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Diarrhea, Dehydration, and the Associated Mortality in Children with Complicated Severe Acute Malnutrition: A Prospective Cohort Study in Uganda

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Objective To assess predictors of diarrhea and dehydration and to investigate the role of diarrhea in mortality among children with complicated severe acute malnutrition.

Study design A prospective cohort study, nested in a probiotic trial, was conducted in children with complicated severe acute malnutrition. Children were treated according to World Health Organization and national guidelines, and diarrhea and dehydration were assessed daily. Multiple linear and log-linear Poisson regression models were used to identify predictors of days with diarrhea and dehydration, respectively, and multiple logistic regression was used to assess their role in mortality.

Results Among 400 children enrolled, the median (IQR) age was 15.0 months (11.2-19.2 months), 58% were boys, and 61% had caregiver-reported diarrhea at admission. During hospitalization, the median (range) number of days with diarrhea was 5 (0-31), the median duration of hospitalization was 17 days (1-69 days), and 39 (10%) died. Of 592 diarrhea episodes monitored, 237 were admission episodes and 355 were hospital acquired. During hospitalization, young age was associated with days with diarrhea, and young age and HIV infection were associated with dehydration. Both days with diarrhea and dehydration predicted duration of hospitalization as well as mortality. The odds of mortality increased by a factor of 1.4 (95% CI, 1.2-1.6) per day of diarrhea and 3.5 (95% CI, 2.2-6.0) per unit increase in dehydration score.

Conclusions Diarrhea is a strong predictor of mortality among children with complicated severe acute malnutrition. Improved management of diarrhea and prevention of hospital-acquired diarrhea may be critical to decreasing mortality. *(J Pediatr 2019;210:26-33)*.

Global childhood mortality attributable to undernutrition was estimated at 3.1 million in 2011, corresponding with 45% of deaths in children less than 5 years of age.[1] Children with complicated severe acute malnutrition (cSAM) are particularly vulnerable. Despite improvement of treatment procedures, mortality rates are still unacceptably high with case fatality rates of 20% or more.[2-4]

There is a vicious cycle between malnutrition and diarrhea.[5-8] Malnutrition impairs immune function and thereby increases the risk of enteric (and other) infections. Enteric infections, in turn, disrupt the intestinal barrier function and decrease the absorption of nutrients, leading to or aggravating malnutrition. The long-term effects of multiple enteric infections are stunting and potentially reduced cognitive development.[6] Finally, diarrhea and malnutrition act synergistically, increasing the mortality risk of both conditions.[9,10]

The immediate danger from diarrhea is caused by the loss of body fluids, which may result in dehydration and electrolyte imbalance and eventually cause shock and death.[11,12] To prevent this, children with diarrhea are treated with rehydration solution according to standard protocols.[13] However, the rehydration of malnourished children is much more challenging than rehydration of well-nourished children. Malnourished children often have high total body sodium, increasing the risk of fluid overload and heart failure.[12,14] In addition, dehydration is difficult to identify in malnourished children owing to overlapping signs of dehydration and malnutrition, such as sunken eyes and reduced skin turgor.[11] With limited resources, appropriate treatment of these children may, therefore, be difficult to achieve.

cSAM	Complicated severe acute malnutrition
HAZ	Height-for-age z-score
MUAC	Mid-upper arm circumference
ReSoMal	Rehydration Solution for Malnourished (children)
SAM	Severe acute malnutrition
WHO	World Health Organization
WHZ	Weight-for-height z-score

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Funded by University of Copenhagen, Chr. Hansen A/S, Denmark and Innovation Fund Denmark.

The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2019.03.014

Many hospitalized children with severe acute malnutrition (SAM) present with diarrhea at admission. In studies from Zambia,[15] Uganda,[16] Kenya,[17] and India,[18] a minimum of 50% presented with diarrhea, and 2 studies that assessed the association with mortality both reported increased mortality.[15,17] We have previously described an association of diarrhea present at admission with increased mortality.[19] In the current study, we investigated the same cohort of children with cSAM further. The aim was to identify factors that may be important for future reduction of a potentially life-threatening combination of diarrhea and malnutrition. We assessed hospital acquired vs admission diarrhea, predictors of days with diarrhea and dehydration, and the role of diarrhea and dehydration in the duration of hospitalization and mortality.

