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Risk Factors and Gender Differentials for Death among Children Hospitalized with Diarrhoea in Bangladesh

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ABSTRACT

To identify risk factors for death among children with diarrhoea, a cohort of 496 children, aged less than 5 years, admitted to the intensive care unit of a diarrhoeal disease hospital in Bangladesh, was studied during November 1992-June 1994. Clinical and laboratory records of children who died and of those who recovered in the hospital were compared. Deaths were significantly higher among those who had altered consciousness, hypoglycaemia, septicaemia, paralytic ileus, toxic colitis, necrotizing enterocolitis, haemolytic-uraemic syndrome, invasive or persistent diarrhoea, dehydration, electrolyte imbalances, and malnutrition. Females experienced a 2-fold higher risk of death than males (p=0.003). Several indices of severe infections were identified more frequently among females than males. Females with severe infections were less frequently brought to the hospital than their male counterparts. The time lapse between onset of symptoms and hospital admission was significantly higher in females than males. This study suggests initiation of programmes to alleviate social disparity between genders for healthcare in poor communities. The study-results may also help physicians identify either prognostic indicators or risk factors for death among children hospitalized with severe illnesses associated with diarrhoea.

Key words: Diarrhoea; Diarrhoea, Infantile; Infant mortality; Child mortality; Gender issues; Risk factors

INTRODUCTION

Diarrhoeal diseases are a leading cause of childhood morbidity and mortality, specially in developing countries (1). About 4 million children, aged less than 5 years, die due to diarrhoea annually (1). Although dehydration is still the leading cause of death in diarrhoeal patients, several other complications, including septicaemia, pneumonia, electrolyte imbalances, and malnutrition, have been identified as important risk factors of death in hospitalized patients with diarrhoea in Bangladesh (2-6). In this country, the risk of death is nearly 30% among children who are admitted to the intensive care unit (ICU) because of complications associated with diarrhoea, whereas the death rate in hospitalized children with uncomplicated diarrhoea is less than 1% (3). In Bangladesh, there is a paucity of research examining the factors associated with death among children who are admitted to the ICU with complications of diarrhoea. Furthermore, community-based studies raised a concern that females die more often than males in Bangladesh and in other developing countries (7,8). These studies have not been supported by sufficient clinical data.

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The present study was carried out to identify possible risk factors for death among a cohort of very sick children who were admitted to the ICU with complications associated with diarrhoea in Bangladesh, and to examine gender differences for the risks.

METHODS AND MATERIALS

The study was conducted at the Clinical Research and Service Centre of ICDDR,B: Centre for Health and Population Research during November 1992-June 1994. Children, aged less than 5 years, admitted to the ICU of the hospital, were eligible. Patients with systemic diseases or complications, in addition to diarrhoea, were admitted to an in-patient unit. Those with clinical evidence of serious complications, including shock, respiratory distress, convulsions, hypoglycaemia, altered consciousness, septicaemia, meningitis, and renal failure were admitted to the ICU. Patients were discharged from the ICU based on the physician's assessment of clinical improvement and followed in an in-patient unit until recovery. Clinical and laboratory records of all children were analyzed retrospectively. Children referred to another hospital and those released from the hospital against doctor's advice were excluded from the study, since their outcome could not be ascertained. The study was approved by the Ethical Review Committee of ICDDR,B.

Diarrhoea and severity of dehydration were defined according to the World Health Organization-recommended criteria (1). Stool cultures were done for *Vibrio cholerae*, *Salmonellae*, and *Shigellae* using standard methods (9). Blood cultures were performed in subjects who were clinically suspected to have septicaemia. Patients with lethargy, convulsions, or low pulse volume not attributable to dehydration were measured for their blood glucose using a bedside instrument (Reflolux®, Mannheim Boehringer, Germany). The children had their nude body weight measured to the nearest 0.01 kg using a baby scale (model 727; Seca Corporation, Columbia, MD). Weight-for-age percentages and z-scores were determined and compared using the National Center for Health Statistics standards (10,11).

The following case definitions were used: watery diarrhoea–3 or more watery or liquid stools in 24 hours; invasive diarrhoea–stools having visible blood or mucus; persistent diarrhoea–diarrhoea lasting for more than 14 days; hypoglycaemia–a blood glucose of <3 µmol/L; hyponatraemia–blood sodium £130 µmol/L; hypernatraemia–blood sodium >150 µmol/L; hypokalaemia–blood potassium <3.5 µmol/L; hyperkalaemia–blood potassium >5.5 µmol/L; acidosis–blood bicarbonate <18 µmol/L; alkalosis–blood bicarbonate >24 µmol/L; high serum creatinine– >62 µmol/L (>0.7 mg/dL); acute otitis media–infection of the middle ear, having clinical evidence of otalgia, fever, with/without ear discharge, and evidence of fluid in the middle ear and congestion of the tympanic membrane; toxic colitis–systemic toxicity, fever, tachycardia, abdominal distension, leukocytosis, and colonic dilatation by radiology; necrotizing enterocolitis–abdominal distension, retention of food with ileus, and rectal bleeding; haemolytic-uraemic syndrome–haemolytic anaemia, thrombocytopenia, and renal failure (12).

