Association between cholera treatment outcome and nutritional status in children aged 2–4 years in Nigeria

M. V. Bragança Lima,[1] S. G. Hinderaker,[2] O. F. Ogundipe,[1] P. O. Owiti,[3] B. Kadai,[4] J. Maikere[1]

SETTING: Cholera can aggravate or precipitate malnutrition, and children with severe acute malnutrition (SAM) have a higher incidence and longer duration of diarrhoea.

OBJECTIVE: To describe 1) characteristics of and treatment outcomes in children aged 2–4 years with cholera, 2) the case fatality rate (CFR) in all children treated, and 3) the associations between nutritional status, hydration status, treatment administered and hospital outcomes.

DESIGN: An observational cohort study of children admitted to one cholera treatment centre in Maiduguri, Nigeria, with a focus on children aged 2–4 years. CFRs were examined by cross tabulation and mean length of stay (LOS) using analysis of variance.

RESULTS: SAM was identified in 24% of children aged 2–4 years. The CFR for children aged 2–4 years was 1.4%. As the sample size was small, we did not find any association between nutritional status and death due to cholera. The proportion of children discharged within 2 days was 79%, and the longest stay was 8 days. In general, health facility LOS increased with severity of malnutrition.

CONCLUSION: Our study found that nutritional status affected the LOS, but was unable to find an association between malnutrition and fatality among children aged 2–4 years.

Cholera is a water-borne diarrhoeal disease caused by the Gram-negative bacterium *Vibrio cholerae*. It is an ancient illness, first described in the fifth century BC.[1,2] The disease causes severe dehydration that can lead to death in a few hours,[3] but dehydration can be resolved by giving large amounts of fluids, including oral rehydration therapy (ORT). The case fatality rate (CFR) for untreated cholera can be up to 10%,[1] but once appropriate therapy is implemented, it falls to less than 0.2%.[1]

Currently, 47 countries are affected by cholera,[2] and Nigeria's Federal Ministry of Health considers the disease endemic in the country.[4] In recent years, the country has faced prolonged internal conflicts, with a decade of fighting in the north-eastern region.[5] The conflicts have generated a population of internally displaced people, with accompanying problems such as malnutrition.

Historically, children have had the greatest burden of cholera.[6–8] It is estimated that in endemic countries, children under 5 have an incidence of 7.0 cases per 1,000,[9] while children above 15 have an incidence of 0.9 per 1,000 annually.[9] The estimated annual mortality rate for endemic countries in children aged 1–4 years is 23.2 deaths/100,000, while the mortality is 2.7 deaths/100,000 for the population above 15 years.[9]

Diarrhoeal illnesses such as cholera can aggravate or precipitate malnutrition,[10] and conversely, children with severe acute malnutrition (SAM) have a higher incidence and longer duration of diarrhoea.[10] The pathophysiological explanation for these interactions is mainly electrolyte imbalance, which affects the treatment of dehydration, especially in severely malnourished individuals.[10]

Many countries where cholera is endemic also report high rates of malnutrition.[11] In 2017, Asia and Africa together reported 99% of global cholera cases,[12] and in 2018, both continents also housed 96% of the wasted (weight-for-height <-2 standard deviations [SDs] below the median) children worldwide.[13]

Despite the recognised geographical intersections of cholera with malnutrition, data on the two together are limited.[14–16] Some studies have been undertaken to examine the associations between cholera and malnutrition,[17–19] but to date the evidence is too limited to enable firm conclusions to be drawn on the associations or to recommend changes in current treatment practices of cholera in malnourished populations.[10,16,20]

We aimed to conduct this observational study to examine the association between nutrition status and cholera outcomes. Specific objectives were 1) to describe the characteristics of and treatment in children aged 2–4 years; 2) to report on the CFR in all children treated at the CTC; and 3) to measure associations between nutritional status, hydration status, treatment given and hospital outcome (length of stay [LOS] and deaths) in children aged 2–4 years admitted to one cholera treatment centre (CTC) in Maiduguri, Nigeria, in 2018.

METHOD

Study design

This was a retrospective cohort study using secondary data.

