Am. J. Trop. Med. Hyg., 97(5), 2017, pp. 1345–1354
doi:10.4269/ajtmh.17-0277

The Effects of Malnutrition and Diarrhea Type on the Accuracy of Clinical Signs of Dehydration in Children under Five: A Prospective Cohort Study in Bangladesh

Kelly Skrable,[1]* Saadiyah Bilal,[1] Rashmi Sharma,[1] Sarah Robertson,[2] Yokabed Ashenafi,[3] Sabiha Nasrin,[4] Nur H. Alam,[4] and Adam C. Levine[1]

[1]*Warren Alpert Medical School of Brown University, Providence, Rhode Island;* [2]*Brown University School of Public Health, Providence, Rhode Island;* [3]*Brown University, Providence, Rhode Island;* [4]*International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh*

INTRODUCTION

Acute diarrhea and malnutrition remain significant burdens of disease for children under five and disproportionately affect children living in low- and middle-income countries. Children under five have an estimated 2.9 episodes of diarrhea every year or nearly 1.7 billion episodes of diarrhea in 2010, with the highest burden of disease in Africa and southeast Asia.[1] Cholera infection, caused by the O1 or O139 subgroups of the bacterium *Vibrio cholerae*, is of particular concern because of the severe onset of profuse diarrhea that can cause death from dehydration within hours if untreated.[2] Three out of five subregions in Africa report rising numbers of children under five with stunting, a measure of chronic malnutrition, from 46% in 1990 to 58% in 2014.[3] Acute malnutrition shows similar geographic distribution, with 68% of children under five suffering from wasting living in Southern Asia and 28% living in Africa.[3]

Malnutrition is particularly deleterious as it increases the risk of all-cause mortality and can increase the severity and the risk of mortality from common childhood illnesses, including diarrhea. The World Health Organization (WHO) estimates that almost half (45%) of all deaths of children under five are linked to malnutrition.[4] Acute and chronic malnutrition as well as micronutrient deficiencies are estimated to contribute to almost 3.1 million child deaths annually.[5] In 2013, a pooled analysis of ten prospective studies examining the association of malnutrition and disease-specific mortality found that the largest effects of malnourishment seen in mortality were from diarrheal diseases.[6] Conversely, diarrhea can also cause acute malnutrition and, if not addressed properly, frequent bouts can negatively affect child development and lead to chronic malnutrition.[7]

Prompt and appropriate treatment of dehydration among children under five presenting with acute diarrhea is critical. Several scales have been developed to assess dehydration among children using various clinical signs of dehydration. The Dehydration: Assessing Kids Accurately (DHAKA) Score is an empirically derived scale that was developed and internally validated through the 2014 DHAKA study[8] and externally validated in a 2015 validation study.[9] The integrated management of childhood illnesses (IMCI) algorithm is a standard algorithm developed by WHO that has been in clinical use for more than a decade.[10] The clinical dehydration scale (CDS) was originally developed for use in children under 36 months in 2004 and has since been externally validated for children under five.[11,12]

Despite the widespread use of these and other clinical scales for assessing the extent of dehydration among children under 5 years in areas in which malnutrition and cholera are endemic, the predictive value of these scales has previously not been independently evaluated in children with malnutrition or those with diarrhea due to cholera. Given the large body of evidence indicating that children with malnutrition are at greater risk of severe morbidity and mortality from diarrheal disease and the substantial global burden of seasonal cholera outbreaks, it is important to ensure that diagnostic tools used to assess the degree of dehydration in children are also accurate in these populations.

MATERIALS AND METHODS

Study design and patient population. This study is a planned secondary analysis of data collected from two prospective cohort studies conducted in Dhaka, Bangladesh, at the International Center for Diarrheal Disease Research, Bangladesh (icddr,b). The icddr,b provides free clinical services to Dhaka and its surrounding urban and rural areas, serving a catchment area of more than 17 million people.[13] The first study, the DHAKA derivation study, included children presenting with acute diarrhea to the rehydration (short stay) unit at the icddr,b from February to June 2014. The second study, a validation study conducted to confirm the findings of the original 2014 DHAKA study, replicated the 2014 methodology and collected data from a second sample of children who presented to the icddr,b with acute diarrhea from March to May 2015.

The two DHAKA studies and this planned secondary analysis were preregistered at ClinicalTrials.gov (NCT02007733), and ethical approval was obtained from the icddr,b Ethical Review Committee and the Rhode Island Hospital (Lifespan) Institutional Review Board.

Participant selection. All children younger than 60 months presenting to the icddr,b rehydration unit (short stay) with acute diarrhea during the aforementioned study periods were eligible for enrollment. Acute diarrhea was defined using the WHO definition of three or more loose stools per day.[14] Research staff randomly selected eligible participants by pulling colored marbles from a black pouch. The exclusion criteria included fewer than three loose stools per day, diarrhea lasting for more than 14 days, a diagnosis other than gastroenteritis as per the examining physician, edema and previous enrollment in either the 2014 DHAKA derivation study or the 2015 validation study.

Data collection. After obtaining informed consent in Bangla, the local language, children were immediately undressed and weighed using an electronic scale to the nearest tenth of a

*Address correspondence to Kelly Skrable, Brown University, Box G-9999, Providence, RI 02912. E-mail: kelly_skrable@brown.edu

kilogram. A study nurse clinically assessed the participant and classified the dehydration status. In the 2014 DHAKA study, dehydration was assessed using eight clinical signs of dehydration, namely general appearance, skin pinch, sunken eyes, tears, radial pulse, deep breathing, heart rate, and mucus membranes as described previously.[8] An additional clinical sign, thirst, was collected to score participants based on the IMCI algorithm and used as a part of the current analysis. The 2015 validation study assessed dehydration by first applying the DHAKA score, which was empirically derived through the 2014 DHAKA study, followed by the IMCI algorithm as described previously.[9] Scoring both of these assessments required assessment using the same clinical signs of dehydration as the 2014 DHAKA study. When available, a second study nurse who was blinded to the assessment of the first study nurse also clinically assessed each participant in both cohorts.

Study nurses assessed malnutrition by measuring the mid-upper arm circumference (MUAC) at admission using a standardized measuring tape. Study nurses also collected additional baseline historical and demographic data on participants, including age, sex, home district, days of diarrhea, the number of diarrheal episodes in the previous 24 hour period, and classified the type of diarrhea as one of three categories (watery, bloody, and rice water).

Clinicians followed established iccdr,b protocols for rehydrating all participants and weighed them, undressed, on the same scale every 8 hours to determine their post-rehydration stable weight. Study staff telephoned the families of participants who did not achieve a stable weight before discharge daily and asked them to return for a post-illness weight check once their diarrhea had resolved completely.

