MAJOR ARTICLE

Contribution of Enteric Infection, Altered Intestinal Barrier Function, and Maternal Malnutrition to Infant Malnutrition in Bangladesh

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Background. Malnourished children are at increased risk for death due to diarrhea. Our goal was to determine the contribution of specific enteric infections to malnutrition-associated diarrhea and to determine the role of enteric infections in the development of malnutrition.

Methods. Children from an urban slum in Bangladesh were followed for the first year of life by every-other-day home visits. Enteropathogens were identified in diarrheal and monthly surveillance stools; intestinal barrier function was measured by serum endocab antibodies; and nutritional status was measured by anthropometry.

Results. Diarrhea occurred 4.69 ± 0.19 times per child per year, with the most common infections caused by enteric protozoa (amebiasis, cryptosporidiosis, and giardiasis), rotavirus, astrovirus, and enterotoxigenic *Escherichia coli* (ETEC). Malnutrition was present in 16.3% of children at birth and 42.4% at 12 months of age. Children malnourished at birth had increased *Entamoeba histolytica*, *Cryptosporidium*, and ETEC infections and more severe diarrhea. Children who became malnourished by 12 months of age were more likely to have prolonged diarrhea, intestinal barrier dysfunction, a mother without education, and low family expenditure.

Conclusions. Prospective observation of infants in an urban slum demonstrated that diarrheal diseases were associated with the development of malnutrition that was in turn linked to intestinal barrier disruption and that diarrhea was more severe in already malnourished children. The enteric protozoa were unexpectedly important causes of diarrhea in this setting. This study demonstrates the complex interrelationship of malnutrition and diarrhea in infants in low-income settings and points to the potential for infectious disease interventions in the prevention and treatment of malnutrition.

By age 15 months, nearly one-third of children in the developing world are undernourished. Stunting, wasting, and intrauterine growth retardation in the first 5 years of life are estimated to be present in half of all children dying of diarrhea, pneumonia, and malaria, resulting in 2.2 million annual deaths and 21% of all disability-adjusted life-years [1, 2]. Morbidity from undernutrition in the first 5 years of life affects 200 million children and includes damage to cognitive function and physical capacity. The Indian subcontinent has the most severe problem with undernutrition, with half of children (86 million in that subcontinent) undernourished [1, 2].

We have been studying the impact of diarrheal diseases on malnutrition in Dhaka, Bangladesh, for the last decade [3–6]. We discovered that malnourished preschool children were at increased risk for diarrhea due to *Entamoeba histolytica*, *Cryptosporidium parvum/hominis*, and enterotoxigenic *Escherichia coli* (ETEC) [3]. We further demonstrated that the increased susceptibility of malnourished children to *E. histolytica*

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infection was due to the role of leptin in providing mucosal immunity to the parasite [7, 8]. However, a causal role for diarrheal infections in malnutrition could not be established by our previous studies, which included children only after the critical first 2 years of life when malnutrition has its onset. In addition, these studies of preschool children gave no information on the etiologies of diarrhea contributing to infant morbidity [1, 2]. Here we report the findings from our prospective observation of 147 low-income children followed from birth to age 12 months in Bangladesh.

METHODS

Study Area and Population

The study was conducted in Mirpur, an urban slum in Dhaka. One hundred forty-seven infants (77 male and 70 female) were enrolled in the study the first week after birth, beginning in January 2008, and followed until 12 months of age. The study period reported here ended in September 2009, when all 147 children had been followed until their first birthday. We defined no maternal education as the lack of any formal education, even primary school. Subjects were identified by trained field research assistants (FRAs) who did a census for pregnant women in the study area. FRAs kept in touch with the families of those pregnant women who consented to participate in the study. In most cases, the study medical officer visited the study household to assess the health status of the newborn within the first 72 hours after the birth of the baby. In some cases, the parents or guardians visited the study field clinic for the assessment of newborn health status. If the study medical officer found the baby clinically healthy, the baby was enrolled to the study after obtaining written consent from the parents or eligible guardian.