Methods

The study was a prospective cohort study nested in a randomized, controlled intervention trial assessing the effect of probiotics on diarrhea in 400 children with cSAM.[20] The study was conducted at Mwanamugimu Nutrition Unit, Mulago National Referral Hospital, Kampala, Uganda, between March 2014 and September 2015. Children aged 6-59 months with cSAM were eligible for the study. SAM was defined as weight-for-height z-score (WHZ) of less than −3 or a mid-upper arm circumference (MUAC) of less than 11.5 cm or bipedal pitting edema. Children with SAM and medical complications were hospitalized according to the national guidelines[19] and were considered to have cSAM. Children were excluded from the study if they were in shock, had severe respiratory distress, significant disability, congenital or malignant disease, or had a weight of less than 4.0 kg at admission. The study was conducted according to the principles of the Declaration of Helsinki. Ethical approval was obtained from the School of Medicine Research and Ethics Committee at Makerere University, Kampala (REC REF 2013-134), and a consultative approval was given by The National Committee of Health Research Ethics in Denmark (Case no. 1306195). Study clearance was also obtained from Uganda National Council of Science and Technology and the Uganda National Drug Authority. The study was registered at http://www.isrctn.com, ISRCTN16454889.

Study Procedures

Children were treated according to the Ugandan protocol based on World Health Organization (WHO) guidelines for inpatient management of children with SAM.[11,21] This involved a stabilization phase where children received a liquid, low-protein, low-energy F-75 formula followed by a gradual transition to a semisolid, lipid-based, energy-dense, ready-to-use therapeutic food.[22] If transition to ready-to-use therapeutic food failed, a liquid F-100 formula was given.

A baseline questionnaire was completed at admission. Among others, caregivers provided information on their child, including presenting symptoms at admission (fever, cough, vomiting, weight loss, lack of appetite, change of mood, and how ill their child was on a 10-point visual analogue scale). In addition, information about the caregiver (who lived with the child, caregiver education), household information (number of people in the household, water and sanitation facilities), and the child's breastfeeding status were obtained.

A physical examination was performed at admission covering the assessment of vital signs, presence and degree of edema, anthropometry, and systemic examination to make a diagnosis. A blood sample was collected to measure C-reactive protein, hemoglobin, and HIV status.

HIV testing was routinely performed on all admitted children with standard HIV serology testing (Determine [Abbott Laboratories, Abbott Park, Illinois]), Stat pack [Chembio Diagnostic systems, Medford, New York], and Uni-Gold [Trinity Biotech, Bray, Ireland]). Children younger than 18 months of age who were positive according to these standard HIV tests had a DNA polymerase chain reaction test performed to confirm the diagnosis.

The presence of diarrhea at admission was based on the baseline questionnaire, where caregivers were asked if their child had diarrhea. If the answer was positive, the duration of diarrhea was noted.

During hospitalization, diarrhea data were collected using a validated stool diary collecting data on stool frequency and consistency.[23] Stool consistency was categorized as watery, abnormally loose, loose, or normal according to a 4-point photo scale.[23] Loose, abnormally loose, and watery stools were counted as diarrheal stools. Caregivers were thoroughly trained in how to use the diary and nutritionists supported and evaluated the caregivers' ability to score stool consistency and fill out the stool diary correctly every day. Vomiting was also recorded in the diary.

Diarrhea was defined as 3 or more loose or watery stools per 24 hours in accordance with the WHO definition.[24] When the child passed fewer than 3 loose or watery stools per day for a minimum 48 hours, diarrhea was defined to have stopped. If diarrhea reappeared after less than 48 hours, it was considered part of the same episode, but only days with 3 or more loose or watery stools were included in the number of days with diarrhea.

Diarrhea episodes recorded in the stool diaries were categorized as admission diarrhea episodes if they were observed from day 1 or 2 and hospital-acquired episodes if they started on day 3 or later. The Vesikari scale was used to calculate the severity of each diarrheal episode.[25] The scale is a composite score consisting of diarrhea duration, maximum stool frequency, vomit duration, maximum vomits per day, maximum temperature, degree of dehydration, and need of hospitalization. The score ranges from 0 to 20 and scores of 7 or less are categorized as mild, 7-10 as moderate, and 11 or greater as severe diarrheal episodes.

Dehydration was evaluated daily by a medical doctor according to WHO guidelines.[13] Prescription of Rehydration

Solution for Malnourished children (ReSoMal) was used as a surrogate marker of dehydration. ReSoMal was prescribed according to the Ugandan protocol[21] based on WHO guidelines: no treatment (score 0) was prescribed if the child did not have diarrhea and was not dehydrated. Treatment plan A (score 1) was prescribed if the child had diarrhea but no visible signs of dehydration. ReSoMal was administered orally after each diarrheal stool. Treatment plan B (score 2) was prescribed in case of diarrhea with some or severe dehydration and ReSoMal was administered orally according to a fixed regimen. Treatment plan C (score 3) was given to children in shock and included intravenous rehydration and follow-up according to guidelines.

Weight, length, height, and MUAC were measured in triplicate at admission and the mean was calculated. The maximum difference between 3 measurements was 0.2 cm for MUAC, 0.5 cm for length and height, and 0.5 kg for weight. Height-for-age z-scores (HAZ) and WHZ were calculated using WHO Anthro 3.1.1. A clinical evaluation of the child was performed daily including assessment of dehydration. For additional study information, please refer to an earlier publication.[20]

Measured outcomes were number of days with diarrhea during hospitalization, dehydration score (defined as the maximum level of rehydration treatment during hospitalization; score 0-3), duration of hospitalization, and mortality.