Setting

General setting

Nigeria is in Western Africa and has a population of 196 million.[21] The first case of cholera was recorded in December 1970,[22] and since then there have been numerous outbreaks with CFRs ranging from 13% in earlier years to 1.9%, as in the 2018 outbreak.[22,23]

Specific setting

Maiduguri is the capital of Borno State in north-eastern Nigeria, and together with Adamawa and Yobe States, has experienced severe humanitarian crises due to armed conflicts,[24] with a displaced population of 1.8 million.[24] The Borno, Adamawa and Yobe (BAY) states have an estimated 3,500,000 people in need of humanitarian nutritional assistance, with around 440,000 children with SAM.[24] During the 2018 cholera outbreak, the BAY states had a CFR of 1.6%.[23]

During the 2018 cholera outbreak, there were three CTCs with 50–100 beds and 10 cholera treatment units (CTU) with 7–22 beds in the city of Maiduguri. All centres had an inpatient capacity with 24-hour care provided by medical doctors and nurses, and were run by international non-governmental organizations (INGOs). Oral rehydration points (ORPs) were also organised by different partners for short-term observation and oral rehydration of people with suspected cholera.

During the study period, the INGO Médecins Sans Frontières (MSF) Operational Centre Brussels, managed a 100-bed CTC. This centre was also operational during a 2017 cholera outbreak in Maiduguri. MSF also runs an inpatient treatment feeding centre (ITFC) in the city, which made it possible to follow malnourished patients after transfer. Selected children who needed further malnutrition treatment when they were considered clinically cured for cholera and not infectious (general improvement and decreased frequency of stools) were transferred.

Case management of cholera

The case definitions for cholera in Nigeria (suspected or confirmed) depend on whether an outbreak has been declared or not. If an outbreak has not been declared, a suspected cholera case is any person aged ≥2 years with acute watery diarrhoea (AWD) and severe dehydration or any person dying from AWD. If an outbreak has been declared, all cases or deaths due to acute watery diarrhoea are considered cholera suspects.[2,4] AWD is defined as the passage of three or more loose or liquid stools within 24 hours,[2,4] or increased stool frequency above normal for the individual.[4] A confirmed case of cholera is defined as a suspected case with *V. cholerae* O1 or O139 isolated from stool samples using culture or polymerase chain reaction (PCR).[2,4] None of the cases in our study had culture- or PCR-confirmed cholera.

Treatment for suspected and confirmed cholera cases involves assessment and determination of levels of dehydration, rehydration with replacement of ongoing fluid losses until the diarrhoea subsides, and frequent reassessment of vital signs and hydration status. Oral antibiotics are given only if the patient is severely dehydrated to reduce stool volume, duration of diarrhoea and infectivity.[20]

The children at the study site had their level of dehydration assessed and were observed for at least 4 hours (this is the minimal time of observation for patients treated with plan B (Table 1) for the presence of loose stools before admission.[4] The patients admitted after this assessment were those with dehydration and AWD, regardless of age. The facility also managed patients with cholera and other concomitant diseases, resulting in other treatments being given in addition to standard cholera treatments (Table 1). The treatment of the children in the MSF-run CTC was based on dehydration status as outlined in Table 1.

Case management of malnutrition

According to the WHO, the definition of SAM in children aged 6–59 months is weight-for-height 3 SDs below the median, presence of bilateral oedema or mid-upper-arm-circumference (MUAC) <115 cm.[25] The definition of moderate acute malnutrition (MAM) is weight-for-height between –3 and –2 SDs below the median.[26] No clear consensus definition has been established yet for MUAC for MAM, but MSF uses an MUAC of 115–125 cm as the cut-off for MAM.

The CTC routinely screened children aged 6 months to less than 5 years for malnutrition at intake, but screening could also have been before, during or after the rehydration therapy. Children aged 5–14 years were not routinely screened, and only 71% of them had a recorded nutritional status.

The CTC admitted patients with AWD with and without dehydration. Patients aged 2–4 years admitted to the centre underwent fairly complete nutritional assessment and could be analysed further. A SAM or MAM diagnosis was assessed according to information provided by the health staff in the patient's files.

Study population

Records of all children admitted to a single CTC in Maiduguri, Nigeria, between 1 August and 30 November 2018, were reviewed for the study, with more detailed analyses conducted on those aged 2–4 years. Outpatient children were not included.

Data variables, data sources and data collection

Data encoders and/or medical staff recorded the data from the patient's clinical files, and these were entered in a digital archive (Microsoft Excel v97-2003; Microsoft, Redmond, WA, USA). Patient files were cross-checked against the digital archives, and corrections made as necessary. Laboratory testing, specifically rapid diagnostic testing for cholera and stool culture samples, was not available during the entire study period. Study variables included registration number, age, sex, place of origin, cholera test result, nutritional status and type of treatment given. The rehydration treatment plan (Table 1) was used as a proxy to determine the dehydration status of the patient (Plan A: no

TABLE 1 Standard treatment for cholera provided to patients based on their hydration status when admitted to a CTC, Maiduguri, Nigeria, 2018[20]

Dehydration status	Treatment
No dehydration	Plan A: Observation and ORT
Moderate dehydration	Plan B: Observation in the CTC for at least 4 hours and ORT
Severe dehydration	Plan C: Admission to CTC, intravenous rehydration and antibiotic therapy

CTC = cholera treatment centre; ORT = oral rehydration therapy.

dehydration; Plan B: treated for moderate dehydration; Plan C: treated for severe dehydration), as the electronic record did not indicate the rehydration status but only the treatment plan used. The treatment outcome variables included discharged, transferred to an MSF facility or another facility, left against medical advice and death) and LOS in days. All the data were collected from the MSF electronic database (Microsoft Excel 97-2003).