Variables of interest. *Dehydration.* The two highest consecutive weight measurements that differed by < 2% were averaged to establish each participant's stable weight as described previously.[9] We calculated the percent dehydration from the percent weight change with rehydration as follows:

$$\text{Percent dehydration} = \frac{(\text{stable weight} - \text{admission weight})}{\text{stable weight}} \times 100$$

Dehydration was categorized as no dehydration (< 3% weight change), any dehydration (≥ 3% weight change), and severe dehydration (> 9% weight change).

Clinical signs. Nine clinical signs of dehydration were assessed in both the 2014 and 2015 studies, namely general appearance, thirst, skin pinch, sunken eyes, tears, radial pulse, deep breathing, heart rate, and mucus membranes. In the initial studies, clinical signs were classified into three categories (i.e., normal skin pinch, slow skin pinch, and very slow skin pinch). For the purposes of these analyses, the assessments of the clinical signs were recoded as dichotomous variables, with the presence of any degree of the clinical sign categorized as the patient having the sign and the absence of the sign categorized as the patient not having the sign.

Malnutrition. The nutrition status was calculated using the MUAC as measured by the study nurses at admission. The MUAC has previously been established as the most accurate predictor of undernutrition in children with dehydration.[15–17] As per WHO guidelines, nutritional status was categorized as no acute malnutrition (MUAC ≥ 125 mm), any acute malnutrition (MUAC < 125 mm), and severe acute malnutrition (MUAC < 115 mm).[18] Children with edema were excluded from enrollment in both DHAKA studies.

Diarrhea type. Study nurses classified the diarrhea type at presentation as bloody, watery, or rice-water based on the description of the stool color provided by the patient's parent or guardian or directly observed by the nurse. Rice-water diarrhea, which appears white or milky in appearance, is typically associated with diarrhea due to *V. cholerae*.[19] Because of logistical constraints, stool cultures were not performed to definitively identify the etiology of diarrhea in any of the children enrolled in these studies.

Data analysis. Demographic and presenting clinical characteristics were analyzed using descriptive statistics, including median/interquartile range (IQR) and number/proportion. Associations between demographic and presenting clinical characteristics, nutritional status, and diarrhea type were assessed using the χ^2 tests of independence for categorical variables and the Wilcoxon rank-sum tests for continuous variables. We assessed the effects of nutritional status and diarrhea type (rice-water versus watery) on the accuracy of the aforementioned nine clinical signs for predicting the presence of any dehydration by conducting separate stratified bivariate analyses for each of the dichotomous clinical signs. Effect modification was assessed using the Cochran–Mantel–Haenszel (M-H) test for the homogeneity of stratified risk ratios. In addition, we assessed for confounding by malnutrition and diarrhea type by calculating and comparing the crude and adjusted (M-H combined) risk ratios for each clinical sign.

We compared the accuracy of three clinical diagnostic models of dehydration, namely the DHAKA Score (Figure 1), the IMCI algorithm (Figure 2), and the CDS (Figure 3), in children with and without acute malnutrition and by diarrhea type (rice-water versus watery) by calculating each participant's score using the individual scale's scoring criteria. We then calculated the areas under their receiver-operating characteristic (ROC) curves for each scale stratified by nutrition status and diarrhea type. Statistical significance was established at 0.05. Data analyses were conducted in the Stata 14.2 (StataCorp).

RESULTS

The complete dataset included data for 1,396 participants of which 850 were from the 2014 DHAKA derivation study and

Clinical Sign	Finding	Points
General appearance	Normal	0
	Restless/irritable	1
	Lethargic/unconscious	2
Tears	Normal	0
	Decreased	2
	Absent	4
Skin pinch	Normal	0
	Slow	2
	Very Slow	4
Respirations	Normal	0
	Deep	2

Total: ≥ 4 severe dehydration, 2-3 some dehydration, 0-1 no dehydration

FIGURE 1. Dehydration: Assessing Kids Accurately (DHAKA) score.

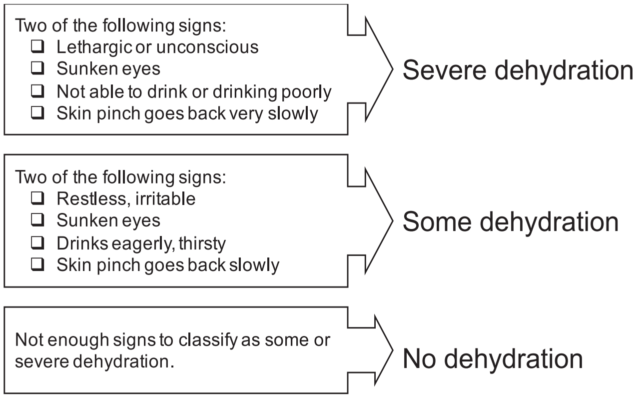

FIGURE 2. Integrated Management of Childhood Illness (IMCI) algorithm.

546 were from the 2015 validation study (Figure 4). Of these patients, one participant did not record the nutrition status, and 113 participants did not have a final stable weight recorded because of loss to follow up, leaving 1,282 participants for malnutrition analysis. In addition, one participant did not record the diarrhea type, and seven participants had bloody diarrhea. These patients were excluded in the analysis by diarrhea type because of the small number involved, leaving a total of 1,274 participants included in the latter analysis.

Table 1 provides information on the baseline demographic and initial clinical characteristics of the study population. The median participant age was 15 months (IQR = 10–20 months). Overall, 44% (558) of the participants were female. A total of 47% (597) had no dehydration, 41% (530) had some dehydration, and 12% (155) had severe dehydration. Among all children enrolled, 81% (1,042) had no acute malnutrition, 14% (N = 182) had moderate and acute malnutrition, and 5% (58) had severe and acute malnutrition. Of the 1,281 participants with a recorded diarrhea type, < 1% (7) had bloody diarrhea, 65% (828) had watery diarrhea, and 35% (446) had rice-water diarrhea.

Table 2 presents an analysis of differences in baseline characteristics between malnourished and nonmalnourished children enrolled in the study. There were no significant differences between the two groups with respect to dehydration status, diarrhea type, or episodes of diarrhea. Females were more likely to be malnourished (P = 0.002). Malnourished children were significantly younger, with a median age of 9 months versus 18 months for nonmalnourished children (P = 0.000). The malnourished children had a statistically significantly longer median number of days of diarrhea before arrival (3) than nonmalnourished children (2; P = 0.000).

