

Original Article

Death in severely malnourished hospitalized children presenting with diarrhea and vomiting

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Abstract

Introduction: There is lack of data on outcomes of severely malnourished children who are hospitalized with concomitant diarrhea and vomiting. We sought to evaluate outcomes of such children.

Methodology: In this retrospective chart review, we used electronic databases to evaluate children aged 0-59 months and admitted to the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh, with diarrhea and severe malnutrition between April 2011 and August 2012. Outcomes of children with and without vomiting were compared. The primary outcome was death. A probability of ≤ 0.05 was considered statistically significant.

Results: Out of 306 enrolled children, 51 (17%) had vomiting and 255 (83%) did not have vomiting. A total of 31 (10%) children died, 12 (24%) of them had vomiting and 19 (8%) did not have vomiting. Death was significantly higher in severely malnourished diarrheal children with vomiting (12/51 (24%)) compared to those without vomiting (19/255 (8%)) (Relative risk [RR] 2.73, 95% confidence interval [CI] 1.61–4.64; $p < 0.001$). We used Log linear bi-nominal regression after adjusting for potential confounders such as metabolic acidosis and hypoglycemia, and found that vomiting was significantly associated with deaths in severely malnourished diarrheal children (RR 1.89, 95% CI 1.01–1.33; $p = 0.05$).

Conclusions: Our analysis showed that children with diarrhea and severe malnutrition who had vomiting during hospitalization were at a higher risk of death compared to those without vomiting. The results underscore the importance of prompt identification and management of vomiting to reduce deaths in such children.

Key words: children; death; diarrhea; severe malnutrition; vomiting.

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Introduction

Severe acute malnutrition (SAM) is one of the leading causes of death in children under five years of age in developing countries [1]. The risk of death from any cause was 9 times higher for SAM compared to non-SAM children [2]. When children with SAM presented with concomitant diarrhea, mortality was also high [3]. Vomiting was found to be a common manifestation in children hospitalized for diarrhea [4]. Vomiting in hospitalized diarrheal children was also identified to be associated with high fatality [4]. However, when children have SAM in addition to diarrhea, the complication of vomiting is presumed to be more fatal.

Children with diarrhea and vomiting are hospitalized when their caregivers become anxious about the potential consequences of vomiting. Many of these children are reluctant to eat due to vomiting and experience hypoglycaemia, convulsion, and even death

[5]. However, to our current knowledge, no published data are available on the outcomes of children with diarrhea who are hospitalized for severe malnutrition and vomiting.

The Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) treated a number of diarrheal children with severe malnutrition [6]. Several of these children were hospitalized due to vomiting and often experienced fatal consequences. Thus, we intended to evaluate the outcomes of hospitalized severely malnourished diarrheal children with vomiting symptoms in our hospital.

Methodology*Ethical Statement*

The study (protocol number: PR-10067) was approved by the Institutional Review Board (IRB) of icddr,b. The IRB of icddr,b comprises of two bodies,

Research Review Committee and Ethical Review Committee and the study was approved by both the committees.

Study Setting

The study was performed at the Dhaka hospital of icddr,b. The Dhaka Hospital was established in 1962, mostly to meet the needs of critical patients, and specifically the children, with severe diarrheal disease. This hospital is the world's largest diarrheal treating center and treats more than 180,000 patients every year [7], free of cost. The patients come from all over Bangladesh and are mostly of low socio-economic background. The hospital has three different units to treat these patients, the short stay unit (SSU), long stay unit (LSU) and the intensive care unit (ICU). More than 90% of the patients who did not have any complication of diarrhea or any other problem were treated at the SSU and the median duration of stay there was less than 24 hours. Patients who presented at the triage with concomitant complications of diarrhea or other associated problems were admitted to LSU or ICU according to severity of the illnesses. About 8000 patients were treated in the LSU and 1200 patients were treated in the ICU in the previous each year [8]. The hospitalized patients included a higher proportion of infants and children. An estimated 40,000 lives were saved in the previous year by the hospital's clinicians' outstanding care. The hospital has pioneered numerous innovations including the oral rehydration salt (ORS) solution. It has a paperless patient record system, which has also been adopted at the Matlab Hospital of icddr,b.

Study design and participants

Relevant data between April 2011 and August 2012 were obtained from the electronic database of the Dhaka Hospital of the icddr,b. Our inclusion criteria for the study were (i) children aged 0-59 months, (ii) diarrhea, (iii) vomiting, and (iv) severe malnutrition. We excluded the children whose records had no information on vomiting. Outcomes of the study children with and without vomiting were compared. Diarrhea was defined as passage of three or more abnormally loose stools in 24 hours [9]. Severe malnutrition included the children who had SAM and severe underweight, both defined by the WHO [9].