Household Information and Active Surveillance

The study medical officer collected socioeconomic information about the study household using a structured questionnaire. FRAs visited each study house every other day and collected information related to child morbidity, especially for diarrheal illness, using a structured questionnaire. If the FRA found any child with an acute illness, he/she referred the child to the study clinic for further management by the medical officer. Parents or guardians were also encouraged to visit the study clinic for medical assistance if the study child became sick.

Sampling and Specimen Transport

FRAs collected nondiarrheal monthly stool specimens from the study child according to schedule. The FRAs also collected diarrheal stool specimens from the home or in the study field clinic. All stool specimens were transported from the field to the clinic using a cold box. In the field clinic, an aliquot of the diarrheal stool specimens was placed into Cary-Blair medium. All specimens were transported from the field clinic to the International Centre for Diarrhoeal Disease Research, Bangladesh parasitology laboratory within 3 hours of collection, with a cold chain maintained.

Anthropometry

Anthropometric measurements were taken by FRAs at the time of enrollment and then every 3 months. Each child was weighed in light clothes on an electronic scale (Digital Baby & Toddler Scales, Seca 354). The length of the children was measured to the nearest centimeter (Infantometer Baby Board, Seca 416). Nutritional status was assessed by comparing weight and height with the weight and height of the World Health Organization (WHO) reference population of the same age and sex, using WHO Anthro software, version 3.0.1.

Detection of Enteropathogens

Stool samples were cultured for enteric pathogens including *Vibrio cholerae* O1/O139, *Salmonella* species, *Shigella* species, and *Campylobacter jejuni* [3]. Enzyme-linked immunosorbent assay (ELISA) methods were used to detect heat labile toxin and heat stable toxin producing ETEC [5]. *E. histolytica*, *Cryptosporidium*, and *Giardia* were identified using real-time polymerase chain reaction, as described previously [9]. Rotavirus, astrovirus, and adenovirus were detected with ELISA using commercial kits (ProSpectT Rotavirus Catalog No. R240396, ProSpectT Astrovirus Catalog No. R240196, and ProSpectT Adenovirus Catalog No. R240096, respectively).

Measures of Intestinal Barrier Dysfunction

Sera were tested for antibodies against the endotoxin core using a Hycult Biotech EndoCab ELISA and expressed in arbitrary units. Similarly, sera were tested for zonulin using a commercial kit (Immundiagnostik) and expressed as micrograms per microliter sera.

Clinical Definitions

Diarrhea was defined as having 3 or more unformed or abnormal stools (as perceived by the mother) in a 24-hour period. A diarrheal episode was defined as being separated from another episode by at least 3 diarrhea-free days. Diarrheal episodes were defined as acute ($<$14 days), persistent (14–29 days), and chronic ($\geq$30 days). Colonization or asymptomatic infection with a given pathogen was calculated by dividing the total number of infections by the given pathogen detected in monthly surveillance stools divided by the number of children observed. An enteropathogen detected on 2 sequential monthly stool samples was counted as a single episode of either diarrhea or colonization. Fever was defined according to the mother's assessment or assessed by the medical staff in the study clinic and dehydration was defined using WHO criteria. The severity of each diarrheal disease episode was calculated using a numeric scoring system [10].

Table 1. Sociodemographic Characteristics of the Study Population Including Nutrition Status at Birth

Characteristic	Children, No. (%)[a]
Male sex	77 (52.4)
Family monthly expenditure <6000 BDT[b]	83 (56.5)
No maternal education	58 (39.5)
Family size ≤5[c]	97 (66.0)
Maternal BMI <18.5	28 (19.0)
Malnourished at birth (weight for age *z* score <−2)	42 (28.6)
Stunted at birth (height for age *z* score <−2)	24 (16.3)
Household water supply from municipality	135 (91.8)
Food covering practiced at household	140 (95.2)
Having animal at house	9 (6.1)
Exclusively breastfed	38 (25.8)

Abbreviations: BDT, Bangladeshi Taka (currency); BMI, body mass index.