Data analysis

Data were analyzed using SPSS Windows version 10.0 (SPSS Inc., Chicago, Illinois). Continuous variables were compared using Student's *t*-test or Mann-Whitney test depending on the distribution of data. Categorical variables were compared using chi-square test and Mantel-Haenszel stratified analysis. The Fisher exact 2-tailed test was done for those categories having insufficient numbers. Multivariate logistic regression was done for prediction analysis of outcome among the study subjects. Probability levels of <0.05 were considered to be statistically significant.

RESULTS

In total, 559 patients (354 males and 205 females) were admitted to the ICU of the hospital with a history of diarrhoea; of them, 496 (89%) were aged less than 5 years. Thirty children were excluded, since their outcome could not be ascertained as they were either referred to another hospital (n=10) or parents had their children taken home against doctor's advice (n=20). Of the 466 children included, 199 died and 267 recovered.

Males were admitted at a higher proportion than females to the ICU (64% vs 36%). However, females had about 2 times higher odds of dying than males (p=0.003) (Table 1). The severity of malnutrition was significantly greater among those who died than those who recovered (p<0.001). Some other significant risk factors for death were: incomplete or no immunization (p=0.003), symptoms of rapid breathing at admission (p=0.004), and acute otitis media (p=0.039). The children who died presented with either invasive or persistent diarrhoea significantly more often than did those who recovered (p=0.002). However, the children who died had fewer isolates of *V. cholerae* (0.6% vs 5%, p=0.018) compared to those who survived. The presence of moderate or severe dehydration, irrespective of the type of diarrhoea, was about 3 times as common as among those who died than those who recovered (p<0.001). Several other clinical presentations predicted significantly a fatal outcome: altered consciousness (lethargy, semiconscious, or unconscious) (p<0.001); hypoglycaemia (p<0.001); septicaemia (p<0.001); paralytic ileus (p=0.05); toxic colitis (p<0.001); necrotizing enterocolitis (p<0.001); bleeding

Table 1. Clinical presentations and complications among children who died and those who survived

Features	Children who died	Children who survived	Odds ratio	95% CI for mean difference	p value
Age (months)[a]	5 (2,6) (n=199)	4 (1,6) (n=267)	-	-0.2, 1.1	0.08[b]
Female	88/199 (44%)	82/267 (31%)	1.8	1.2, 2.7	0.003[c]
Weight-for-age z-score[d]	-3.75±1.11 (n=181)	-3.00±1.35 (n=260)	-	-1.0, -0.5	<0.001[e]
Incomplete or no immunization	115/126 (91%)	132/168 (79%)	2.9	1.3, 6.3	0.003[c]
Rectal temperature (℃)[d]	37.5±1.3 (n=195)	37.8±1.4 (n=264)	-	-0.5, 0.1	0.06[e]
Respiration per minute[d]	46±13 (n=193)	43±11 (n=261)	-	1.0, 5.5	0.004[e]
Acute otitis media	34/197 (17%)	25/239 (10%)	1.8	1.0, 3.2	0.039[c]
Invasive or persistent diarrhoea	91/195 (47%)	86/267 (32%)	1.8	1.2, 2.8	0.002[c]
Cholera	1/156 (0.6%)	13/264 (5%)	0.1	0.1, 0.9	0.018[c]
Altered consciousness	137/183 (75%)	129/256 (50%)	2.9	1.9, 4.5	<0.001[c]
Hypoglycaemia	115/179 (64%)	31/266 (12%)	13.6	8.2, 22.8	<0.001[c]
Septicaemia	183/185 (99%)	242/266 (91%)	9.1	2.0, 56.3	<0.001[c]

CI=Confidence interval; [a] Median (quartile); [b] Mann-Whitney test; [c] Mantel-Haenszel stratified analysis; [d] Mean±SD; [e] Student's *t*-test

manifestations, including skin purpura or gastric bleeding (p=0.05); and presence of haemolytic-uraemic syndrome (p=0.05). Past history of measles and xerophthalmia were not found as risk factors for death.

Table 2 shows the laboratory features that were more common among the children who died. These included low haematocrit (p=0.03); thrombocytopenia (p<0.001); polymorphoneuclear leukocytosis (p=0.02); presence of bands in peripheral blood counts (p=0.01); hyponatraemia (p=0.002); acidosis (p<0.001); uraemia (p<0.001); and features of invasive diarrhoea (pus cells >20 per high power field, p=0.03; and RBC in stool microscopy, p=0.002).