Table 3 presents an analysis of differences in the baseline characteristics between children with watery versus rice water diarrhea. There were no significant differences between the two groups with respect to sex, malnutrition status, days of diarrhea before arrival, or episodes of diarrhea. Children with rice water diarrhea were significantly older (median age = 17 months) than children with watery diarrhea (median age = 15 months; P = 0.009). In addition, children with rice water diarrhea were significantly more likely to be moderately or severely dehydrated than children with watery diarrhea (P = 0.000).

Stratification of patients with any acute malnutrition (MUAC < 125 mm) and without any acute malnutrition (MUAC ≥ 125 mm) showed no evidence of effect modification by nutrition status on any of the nine clinical signs of dehydration (Table 4). In addition, a comparison of the crude versus M-H combined risk ratios did not indicate any confounding by nutritional status. Stratification by severe acute malnutrition (MUAC < 115 mm) rather than any acute malnutrition also did not show evidence of effect modification.

By contrast, there was a significant effect modification by type of diarrhea on all of the clinical signs with the exception of sunken eyes and thirst (Table 5). In all instances, the clinical signs were significantly less predictive of dehydration status among those with rice water diarrhea as compared with those with watery diarrhea. A comparison of the crude versus M-H combined risk ratios did not indicate any confounding by diarrhea type.

Acute malnutrition did not have a significant effect on the accuracy of the DHAKA Score (Figure 5A), the IMCI algorithm (Figure 5B), or the CDS (Figure 5C) as per comparisons of their area under the curve (AUC) (Table 6). Diarrhea type did not significantly affect the accuracy of the DHAKA Score (Figure 6A) or the IMCI algorithm (Figure 6B). The AUC for the CDS was significantly less (P = 0.03) for patients with rice water diarrhea (0.72, 95% CI = 0.67–0.77) than that of patients with watery diarrhea (AUC = 0.78, 95% CI = 0.75–0.82 as shown in Figure 6C and Table 7.

Clinical Sign	Finding	Points
General appearance	Normal	0
	Thirsty, restless, or irritable	1
	Lethargic or unconscious	2
Eyes	Normal	0
	Slightly sunken	1
	Very sunken	2
Mucus membranes	Moist	0
	Dry	1
	Very dry	2
Tears	Tears present	0
	Decreased tears	1
	Absent tears	2

Total: 5-8 moderate/severe dehydration, 1-4 some dehydration, 0 no dehydration

FIGURE 3. Clinical dehydration scale (CDS).

DISCUSSION

Initial accurate assessment of the hydration status in children suffering from diarrhea is a challenging yet critical task. It determines patient treatment and disposition as well as healthcare resource use; while children with no dehydration can be treated as outpatients and those with some dehydration can be treated using oral rehydration solution alone in a primary care setting, those with severe dehydration require hospital admission and treatment with intravenous fluids. Inappropriate triaging of patients based on the misclassification of their hydration status can cause harm to patients by either insufficient treatment of their dehydration or alternatively unnecessary and invasive interventions. Numerous studies have documented the modest utility of laboratory tests in assisting with the determination of hydration status; individual clinical findings generally have low sensitivity and most authors have concluded that the diagnosis of clinically important dehydration should rely on a combination of clinical

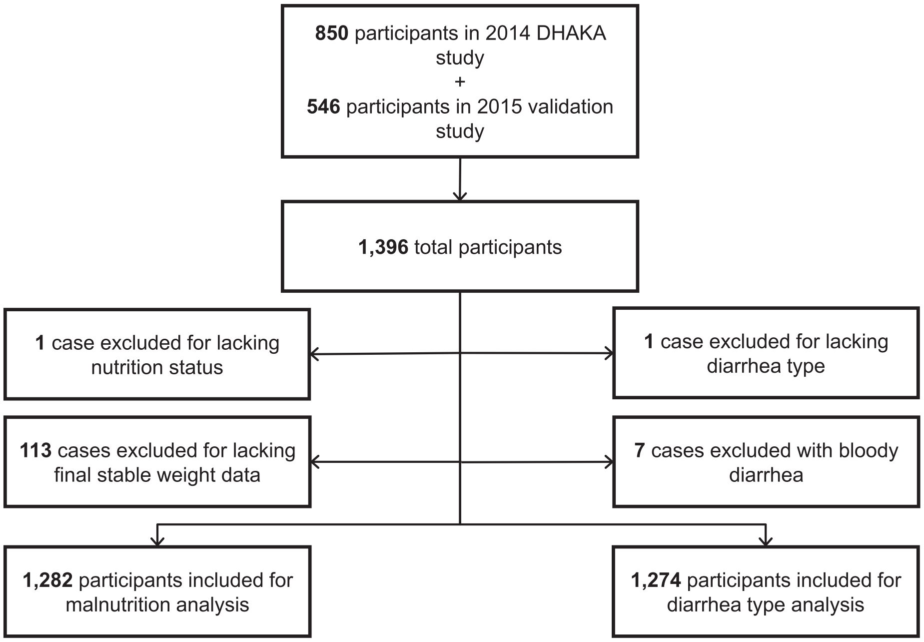

Figure 4. Study flow diagram for patient enrollment in the 2014 DHAKA study and 2015 validation study.

signs.[20–22] Levine et al.[9] have described one of the first empirically derived and validated clinical models for assessment of dehydration in children with acute diarrhea aimed at use by healthcare workers in resource-limited settings.

To our knowledge, our secondary analysis of data from the two prospective cohort studies is one of the first to compare the accuracy of three clinical diagnostic models of dehydration, the DHAKA Score, the IMCI algorithm, and the CDS in children by nutritional status and diarrhea type (rice water versus watery).