[a] Sample size was 147.

[b] Average family expenditure was 6000 BDT per month (range, 2000–14 000).

[c] Average family size was 5 (range, 3–14).

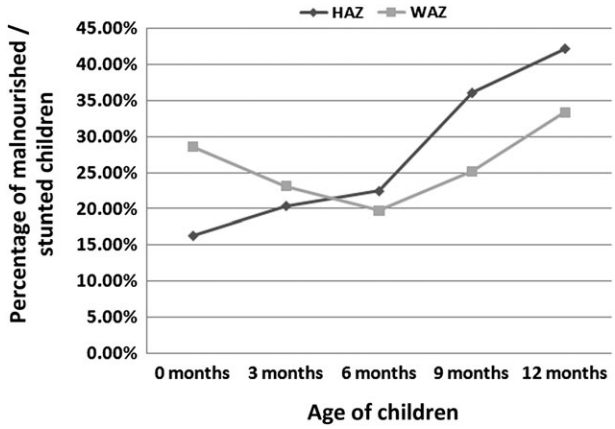

Figure 1. Percentage of malnourished (WAZ <−2) and stunted (HAZ <−2) children with increasing age, from birth to 12 months. Infants were weighed and measured every 3 months, and HAZ and WAZ scores determined using the World Health Organization's Anthro software, version 3.0.1.

Statistical Methods

Demographic information, surveillance data, and clinical and laboratory findings were computed in data files using Fox-Pro (Microsoft Corp). All data were double-checked before analysis. Categorical data were compared by χ^2 analysis and Fisher exact test. Comparisons between means were made using 2-sample *t* test or nonparametric test where applicable. Logistic regression was used to study the relationship between malnutrition and enteropathogenic infections.

Ethical Considerations

The study was approved by the Institutional Review Board of the University of Virginia and the Ethical Review Committee of the International Centre for Diarrhoeal Disease Research, Bangladesh. Informed written consent was obtained from the parents or guardians for the participation of their child in the study.

RESULTS

Study Population

The 147 children were enrolled within the first week of life starting in January 2008. The study ended in September 2009 when 12 months of follow-up had been completed on all 147 children. The majority of newborns were from poor families, as indicated by the median household expenditure of <6000 Bangladeshi Taka (BDT; <$100 USD) per month and range of 2000–14 000 BDT per month. In addition, 39.5% (58) of the mothers had no education. The average family size was 5 (range, 3–14. The vast majority of households had access to municipal water supplies and used safe food-handling practices. Nineteen percent (28 of 147) of the mothers were underweight with a body mass index (BMI) of <18.5 (Table 1).

Nutritional Status of Study Children at Birth and During Follow-Up

Poor nutritional status was common at birth and increased by 12 months of age (measured both by underweight WAZ <−2 and stunted HAZ <−2). There was a brief period from ages 3 to 6 months where catch-up weight gain was seen; however, this was not sustained. At birth, 28.6% and 16.3% of the newborns had WAZ and HAZ scores of <−2, respectively. This worsened at 1 year of age to 34.0% and 42.4% of the children underweight or stunted, respectively (Figure 1).

Association of Sociodemographic Factors With Nutritional Status at Birth

We examined the association of sex, monthly family expenditure, mother's education, family size, and mother's nutritional status with the nutritional status of the children at birth (Table 2). Underweight was associated with household income of <6000 BDT per month ($P = .003$). In addition, underweight and stunting at birth was associated with an underweight mother (BMI <18.5; Table 2).

