

Original Article

Fatal outcome related risks in severely malnourished children with pneumonia in an urban critical care ward of Bangladesh

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Abstract:

Background: Fatal outcome related risks are high when children with pneumonia present with severe acute malnutrition (SAM). However, data are limited on fatality related risk factors from pneumonia in Children with SAM especially those who attended in critical care ward. We evaluated clinically identifiable risks for fatal outcome in under-five Children with SAM with pneumonia at a critical care ward in an urban hospital.

Methods: This study was of unmatched case-control design and Children with SAM of either sex, aged 0-59 months, admitted to the Intensive Care Unit (ICU) of Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) from April 2011 through July 2012 with radiological pneumonia were studied. The study children who had fatal outcome constituted the cases (n=35), and randomly selected children who survived constituted the controls (n=105).

Results: The age (months) among the cases and the controls [median (inter-quartile range)] was comparable [8.0 (4.9, 11.0) vs. 9.7 (5.0, 18.0); p=0.210]. In multivariate logistic regression analysis, after adjusting for potential confounders, such as abnormal mental status, vomiting, and systolic hypotension (<70 mm of Hg) in absence of dehydration, severely malnourished under-five children with pneumonia having fatal outcome more often had hypoxemia (OR=23.15, 95% CI=4.38-122.42), dehydrating (some/severe) diarrhea (OR=9.48, 95% CI=2.42-37.19), abdominal distension at admission (OR=4.41, 95% CI=1.12-16.52), and received blood transfusion (OR=5.50, 95% CI=1.21-24.99) for the management of crystalloid resistant systolic hypotension.

Conclusion: The results of our data revealed hypoxemia, clinical dehydration, and abdominal distension as the independent risk factors for fatal outcome in Children with SAM with pneumonia. Severely malnourished children with pneumonia who required blood transfusion for the management of crystalloid resistant systolic hypotension were also at risk of fatal outcome. Thus, early identification and prompt management of these simple clinically recognizable risk factors for fatal outcome and avoiding the use of blood transfusion for the management of crystalloid resistant systolic hypotension may help reduce death in such population.

Key Words: Bangladesh; children; hypoxemia; pneumonia; severe acute malnutrition

Introduction

Pneumonia still remains as the leading cause of global under-five childhood fatality,^{1,2} representing an estimated 1.4 million out of the total 7.6 million deaths in this

population in 2010.³ The risk of fatal outcome is high when children with pneumonia have the co-morbidity of severe acute malnutrition (SAM)^{4,5} and fatality could be as high as 15 times compared to those who did not have SAM.⁶ Most

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of these pneumonia and diarrhea related fatal outcome in Children with SAM occur in the critical care wards of developing countries.⁴ However, clinical features of pneumonia in severely malnourished children often remain subtle.^{6,7} As a consequences, health professionals, particularly in resource poor settings may be less confident in identifying clinical features for the diagnosis of pneumonia in such children and if the Children with SAM do not have any complication, they potentially offer only oral antibiotics following recent WHO recommendations.⁸ The bacterial pathogens causing pneumonia in severely malnourished children are frequently different than those in better-nourished children.^{6,9,10} Therefore, the delicate clinical signs and diverse etiology of pneumonia in Children with SAM may require first dose of parenteral antibiotics before their referral to tertiary hospitals with the objectives to reduce fatal outcome. However, this management approach might not be feasible at every health care facility in resource limited settings due to lack of fund. Thus, identification of simple clinical features for fatal outcome in severely malnourished children with pneumonia may demonstrate very valuable to health professionals, particularly health workers in making referral decisions. However, data are insufficient on risk factors for fatal outcome in such children. From this perspective, we sought to identify simple clinically recognizable risk factors for fatal outcome in hospitalized, under-five severely malnourished children with pneumonia.

Materials and Methods

Ethics statement

The study was approved by the Research Review Committee (RRC) and the Ethical Review Committee (ERC) of International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b). A written informed consent was obtained from parents/caregivers of all participating children. Children whose parents/caregivers did not provide consent were not included in the study.