Case management

All of our study children with and without vomiting received standard treatment following hospital guidelines that were derived from Ahmed *et al.* [3]. Standardized care was given to patients admitted to

SSU, LSU and the ICU, following hospital protocols including antibiotic therapy, supportive care such as intravenous fluids and oxygen, daily monitoring and nutritional support (breast milk, formula, solid and semisolids diets, micronutrients and zinc). SSU was the entry point of the hospital and less complicated patients with diarrhea were treated there. An attending nurse followed by a physician checked all the vital signs including the Z score of all children who visited the hospital. Children with acute diarrhea with or without dehydration but essentially without any potential complication or concomitant severe illness were treated at the SSU. Correction of dehydration was done following WHO guidelines [9]. More complicated patients such as those with persistent diarrhea, sepsis, acute respiratory illness, electrolyte imbalance and severe acute malnutrition were treated in the LSU. Mechanical ventilation was used in the treatment of children with respiratory failure admitted to the ICU. The attending ICU doctors, who maintained the medical records, carried out clinical examinations of all children and determined the management strategy. A portable pulse oximeter (OxiMax N600, Nellcor, Boulder, CO, USA) was used to measure arterial oxygen saturation (SpO₂) and blood glucose was estimated using the bedside Gluco-check system (STADA, Bad Vilbel, Germany). Children with diarrhea, sepsis, severe cholera, dysentery, severe malnutrition and other respiratory infection were treated with antibiotics. Patients with pneumonia were handled in compliance with WHO algorithm [9] and treatment for extreme protein energy malnutrition (PEM) was done in accordance with the hospital guidelines [8,10]. Oxygen therapy was given using innovative low-cost bubble continuous positive airway pressure to children with severe pneumonia and hypoxemia in the ICU [8].

Measurements

Case report forms (CRF) were developed, pretested, and finalized for relevant data collection. We mainly analyzed the outcomes of death and treatment failure. Other characteristics in our analysis included demographic information on admission (age, gender, residence, vaccinations, exclusive breast feeding, use of antibiotics at home), clinical features (duration of diarrhea, fever, difficulty in breathing, abdominal distension, hypoxemia), and laboratory parameters (hypoglycemia, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, metabolic acidosis, and metabolic alkalosis) (Table 1). Treatment failure was defined if the patient deteriorated within 24 hours of

initiation of treatment or did not improve after 48 hours of treatment.

Outcomes

The primary outcome of the study was death during hospitalization which was determined during chart analyses of our hospital data. The analyses were not pre-specified and considered exploratory. As it was not an interventional study and the participants were not prospectively assigned in this study and it was not designed to evaluate the effect of the intervention on the participants. This was not a clinical trial and thus, this study did not require to be registered in clinicaltrials.gov.

Analysis

All data were analyzed with SPSS for Windows (version 20.0; SPSS Inc, Chicago, USA) and Epi-Info (version 7.0, USD, Stone Mountain, GA, USA). These data from the icddr,b electronic database were cleaned and re-checked. Differences in proportion were compared by the Chi-square test. Student's t-test was used to compare the means of normally distributed data and Mann-Whitney test was used for comparison of data that were not normally distributed. A probability

of ≤ 0.05 was considered statistically significant. Strength of association was determined by calculating relative risks (RR) and their 95% confidence intervals (CIs). In analyzing deaths and treatment failure of diarrheal children having severe malnutrition and vomiting compared to those without vomiting, variables were initially analyzed in a bi-variate model. We also analyzed baseline characteristics between the study children with and without vomiting using the bi-variate model. Finally, we have performed multivariate log linear binomial regression analysis with the assessed variables in bi-variate model, where we considered deaths as dependent variable whereas significantly associated factors ($p = 0.05$) with deaths compared to those who survived in children with diarrhea and severe malnutrition by bi-variate analysis were considered as independent variables. This model helped us assess the true association of vomiting with deaths in children with diarrhea and severe malnutrition.