Data Handling and Statistical Analyses

Data were double-entered in EpiData v.3.1 (EpiData, Odense, Denmark) and analyzed using the statistical software R version 3.1.1 (2014-07-10).[26] A cross-sectional analysis of the baseline data from children admitted with and without diarrhea was carried out using χ^2 tests and the Wilcoxon rank-sum test for categorical and continuous variables, respectively. The proportion of children with admission and hospital-acquired diarrhea and treatment for dehydration from day 1 to 21 was computed graphically. Likewise, the distribution of stool consistency and frequency among study children was also shown. Paired Wilcoxon rank-sum tests were used to compare stool frequency and stool consistency between day 2 and discharge. The duration, dehydration, and severity scores of admission vs hospital-acquired diarrhea episodes were analyzed using linear mixed models with subject-specific random effects and adjustment for sex and age. Associations of age, sex, admission anthropometric values (HAZ, WHZ, MUAC), admission edema, presence of diarrhea at admission, and HIV status with the number of days with diarrhea during hospitalization were analyzed using multiple linear regression models, adjusted for sex, age, and the probiotic intervention. Associations of the same exposures and the dehydration score were analyzed by log-linear Poisson regression models with adjustment for overdispersion and adjusting for sex, age, and the probiotic intervention. Intermittent missing data in stool diaries were imputed to obtain complete episodes, as described previously.[20] Associations of days with diarrhea with duration of hospitalization and weight gain were analyzed by multiple linear regression models adjusted for sex, age, and the intervention. The association of dehydration with duration of hospitalization was analyzed with a log-linear Poisson regression model with adjustment for overdispersion and adjusting for sex, age, and the intervention. Logistic regression models, adjusted for sex, age, duration of hospitalization, the presence of diarrhea at admission, and the probiotic intervention were used to evaluate whether days with diarrhea and the dehydration score were associated with mortality.

Results

Of 400 children enrolled, the median age was 15.0 months (IQR, 11.2-19.2 months) and 58% were boys. Two-thirds (66%) had edematous malnutrition, 11% (n = 43) were confirmed to have HIV, and 61% (n = 244) were reported by caregivers to have diarrhea at the time of admission. The median duration of diarrhea present at admission was 7 days (IQR 4-21 days) and 43% of the 244 children (n = 103) presenting with diarrhea reported persistent diarrhea with 14 or more days of diarrhea before admission. During hospitalization children had a median number of days with diarrhea of 5.0 (range 0-31) and the median dehydration score was 1 (range 0-3). Among the 39 children (10%) who died in the hospital, 29 (74%) had diarrhea at admission[19] and 37 (95%) had at least 1 day of diarrhea during hospitalization. The median duration of hospitalization was 17.0 days (IQR, 1-69 days) and 327 children were discharged from the hospital.

Diarrhea Episodes

A total of 592 diarrhea episodes were reported in 346 children using stool diaries. Of these, 237 episodes were categorized as admission diarrhea and 355 as hospital-acquired (**Table I** and **Figure 1**; available at www.jpeds.com). Stool diary data were available for 396 children. The proportion of children where caregivers reported diarrhea in the stool diary was approximately 50% at admission, decreasing to 20% after 3 weeks of hospitalization (**Figure 2**, A). Diarrhea reported by caregivers at admission did not match admission diarrhea episodes captured in stool diaries completely. The percentage of children with diarrhea and no signs of dehydration who received rehydration treatment A decreased from 33% to 10% during the first 3 weeks of hospitalization, whereas the percentage with some to severe dehydration receiving treatment B was approximately 3%-5% during the first 2 weeks and thereafter it declined. During the study, 8 children were noted to receive plan C (**Figure 2**, B). Stool consistency increased and stool frequency decreased (**Figure 3**; available at www.jpeds.com) during hospitalization (both $P < .001$). Admission episodes were longer (+3.4 days [95% CI, 2.6-4.1]), had more dehydration (+0.6 dehydration points [95% CI, 0.5-0.7]), and a higher Vesikari severity