Study design

This was an unmatched case control study which was conducted at the Dhaka Hospital of icddr,b. Severely malnourished children of either sex, aged 0-59 months, admitted to the Intensive Care Unit (ICU) of the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) during April 2011 to July 2012 with radiological pneumonia were eligible. Children with SAM with pneumonia who had fatal outcome constituted the cases, and Children with SAM with pneumonia who survived constituted controls. Controls were randomly selected by computer randomization using SPSS (version 17.0; SPSS Inc, Chicago) from a personal computerized data source of this study. This database identified 370 controls, and 1:3 unmatched case-control ratios were used to increase the statistical power of our

analyses. Pneumonia was defined radiologically as the presence of end-point consolidation or other (non-end-point) infiltrate in lungs according to the WHO radiological classification of pneumonia¹¹ and the finding was confirmed independently by a qualified radiologist (FBM) and a pediatric respiratory physician (MJC). When there was any disagreement on radiological classification of pneumonia we did not include them in our study. Children with severe wasting [weight for height z score (WHZ) < -3 of the median of the WHO anthropometry] or severe under-nutrition [weight for age z score (WAZ) < -4 of the median of the WHO anthropometry], or nutritional edema were considered as SAM.

Setting

The Dhaka Hospital of icddr,b provides care and treatment to around 140,000 per annum patients of all ages and either sex with diarrhea, with or without associated complications or health problems. Diarrhea and/or acute respiratory infection (ARI) are the entry points for admission to the Dhaka Hospital of icddr,b. Children with complications of diarrhea, or those with respiratory distress, cyanosis, apnea, hypothermia, sepsis, shock, impaired consciousness, convulsion, severe/very severe pneumonia with hypoxemia or respiratory failure are admitted to the ICU of the hospital. The vast majorities of the patients visiting the hospital have poor socio-economic backgrounds and most live in urban and peri-urban Dhaka.

Patient management

Patients admitted to the ICU receive standardized care and treatment, following hospital guidelines that include antibiotic therapy, supportive care such as intravenous fluids and oxygen, frequent monitoring, and nutritional support (breast milk, formula, solid and semisolid diets, micronutrients, and zinc). Mechanical ventilation is used for management of children admitted to ICU with respiratory failure. All children in the study were assessed by the regular ICU physicians, who recorded medical history, performed clinical examinations, and determined management plan. Arterial oxygen saturation (SpO₂) was measured using a portable pulse oximeter (OxiMax N-600, Nellcor, Boulder, CO) and blood glucose was estimated using a bedside Gluco-check machine (STADA, Bad Vilbel, Germany).

Children with hypoxemia received O₂ supplementation through nasal prongs (2L/min) or mask (5L/min). Antibiotics were prescribed for children with pneumonia, sepsis, severe cholera, dysentery and other bacterial infections. Dehydration was corrected using ORS solution, orally or through NG tube, or appropriate intravenous fluid when dehydration was severe or when children had severe respiratory distress. Pneumonia was managed according to the WHO algorithm¹⁹ and management of severe

protein-energy malnutrition (PEM) was done following the hospital guidelines.^{12,13}

Measurements

Case report forms (CRF) were developed, pretested, and finalized for acquisition of study relevant data. We analyzed admission characteristics at ICU of the Dhaka Hospital of icddr, which included demographic information (age, gender, residence, socio-economic status, working mother, lack of vaccinations, non-breast-feeding), clinical signs {AWD, vomiting, dehydration (defined by "Dhaka methods" of assessment of dehydration that is almost similar to WHO method and approved by WHO¹⁴), nutritional edema, WHZ and WAZ, abnormal mental status (irritable / lethargy / convulsion), abdominal distension, hypoxemia [arterial oxygen saturation (SPO₂) <90% in air⁸], systolic hypotension (<70 mm of Hg), refractory/crystalloid resistant systolic hypotension [unresponsive to crystalloid, i.e. unresponsive to 20ml per kg per hour physiological saline (sodium: 154 mMol/L and chloride: 154 mMol/L) or cholera saline (sodium: 133 mMol/L, potassium: 13 mMol/L, chloride: 98 mMol/L, acetate: 48 mMol/L)⁵ (maximum 40 ml over 2 hours)], heart failure (defined as tachypnea, tachycardia, enlarged tender liver, gallop, basal rales, non-pitting edema)}, blood transfusion, hypoglycemia and hematocrit (Hct%).

Analysis

All data were entered into SPSS for Windows (version 15.0; SPSS Inc, Chicago) and Epi-Info (version 6.0, USD, Stone Mountain, GA). Differences in proportions 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 less than 0.05 was considered statistically significant. Strength of association was determined by calculating odds ratio (OR) and their 95% confidence intervals (CIs). In identifying risks of death in children with SAM and pneumonia, variables were initially analyzed in a uni-variate model, and then predictors independently associated with deaths were identified using logistic regression after controlling for the co-variables.

Results

We were able to identify 35 cases and 105 controls. Cases more often had abnormal mental status, vomiting, and systolic hypotension compared to the controls (Table 1).