Results

During the study period a total of 1482 children were identified to have severe malnutrition. Among them 306 records had the complete information of

Table 1. Baseline characteristics of participants with diarrhea, severe malnutrition, and vomiting compared to participants without vomiting

Characteristics	Diarrheal children having vomiting n = 51 (%)	Diarrheal children without vomiting n = 255 (%)	RR	95% CI	p value
Duration of diarrhea in hours (median, IQR)	4.0 (3.0, 6.0)	4.0 (3.0, 5.0)	-	-	1.00
Age in months	8.0 (4.0, 14.0)	10.0 (5.0, 18.0)			0.240
Male Gender	32 (63)	139 (55)	1.33	0.79 – 2.24	0.279
Residence in slum area	24 (47)	114 (45)	1.08	0.66 – 1.79	0.758
Exclusively breast feeding	11 (22)	78 (31)	0.67	0.36 – 1.25	0.195
Vaccinated following EPI schedule	29 (57)	165 (65)	0.89	0.51 – 1.59	0.718
Antibiotic prior to hospitalization	4 (8)	26 (10)	0.81	0.31 – 2.11	0.797
Dehydration	20 (39)	32 (12)	3.10	1.96 – 5.07	< 0.001
Fever (≥ 38 °C)	25 (49)	143 (56)	0.79	0.48 – 1.30	0.355
Difficulty in breathing	17 (33)	95 (37)	0.87	0.51 – 1.48	0.596
Abdominal distension	10 (20)	35 (14)	1.41	0.77 – 2.62	0.278
Hypoxemia ($SpO_2 < 90\%$)	6 (12)	24 (9)	1.23	0.57 – 2.63	0.606
Hypoglycemia (RBS < 3.0 mmol/L)	3 (6)	3 (1)	3.13	1.35 – 7.25	0.027
Hypernatremia (S Sodium ≥ 150.0 mmol/L)	6 (12)	25 (10)	1.18	0.55 – 2.55	0.672
Hyponatremia (serum sodium < 130.0 mmol/L)	11 (22)	42 (17)	1.31	0.72 – 2.39	0.379
Hypokalemia (serum potassium < 3.5 mmol/L)	23 (45)	96 (38)	1.29	0.78 – 2.13	0.319
Hyperkalemia (serum potassium ≥ 5.5 mmol/L)	8 (16)	32 (13)	1.23	0.73 – 1.44	0.544
Metabolic acidosis (serum $TCO_2 < 17.0$ mmol/L)	34 (67)	128 (50)	1.78	1.04 – 3.04	0.031
Metabolic alkalosis (serum $TCO_2 > 24.0$ mmol/L)	4 (8)	28 (11)	0.73	0.28 – 1.89	0.622

Table represents n (%), unless specified. RR: relative risk. CI: confidence interval. IQR: inter-quartile range.

diarrhea and vomiting and were enrolled in the study. Among 306 enrolled children with diarrhea, 51 (17%) had vomiting and 255 (83%) did not have vomiting.

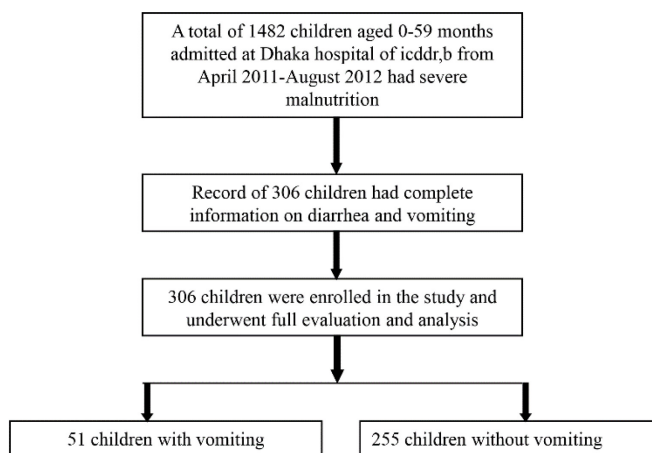
A flowchart of the study participants is shown in Figure 1. Comparison of baseline characteristics between severely malnourished diarrheal children with and without vomiting revealed that the study children with vomiting often had metabolic acidosis and hypoglycemia (Table 1). A total of 88 (29%) children experienced treatment failure, out of which 21 (41%) had vomiting and 67 (26%) did not have vomiting (Table 2). The treatment failure was significantly higher in children who had vomiting than those without vomiting (Table 2). Simultaneously, a total of 31 (10%) children died, 12 (24%) of them had vomiting and 19 (8%) did not have vomiting. Death was significantly higher in children with diarrhea and severe malnutrition along with vomiting, compared to those without vomiting (Table 2). Using log linear bi-nominal regression after adjusting for potential confounders such as metabolic acidosis and hypoglycaemia, we found that vomiting was significantly associated with deaths in severely malnourished diarrheal children (Table 3).