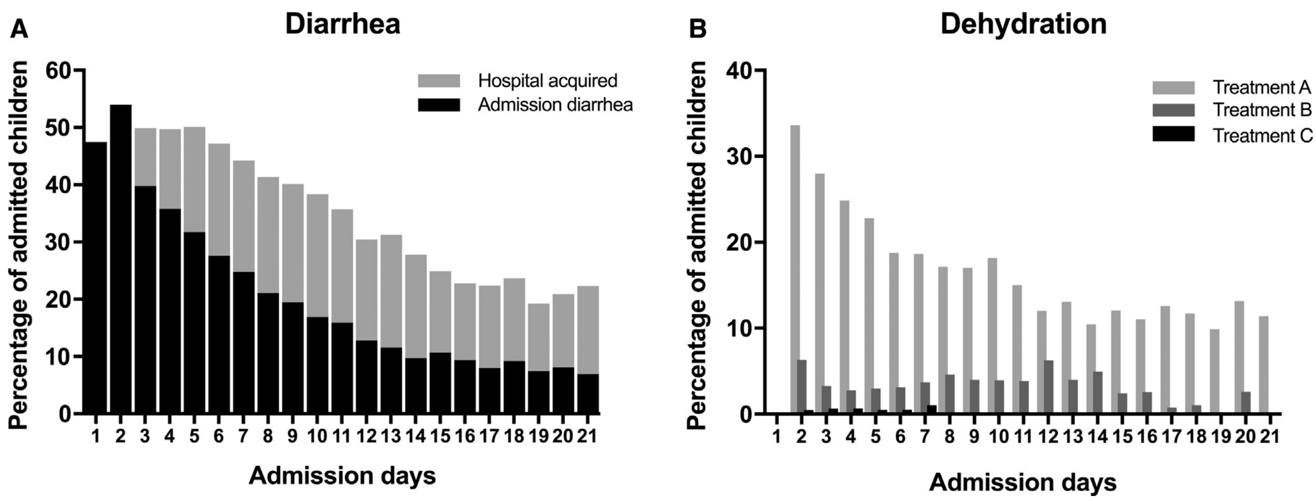

Figure 2. Percentage of children with diarrhea (*left*) and dehydration (*right*) on days 1-21 of admission. Treatment A: No to mild dehydration requiring rehydration solution after each diarrheal stool. Treatment B: Moderate to severe dehydration requiring rehydration according to a fixed schedule. Treatment C: Shock requiring intravenous rehydration according to guidelines.

score than hospital-acquired episodes (**Table I**; +2.7 Vesikari points [95% CI, 2.0-3.3]), and with 51% vs 27% categorized as severe ($P < .001$).

Associations with Diarrhea and Dehydration

In univariate analysis (**Table II**) higher HAZ ($P < .001$), lower WHZ ($P < .001$), and lower MUAC ($P = .03$) correlated with diarrhea at admission. In addition, the presence of HIV ($P = .05$), absence of edema ($P = .03$), hemoglobin ($P = .02$), and a range of illness symptoms reported by the caregiver correlated with the presence of diarrhea at admission (vomiting, $P < .001$; weight loss, $P < .001$; lack of appetite, $P = .01$; changed mood, $P = .02$).

In multivariate analysis adjusting for age and/or sex and the intervention of the original trial, age was associated with a lower number of days with diarrhea and less dehydration during hospitalization (**Table III**). The regression coefficients of −1.3 (95% CI, −2.1 to −0.4) and -0.2 (95% CI, −0.3 to −0.1) reflect a 1.3-day shorter duration of diarrhea and 0.2 dehydration points less per year of age. HIV was associated with 0.6 more dehydration points (95% CI, 0.3-1.1). In addition, WHZ, MUAC, and edema were associated with less dehydration with −0.1 dehydration points (95% CI, −0.2 to −0.07) for each WHZ, −0.1 dehydration points (95% CI, −0.1 to −0.04) per centimeter MUAC increased and −0.2 (95% CI, −0.4 to −0.03) to −0.3 (95% CI, −0.4 to −0.1) dehydration points, depending on edema grade.

Associations of Diarrhea and Dehydration with Hospitalization and Mortality

Days with diarrhea were strongly associated with duration of hospitalization with 1.0 day (95% CI, 0.9-1.1; $P < .001$) of hospitalization per diarrhea day. A 1-unit increase in the dehydration score was associated with 3.3 days (95% CI, 2.0-4.5; $P < .001$) of hospitalization. There was no association between days with diarrhea and weight gain ($P = .17$). The number of days with diarrhea as well as the dehydration score of each child were strongly associated with mortality. For days with diarrhea, the OR was 1.4 (95% CI, 1.2-1.6; $P < .001$), reflecting a 1.4 times increased odds of death for each additional day of diarrhea. Similarly, the odds of death increased 3.5 times (95% CI, 2.2-6.0; $P < .001$) for each unit increase in the dehydration score.