Association of Sociodemographic Factors With Nutritional Status at 12 Months of Age

Newborns who were male ($P = .035$), had a WAZ score <−2 at birth ($P = .001$), had a mother with no education ($P = .021$), and/or had an underweight mother ($P = .001$) were more likely to be underweight (WAZ<−2) at 12 months of age. In addition, there was an association of stunting at 12 months of age with HAZ<−2 at birth ($P = .012$), monthly family expenditure of <6000 BDT ($P<.001$), a mother with no education ($P = .028$), and an underweight mother ($P = .034$) (Table 3).

Table 2. Association between Major Sociodemographic Characteristics of the Study Population and Nutritional Status at Birth[a]

Characteristic	WAZ ≥−2 (n = 105)	WAZ <−2 (n = 42)	HAZ ≥−2 (n = 123)	HAZ<−2 (n = 24)
Male sex	55 (52.4)	22 (52.4)	65 (52.8)	12 (50.0)
Family monthly expenditure ≤6000 BDT	51 (48.6)*	32 (76.2)*	66 (53.7)	17 (70.8)
No maternal education	38 (36.2)	20 (47.6)	48 (39.0)	10 (41.7)
Family size ≤5	69 (65.7)	28 (66.7)	80 (65.0)	17 (70.8)
Maternal BMI <18.5	12 (11.4)**	16 (38.1)**	19 (15.4)***	9 (37.5)***

χ^2 *P* values: $^{*}P = .002$, $^{**}P < .001$, $^{***}P = .012$; Fisher exact test *P* values: $^{*}P = .003$, $^{**}P < .001$, $^{***}P = .021$.

Abbreviations: BDT, Bangladeshi Taka (currency); BMI, body mass index; HAZ, height for age Z score; WAZ, weight for age Z score.

[a] All data are no. (%).

Diarrhea Morbidity in the First Year of Life

The total number of diarrheal episodes suffered by 147 children in the first year of life was 689 (standard error, 4.69 ± 0.19 per child per year). Of these 689 episodes, stool specimens from 420 diarrheal episodes (61%) were available for laboratory analysis. Protozoa, rotavirus, and ETEC were the most common pathogens isolated from the diarrheal stool specimens (Table 4; Figure 2). The majority of diarrheal episodes were of short duration (≤3 days) (Supplementary Figure 1) with mild to moderate severity; the Ruuska score was 4 (Supplementary Figure 2) [10]. There was no significant association between nutritional status at birth and duration of diarrheal episodes >3 days or >14 days. However, children who were stunted at birth were at increased risk for severe diarrhea ($P = .019$).

Relationship of Enteropathogen Infections and Nutritional Status at Birth

Children who were underweight and stunted at birth had more *E. histolytica* colonization during their first year of life. However, only children stunted at birth had more *Cryptosporidium* and ETEC diarrhea during their first year of life (Table 5). As noted previously, the percentage of underweight (28.6%–34.0%) and stunted (16.3%–42.4%) children increased during the first year (Figure 1). Being stunted at 12 months of age was associated with diarrhea lasting >14 days and with intestinal barrier dysfunction, as marked by increased levels of serum antibodies against bacterial endotoxin (endocab antibodies) (Table 6).

Independent Predictors for Nutritional Status at 12 Months of Age

Logistic regression was used to find the independent predictors for nutritional status at 12 months of age. Sex of the child, nutritional status at birth, family monthly expenditure, mother's education, mother's BMI, diarrhea >14 days, and endocab antibodies were included in the model because they showed association with nutritional status at 12 months of age in the bivariate analysis. Independent predictors for underweight and stunting at 12 months of age were mother's lack of education and mother's BMI <18.5. In addition, independent predictors for underweight were male sex and being underweight at birth; for stunting, predictors were monthly expenditure ≤6000 BDT, being stunted at birth, diarrhea >14 days, and endocab antibodies at 6 months of age (Table 7).

