 7.

121   Differences in the proportion were compared by the Chi-square test. A probability value of <

122   0.05 was considered as statistically significant. Strength of association was determined by

123   calculating odds ratios (OR) and their 95% confidence intervals (CI). Logistic regression was

124   performed to identify factors that were considered significantly associated with malnourished

125   cholera children after adjusting for potential confounding variables. Multicollinearity between

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126   independent variables was also checked before constructing logistic regression models having a

127   variance inflation factor (VIF) of < 3.0.

Results

129   A total of 14, 403 under-five children were enrolled in the DDSS during the study period and

130   581 children were found to have culture proven cholera. Out of them, according to the eligibility

131   criteria 305 belonged to the study group (cases) while the rest 276 constituted the comparison

132   group (controls). Bi-variate analysis revealed that the cases more often had illiterate mothers and

133   lived in slum settlements compared to the controls. The cases compared to their counterpart

134   commonly reported to the facility at evening hours (6 pm -12 mid-nights), often had history of

135   cough within the last seven days, and were found to seek out care for dehydrating diarrhea. The

136   cases often required longer hospitalization than the controls (Table 1).

137   **Table 1. Clinical findings of cholera children with or without malnutrition (2008-2017)**

Variable	Malnourished cholera children (n=305) (%)	Non-malnourished cholera children (n=276) (%)	OR	95%CI	P value
Male	186 (61%)	169 (61.2%)	0.99	0.71-1.38	0.981
Illiterate mother	105 (34.4%)	70 (25.4%)	1.55	1.08-2.21	**0.022**
Illiterate father	117 (38.4%)	68 (24.6%)	1.9	1.33-2.72	**0.001**
Slum area	41 (13.4%)	22 (8%)	1.8	1.04-3.10	**0.047**

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Non-sanitary Toilet	68 (22.3%)	51 (18.5%)	1.27	0.84-1.90	0.300
Use of untreated drinking water	197 (64.6%)	161 (58.3%)	1.3	0.93-1.82	0.143
No use of antibiotic at home	115 (37.7%)	110 (39.9%)	0.91	0.65-1.28	0.656
Presence of vomiting	265 (86.9%)	237 (85.9%)	1.1	0.68-1.8	0.814
Presence of fever	15 (4.9%)	9 (3.3%)	1.53	0.7-3.57	0.427
Presence of abdominal pain	87 (28.5%)	83 (30.1%)	0.93	0.65-1.33	0.750
History of cough within last 7 days	93 (30.5%)	57 (20.7%)	1.69	0.33-14.29	**0.009**
History of measles	11 (3.6%)	12 (4.3%)	0.82	0.36-1.9	0.807
Diarrheal duration < 24hours	129 (42.3%)	135 (48.9%)	0.77	0.55-1.06	0.129
Dehydration (some/severe)	242 (79.3%)	184 (66.7%)	1.9	1.32-2.8	**0.001**
Watery stool	291 (94.4%)	267 (96.7%)	0.7	0.3-1.63	0.543
Use of IV fluid	145 (47.7%)	123 (44.7%)	1.13	0.81-1.56	0.527
Reporting time (6.00 pm to 12.00 mid-night)	76 (24.9 %)	41(14.9 %)	1.89	1.24 -2.88	**0.004**
Length of stay > 24hours	143(47.4 %)	96(36 %)	1.14	1.14-2.24	**0.008**
Death	0 (0%)	1 (0.4%)	-	-	0.948

138   % denotes percentage of cholera positive malnourished and non-malnourished group until

139   mentioned otherwise

140   Logistic regression analysis adjusting for potential covariates such as maternal illiteracy, and

141   slum dwelling revealed that malnourished children under 5 years of age with cholera

142   significantly more often had paternal illiteracy, history of cough, reported to the hospital in

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143   evening hours, presented with dehydrating diarrhea, and had longer stay at hospital (Table 2).

144   Another logistic regression revealed no significant association between untreated drinking water,

145   non-sanitary toilet use, febrile illness and cholera in malnourished children.

146   **Table 2. Logistic regression analysis to find out independent factors associated with**

147   **cholera in malnourished children**

Characteristic	Adjusted OR	95%CI	P value
Illiterate mother	0.98	0.63-1.54	0.943
Illiterate father	1.74	1.13-2.67	**0.012**
Slum dwelling	1.75	0.97-3.21	0.071
History of cough within last 7 days	1.61	1.08-2.39	**0.019**
Reporting time (6.00 pm to 12.00 mid night)	1.76	1.14-2.73	**0.011**
Dehydration (some/severe)	1.67	1.13-2.48	**0.011**
Length of stay > 24hours	1.51	1.06-2.15	**0.022**

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Discussion

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150   The present study observed different features of cholera in children with or without malnutrition.

151   The most important significant observation is the 67% excess risk of dehydrating diarrhea in

152   malnourished cholera children than non-malnourished cholera children. Other important

153   observations in malnourished cholera children with dehydrating diarrhea than non-malnourished

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154   cholera children were: i) most often care seeking at evening-night hours, and iii) longer

155   hospitalization of malnourished cholera children.

156   As expected in malnourished children, lack of immune responses particularly the reduced

157   secretory IgA levels in the gut mucosa along with hypochlorhydria or achlorhydria made these

158   study children more vulnerable to diarrheal illnesses with relatively lower inoculums. Possible

159   explanation for more dehydrating diarrhea in malnourished cholera children are: these children

160   are more often slum dwellers with poor water-sanitation and hygienic practices that might have

161   caused the ingestion of larger inoculums of *Vibrio cholerae* resulting in greater challenging dose

162   of cholera toxin. Moreover, since malnourished children are likely to have an increased area of

163   gut mucosal surface compared to their body weight than the non-malnourished children they are

164   more vulnerable to higher purging rate and resultant greater stool output during diarrhea [4]. In

165   case of malnourished children with cholera, slower turnover rate of gut mucosal cells,

166   deficiencies of intestinal enzymes, micronutrients, and impaired immune responses with

167   exposures to larger inoculums because of their dwelling in more contaminated environments in

168   the slums might have caused more severe disease and delayed recovery, thereby, longer

169   hospitalization.