Discussion

In our study, days with diarrhea during hospitalization were strongly correlated with mortality. The OR for mortality was 1.4 for each additional day of diarrhea during hospitalization. As reported elsewhere from this study, children admitted with diarrhea had a 2.2-fold higher hazard ratio of dying compared with children admitted without diarrhea.[19] In Kenya, Talbert et al found a higher mortality in children with SAM admitted with or having any diarrhea during the hospitalization period compared with those without diarrhea.[17] Similarly, Irena et al reported a 2.5 times increased odds for mortality in children admitted with diarrhea in Zambia.[15]

Dehydration is likely to be a key factor mediating the effect of diarrhea on mortality. We found an OR of 2.3 of mortality for each unit increase in the dehydration score. The Kenyan study[17] showed an association between severe dehydration and mortality with an OR of 1.7. As diarrhea results in loss of both water and electrolytes (including sodium) and SAM conversely is associated with increased body sodium and retention of water, it is difficult to rehydrate a child with profuse diarrhea and SAM owing to the risk of fluid overload and congestive heart failure.[12,14] The perception among specialists of a high risk of fluid overload in children with SAM and diarrhea has recently been questioned.[27]

Table II. Correlates of diarrhea among children admitted with severe acute malnutrition

Admission characteristics	Admitted with diarrhea* (n = 244)	Admitted without diarrhea* (n = 155)	*P* value†
Age (mo)	14.0 (11.0 to 19.0)	16.0 (12.0 to 20.0)	.15
Female sex	40 (97)	47 (73)	.18
Anthropometry			
HAZ	−2.9 (−3.8 to −1.9)	−3.4 (−4.4 to −2.4)	<.001
WHZ	−3.1 (−4.0 to −1.9)	−2.2 (−3.3 to −0.8)	<.001
MUAC (cm)	11.3 (10.4 to 12.3)	11.6 (10.6 to 12.9)	.03
Caregiver reported symptoms at admission			
Fever	55 (133)	50 (78)	.48
Cough	69 (168)	61 (94)	.12
Vomit	56 (137)	22 (34)	<.001
Weight loss	74 (178)	53 (81)	<.001
Lack of appetite	65 (159)	50 (81)	.01
Mood changed	85 (206)	75 (115)	.02
General illness level VAS score‡	6.0 (5.0 to 8.0)	6.0 (5.0 to 7.0)	.17
Physical examination findings			
Edema			
Any edema	61 (148)	72 (112)	.03
Grade 1	8 (19)	5 (7)	.28
Grade 2	19 (45)	19 (30)	.92
Grade 3	35 (84)	48 (75)	.008
Pneumonia	17 (42)	17 (26)	>.99
Temperature	36.6 (36.2 to 37.0)	36.6 (36.1 to 37.1)	.88
HIV			
Negative	64 (141)	76 (112)	.03
Positive	15 (32)	7 (11)	.05
Exposed	21 (46)	17 (25)	.40
Biochemistry: median, (IQR)	n = 123	n = 174	
C-reactive protein (mg/L)	16.3 (7.0 to 38.9)	14.2 (4.5 to 36.7)	.38
Hemoglobin (mg/dL)	9.2 (8.0 to 10.3)	8.8 (7.2 to 9.6)	.02
Social factors			
Child lives with mother	85 (198)	82 (127)	.67
Mother education, primary school completed or lower	56 (130)	52 (80)	.55
Total no. in the household	4.5 (3.8 to 6.0)	4.0 (3.0 to 6.0)	.64
Children <5 years in household	2.0 (1.0 to 2.0)	2.0 (1.0 to 2.0)	.61
Water and sanitation			
Access to safe water	87 (203)	88 (136)	.77
Use of pit latrine	92 (216)	95 (147)	.07
Breastfeeding			
Ever breastfed	98 (223)	97 (147)	>.99
Currently breastfeeding	14 (32)	15 (22)	.98

VAS, Visual analogue scale.
*Data are expressed as median (IQR) or % (n). For some categorical variables, numbers do not add up to 400 owing to missing data.
†A χ^2 test or Wilcoxon rank-sum test for categorical and continuous variables, respectively.
‡VAS score from 0 to 10 with faces indicating different levels of illness, where 0 was perfectly healthy and 10 was as sick as the caregiver could imagine.

A small review found no evidence of fluid overload in children with SAM, diarrhea, and severe dehydration if intravenous rehydration was applied. The authors suggest that current conservative rehydration regimens of children with SAM and severe dehydration may be too restrictive and urgently needs to be tested in clinical trials.[27] However, for children with SAM and presumptive septic shock, conservative fluid resuscitation is still recommended. This recommendation is in line with findings of the large FEAST trial.[28]

To manage the fluid and electrolyte balance, skilled health professionals are needed. But often, the required close monitoring of children is impossible owing to a lack of resources and/or high turnover of doctors, resulting in suboptimal treatment.[29] Overlapping signs of dehydration and malnutrition may further contribute to complicating the identification of dehydrated children.[11]

Correlates of Diarrhea and Dehydration

It is well-described that young children (<2 years of age) have a greater incidence of diarrhea and mortality attributable to diarrhea than older children.[9] In line with this finding, we found negative associations between age and days with diarrhea as well as dehydration score during hospitalization. However, the age of children with diarrhea at admission did not differ from children admitted without diarrhea. We also did not find a correlation between breastfeeding and the presence of diarrhea at admission, although very strong correlations have been described in the literature.[10,30] However, the number of children breastfed during the study was low (14%-15%), probably owing to the age of the children.

