J HEALTH POPUL NUTR 2005 Sep;23(3):259-265 © 2005 ICDDR,B: Centre for Health and Population Research
ISSN 1606-0997 $ 5.00+0.20

Risk Factors for Mortality Due to Shigellosis: A Case-Control Study among Severely-malnourished Children in Bangladesh

J.M. van den Broek[1], S.K. Roy[2], W.A. Khan[2], G. Ara[2], B. Chakraborty[2], S. Islam[2], and B. Banu[2]

[1]Academical Medical Centre, University of Amsterdam, The Netherlands, and [2]ICDDR,B: Centre for Health and Population Research, GPO Box 128, Dhaka 1000, Bangladesh

ABSTRACT

To determine the risk factors for death of severely-malnourished Bangladeshi children with shigellosis, a case-control study was conducted at the Clinical Research and Service Centre of ICDDR,B: Centre for Health and Population Research in Dhaka, Bangladesh. One hundred severely-malnourished children (weight-for-age <60% of median of the National Center for Health Statistics), with a positive stool culture for *Shigella dysenteriae* type 1 or *S. flexneri*, who died during hospitalization, were compared with another 100 similar children (weight-for-age <60% and with *S. dysenteriae* type 1 or *S. flexneri*-associated infection) discharged alive. Children aged less than four years were admitted during December 1993−January 1999. The median age of the cases who died or recovered was 9 months and 12 months respectively. Bronchopneumonia, abdominal distension, absent or sluggish bowel sound, clinical anaemia, altered consciousness, hypothermia, clinical sepsis, low or imperceptible pulse, dehydration, hypoglycaemia, high creatinine, and hyperkalaemia were all significantly more frequent in cases than in controls. In multivariate regression analysis, altered consciousness (odds ratio [OR]=2.6, 95% confidence interval [CI] 1.0-6.8), hypoglycaemia (blood glucose <3 mmol/L (OR=7.8, 95% CI 2.9-19.6), hypothermia (temperature <36 °C) (OR=5.7, 95% CI 1.5-22.1), and bronchopneumonia (OR=2.5, 95% CI 1.1-5.5) were identified as significant risk factors for mortality. Severely-malnourished children with shigellosis having hypoglycaemia, hypothermia, altered consciousness and/or bronchopneumonia were at high risk of death. Based on the findings, the study recommends that early diagnosis of shigellosis in severely-malnourished children and assertive therapy for proper management to prevent development of hypothermia, hypoglycaemia, bronchopneumonia, or altered consciousness and its immediate treatment are likely to reduce *Shigella*-related mortality in severely-malnourished children.

Key words: *Shigella*; Dysentery, Bacillary; Infant nutrition disorders; Child nutrition disorders; Infant mortality; Child mortality; Risk factors; Case-control studies; Bangladesh

INTRODUCTION

Shigellosis, prevalent worldwide, is still a major cause of childhood mortality in developing countries. An estimated 667,000 children, aged less than five years, die due to shigellosis each year in developing countries (1). In Bangladesh, *Shigella dysenteriae* causes epidemic dysentery and is associated with more complications than other *Shigella* species, and *S. flexneri* is responsible for endemic infection. Malnutrition is another major public-health problem in developing countries (2), and interaction of malnutrition with shigellosis leads to an even higher mortality (3). Shigellosis causes malnutrition, which is enhanced through reduced food intake (4), increased energy expenditure as a consequence of systemic effects of inflammation and fever, malabsorption, and enteric loss of protein (5).

Correspondence and reprint requests should be addressed to:
Dr. S.K. Roy
Scientist
ICDDR,B: Centre for Health and Population Research
GPO Box 128, Dhaka 1000
Bangladesh
Email: skroy@icddrb.org
Fax: 880-2-8823116, 8812530

Hypothermia, severe malnutrition, severe dehydration, altered consciousness, abdominal distension, thrombocytopaenia, hypoproteinaemia, hyponatraemia, hypoglycaemia, renal failure, and bacteraemia are significantly more common in patients with *Shigella*-associated infection (6). Complications due to shigellosis, such as malnutrition, pneumonia, and septicaemia, predispose children to a higher risk of mortality (7). Frequent resistance to antibiotics (8) and absence of effective vaccines impede the treatment of shigellosis. Although risk factors for the death of children with shigellosis have been described before (6,9), it was not specific for severely-malnourished children. As severe malnutrition is significantly associated with deaths due to dysentery (9), it is necessary to identify the risk factors for mortality of severely-malnourished children to reduce preventable deaths.

We hypothesized that severely-malnourished children, who die of shigellosis, present with some particular characteristics compared to those who are discharged alive. Therefore, to determine the factors responsible for increased mortality, we undertook a case-control study using the hospital records of 200 patients with lethal *S. dysenteriae* type 1 or *S. flexneri*-associated infection admitted to the Clinical Research and Service Centre of ICDDR,B: Centre for Health and Population Research during December 1993–January 1999. Of these patients, 100 died in the hospital, and the remaining 100 matched patients were discharged alive.

MATERIALS AND METHODS

Although all *Shigella* species are endemic in Bangladesh, *S. flexneri* and *S. dysenteriae* are the most commonly-isolated species from culture of stools of patients who attended the treatment centre of ICDDR,B during 1983-1987 (6). These two also cause a more severe form of dysentery with more gastrointestinal and extraintestinal manifestations than *S. boydii* and *S. sonnei* (10,11).