The WHO criteria for diagnosis of severe and acute malnutrition includes MUAC of less than 125 mm, the presence of bilateral pitting edema of nutritional origin, or the weight-for-height z-score below –3.[23] The presence of acute malnutrition is thought to present an extra challenge when clinically assessing hydration status in a child with acute diarrhea. It has been hypothesized that the overall appearance and abnormal physiological responses associated with acute malnutrition distort clinical signs such as skin pinch or general appearance that are used to help establish hydration status. In its guidelines for the treatment of malnourished children, the WHO cites difficulty in using clinical signs alone to estimate the dehydration status in severely malnourished children.[24,25] The WHO further recommends that healthcare providers "assume all children with watery diarrhea may have dehydration" and exhorts vigilance in clinical care and laboratory monitoring of electrolyte disturbances of severely malnourished children with comorbid diarrhea.[25,26]

Table 1
Baseline characteristics of children enrolled in the study

	Total participants (N = 1,396)	Included in final malnutrition analysis (N = 1,282)	Included in final diarrhea type analysis (N = 1,274)
Age in months, median (IQR)	16 (9–30)	15 (10–20)	15 (9–30)
Sex			
Female, No. (%)	611 (44)	558 (44)	553 (43)
Male, No. (%)	785 (56)	724 (56)	721 (57)
Dehydration status			
No dehydration, No. (%)	597 (47)	597 (47)	589 (46)
Some dehydration, No. (%)	531 (41)	530 (41)	530 (42)
Severe dehydration, No. (%)	155 (12)	155 (12)	155 (12)
Nutritional status (MUAC)	135 (126–144)	135 (125–144)	135 (125–144)
Malnutrition status			
No malnutrition, No. (%)	1,137 (82)	1,042 (81)	1,035 (81)
Some malnutrition, No. (%)	196 (14)	182 (14)	182 (14)
Severe malnutrition, No. (%)	62 (4)	58 (5)	57 (4)
Diarrhea type			
Bloody, No. (%)	7 (0.50)	7 (0.55)	–
Watery, No. (%)	896 (64)	828 (65)	828 (65)
Rice water, No. (%)	491 (35)	446 (35)	446 (35)
Days of diarrhea before arrival, median (IQR)	2 (1–3)	2 (1–4)	2 (1–4)
Episodes of diarrhea, median (IQR)	15 (10–20)	15 (9–30)	15 (10–20)

IQR = interquartile range; MUAC = mid-upper arm circumference.

TABLE 2
The analysis of differences in baseline characteristics between malnourished and nonmalnourished children enrolled in the study

	Not malnourished (*N* = 1,042)	Malnourished (*N* = 240)	*P* value
Age in months, median (IQR)	18 (10–30)	9 (7–16)	0.000*
Sex	–	–	0.002†
Female, No. (%)	432 (41)	126 (53)	–
Male, No. (%)	610 (59)	114 (48)	–
Dehydration status	–	–	0.327†
No dehydration, No. (%)	491 (47)	106 (44)	–
Some dehydration, No. (%)	421 (40)	109 (45)	–
Severe dehydration, No. (%)	130 (13)	25 (10)	–
Diarrhea type	–	–	0.577†
Bloody, No. (%)	6 (1)	1 (0.4)	–
Watery, No. (%)	666 (64)	162 (68)	–
Rice water, No. (%)	369 (35)	77 (32)	–
Days of diarrhea before arrival, median (IQR)	2 (1–3)	3 (2–4)	0.000*
Episodes of diarrhea, median (IQR)	15 (10–20)	15 (10–20)	0.661*

IQR = interquartile range.
* Wilcoxon Rank-Sum Test.
† χ^2.

In contrast to these studies and WHO recommendations, our study demonstrates that clinical signs of dehydration are as accurate in children with acute malnutrition as in children without acute malnutrition, with the caveat that children with bilateral pitting edema were excluded from our study. Stratification by those with any acute malnutrition and without acute malnutrition showed no effect modification on any of the nine clinical signs of dehydration. In addition, acute malnutrition did not have a significant effect on the accuracy of the DHAKA score, the IMCI algorithm, or the CDS to predict any dehydration. Although we do not have the number of children excluded for edema, a recently published study of children admitted to icddr,b between January 2012 and December 2013 for persistent diarrhea found that 3.8% had bipedal edema.[27] Based on these findings we can conclude that healthcare workers worldwide should feel confident in using the standard clinical diagnostic models for predicting dehydration severity in guiding rehydration treatment in children with acute malnutrition as long as they do not have bilateral edema. We hope that this finding will allow for more efficient and effective resuscitation of acutely malnourished children with acute diarrhea and that healthcare providers on the frontlines of providing care to malnourished children will use the clinical diagnostic tools at their disposal to inform their clinical assessments.

Of note, we identified some significant differences among children with and without acute malnutrition that warrant special consideration when providing clinical care and developing targeted health outreach interventions in Bangladesh. Females were significantly more likely to be malnourished than males, which is consistent with previous research indicating that females are more likely to be underweight than their male counterparts in Bangladesh.[28] Malnourished children presented for medical care significantly later in the course of their illness than nonmalnourished children, possibly because of resource constraints impacting both their nutritional status as well as their ability to seek timely care. The median age of malnourished children seeking care for diarrhea was 9 months, which was half of that (18 months) of nonmalnourished children. While analyses of malnutrition in Bangladesh indicate that younger children are at greatest risk for malnutrition,[28] no data were identified that empirically addressed potentially higher rates of malnutrition specifically in children under 1 year of age. This finding merits further research to explore the potential relationship between

TABLE 3
The analysis of differences in baseline characteristics between children with watery and rice water diarrhea enrolled in the study

	Watery diarrhea (*N* = 828)	Rice water diarrhea (*N* = 446)	*P* value
Age in months, median (IQR)	15 (9–25)	17 (9–36)	0.009*
Sex	–	–	0.775†
Female, No. (%)	357 (43)	196 (44)	–
Male, No. (%)	471 (57)	250 (56)	–
Dehydration status	–	–	0.000†
No dehydration, No. (%)	431 (52)	158 (35)	–
Some dehydration, No. (%)	310 (37)	220 (49)	–
Severe dehydration, No. (%)	87 (11)	68 (15)	–
Malnutrition status	–	–	0.550†
No malnutrition, No. (%)	666 (80)	369 (83)	–
Some malnutrition, No. (%)	122 (15)	60 (13)	–
Severe malnutrition, No. (%)	40 (5)	17 (4)	–
Days of diarrhea before arrival, median (IQR)	2 (1–4)	2 (1–3)	0.020*
Episodes of diarrhea, median (IQR)	12 (8–20)	15 (10–25)	0.316*

IQR = interquartile range.
* Wilcoxon Rank-Sum Test.
† χ^2.