DISCUSSION

This intensive observational study of children in the first year of life in an urban slum of Dhaka, Bangladesh, is most important

Table 3. Association between Major Sociodemographic Characteristics of the Study Population and Nutritional Status of Children at Age 12 Months[a]

Characteristic	WAZ ≥−2 (n = 98)	WAZ <−2 (n = 49)	HAZ ≥−2 (n = 85)	HAZ<−2 (n = 62)
Male sex	45 (45.9)*	32 (65.3)*	41 (48.2)	36 (58.1)
WAZ <−2 at birth	19 (19.4)**	23 (46.9)**	20 (23.5)	22 (35.5)
HAZ<−2 at birth	14 (14.3)	10 (20.4)	8 (9.4)[‡]	16 (25.8)[‡]
Family monthly expenditure ≤6000 BDT	51 (52.0)	32 (65.3)	37 (43.5)[§]	46 (74.2)[§]
No maternal education	32 (32.7)***	26 (53.1)***	27 (31.8)[‖]	31 (50.0)[‖]
Family size ≤5	63 (64.3)	34 (69.4)	51 (60.0)	46 (74.2)
Maternal BMI <18.5	11 (11.2)[†]	17 (34.7)[†]	11 (12.9)[¶]	17 (27.4)[¶]

χ^2 *P* values: $^{*}P = .027$, $^{**}P = .001$, $^{***}P = .017$, $^{\dagger}P = .001$, $^{\ddagger}P = .008$, $^{\S}P < .001$, $^{\|}P = .026$, $^{\P}P = .027$; Fisher exact test *P* values: $^{*}P = .035$, $^{**}P = .001$, $^{***}P = .021$, $^{\dagger}P = .001$, $^{\ddagger}P = .012$, $^{\S}P < .001$, $^{\|}P = .028$, $^{\P}P = .034$.

Abbreviations: BDT, Bangladeshi Taka (currency); BMI, body mass index; HAZ, height for age Z score; WAZ, weight for age Z score.

[a] All data are no. (%).

Table 4. Isolation of Diarrheal Pathogens From 420 Diarrheal Stool Specimens and Number of Affected Children for Each Pathogen[a]

Pathogen	Diarrheal Episodes, No. (%)	Affected Children, No. (%)
Giardia	64 (15.2)	50 (34.0)
Rotavirus	42 (10.0)	38 (25.9)
Enterotoxigenic *Escherichia coli*	32 (7.6)	25 (17.0)
Astrovirus	25 (6.0)	21 (14.3)
Cryptosporidium	18 (4.3)	17 (11.6)
Entamoeba histolytica	16 (3.8)	16 (10.9)
Adenovirus	8 (1.9)	8 (5.4)
Campylobacter jejuni	8 (1.9)	8 (5.4)
Vibrio cholerae	2 (0.5)	2 (1.4)
Shigella	0 (0)	0 (0)

[a] Sixty-one percent (420 of 693) of diarrheal stool specimens were analyzed. In 51% (215 of 420) of cases of diarrhea, an enteropathogen was identified.

for the insight that it provides into the complex pathogenesis of malnutrition. We observed that enteric infections, maternal malnutrition, and low socioeconomic status contributed to the nutritional decline observed during the first year of life, as well as to morbidity of children born underweight and stunted. Insight into the mechanism by which infections exacerbate malnutrition was provided by the demonstration that prolonged diarrhea and altered intestinal barrier function predicted the development of malnutrition at 12 months of age. The study thus addressed the 2 interrelated problems of child nutrition in low-income settings: the susceptibility to diarrheal infections of children born with mild to moderate malnutrition and the development of underweight and stunting in up to half of children during the first year of life.

The association of enteric infections with malnutrition was observed in this study both at birth and at 12 months of age. Enteric infections were common, with each child averaging 4 to 5 episodes of diarrhea. Although high rates of diarrhea had been previously observed in low-income settings [1, 2], unique to this study was the comprehensive enteropathogen workup of the etiologies of diarrhea that included the discovery that nearly all children were infected with enteric protozoa by the first year of life. Children born malnourished were more likely to suffer from severe diarrhea, to be infected with *E. histolytica*, and to have diarrhea due to *Cryptosporidium* and ETEC. These studies extended our previous observations in preschool-aged children in the same community into the first year of life when most mortality due to diarrheal disease occurs [6].