HIV correlated with the presence of diarrhea at admission, predicted dehydration, and tended to predict days with diarrhea during hospitalization. Both acute, recurrent, and

Table III. Predictors of number of days with diarrhea and dehydration score* during hospitalization of children with severe acute malnutrition†

Variables	n	Days with diarrhea, adjusted effect size (95% CI)	P value	Dehydration score,* adjusted effect size (95% CI)	P value
Age (y)	400	−1.3 (−2.1 to −0.4)	.004	−0.2 (−0.3 to −0.1)	.002
Female sex	400	−0.1 (−1.3 to 1.1)	.86	0.1 (−0.1 to 0.3)	.26
Height-for-age (z-score)	387	−0.2 (−0.6 to 0.3)	.43	0.03 (−0.03 to 0.1)	.45
WHZ	387	−0.2 (−0.6 to 0.2)	.31	−0.1 (−0.2 to −0.1)	<.001
MUAC (cm)	388	−0.2 (−0.6 to 0.3)	.41	−0.1 (−0.1 to −0.04)	<.001
Presence of diarrhea at admission	399	0.4 (−0.8 to 1.7)	.52‡	0.5 (0.2 to 0.8)	<.001
Edema	399				
Grade I		−0.5 (−3.1 to 2.1)	.68	−0.3 (−0.5 to −0.1)	.021
Grade II		−0.2 (−1.9 to 1.6)	.86	−0.2 (−0.4 to −0.03)	.026
Grade III		0.8 (−0.7 to 2.2)	.30	−0.3 (−0.4 to −0.2)	<.001
HIV	368				
HIV exposed		−0.1 (−1.7 to 1,5)	.88	−0.1 (−0.2 to 0.2)	.53
HIV positive		1.8 (−0.2 to 3.8)	.08	0.6 (0.3 to 1.1)	<.001

*Dehydration score: Prescribed rehydration was used as a surrogate marker of dehydration. The dehydration score was defined as the maximum rehydration level of each child during hospitalization (0, no treatment; 1, treatment A, treatment of diarrhea with no signs of dehydration, requiring oral rehydration after each diarrheal stool; 2, treatment B, treatment of diarrhea with some to severe dehydration, requiring oral rehydration according to a fixed schedule; 3, treatment C, child in shock requiring intravenous rehydration).
†Predictors of days with diarrhea were analyzed using multiple linear regression models adjusted for age, sex, and the intervention of the original trial. Predictors of the dehydration score was analyzed using log-linear Poisson regression models with adjustment for over-dispersion and adjusting for age, sex and the original trial.
‡Presence of diarrhea at admission was associated with days with diarrhea in a fully adjusted model (adjusted for age, sex, HIV, WHZ, MUAC, edema, and duration of hospitalization and the intervention).

chronic diarrhea have been reported to be common in children with HIV.[12,31] HIV enteropathy, which involves intestinal inflammation, increased gut permeability and malabsorption caused by HIV-mediated damage to the intestinal mucosa can lead to diarrhea and aggravate malnutrition and increase susceptibility to infections, thereby reinforcing the vicious cycle between malnutrition and infections.[31] In addition, children with HIV have a higher prevalence of persistent diarrhea owing to *Cryptosporidium*.[13]

Wasting and a low MUAC correlated with the presence of diarrhea reported at admission. This finding may partly be due to the presence of dehydration at admission. A dehydrated child presents with a lower WHZ or MUAC than after rehydration.[32,33] Possible dehydration in children admitted with diarrhea may also explain why hemoglobin levels were higher.[34]

Edema was negatively associated with the presence of diarrhea at admission. It is speculated that caregivers with an edematous child would take their child to a hospital whether or not the child had diarrhea (or other infections), whereas caregivers with a nonedematous child would only take the child to a hospital if the child was overtly ill, for example, with severe diarrhea. Talbert et al also found a lower MUAC and less edema in children admitted with diarrhea than children without diarrhea.[17] In our longitudinal analyses, WHZ, MUAC, and edema were similarly negatively associated with dehydration during hospitalization; however, there was no association with the number of days with diarrhea. In a prospective, longitudinal, community-based study in rural Bangladesh, children with low weight-for-length (<80% of the National Center for Health Statistics reference population median) had longer durations of diarrhea, but a similar diarrhea incidence as better nourished children.[35]

The number of days with diarrhea and the dehydration score were both associated with longer hospitalization. Each day of diarrhea increased the duration of hospitalization by 1 day and each unit increase in the dehydration score increased hospitalization by 3 days. Because a longer hospitalization increases the risk of nosocomial infections and hospital costs and adds to the burden of implicated families,[11] it is important to focus on diarrhea and dehydration management throughout the hospitalization period to decrease it to the extent possible.