Analysis and statistics
The electronic data were exported to and analysed using EpiData software v2.2.3.187 (EpiData Association, Odense, Denmark). De-

scriptive statistics were used for patient characteristics. The CFR was calculated. We analysed CFR using cross tabulation and Fisher's test and mean LOS using the Kruskall-Wallis test. Significance levels were set at 5% ($P < 0.05$).

Ethics
The Borno State Ethical Approval Committee (Maiduguri, Nigeria; MOH/GEN/6678/1) approved this research. This research fulfilled the exemption criteria set by the MSF Ethics Review Board (ERB) for a posteriori analyses of routinely collected clinical data, and thus did not require MSF ERB review. The study was conducted with permission from the Medical Director, Operational Center Brussels, MSF, Brussels, Belgium.

RESULTS

At the CTC, 2744 persons were admitted during the outbreak, of whom 1599 were under 18 years (Table 2). For further analyses, we included the 500 children aged 2–4 years (Table 3). SAM was present in 24% of the children, and 34% had severe dehydration. In the population aged 2–4 years, 34% ($n = 171$) was treated for severe dehydration, 31% ($n = 53$) of whom were also classified as SAM, while 21% ($n = 36$) were MAM and 48% ($n = 82$) were not malnourished.

The CFR for all cholera cases was less than 1% (0.8%, 13/1,599). Of the 500 children aged 2–4 years, seven died, resulting in a CFR of 1.4%. CFR was higher in children under 2 years (1.6%) than the rest of the study population. Two of the patients who died were excluded from subsequent analyses because of missing data, and one died after transfer. Nutritional status was not associated with death from cholera in this study even after adjusting for hydration status and treatment regimen.

Table 3 shows the associations of death as an outcome and LOS with nutritional status, hydration status and treatment regimen. The proportion of patients discharged within 2 days was 79%, and the longest stay was 8 days. Longer stays at the CTC

TABLE 2 Demographic characteristics of patients admitted to a cholera treatment centre in Maiduguri, Nigeria, 2018

	n	(%)
Total	1,599	
Sex		
Male	893	(55.8)
Female	706	(44.1)
Age, years		
<2	308	(19.3)
2–4	500	(31.2)
5–14	699	(43.7)
>15	92	(5.7)
Area of origin		
Bama	1	(0.0)
Gubio	0	(0.0)
Jere	860	(53.8)
Kaga	2	(0.1)
Konduga	85	(5.4)
Mafa	6	(0.3)
Magumeri	3	(0.2)
Maiduguri	636	(39.7)
Monguno	1	(0.0)
Nganzai	2	(0.1)

TABLE 3 Association of death and length of stay by nutritional status and hydration status among children aged 2–4 years in a cholera treatment centre in Maiduguri, Nigeria, 2018

	Total (n = 500)		Died (n = 5)		Length of stay		
	n	(%)	n	P value*	Mean (days)	(95% CI)	P value†
Nutritional status				0.44			<0.001
Not malnourished	250	(50)	4		1.5	(1.4–1.6)	
Moderate acute malnutrition	127	(25)	0		2.0	(1.8–2.2)	
Severe acute malnutrition	121	(24)	1		2.3	(2.0–2.6)	
Not recorded	2	(0.4)					
Treated for dehydration‡				0.07			0.02
Mild dehydration	31	(6)	1		1.9	(1.5–2.4)	
Moderate dehydration	297	(59)	1		1.7	(1.5–1.8)	
Severe dehydration	171	(34)	3		2.0	(1.8–2.3)	
Not recorded	1	(0.2)	1				
Treatments given				0.34			<0.001
Standard cholera	264	(53)	1		1.5	(1.4–1.6)	
Other§	230	(46)	3		2.2	(2.0–2.4)	
Not recorded	6	(1.2)					

* P value for number of deaths from Fisher's test.
† P value for length of stay using the Kruskall-Wallis test.
‡ Dehydration categorised by treatment given.
§ Other treatments for concomitant diagnoses.
CI = confidence interval.

was associated with increasing severity of malnutrition. This trend remained significant after adjusting for hydration and treatment given. Children with moderate dehydration had a significantly shorter stay than those who had severe dehydration and no dehydration. No significant associations were found between exposure variables (nutritional status, hydration status and treatments given) and mortality (Table 3).