Existing data on the role of enteropathogens in malnutrition had been limited by small sample sizes, limited geographic locales, and robustness of diagnostic tests [2, 11]. In Bangladesh, *E. histolytica*–caused diarrhea was associated with lower WAZ and HAZ scores [6]. In Nepal, *Giardia* infection correlated with a higher lactulose-to-mannitol ratio, a marker for intestinal permeability [12]. In Brazil, children with intestinal enteroaggregative *E. coli* infection exhibited significant growth impairment, regardless of the presence or absence of diarrhea [13]. In Peru and Brazil, *Cryptosporidium* infection was associated with impaired growth and development, also with or without overt diarrhea [14, 15]. Others have postulated that *Ascaris*

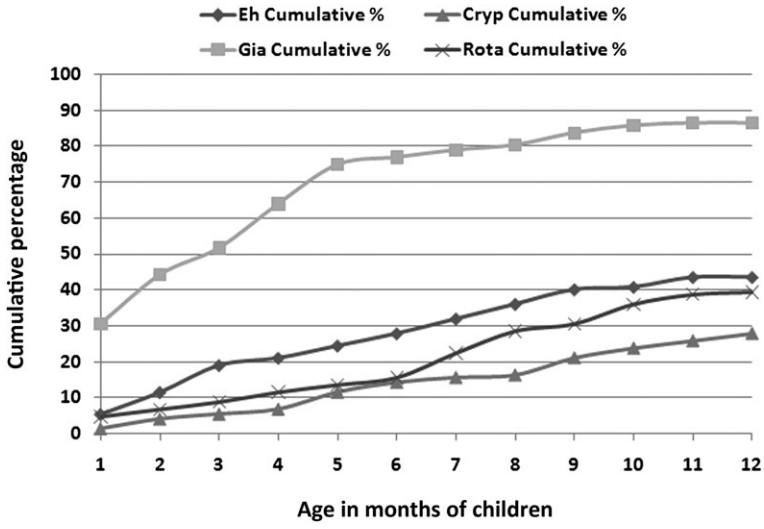

Figure 2. Cumulative percentage of children infected with *Entamoeba histolytica*, *Giardia lamblia*, *Cryptosporidium*, and rotavirus. Monthly surveillance and diarrhea stools were tested for *Entamoeba histolytica*, *Giardia lamblia*, and *Cryptosporidium* infection by real-time polymerase chain reaction and rotavirus by antigen detection.

Table 5. Association of Nutritional Status at Birth With Morbidity in the First Year of Life[a]

Condition	WAZ ≥−2 (n = 105)	WAZ <−2 (n = 42)	HAZ ≥−2 (n = 123)	HAZ<−2 (n = 24)
Overall diarrhea[b]	4.53 (0.19)	5.07 (0.45)	4.68 (0.20)	4.71 (0.53)
Colonization[b]				
Entamoeba histolytica	0.38 (0.06)*	0.69 (0.15)*	0.41 (0.06)**	0.75 (0.22)**
Giardia	2.04 (0.16)	2.21 (0.35)	2.11 (0.17)	1.96 (0.24)
Cryptosporidium	0.29 (0.05)	0.26 (0.10)	0.28 (0.05)	0.29 (0.11)
Rotavirus	0.19 (0.04)	0.07 (0.04)	0.17 (0.03)	0.08 (0.06)
Diarrhea[b]				
E. histolytica	0.11 (0.03)	0.10 (0.05)	0.12 (0.03)	0.04 (0.04)
Giardia	0.40 (0.07)	0.52 (0.11)	0.45 (0.07)	0.38 (0.12)
Cryptosporidium	0.11 (0.03)	0.14 (0.06)	0.10 (0.03)	0.25 (0.11)***
ETEC	0.18 (0.05)	0.31 (0.09)	0.18 (0.04)†	0.42 (0.15)†
Campylobacter jejuni	0.05 (0.02)	0.07 (0.04)	0.06 (0.02)	0.04 (0.45)
Rotavirus	0.28 (0.05)	0.31 (0.08)	0.32 (0.05)	0.13 (0.07)
Astrovirus	0.16 (0.04)	0.19 (0.08)	0.17 (0.04)	0.17 (0.10)
Adenovirus	0.06 (0.02)	0.05 (0.03)	0.06 (0.02)	0.04 (0.04)