Admission Diarrhea vs Hospital-Acquired Diarrhea

Of a total of 592 diarrhea episodes, 237 episodes were categorized as admission diarrhea with 51% being severe according to the Vesikari scale and an additional 355 diarrhea episodes developed during hospitalization, of which 27% were severe. Talbert et al found 49% of children to present with diarrhea at admission.[17] An additional 16% developed diarrhea at least 48 hours after admission, indicating that hospital-acquired diarrhea is a common phenomenon. The causes of hospital-acquired diarrhea were not assessed, but diarrhea episodes occurred throughout the hospitalization. Such episodes could be caused by hygiene issues in the hospital environment, among caregivers, or owing to cross-contamination from other children with diarrhea. Some researchers found a worsening of diarrhea just after initiation of F-75 or F-100 treatment, indicating that therapeutic feeds used in treatment of SAM could cause looser stools, for example, owing to lactose intolerance.[16]

Stool frequency and consistency data (**Figure 3**) confirmed that diarrhea was more severe at admission compared with later during hospitalization. One-half of the children had watery or abnormally loose stool at admission. Although this number decreased, a minimum of 20% of the children had watery or abnormally loose stool during the first 2 weeks of hospitalization, which indicates a risk of dehydration and requirement of more intensive medical supervision.

This study was nested in a probiotic intervention trial that could potentially affect the results. However, the probiotics did not have any effect on diarrhea during inpatient treatment[20] and adjustment for the probiotic intervention did not modify the reported results. Daily registration of rehydration treatment (treatment plan A, B, or C) as a surrogate marker of dehydration status was another limitation of this study. Because both some and severe dehydration was treated according to treatment plan B, it was not possible to distinguish between these 2 conditions. In addition, dehydration was assessed by medical doctors and noted in the study case report forms during morning ward rounds. If dehydration developed later during the day or night and rehydration was initiated and stopped before the following morning, it may not always have been captured in the study records. On the positive side, the diarrhea data were collected using a validated stool diary[20] and experienced study staff trained caregivers and supported them in collecting as thorough and complete registration of diarrhea data as possible.

The study confirmed that diarrhea is a life-threatening condition in children with SAM. Young children had more days with diarrhea and were more dehydrated than older peers and children with HIV were more dehydrated than children without HIV. In addition, the study showed that admission diarrhea episodes were more severe than hospital-acquired episodes.

Improvement of diarrhea and dehydration management is important to decrease mortality in children with cSAM and should be given high priority. A focus on rehydration seems to be important and this process could be facilitated by more supervision of dehydrated children and improved education of staff. More studies are needed to find the most common cause(s) of hospital-acquired diarrhea in this type of setting to prevent them. According to Chopra et al, 95% of diarrhea deaths are preventable, but to achieve this ambitious goal, it requires that already known interventions be scaled up substantially.[36] The management of severe diarrhea in children with SAM is a challenge but because mortality is so high, efforts should focus both on prevention and improved treatment of these cases. ■

Submitted for publication Sep 28, 2018; last revision received Feb 26, 2019; accepted Mar 12, 2019.

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *The Journal of Pediatrics*

The Expanded Lung of the Term Fetus

Adams FH, Latta H, el-Salawy A, Nozaki M. J Pediatr 1969;75:59-66.

Adams et al performed a simple experiment to demonstrate that the normal fetal lung at term was well expanded in utero. They simply exteriorized term fetal lambs while on placental perfusion and ligated the trachea. They then performed a biopsy of the left lung with a clamp on the cut surface to prevent fluid loss and fixed the lung for histopathology. The tracheal obstruction was then removed; fetal lung fluid was drained passively for a similar biopsy of the right lung. Samples from air breathing lambs without tracheal obstruction were used for comparison. The fetal left lung was fully expanded with no collapsed alveoli. In contrast, drainage of the fetal lung fluid resulted in partially collapsed alveoli similar to lung samples from term lamb lungs sampled after breathing had stopped and without tracheal obstruction. The explanation of the expanded fetal lung was regulated airway closure by the fetus. This early observation that the fetal lung was inflated with fluid was 10 years after the identification of the association of surfactant deficiency with respiratory distress syndrome and concurrently with early attempts to mechanically ventilate preterm infants. The importance of fetal lung inflation with fluid for the normal growth and development was not yet appreciated. Adams et al got the physiology of airway closure right but were not aware that the fetus breathed intermittently in utero, which also is essential for normal lung development. The importance of airway closure and of clearance of fetal lung fluid to the physiology of respiratory adaptation to delivery remains relevant to neonatal resuscitation today.