Table 1. Admission features in severely malnourished children with pneumonia with (cases) and without fatal outcome (controls)

Characteristic	Cases (n= 35)	Controls (n= 105)	OR	95% CI	p
Male sex	23 (66)	62 (59)	1.33	0.56 - 3.19	0.617
Age in months (median, IQR)	8.0 (4.9, 11.0)	9.7 (5.0, 18.0)	-	-	0.210
Non-breastfed (up to 6 months of age)	5 (14)	17 (16)	0.86	0.25 - 2.78	1.00
Acute Watery Diarrhea	31 (89)	82 (78)	2.17	0.64 - 8.10	0.266
Children with vomiting	12 (34)	15 (14)	3.13	1.18 - 8.32	0.019
Clinical dehydration (some/severe)	16 (46)	9 (9)	8.98	3.16 - 26.16	<0.001
Nutritional edema	5 (14)	5 (5)	3.33	0.77 - 14.50	0.121
weight for height z score (mean ± SD)	-3.75 ± 1.83	-3.73 ± 1.37	-0.02*	-1.28 - 0.06	0.943
weight for age z score (mean ± SD)	-5.58 ± 1.69	-4.98 ± 1.74	-0.61*	-0.60 - 0.56	0.073
Abnormal mental status	19 (54)	12 (11)	9.20	3.45 - 25.06	<0.001
Abdominal distension	10 (29)	10 (10)	3.80	1.29 - 11.30	0.012
Presence of hypoxemia	14 (40)	3 (3)	22.67	5.39 - 110.01	<0.001
Systolic hypotension (<70 mm of Hg) after correction of dehydration or in absence of dehydration	6 (18)	4 (4)	5.61	1.28 - 25.90	0.012
Hypoglycemia (random blood sugar <3.0mmol/L) on admission	2 (6)	1 (1)	6.30	0.43 - 181.82	0.154
Blood transfusion done for management of refractory systolic hypotension (<70 mm of Hg even after 40 ml/kg bolus fluid)	11 (31)	5 (5)	9.17	2.61 - 33.92	<0.001
Heart failure	1 (3)	3 (3)	1.0	(0.18 - 5.60)	1.00

Figures represent n (%), unless specified. OR: odds ratio. CI: confidence interval. IQR: inter-quartile range. SD: standard deviation. SpO₂: transcutaneously measured blood oxygen concentration; *: mean difference

Cases more often presented with lower Hct% on admission compared to controls (27.7±6.1 vs. 31.5±6.1; p<0.001), but admission Hct% of the children who received blood transfusion was comparable among the cases and the controls (26.3±6.6 vs. 20.8±8.4; p=0.176). In multivariate logistic regression analysis, after adjusting for potential

confounders, such as abnormal mental status, vomiting, and systolic hypotension, under-five severely malnourished children with pneumonia more often had hypoxemia, dehydrating (some/severe) diarrhea, and abdominal distension at admission, and received blood transfusion (Table 2).

Table 2. Multiple logistic regression analysis to disclose the fatal outcome related independent risks in severely malnourished children with pneumonia

Characteristics	OR	95% CI	p
Abnormal mental status	1.84	0.45 - 7.60	0.400
Children with vomiting	1.09	0.25 - 4.74	0.912
Clinical dehydration (some/severe)	9.48	2.42 - 37.19	0.001
Abdominal distension	4.41	1.12 - 16.52	0.028
Presence of hypoxemia	23.15	4.38 - 122.42	<0.001
Systolic hypotension (<70 mm of Hg) after correction of dehydration or in absence of dehydration	1.50	0.17 - 13.59	0.721
Blood transfusion used for the management of refractory systolic hypotension (<70 mm of Hg)	5.50	1.21 - 24.99	0.027

Other parameters those were compared among the cases and the controls showed comparable results (Table 1).

Discussion

Our observation of blood transfusion used for the management of crystalloid resistant systolic hypotension revealed as the independent predictor for death in under-five Children with SAM with pneumonia which is very important information for clinicians in critical care wards of developing countries. World Health Organization (WHO) recommends blood transfusion in severely malnourished children who do not recover from septic shock by consecutive two boluses of isotonic fluid.⁸ The protocolized management of such children in our hospital followed this recommendation.¹³ Systolic hypotension, in addition to features of sepsis (endorsed by our local evidence),^{15,16} are used as the marker of septic shock in Children with SAM, especially in resource limited settings. Children with systolic hypotension and unresponsive to crystalloid received blood transfusion but did not receive diuretics and more often had fatal outcome. We do not have any ready explanation for this finding. All our study children received blood transfusion due to septic shock refractive to fluid therapy, which might be due to septic myocardial dysfunction characterized by decrease in ejection fraction with dilatation of ventricles.¹⁷⁻¹⁹ Death in this special population is often very high even with adequate treatment not only in developing countries¹⁶ but also in developed countries.²⁰ However, the impact of blood transfusion on deterioration in heart function in Children with SAM is unclear to us. Recent data suggest that reduction of alveolar epithelial sodium and chloride transport in pneumonic