Discussion

To our knowledge this is the only study that evaluated the outcome of hospitalized children with diarrhea and severe malnutrition who had vomiting compared to those without vomiting. Vomiting was found to be significantly associated with death in these children even after adjusting for potential confounders.

The study children in both the groups were sick as both the groups had the co-morbidity of severe malnutrition. Children with severe malnutrition were found to be vulnerable to death [11]. However, mortality of severely malnourished children who required hospitalization for diarrhea was very high [3].

Figure 1. Participants’ flow chart.



Thus, our observation of higher treatment failure and deaths in hospitalized children with diarrhea and severe malnutrition who also had vomiting compared to those who did not have vomiting was interesting. We had already observed that our study children with vomiting often had metabolic acidosis and hypoglycemia compared to those without vomiting. Vomiting is responsible for the loss of hydrogen and chloride ions, and thereby allows the stomach to add new bicarbonate to the body leading to transient gastric alkalosis [12]. Simultaneously, vomiting in metabolic acidosis occurs as a result of compensatory mechanism reinforcing the renal response [13] and removal of gastric juice and that has been recommended as a treatment for metabolic acidosis [14]. Thus, vomiting is a physiological response in metabolic acidosis [15]. However, presence of vomiting in addition to severe malnutrition and diarrhea in these children potentially prevented them to have oral feeding at home and that contributed in developing hypoglycemia which was noticed during hospitalization. Hypoglycemia in severely malnourished children with diarrhea was often found to

Table 2. Outcomes of participants with diarrhea, severe malnutrition, and vomiting compared to participants without vomiting.

Characteristics	Total n = 306 (%)	Diarrheal children having vomiting n = 51 (%)	Diarrheal children without vomiting n = 255 (%)	RR	95% CI	p value
Treatment failure	88 (29)	21 (41)	67 (26)	1.73	1.05 – 2.86	0.032
Deaths	31 (10)	12 (24)	19 (8)	2.73	1.61 – 4.64	< 0.001

Table 3. Results of log linear bi-nominal regression to evaluate whether vomiting in children hospitalized for diarrhea and severe acute malnutrition was independently associated with deaths after adjusting for potential confounders.

Characteristics	RR	95% CI	p value
Hypoglycemia (RBS < 3.0 mmol/L)	1.03	0.74 – 2.63	0.30
Metabolic acidosis (serum TCO ₂ < 17.0 mmol/L)	2.82	1.03 – 1.18	0.005
Vomiting	1.89	1.01 – 1.33	0.05

be associated with a fatal outcome [16]. Moreover, metabolic acidosis had also been associated with deaths in diarrheal children [17].

Thus, our observation of independent association of vomiting with deaths even after adjusting for metabolic acidosis and hypoglycemia in children with diarrhea and severe malnutrition indicates that vomiting is a serious symptom of underlying pathologies. This observation is critical and has high clinical relevance in diarrheal children with severe malnutrition, especially in a resource limited setting where there is a lack of opportunity in performing laboratory investigations. Early identification of vomiting by the health professionals helps in taking decision for prompt rehydration and subsequent early referral to tertiary hospitals for further and appropriate management in order to reduce morbidity and deaths in such children especially in resource poor settings.

The main limitations of the study were the retrospective nature and small sample size which may have prevented some of our variables of interest to be significantly associated with vomiting. However, we feel that despite the limitations, the results still have the clinical relevance in resource poor settings where there is lack of opportunity to have laboratory investigations.

Conclusions

Vomiting in children under five years of age with diarrhea and severe malnutrition was associated with poor outcome. This underscores the importance of early identification of vomiting and prompt initiation of oral rehydration solution or intravenous fluid as indicated, to curb vomiting in an effort to reduce morbidity and deaths in such children especially in resource limited settings. However, further research with a larger sample may strengthen or refute our observation.

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Authors' contributions

MTF, MK, ASMSBS, KMS, MTA, IJK, and MJC conceived and designed the study. ASMSBS, KMS, and MJC were involved in the collection and cleaning of data. MTF and MJC analyzed the data. MTF, MK, ASMSBS, KMS, MTA, IJK, and MJC interpreted the data. MJC provided the conceptual advice and MTF provided the technical support. MTF, MK, ASMSBS, KMS, MTA, IJK, and MJC contributed to the manuscript. All the authors approved the final version of the manuscript. MJC supervised and approved the final draft.

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