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Table I. Comparison of admission vs hospital acquired diarrhea episodes

Episodes	At admission* (n = 237)	Hospital acquired* (n = 355)	Admission vs hospital-acquired diarrhea,† adjusted difference (95% CI)
Duration (d)	6.5 (1-31)	3.1 (1-23)	+3.4 (2.6-4.1)‡
Dehydration score			+ 0.6 dehydration points (0.5-0.7)‡
0	30 (65)	70 (248)	
1	47 (103)	22 (77)	
2	19 (41)	8 (30)	
3	4 (8)	0 (0)	
Vesikari score	11.1 (5-20)	8.4 (4-18)	+2.7 Vesikari points (2.0-3.3)‡
Mild	13 (26)	47 (125)	
Moderate	37 (75)	26 (69)	
Severe	51 (104)	27 (73)	

*Data are presented as mean (range) or percentage (n) unless otherwise stated. Some numbers do not add up to n = 237 or n = 355 because some diarrhea episodes had missing data.
†Comparisons of duration, dehydration, and Vesikari scores of admission vs hospital-acquired diarrhea episodes were analyzed using linear mixed models with subject-specific random effects and adjustment for sex and age. The dehydration score was defined as the maximum level of rehydration treatment during hospitalization (score 0-3). The Vesikari score is a composite score evaluating severity of diarrhea episodes.[25] It ranges from 0 to 20 and scores of ≤7 are categorized as mild, 7-10 as moderate, and ≥11 as severe diarrheal episodes.
‡$P < .001$.

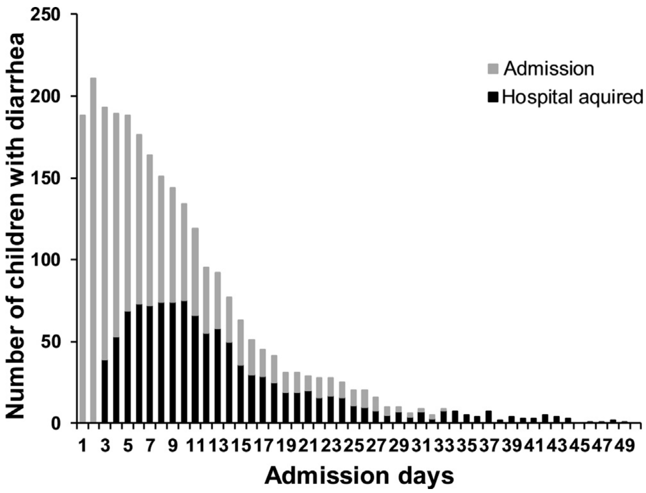

Figure 1. Number of children with diarrhea as a function of admission days. Grey: Admission diarrhea starting day 1 or 2. Black: Hospital-acquired diarrhea starting day 3 or later.

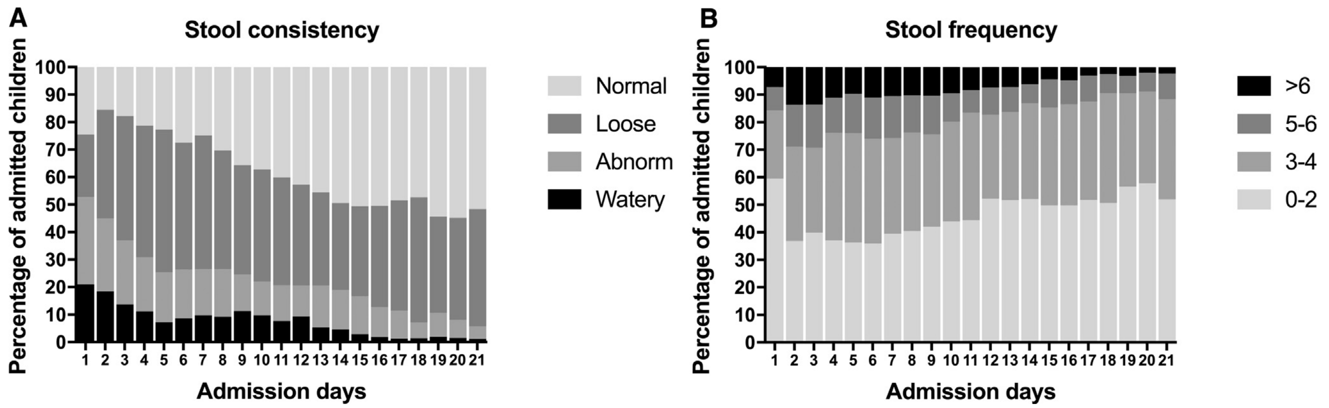

Figure 3. Stool consistency (*left*). The percentage of children with their most liquid stool consistency on days 1-21. Stool frequency (*right*). The percentage of children with 0-2 stools/day, 3-4 stools/day, 5-6 stools/day, or >6 stools/day during days 1-21 of admission.