Children with SAM impedes clearance of fluid from the alveolar exudates.^{21,22} This may contribute to development of interstitial edema/heart failure in our study children who received blood transfusion in addition to receiving crystalloid fluids. However, clinical evidence of fluid overload/ heart failure was not different among the cases and controls. Thus, pulmonary edema, a common etiology for death in pneumonic children with SAM,²³ might not be responsible for the detrimental effect of blood transfusion in our study population. Although an earlier study conducted in Mulago hospital, Uganda had experienced significant higher deaths after blood transfusion related pulmonary edema in Children with SAM compared to those who did not receive blood transfusion, most of the indications of blood transfusions in that study were other than septic shock and often the use of blood transfusion was not judicious.²⁴ We did not evaluate the cardiac function of these children to exclude fluid overload as a consequence of blood transfusion. A recent study has reported cardiovascular collapse rather than fluid overload to contribute to excess death from rapid fluid resuscitation in well nourished children with septic shock;²⁵ however, cardiac function in Children with SAM with septic shock has not been explored yet, which needs to be addressed in carefully conducted patho-physiological studies in future.

Although, admission Hct% was significantly lower in fatal cases than the survivors, Hct% of the children who received blood transfusion was comparable among the fatal cases and the survivors which indicate that Hct% might not have any impact on case-fatality among the children who received blood transfusion.

Systolic hypotension after adequate rehydration along with replacement of ongoing fluid losses is likely to be secondary to impaired vaso-regulation and cardiac function as a result of sepsis and is often associated with death,^{26,27} which is similar to our earlier observations.^{16,28} This event was significantly associated with deaths in univariate analysis (Chi-square test) but after adjusting the potential confounders in logistic regression it failed to remain as an independent predictor for death in under-five Children with SAM with pneumonia, but blood transfusion remained as one of the independent predictors for death in such children indicating the strong association of blood transfusion with deaths, although it seems like blood transfusion is a proxy for late treatment of systolic hypotension and it would be more important for quick recognition and intervention for symptoms of shock.

Our observation of strong association between admission hypoxemia, clinical dehydration (some/severe), and abdominal distension in pneumonic under-five SAM and fatal outcome are understandable. In pneumonic children, hypoxemia may occur as a consequence of impairment of alveolar-arterial oxygen diffusion and concomitant increase in the partial pressure of carbon-dioxide (CO₂) due to abnormally lower alveolar ventilation.^{20,30} This phenomenon in Children with SAM with pneumonia represents very severe illness often with fatal outcome. The association of hypoxemia and death has been reported by a number of earlier studies without describing nutritional status of the children.^{31,32} Abdominal distension is one of the common consequences of severe form of sepsis³³ due to compromised splanchnic circulation, often leading to paralytic ileus and death.^{34,35} Clinical dehydration is also associated with poor peripheral circulation,³⁶ which might aggravate myocardial dysfunction in the septic Children with SAM with fatal outcome.

The observation of indifference distribution of baseline characteristics on admission such as age, WAZ, WHZ, sex, residence, socio-economic status, working mother, lack of vaccinations, non-breast-feeding, AWD, nutritional edema, and bedside hypoglycemia potentially eliminates the chances of biasness of selection of controls and thus validate the study results.

In summary, under-five severely malnourished children with pneumonia having admission hypoxemia, clinical dehydration, abdominal distension, and those who require blood transfusion for the management of crystalloid resistant systolic hypotension during the course of hospitalized treatment are at higher risk of fatal outcome. Thus, identification of these simple, clinically recognizable features in such children may make vigilant health professionals, especially health workers to administer the first dose of parental broad spectrum antibiotics before their

referral to the critical care medicine words. The clinicians in the critical care ward should be cautious in using blood transfusion for the management of crystalloid resistant systolic hypotension in an effort to reduce morbidity and deaths in such population, especially in resource limited settings.

Acknowledgement

We would like to express our sincere thanks to study physicians as well as all clinical fellows, nurses, members of feeding team and cleaners of the hospital for their invaluable support and contribution during patient enrollment and data collection. We would also like to express our sincere thanks to care givers/parents for proving consent for the enrolment of their children in the study.

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