Since females died more frequently than males, attempts were made to identify risk factors for death by gender (Table 3). Girls more commonly presented features of severe infections, including higher body temperatures (p=0.01); faster respirations (p=0.04); and increased polymorphs in peripheral blood counts (p<0.001) compared to boys. The girls also showed any electrolyte imbalance (p=0.05), hypoglycaemia (p=0.004), and stool pus cells >20 per high power field (p=0.03) significantly more often than did the boys. The time lapse between onset of symptoms and hospital admission was significantly higher in girls than boys (p<0.001).

In multiple logistic regression analysis, the significant predictors of death in all children were: younger age (p=0.043), lower weight-for-age z-score (p<0.001), faster respiration (p=0.041), increased total counts of white blood cells in peripheral blood (p=0.031), presence of septicaemia (p<0.001), and presence of hypoglycaemia (p<0.001). Deaths in females were significantly predicted by the time lapse between onset of symptoms and hospitalization (p<0.001) and higher body temperatures (p=0.038) than males.

DISCUSSION

In this study, the predominant risk factors associated with death in hospital children in Bangladesh were: female gender, incomplete or no immunization, malnutrition, electrolyte imbalances, septicaemia, invasive or persistent diarrhoea, increased polymorphs in blood count, and hypoglycaemia.

Some risk factors, including severe dehydration, malnutrition, electrolyte imbalances, and septicaemia,

Table 2. Laboratory features among children who died and those who survived

Features	Children who died	Children who survived	Odds ratio	95% CI for mean difference	p value
Haematocrit (%)[a]	32.5±6.5 (n=178)	34.0±7.0 (n=251)	-	-2.8, -0.2	0.03[b]
Platelet[a]x1000/mm^3	103.3±52.6 (n=36)	182.1±85.8 (n=22)	-	-115.1, -42.5	<0.001[b]
WBC[a]x1000/mm^3	14.9±8.5 (n=161)	16.2±7.3 (n=234)	-	-2.9, 0.3	0.11[b]
Polymorph (%)[c]	52 (36,68) (n=178)	46 (29,62) (n=251)	-	0.8, 8.4	0.02[d]
Leukaemoid reaction	8/152 (5%)	7/266 (3%)	2.1	0.7, 6.4	0.16[e]
Hyponatraemia	81/179 (45%)	63/212 (30%)	2.0	1.3, 3.0	0.002[e]
Hypernatraemia	17/179 (9%)	20/212 (9%)	1.0	0.5, 2.1	0.98[e]
Hypokalaemia	84/179 (47%)	91/211 (43%)	1.2	0.8, 1.8	0.45[e]
Hyperkalaemia	34/179 (19%)	29/211 (14%)	1.5	0.8, 2.6	0.16[e]
Acidosis	141/170 (83%)	137/204 (67%)	2.4	1.4, 4.0	<0.001[e]
Alkalosis	5/170 (3%)	10/204 (5)	0.6	0.2, 1.9	0.34[e]
High serum creatinine	52/88 (59%)	13/66 (20%)	5.9	2.7, 13.3	<0.001[e]
Presence of RBC in stool	77/129 (60%)	76/183 (42%)	2.1	1.3, 3.4	0.002[e]
Stool pus cells >20 per high power field	48/129 (37%)	47/183 (26%)	1.7	1.0, 2.9	0.03[e]

CI=Confidence interval; [a] Mean±SD; [b] Student's *t*-test; [c] Median (quartile); [d] Mann-Whitney analysis; [e] Mantel-Haenszel stratified analysis

identified in this study were consistent with previous findings in this population (5). Our study also confirmed the earlier autopsy results of septicaemia, hypoglycaemia, and hypokalaemia as being the immediate causes of death (2). Over 90% of our children admitted to the ICU were clinically diagnosed as having septicaemia, although a previous report showed that only 12% of blood cultures grew organisms (4). The predominant organisms identified from blood cultures were *Salmonella typhi, Escherichia coli, Streptococcus pneumoniae, Pseudomonas aeruginosa, Acinatobacter, Klebsiella,* and *Shigella* spp.