TABLE 4
The analysis of clinical signs of dehydration by nutrition status among children < 60 months with acute diarrhea in Dhaka, Bangladesh, 2014 and 2015

		P value		
	Risk ratio (95% confidence interval)	M-H test of homogeneity	Crude risk ratio	M-H combined risk ratio
Eyes	–	0.130	1.926	1.923
Not malnourished	2.088 (1.588–2.745)	–	–	–
Malnourished	1.397 (0.893–2.188)	–	–	–
General appearance	–	0.581	2.323	2.324
Not malnourished	2.364 (2.049–2.727)	–	–	–
Malnourished	2.167 (1.649–2.849)	–	–	–
Heart rate	–	0.263	1.666	1.666
Not malnourished	1.715 (1.523–1.932)	–	–	–
Malnourished	1.482 (1.182–1.859)	–	–	–
Mucous membranes	–	0.790	1.728	1.726
Not malnourished	1.739 (1.525–1.984)	–	–	–
Malnourished	1.667 (1.257–2.212)	–	–	–
Radial pulse	–	0.195	1.856	1.855
Not malnourished	1.911 (1.727–2.115)	–	–	–
Malnourished	1.642 (1.337–2.017)	–	–	–
Respirations	–	0.298	2.130	2.132
Not malnourished	2.186 (1.952–2.448)	–	–	–
Malnourished	1.923 (1.554–2.382)	–	–	–
Skin pinch	–	0.112	2.429	2.425
Not malnourished	2.549 (2.205–2.947)	–	–	–
Malnourished	1.947 (1.443–2.627)	–	–	–
Tears	–	0.129	1.741	1.742
Not malnourished	1.661 (1.451–1.902)	–	–	–
Malnourished	2.127 (1.594–2.838)	–	–	–
Thirst	–	0.210	1.815	1.818
Not malnourished	1.632 (1.171–2.273)	–	–	–
Malnourished	2.955 (1.221–7.147)	–	–	–

M-H = Cochran-Mantel-Haenszel.

malnutrition and acute diarrhea in children under 1 year of age in Bangladesh.

While the clinical signs for dehydration were significantly associated with the presence of dehydration in all children, their risk ratios tended to be somewhat smaller in those with rice water diarrhea. While we did not use microbiological testing on stool samples to determine diarrhea types, studies examining the pathogenesis and seroepidemiologic

TABLE 5
The analysis of clinical signs of dehydration by diarrhea type among children < 60 months with acute diarrhea in Dhaka, Bangladesh, 2014 and 2015

		P value		
	Risk ratio (95% confidence interval)	M-H test of homogeneity	Crude risk ratio	M-H combined risk ratio
Eyes	–	0.069	1.914	1.868
Watery diarrhea	2.193 (1.584–3.037)	–	–	–
Rice water diarrhea	1.458 (1.064–1.999)	–	–	–
General appearance	–	0.002	2.314	2.237
Watery diarrhea	2.631 (2.221–3.116)	–	–	–
Rice water diarrhea	1.766 (1.473–2.117)	–	–	–
Heart rate	–	0.044	1.667	1.674
Watery diarrhea	1.826 (1.573–2.120)	–	–	–
Rice water diarrhea	1.489 (1.296–1.710)	–	–	–
Mucous membrane	–	0.017	1.725	1.666
Watery diarrhea	1.861 (1.588–2.181)	–	–	–
Rice water diarrhea	1.406 (1.185–1.669)	–	–	–
Radial pulse	–	0.003	1.854	1.785
Watery diarrhea	2.025 (1.789–2.291)	–	–	–
Rice water diarrhea	1.537 (1.351–1.749)	–	–	–
Respirations	–	0.018	2.123	2.076
Watery diarrhea	2.295 (2.001–2.631)	–	–	–
Rice water diarrhea	1.817 (1.580–2.089)	–	–	–
Skin pinch	–	0.004	2.418	2.365
Watery diarrhea	2.766 (2.310–3.311)	–	–	–
Rice water diarrhea	1.907 (1.592–2.283)	–	–	–
Tears	–	0.011	1.743	1.730
Watery diarrhea	1.966 (1.654–2.338)	–	–	–
Rice water diarrhea	1.457 (1.239–1.714)	–	–	–
Thirst	–	0.428	1.806	1.731
Watery diarrhea	1.868 (1.263–2.763)	–	–	–
Rice water diarrhea	1.455 (0.892–2.374)	–	–	–

M-H = Cochran-Mantel-Haenszel.