DISCUSSION

This study shows that nutritional status has some effect on the outcome of cholera. We found that moderately and severely malnourished children stayed in hospital significantly longer than non-malnourished children. There was no association with mortality, but deaths were too few for sub-analyses by nutritional status. Our findings of CFR for all cases (0.8%) and for admitted cases (1.4%) indicate good case management for the overall under 18 population,[27] but not for the cases aged 2–4 years. The CFR of the 2010–2011 outbreak in Nigeria was 3.2%.[22]

The proportion of patients with SAM seen in our study (24%) was higher than in a similar study conducted in Yemen (8%).[19] The proportion of children with malnutrition in our CTC was higher than that found in Borno State (above 10%).[28] However, in the Yemenese study the proportion of severely dehydrated children was higher, whereas we had more moderately dehydrated children.[19]

Our study used both weight-for-height and MUAC to diagnose malnutrition, although MUAC is the recommended measurement of nutritional status for children with dehydration.[29] Nutritional status should ideally have been assessed using MUAC on admission, followed by a reassessment with weight-for-height on discharge. Also, as only patients below 5 years of age were routinely assessed for malnutrition in our study, complete and reliable data were not available for older children.

We also found that children without dehydration stayed in the CTC longer than those who were dehydrated. This is probably due to concomitant diseases, but our data does not confirm this. In contrast, patients without dehydration seem not to have been admitted in the studies conducted in Yemen and Sierra Leone.[19,30] Among the dehydrated children, we found as expected longer inpatient stay in the severely dehydrated than in the moderately dehydrated.

We could not fully adjust for the confounding effects of other diseases on mortality rate. We observed that 3 of the 4 patients who died in the final study sample received other treatments for causes that may have contributed to their deaths. The study in Yemen did not report on the presence of concomitant diagnoses in cholera patients,[19] while in Sierra Leone there was a lower proportion of children with concomitant diagnoses than in our study.[30]

Our research did not show that malnourished children had higher mortality than non-malnourished children, although we would have expected otherwise. The small number of deaths, however, in our study does not allow any association between nutritional status and clinical outcome in children with cholera to be made.

A strength of our study was the setting of a busy CTC that included all admissions during the outbreak. There were, however, some limitations. Our study only enrolled patients from one of three CTCs, and we are not sure if the study site was representative of the other two. Our study used both weight-for-height and MUAC to diagnose malnutrition, although MUAC is the recommended measurement for children with dehydration.[29] We were only able to fully analyse data for children below 5 years, as the

CTC only routinely assessed these patients for malnutrition. The inclusion of all children aged <15 years in future studies would make analyses and conclusions more robust and could be useful for clinical care as well.

CONCLUSION

We noted that there is an association between malnutrition and LOS in children with cholera, but were unable to find a clear association with deaths. The CFR for the population studied shows that the treatment might not have been adequate. We think that the routine examination of nutritional status in children in a cholera epidemic is good for clinical care, and would enable us to establish a relationship between nutrition and mortality. This would improve case management and help in attaining a CFR of <1%.

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CONTEXTE : Le choléra peut aggraver ou précipiter la malnutrition et les enfants atteints de malnutrition aiguë grave (SAM) ont une incidence plus élevée et une durée plus longue de diarrhée.
OBJECTIF : Décrire 1) les caractéristiques et les résultats du traitement d'enfants de 2–4 ans atteints de choléra, 2) le taux de mortalité de tous les enfants traités, et 3) les associations entre état nutritionnel, hydratation, traitement administré et évolution à l'hôpital.
SCHÉMA : Cohorte d'observation d'enfants admis au centre de traitement du choléra de Maiduguri, Nigeria, avec un focus sur les enfants de 2–4 ans. Les taux de létalité ont été examinés par tabulation croisée et la durée moyenne de séjour par analyse de la variance.

RÉSULTATS : Une SAM a été identifiée chez 24% des enfants de 2–4 ans. Le taux de létalité des enfants de 2–4 ans était de 1,4%. La petite taille de la population n'a pas permis d'observer d'association entre état nutritionnel et décès dû au choléra. La proportion d'enfants sortis en 48h a été de 79% et la durée la plus longue de séjour de 8 jours. En général, la durée de séjour en structure de santé augmentait avec la gravité de la malnutrition.
CONCLUSION : Notre étude a constaté que l'état nutritionnel affectait la durée de séjour mais n'a pas permis de trouver une association entre malnutrition et létalité parmi les enfants de 2–4 ans.