In their study, which included only 4% of all children attending the hospital, Teka *et al*. have shown that lack of breast-feeding, severe malnutrition, xerophthalmia, dehydration, a longer duration of illness, a recent history of measles, maternal illiteracy, and low income were the significant predictors of death (6). Islam and Shahid (13) showed an increased case fatality in patients with *Shigella* and *V. cholerae* non-O1. A community-based verbal-autopsy study (14) found pneumonia and diarrhoea as the leading causes of death among children aged less than 5 years. Lack of early intervention and an inappropriate choice of antimicrobials by community practitioners may be possible reasons of higher deaths due to diarrhoea and pneumonia in children in the community (15). Although recent progress in the case management of hospital patients has been contributing to reduce the number of deaths due to diarrhoeal diseases, case fatality is still high due to complications of invasive diarrhoea (16,17). In our present study, we found an inverse association of death with watery diarrhoea due to *V. cholerae*, but a direct relationship of death in children with invasive stool pictures is suggestive of shigellosis.

Biologically, females have a greater chance of survival than males (18). However, cross-cultural studies of gender-specific mortality indicated that females experience their greatest mortality in populations with low life-expectancy, whereas males experience their greatest mortality in industrialized societies (18). Excess female deaths, observed in our study, are consistent with previous community-based studies in Bangladesh (14,19,20). The gap in knowledge is that the community-based studies failed to demonstrate any gender difference in severity of illness, probably because these studies did not include clinical details of complications and causes of death. Our study found clinical characteristics that were associated with an increased risk of death in Bangladeshi girls. These risk factors included increased body temperatures, faster respirations, polymorpho-neuclear leukocytosis, electrolyte imbalances, hypoglycaemia, and invasive stool pictures. Also, girls had a significant delay in intervention for their illnesses

Table 3. Gender distribution of selected risk factors for death

Features	Girls	Boys	Odds ratio	95% CI for mean difference	p value
Age (months)[a]	4 (2,6) (n=177)	5 (1,6) (n=309)	-	-0.6, 0.7	0.81[b]
Weight-for-age z-score	-3.4±1.3 (n=169)	-3.3±1.4 (n=288)	-	-0.4, 0.1	0.22[c]
Rectal temperature (°C)	37.9±1.5 (n=176)	37.6±1.5 (n=301)	-	0.1, 0.6	0.01[c]
Respiration per minute	46.1±13.0 (n=173)	43.7±11.4 (n=301)	-	-0.1, 0.5	0.04[c]
Polymorph (%)[a]	55 (38,68) (n=166)	45 (30,62) (n=286)	-	0.1, 4.7	<0.001[b]
Septicaemia	154/162 (95%)	267/285 (94%)	1.3	0.5, 3.3	0.55[d]
Any electrolyte imbalance	128/171 (75%)	198/300 (66%)	1.5	1.0, 2.4	0.05[d]
Hypoglycaemia	69/171 (40%)	81/294 (28%)	1.8	1.2, 2.7	0.004[d]
Presence of RBC in stool	68/124 (55%)	89/197 (45%)	1.5	0.9, 2.4	0.09[d]
Stool pus cells >20 per high power field	46/124 (37%)	51/197 (26%)	1.7	1.0, 2.8	0.03[d]
Time (day) between onset of symptoms and hospitalization	4.2±1.2 (n=166)	2.5±0.9 (n=296)	-	1.5, 1.9	<0.001[c]

CI=Confidence interval; [a] Median (quartile); [b] Mann-Whitney analysis; [c] Student's *t*-test; [d] Mantel-Haenszel stratified analysis

than boys, which indicates a social disparity and gender bias for healthcare.

One limitation of our study is that the rate of hospital admission between boys and girls is likely to suffer from a systematic selection bias, i.e. parents' gender bias in bringing sick male children to the hospital in preference to females. The overall visits of female patients in this hospital were lower than males (43% vs 57%), as found in our previous study (3). In this study, female children with severe illness were also brought less frequently to the hospital compared to male children, as shown by the proportion of females and males admitted to the ICU (37% vs 63%).

In this population, Butler *et al*. (21) showed a significantly higher number of autopsies performed on females than males (c^2=9.0, p<0.05). Among patients with typhoid fever, females had a higher case-fatality rate (6%) than males (3%), although the difference was not statistically significant (21). The results of our study are consistent with the previous findings of an increased death of female children associated with septicaemia due to *S. typhi*.

Community-based studies in Bangladesh demonstrated male preference for better healthcare and better share of foods in the family (19,20). Despite the known biological strength of the female children, chronic neglect of a girl child at home may still make her more vulnerable to severe illness through malnutrition (16,22). A linear association between higher malnutrition and increased death among female children was demonstrated in a recent community-based study in Bangladesh (14). Our study subjects were severely malnourished, but there was no statistical difference of nutritional status by gender. It is likely that the female children developed more severe infections and died more frequently than their male counterparts as a result of delayed initiation of care and prolonged illnesses before admission.

In conclusion, the results of this study may be useful as a prognostic guide for children who are admitted with severe infections complicating diarrhoea. Health-intervention programmes should be aimed at reducing the disparity between genders for healthcare in developing countries.

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