Logistic regression *P* values: *$P = .0128$, **$P = .0274$, ***$P = .0579$, †$P = .0240$.

Abbreviations: ETEC, enterotoxigenic *Escherichia coli*; HAZ, height for age Z score. WAZ, weight for age Z score.

[a] All data are mean (standard error).

[b] Episodes per child per year.

species or *Helicobacter pylori* (via hypochlorhydria) could play a role in malnutrition [16, 17].

Insight into the mechanism by which enteric infection contributes to malnutrition was gained by the discovery that stunting at 12 months was associated with prolonged diarrhea (>14 days) and gut barrier dysfunction (as measured by endocab antibodies). There was no association of zonulin, a tight junction protein, in sera at 12 months with malnutrition (data not shown). This suggests that the gut dysfunction of these infants was distinct from that of diabetic adolescents, where zonulin was a measure of permeability [18]. In contrast, our observation of an association of systemic exposure to endotoxin with growth failure is supported by previous studies. The linear growth failure of pediatric patients with inflammatory bowel disease was linked in 1 study to systemic exposure to bacterial lipopolysaccharide, as measured by endocab antibodies [19]. More closely related to this study, endotoxin core antibody was shown in infants in The Gambia [20] to correlate with linear growth faltering, as well as with other measures of gut permeability, including absorption of lactulose. The prospective nature of our study not only validated the work in The Gambia but enabled the discovery that exposure to endotoxin was a predictor of malnutrition at 12 months of age.

We concluded that enteric infections were more severe in children born malnourished and that enteric infections appeared to contribute to the increase in stunting observed in children during the study period (because prolonged diarrhea and endocab antibodies were associated with worse stunting

Table 6. Stunting at 12 Months of Age is Associated With Prolonged Diarrhea Over the First Year of Life and Level of Endocab Antibodies at 6 Months

	Birth		12 Months		Birth		12 Months	
Variable	WAZ > −2 (n = 105)	WAZ ≤−2 (n = 42)	WAZ > −2 (n = 98)	WAZ ≤−2 (n = 49)	HAZ >−2 (n = 123)	HAZ ≤−2 (n = 24)	HAZ >−2 (n = 85)	HAZ ≤−2 (n = 62)
Exclusive BF, %	26.7	19.1	23.5	26.5	26.8	12.5	24.7	24.2
Diarrhea episodes/year	4.53	5.07	4.68	4.69	4.68	4.71	4.48	4.97
Diarrhea >14 days, %	7.61*	16.71*	9.2	12.2	9.8	12.5	5.92**	16.12**
Endocab GMu/ml at 6 months of age			24	24			17.23***	33.13***
Endocab GMu/ml at 12 months of age			65	60.6			60.4	67.6

Fisher exact test: *$P = .1312$ (not significant), **$P = .055$; χ^2 test: **$P = .043$; logistic regression (adjusted HAZ at birth): ***$P = .009$. (Treat endocab as binary variable, Fisher exact test *P* value = .029.)

Abbreviations: BF, breast feeding; GMu/ml, geometric median unit per ml; HAZ, height for age Z score; WAZ, weight for age Z score.