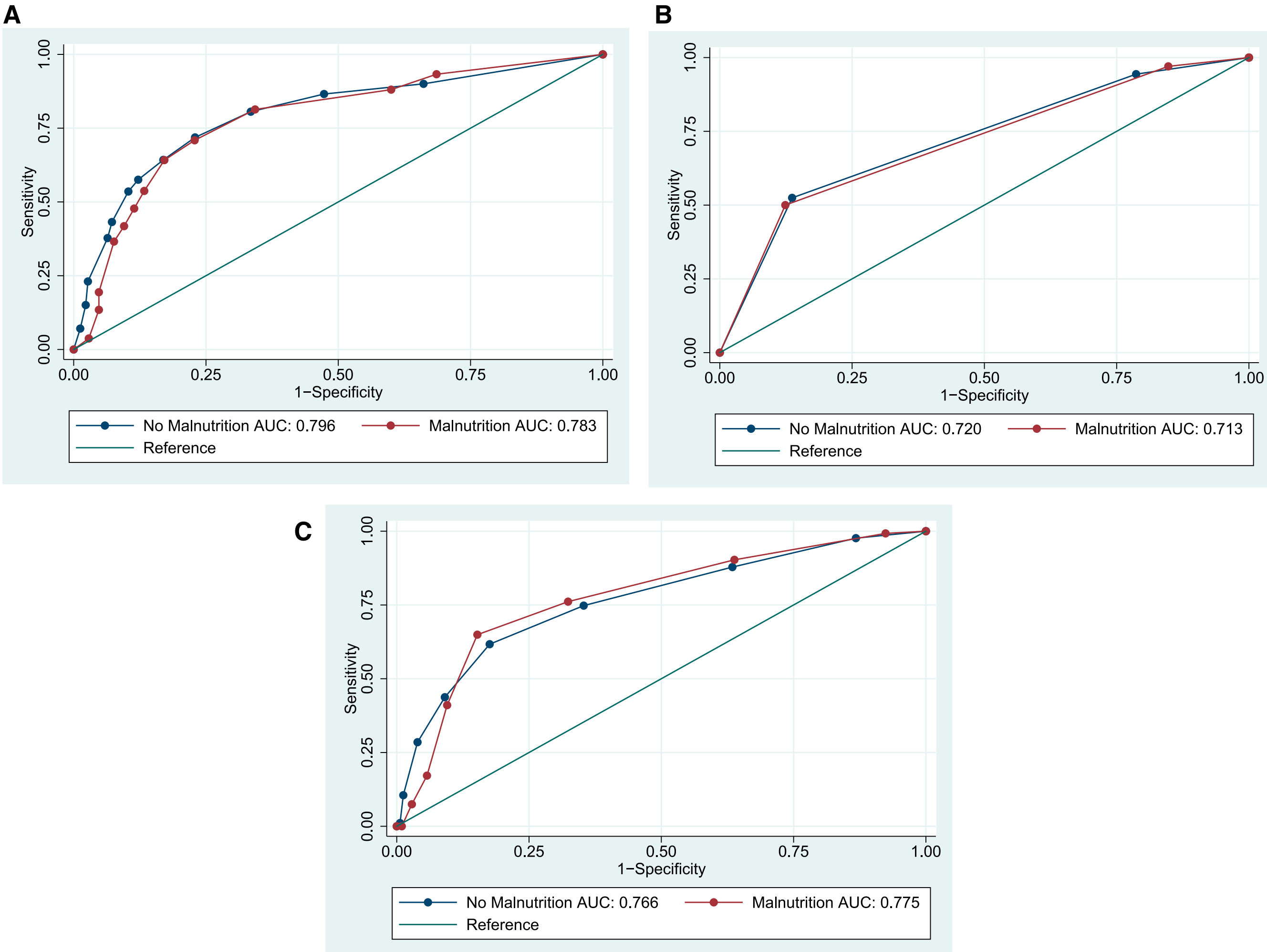

FIGURE 5. Receiver operating characteristic (ROC) curves for dehydration scales by nutrition status among children < 60 months with acute diarrhea in Dhaka, Bangladesh, 2014 and 2015. (**A**) The ROC curve for the DHAKA score by nutrition status. (**B**) The ROC curve for the IMCI algorithm by nutrition status. (**C**) The ROC curve for the clinical dehydration scale (CDS) by nutrition status. This figure appears in color at www.ajtmh.org.

characteristics of cholera have noted the rice water stool appearance of cholera diarrhea.[29–31] Ritchie et al.[29] note that as part of its mechanism of action, cholera toxin induces exocytosis of mucins and glycoproteins that coat epithelial surfaces of intestinal goblet cells; flecks of these mucin glycoproteins in the stool likely account for the rice water appearance of cholera diarrhea. Alternatively, laboratory testing of acute watery diarrhea in children without rice-water stools have isolated Rotavirus, *Salmonella*, and Shigella as the most common organisms.[32,33] Further research will be necessary to determine whether the clinical signs of dehydration are truly different in patients infected with *V. cholerae* as opposed to other infectious causes of acute diarrhea and what the reasons might be for these differences. It is not surprising, however, that the CDS performed less well in children with rice-water diarrhea as it was derived and validated in North America, a setting where cholera is a rare cause of acute diarrhea as opposed to the DHAKA score, which was derived and validated in a setting where cholera is common.

TABLE 6

The analysis of the ROC AUC by nutrition status among children < 60 months with acute diarrhea in Dhaka, Bangladesh, 2014 and 2015

	ROC AUC (95% confidence interval)	*P* value χ^2
DHAKA score	–	0.718
Not malnourished	0.795 (0.768–0.822)	–
Malnourished	0.783 (0.723–0.843)	–
IMCI algorithm	–	0.853
Not malnourished	0.719 (0.692–0.746)	–
Malnourished	0.713 (0.659–0.768)	–
CDS	–	0.785
Not malnourished	0.765 (0.737–0.793)	–
Malnourished	0.774 (0.714–0.834)	–

AUC = area under the curve; CDS = Clinical Dehydration Scale; DHAKA = Dehydration: Assessing Kids Accurately; IMCI = Integrated Management of Childhood Illnesses; ROC = receiver-operating characteristic.

LIMITATIONS

There are several limitations associated with our study. Children with bipedal edema were excluded from this study as they are treated in a separate unit for malnutrition at the icddr,b rather than in the rehydration unit used for treatment of acute diarrhea. Therefore, there may be differences in the accuracy