170   Dewan *et al.* reported that children with associated *Vibrio cholerae* infections were significantly

171   more severely underweight, stunted, and wasted. The study indicated that such association may

172   be due to impaired gastric barrier, hypochlorhydria, and prolonged intestinal mucosal injury that

173   are commonly observed in malnourished children [5]. A study in urban Bangladesh evaluated

174   the role of common diarrheal pathogens and revealed that children with *Vibrio cholerae*

175   infections were 5.5 times more likely to be associated with dehydrating diarrhea than that in case

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176   of children without this causative agent [6] and these children were significantly more

177   malnourished. Similar to our findings, other cholera researchers from Bangladesh revealed

178   marked prolongation of duration of diarrhea in undernourished children [7]. Exerting greater

179   emphasis on stool output, Palmer *et al.* indicated that higher inoculum size is likely to cause

180   greater intestinal mucosal surface involvement causing higher stool volume per unit of time than

181   a longer duration of diarrhea [7]. On the basis of a study in the rural settings of Bangladesh,

182   Black *et al.* reported that child's small body size because of young age and low nutritional status

183   are more likely to result in more fluid loss (per kg body weight) during diarrhea and such

184   children are more vulnerable to severe dehydration and death if not properly treated by

185   appropriate rehydration therapy [4]. Most studies that reported association between malnutrition

186   and severity of diarrhea did not take into consideration the role of enteropathogens in causing

187   severity of dehydration and longer duration of the episode [5, 8]. Another study in Brazil

188   reported that children with fever, vomiting or both would capture 75% of the children at risk for

189   dehydrating diarrhea [9]. However, this study compared the inpatient cases versus outpatient

190   controls without relating to the etiology and nutritional status. In our study particularly with

191   cholera positive children, vomiting (86.9% vs 85.9%), fever (4.9% vs 3.3%) or abdominal pain

192   (28.5% vs 30.1%) did not demonstrate any significant difference in cholera children with or

193   without malnutrition.

194   Victora *et al.* observed strong association between low body weight of infants (regardless of

195   age) and risk of higher dehydration. Low body weight was observed to be a superior determinant

196   in comparison to the anthropometric indices for predicting dehydrating diarrhea in children

197   reporting to the health facility. The study mentioned that children with low body weight are

198   young, malnourished or both. These children have larger gut surface compared to their body size

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199 in addition to greater purging rate due to diarrhea as compared to older children [8]. Thus

200 malnourished cholera children during hospitalization require intensive treatment with adjunct

201 appropriate antimicrobial and zinc therapy, careful assessments of dehydration at intervals,

202 appropriate dietary intervention with closer follow-up. Malnourished children are more prevalent

203 in families with low income and poor housing along with compromised water-sanitation and

204 hygienic practices. These children should be targeted for health education at household level

205 along with support for continued breast feeding, initiation of rehydration therapy soon after the

206 onset of diarrheal illnesses to prevent severity of disease with early referral of dehydrating

207 children to appropriate facilities to avoid unnecessary death.

208 These malnourished cholera children were mostly from the urban slums and due to the nature

209 and working hours of the father or mother or both, they presented to the facility during evening

210 hours or later. Another important observation from our study was that the malnourished cholera

211 children had a greater frequency of a history of cough within the last seven days. Cough is one of

212 the key clinical features of respiratory tract infections. The most common infections for

213 malnourished children are gastrointestinal and respiratory infections [10]. The first line of

214 defense mechanism for these infections is the innate immunity, particularly the epithelial

215 barriers and the mucosal immune response [11]. Malnourished children significantly suffer

216 from compromised mucosal barriers of the gastrointestinal, respiratory and urogenital tracts.

217 The study may be replicated in other geographical and cultural settings to see if the same clinical

218 features play a similar role in causing dehydrating diarrhea in malnourished cholera children.

219 Cholera outbreaks in emergency settings, such as settlements for displaced population and in the

220 aftermath of natural calamities, are now commonly encountered. In such situations, the treatment

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221   of children with severe acute malnutrition and cholera is difficult in terms of both competences

222   of clinicians well as coordination of logistics. The findings of our study are likely to be very

223   helpful in such situations emphasizing the critical need in keeping SAM children with cholera for

224   a longer period of time in the diarrhea treatment center before their referral to a nutritional

225   rehabilitation or outpatient treatment center.

226   This study was conducted in an urban hospital and vast majority of the patients represented with

227   poor socio-economic background. Our study children had higher degree of infection that

228   required hospitalization because of severe illness and they represented a relatively small

229   proportion of children while the vast majority of children with less severe disease received care

230   at the household level and did not seek care from the present facility. Respondents were mothers

231   who presented to the facility with their child; 27% had no formal schooling and 60% of their

232   children were malnourished and those who presented from urban slums, 65% were

233   malnourished. Thus our study children might not be representing the greater population.

234   However, our results are likely to generate several hypotheses. Future studies could better

235   describe the changes in presenting features along with etiology specific changes in clinical

236   features in malnourished children over time period. Along with the unbiased systematic

237   collection of data, a larger sample size, high quality laboratory performance and use of probing

238   techniques in interviewing of mothers or caregivers had thus been the strengths of the study.

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