Table 7. Independent Predictors for Underweight and Stunting at 12 Months of Age

Predictor	OR (95% CI) for WAZ, *P* Value	OR (95% CI) for HAZ, *P* Value
Female sex	0.451 (.222–.917), .028	0.673 (.348–1.302), .240
No maternal education	2.331 (1.155–4.705), .018	2.148 (1.093–4.221), .027
Maternal BMI <18.5	4.202 (1.778–9.928), .001	2.541 (1.093–5.911), .030
Family monthly expenditure ≤6000 BDT	1.735 (.853–3.526), .128	3.730 (1.829–7.604), .0003
WAZ ≥−2 at birth	0.272 (.128–.577), .0007	0.559 (.272–1.152), .115
HAZ ≥−2 at birth	0.650 (.265–1.592), .346	0.299 (.119–0.752), .010
Diarrhea >14 days	1.380 (.462–4.126), .565	3.077 (0.995–9.514), .051
Endocab at 6 months (continuous)	1.000 (.989–1.011), .998	1.017 (1.005–1.030), .004

Abbreviations: BDT, Bangladeshi Taka (currency); BMI, body mass index; CI, confidence interval; HAZ, height for age Z score; OR, odds ratio; WAZ, weight for age Z score.

at 12 months). These are significant observations because they indicate that successful treatment of malnutrition will in part require prevention or treatment of enteric infections in order to prevent gut barrier dysfunction. In turn, these findings indicate that improvement in nutrition will decrease the severity of diarrheal illness due to select pathogens.

An additional contribution of the study was the delineation of the causes of diarrhea in low-income children from a developing country in the first year of life. The 147 children experienced 689 episodes of diarrhea in the first year of life. Of these 689 episodes, 420 (61%) samples were collected for pathogen identification. The samples were tested for 10 pathogens in an effort to identify the major causes of early childhood diarrhea. A surprising result was the importance of enteric protozoa, which were 3 of the top 6 identified causes of diarrhea. This work extended previous studies in cases of more severe diarrhea and in older age groups of the importance of enteric protozoa, as well as ETEC and rotavirus, in childhood diarrhea [2, 3].

It was of interest that the overall number of diarrheal episodes, as well as diarrhea due to *C. jejuni*, *Giardia*, and viruses, was not more common in malnourished children, indicating a selective defect in mucosal immunity due to malnutrition. For at least 1 pathogen, *E. histolytica*, the increased intensity of infection in malnourished children can be explained by the role of leptin in mucosal immunity to amebiasis [7, 8]. Children homozygous for an arginine-to-glutamine substitution in the cytokine receptor homology domain 1 of the leptin receptor (223R) were nearly 4 times more likely to have amebiasis, compared to those homozygous for the ancestral glutamine allele (223Q). Studies in murine models demonstrated that leptin receptor expressed in the intestinal epithelium provided protection against amebiasis via a STAT3-dependent signaling pathway. Perhaps amebiasis is more common in these malnourished children in part because they have low levels of leptin.

Maternal nutritional status, as measured by BMI, was also an important predictor of malnutrition in the child, both at birth and again at 12 months of age. Recently, the prolonged impact of maternal malnutrition on child health has been demonstrated through an analysis of demographic and health surveys in 54 countries [21]. An inverse association of maternal height with child mortality, stunting, and underweight was observed. These data point to the contribution of maternal nutritional status in infant low birth weight and subsequent stunting. Finally, socioeconomic factors, including family income and maternal education, were significant predictors of birth weight and height.

There is arguably no problem more important than malnutrition. Almost one-third of children in the developing world are malnourished. Poor nutrition is linked to up to half of all child deaths worldwide. In the first 2 years of life, malnutrition leads to damage in cognitive function and physical capacity [2]. The use of all known effective interventions in 99% of children would reduce stunting by only one-third [22]. The current study contributes to filling the knowledge gap of how to intervene in malnutrition by demonstrating the contribution of enteric infection and altered gut barrier function, as well as socioeconomic status and maternal malnutrition.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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