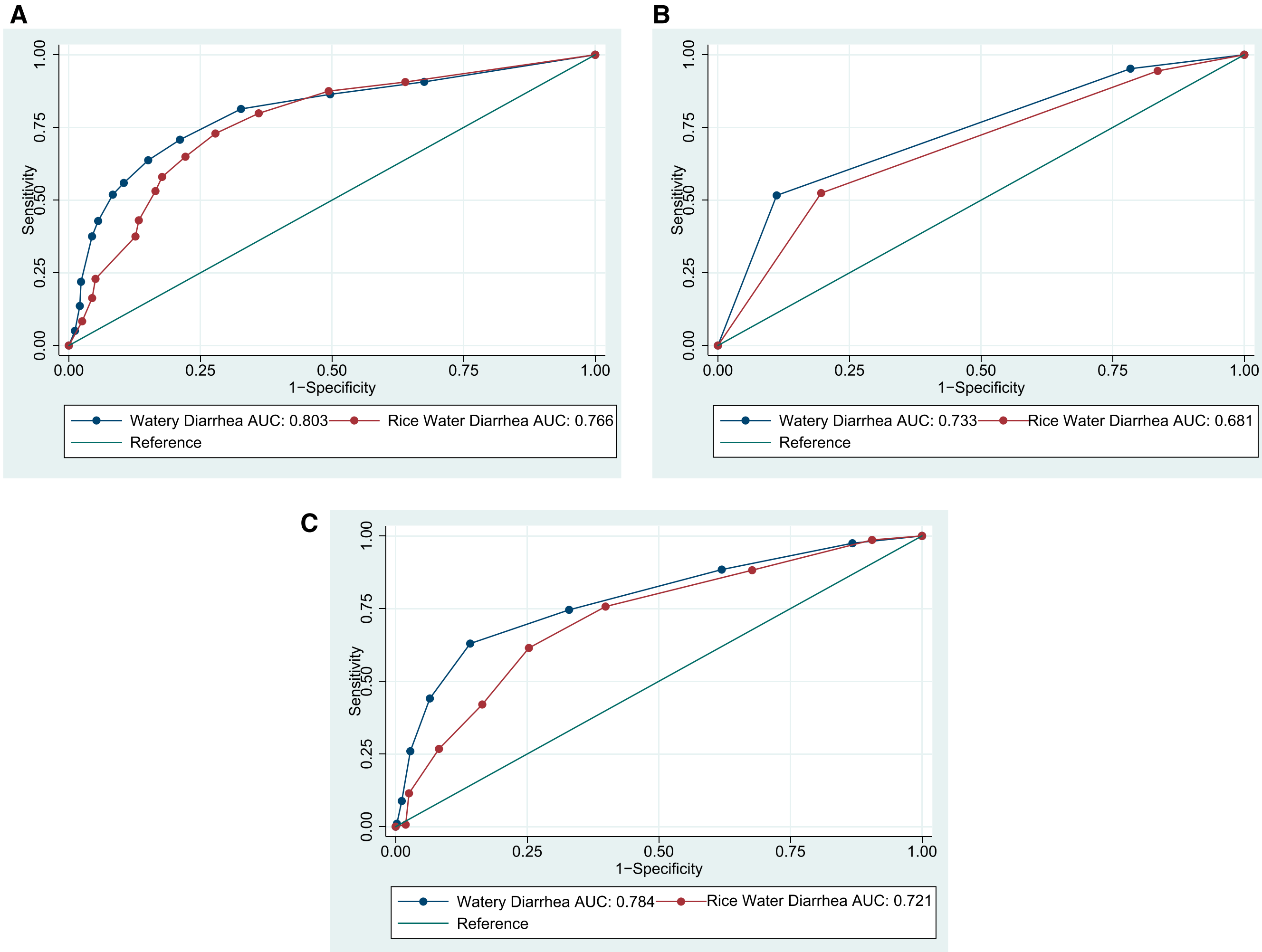

FIGURE 6. The ROC curves for dehydration scales by the type of diarrhea among children < 60 months with acute diarrhea in Dhaka, Bangladesh, 2014 and 2015. (**A**) The ROC curve for the DHAKA score by type of diarrhea. (**B**) The ROC curve for the IMCI algorithm by type of diarrhea. (**C**) The ROC curve for the CDS by type of diarrhea. This figure appears in color at www.ajtmh.org.

of clinical signs of dehydration in children with bipedal edema that our study was unable to detect. As previously noted, however, the percentage of children admitted to icddr,b with persistent diarrhea and bipedal edema was found to be 3.8% and we would expect it to be even lower in acute diarrhea.[27] In addition, stool type was classified by study nurses and was not assessed microbiologically to confirm the presence of *V. cholerae*, although routine stool culture of rectal swabs of patients presenting at the icddr,b is conducted and has documented the presence of endemic *V. cholerae* in the hospital catchment area.[13] While previous studies have established the linkage between cholera and the characteristic rice-water appearance of the stool as noted previously, caution should be taken in applying these results definitively to *V. cholerae*. This study combined the participants from two study populations, increasing the sample size; however, the sample of children who were malnourished was still relatively small (*N* = 240), and the subset of children with severe malnutrition was even smaller (*N* = 58) and may not have been large enough to detect small differences in the accuracy of clinical signs of dehydration between groups. Despite the small sample sizes, the relatively narrow 95% confidence intervals for the risk ratios for most of the clinical signs of dehydration indicate high precision, giving us confidence in our findings. Although both studies were conducted during the same season in sequential years and followed the same protocols, it is possible that there were small differences in the

TABLE 7

The analysis of the ROC AUC by diarrhea type among children < 60 months with acute diarrhea in Dhaka, Bangladesh, 2014 and 2015.

	ROC AUC (95% confidence interval)	*P* value χ^2
DHAKA score	–	0.195
Watery diarrhea	0.803 (0.773–0.834)	–
Rice water diarrhea	0.766 (0.720–0.813)	–
IMCI algorithm	–	0.057
Watery diarrhea	0.733 (0.704–0.763)	–
Rice water diarrhea	0.681 (0.636–0.726)	–
CDS	–	0.032
Watery diarrhea	0.784 (0.753–0.815)	–
Rice water diarrhea	0.721 (0.672–0.770)	–

AUC = area under the curve; CDS = Clinical Dehydration Scale; DHAKA = Dehydration: Assessing Kids Accurately; IMCI = Integrated Management of Childhood Illnesses; ROC = receiver-operating characteristic.

manner in which they were conducted or that there were differences in disease patterns between the study years that may have affected the results.

CONCLUSION

This study demonstrates that there is no significant difference in the accuracy of clinical signs of dehydration in children under five with acute diarrhea based on their nutritional status. Similarly, the DHAKA score, IMCI algorithm, and the CDS perform equally well in children with and without acute malnutrition. However, most clinical signs of dehydration and the CDS were less predictive of dehydration status in children with acute diarrhea likely caused by cholera than diarrhea likely caused by other organisms. Healthcare workers worldwide should feel confident in using standard clinical diagnostic models for predicting dehydration severity and guiding rehydration treatment in children with acute malnutrition. Further research should be conducted to explore potential differences in the accuracy of clinical signs of dehydration and clinical diagnostic models of dehydration among children with culture-confirmed *V. cholerae*.

Received April 5, 2017. Accepted for publication June 19, 2017.

Published online August 21, 2017.

Financial support: This study was funded by the National Institutes of Health Fogarty International Center grant number 1K01TW009208 and the Warren Alpert Medical School of Brown University.

Authors' addresses: Kelly Skrable, Medical School, Brown University Warren Alpert Medical School, Providence, RI, E-mail: kelly_skrable@brown.edu. Saadiyah Bilal, Rashmi Sharma, and Adam C. Levine, Department of Emergency Medicine, Brown University, Providence, RI, E-mails: saadiyah_bilal@brown.edu, doctor.rashmisharma@gmail.com, and adam_levine@brown.edu. Sarah Robertson, Center for Evidence Synthesis, Brown University School of Public Health, Providence, RI, E-mail: sarah_robertson@brown.edu. Yokabed Ashenafi, Undergraduate Studies, Brown University, Providence, RI, E-mail: yokabed_ashenafi@brown.edu. Sabiha Nasrin and Nur H. Alam, International Centre for Diarrhoeal Disease Research, Centre for Nutrition and Food Security, Dhaka, BD, E-mails: sabiha.nasrin@icddrb.org and nhalam@icddrb.org.

REFERENCES

1. Fischer Walker CL, Perin J, Aryee MJ, Boschi-Pinto C, Black RE, 2012. Diarrhea incidence in low- and middle-income countries in 1990 and 2010: a systematic review. *BMC Public Health 12:* 220.
2. Deen JL, von Seidlein L, Sur D, Agtini M, Lucas ME, Lopez AL, Kim DR, Ali M, Clemens JD, 2008. The high burden of cholera in children: comparison of incidence from endemic areas in Asia and Africa. *PLoS Negl Trop Dis 2:* e173.
3. UNICEF-WHO-World Bank Group, 2015. *Levels and trends in child malnutrition*. Geneva, Switzerland: World Health Organization.
4. WHO, 2016. *Children: Reducing Mortality Fact Sheet*. Available at: http://www.who.int/mediacentre/factsheets/fs178/en/. Accessed November 27, 2016.
5. Liu L, et al., Child Health Epidemiology Reference Group of WHO, UNICEF, 2012. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet 379:* 2151–2161.
6. Olofin I, McDonald CM, Ezzati M, Flaxman S, Black RE, Fawzi WW, Caulfield LE, Danaei G, Nutrition Impact Model Study Group, 2013. Associations of suboptimal growth with all-cause and cause-specific mortality in children under five years: a pooled analysis of ten prospective studies. *PLoS One 8:* e64636.
7. Bulled N, Singer M, Dillingham R, 2014. The syndemics of childhood diarrhoea: a biosocial perspective on efforts to combat global inequities in diarrhoea-related morbidity and mortality. *Glob Public Health 9:* 841–853.
8. Levine AC, Glavis-Bloom J, Modi P, Nasrin S, Rege S, Chu C, Schmid CH, Alam NH, 2015. Empirically derived dehydration scoring and decision tree models for children with diarrhea: assessment and internal validation in a prospective cohort study in Dhaka, Bangladesh. *Glob Health Sci Pract 3:* 405–418.
9. Levine AC, Glavis-Bloom J, Modi P, Nasrin S, Atika B, Rege S, Robertson S, Schmid CH, Alam NH, 2016. External validation of the DHAKA score and comparison with the current IMCI algorithm for the assessment of dehydration in children with diarrhoea: a prospective cohort study. *Lancet Glob Health 4:* e744–e751.
10. WHO, 2005. *Handbook: IMCI Integrated Management of Childhood Illness*. Geneva, Switzerland: World Health Organization.
11. Friedman JN, Goldman RD, Srivastava R, Parkin PC, 2004. Development of a clinical dehydration scale for use in children between 1 and 36 months of age. *J Pediatr 145:* 201–207.
12. Bailey B, Gravel J, Goldman RD, Friedman JN, Parkin PC, 2010. External validation of the clinical dehydration scale for children with acute gastroenteritis. *Acad Emerg Med 17:* 583–588.
13. Bardhan P, 2012. *Annual Statistics of Dhaka Hospital*. Dhaka, Bangladesh: International Center for Diarrhoeal Disease Research.
14. WHO, 2005. *The Treatment of Diarrhoea: A Manual for Physicians and Other Senior Health Workers*. Geneva, Switzerland: World Health Organization.
15. Modi P, Nasrin S, Hawes M, Glavis-Bloom J, Alam NH, Hossain MI, Levine AC, 2015. Midupper arm circumference outperforms weight-based measures of nutritional status in children with diarrhea. *J Nutr 145:* 1582–1587.
16. Ali E, et al., 2013. Is mid-upper arm circumference alone sufficient for deciding admission to a nutritional programme for childhood severe acute malnutrition in Bangladesh? *Trans R Soc Trop Med Hyg 107:* 319–323.
17. Briend A, Maire B, Fontaine O, Garenne M, 2012. Mid-upper arm circumference and weight-for-height to identify high-risk malnourished under-five children. *Matern Child Nutr 8:* 130–133.
18. WHO, 2013. *Guideline: Updates on the Management of Severe Acute Malnutrition in Infants and Children*. Geneva, Switzerland: World Health Organization.
19. Nelson EJ, et al., 2007. Complexity of rice-water stool from patients with *Vibrio cholerae* plays a role in the transmission of infectious diarrhea. *Proc Natl Acad Sci USA 104:* 19091–19096.
20. Steiner MJ, DeWalt DA, Byerley JS, 2004. Is this child dehydrated? *JAMA 291:* 2746–2754.
21. Gorelick MH, Shaw KN, Murphy KO, 1997. Validity and reliability of clinical signs in the diagnosis of dehydration in children. *Pediatrics 99:* E6.
22. Hoxha T, Xhelili L, Azemi M, Avdiu M, Ismaili-Jaha V, Efendija-Beqa U, Grajcevci-Uka V, 2015. Performance of clinical signs in the diagnosis of dehydration in children with acute gastroenteritis. *Med Arh 69:* 10–12.
23. WHO, 2009. *WHO Child Growth Standards and the Identification of Severe Acute Malnutrition in Infants and Children*. Geneva, Switzerland: World Health Organization, 2–5.
24. Bhan MK, Bhandari N, Bahl R, 2003. Management of the severely malnourished child: perspective from developing countries. *BMJ 326:* 146–151.
25. Ashworth A, Khanum S, Jackson A, Shorefield C, 2003. *Guidelines for the Inpatient Treatment of Severely Malnourished Children*. Geneva, Switzerland: World Health Organization.
26. Berti A, Bregani ER, Manenti F, Pizzi C, 2008. Outcome of severely malnourished children treated according to UNICEF 2004 guidelines: a one-year experience in a zone hospital in rural Ethiopia. *Trans R Soc Trop Med Hyg 102:* 939–944.

27. Islam SB, Ahmed T, Mahfuz M, Mostafa I, Alam MA, Saqeeb KN, Sarker SA, Chisti MJ, Alam NH, 2017. The management of persistent diarrhoea at Dhaka Hospital of the International Centre for Diarrhoeal Disease and Research: a clinical chart review. *Paediatr Int Child Health*, 10.1080/20469047.2017.1315911.
28. Chowdhury MR, Rahman MS, Khan MM, Mondal MN, Rahman MM, Billah B, 2016. Risk factors for child malnutrition in Bangladesh: a multilevel analysis of a nationwide population-based survey. *J Pediatr 172:* 194–201.e1.
29. Ritchie JM, Rui H, Bronson RT, Waldor MK, 2010. Back to the future: studying cholera pathogenesis using infant rabbits. *mBio 1:* e00047–10.
30. Jackson BR, et al., 2013. Seroepidemiologic survey of epidemic cholera in Haiti to assess spectrum of illness and risk factors for severe disease. *Am J Trop Med Hyg 89:* 654–664.
31. Amin V, Patwari AK, Kumar G, Anand VK, Diwan N, Peshin S, 1995. Clinical profile of cholera in young children–a hospital based report. *Indian Pediatr 32:* 755–761.
32. Maponga BA, Chirundu D, Gombe NT, Tshimanga M, Shambira G, Takundwa L, 2013. Risk factors for contracting watery diarrhoea in Kadoma City, Zimbabwe, 2011: a case control study. *BMC Infect Dis 13:* 567.
33. Houatthongkham S, Sithivong N, Jennings G, Phengxay M, Teepruksa P, Khamphaphongphane B, Vongphrachanh P, Southalack K, Luo D, Chiu CH, 2016. Trends in the incidence of acute watery diarrhoea in the Lao People's Democratic Republic, 2009–2013. *Western Pac Surveill Response J 7:* 6–14.