The hospital records of patients admitted to the Clinical Research and Service Centre of ICDDR,B during December 1993–January 1999 were reviewed. The Centre treated more than 150,000 diarrhoeal patients in 1998. Approximately, 10,000 of them had a positive culture for *Shigella*. Death cases were selected from those cases who died due to shigellosis in the hospital. The probability for the controls to have a risk factor was estimated to be 10%. We planned to identify a risk factor with an odds ratio of size 2.5 or more. This sample size is adequate for 95% level of significance and 80% power of the test. One hundred cases were selected by calculating the sample size. Death cases and controls were selected after matching with the major criteria. Every case was compared with a control, leading to a total sample size of 200 (12).

Patients who attended the Centre were mainly of low socioeconomic status and came either from Dhaka city or from its surrounding areas. Patients with severe diarrhoea or dysentery with complications, such as pneumonia, suspected sepsis, severe malnutrition, or patients of extreme age, such as infants, and those aged over 65 years, were hospitalized. Approximately, 5% of patients who visit the ICDDR,B hospital are admitted to the inpatient ward. It was possible to get clinical findings of patients who died within a short period after admission.

Rectal swabs or stool culture and microscopic examinations were routinely done for all admitted patients. Blood culture, white cell count, and serum electrolytes were analyzed in most cases. On suspicion of a severe respiratory disease or any gastrointestinal complications, an X-ray was taken. Surgery or peritoneal dialysis facilities were not available, and patients who required such treatment were transferred to other hospitals.

All cases were severely malnourished defined by Gomez classification weight-for-age <60% of median of the National Center for Health Statistics. For each case, a matched control was identified who was admitted during the same period (within 3 days) and was of the same sex but recovered from their illness. Patients suffering from any chronic illness or those who were referred to other hospitals or left the hospital against advice of the physicians were not included. To avoid confounding effects, individuals isolated with enteropathogens other than *S. dysenteriae* type 1 or *S. flexneri* were excluded.

Clinical information on age, sex, socioeconomic status, duration of hospitalization, duration of vomiting and diarrhoea prior to admission, history of seizures, and current and past breastfeeding status, when available, was obtained from the records of patients. Clinical findings on admission included signs of kwashiorkor, abdominal distension, absent or sluggish bowel sound, rectal prolapse, xerophthalmia, altered consciousness, lethargy, coma, anaemia, bronchopneumonia, hypothermia, sepsis, pulse rate, and dehydration. Laboratory investigations included stool microscopy, white blood cell and platelet count, haematocrit, blood glucose level, isolation of

bacteria, serum creatinine, and serum electrolytes, such as Na, K, Cl, and TCO_2.

Statistical analysis

Data were entered into the microcomputer and checked using a software (SPSS version 7.5). Comparison of continuous variables between cases and controls was done with the Student's *t*-test for normally-distributed data or with the Mann-Whitney U-test for non-normal distribution. Categorical variables were analyzed with the chi-square test. Fisher's exact *t*-test was used where the expected count was less than five. Two-sided significant test was used. To identify the factors independently associated with an increased risk of death, multiple logistic regression analysis was carried out. In a backward stepwise regression, all non-significant variables were eliminated until a final model with significant p values and odds ratios was accessed.

RESULTS

The clinical characteristics of 52 boys and 48 girls were almost similar (Table 1). The median age of cases and controls was 9 months and 12 months respectively. This difference in age was significant. The proportion of subjects in each age category was comparable between the groups. The average duration of hospital stay was almost two days for the fatal cases and six days ($p<0.001$) for the controls.

Recent medical history showed that complaints of coughing were more common in patients who died than in patients who survived. Patients who had cough before admission had a 2.3-time higher chance of death. The presence and duration of diarrhoea and vomiting prior to admission did not differ very much between the cases and the controls. The presence of mucus in stool was more frequent in controls than in cases. Although not significant, bloody stool was more often found in controls than in cases. History of seizures, breastfeeding status, and socioeconomic status were almost similar between the groups.

Compared to survivors, the higher number of deceased patients had abdominal distension, absent or sluggish bowel sound, altered consciousness, clinical anaemia, bronchopneumonia, hypothermia, clinical sepsis, low or imperceptible pulse, pulse rate of <90 per minute, and dehydration. Abdominal distension and absent or sluggish bowel sound gave a 1.9- and 3.3-time higher risk of death respectively. The presence of clinical anaemia showed a 2.1-time higher risk of mortality. Altered consciousness on admission was highly associated with death with an odds ratio (OR) of 4.2. A similar effect was seen with hypothermia (OR=7.4). The presence of bronchopneumonia, clinical sepsis, dehydration, and a low or imperceptible pulse volume led to an increased risk of death by 2.8, 4.6, 3.1, and 3.9 folds respectively. The highest OR in univariate analysis was found for imperceptible pulse or a pulse rate of <90 per minute (OR= 10.5). Kwashiorkor, rectal prolapse, and xerophthalmia were not associated with a higher risk of mortality (Table 2).

Eighteen patients in the cases and 20 patients in the control group had infection due to *S. dysenteriae* type 1 (Table 3). *S. flexneri* was isolated from the remaining patients. The serum creatinine level of >150 μmol/L was more frequently observed in patients with a fatal outcome ($p<0.001$), and hyperkalaemia was also prominent ($p<0.05$) in the fatal cases. Five patients had *Shigella*-associated bacteraemia, four had bacteraemia with other Enterobacteriaceae, and eight had pneumonia-related species in their blood (4 *Pseudomonas*, 1 *Staphylococcus aureus*, and 3 *Streptococcus pneumoniae*). Double pathogens were isolated from the blood of one patient only.

Haematocrit, white cell, and platelet counts were not positively associated with death in these severely-malnourished children with shigellosis. Hypoglycaemia was significantly more common in cases ($p=0.00$) and was strongly associated with death (OR=6.6).

Multivariate analysis

A list of variables was considered to identify the characteristics, which were independently associated with death. These variables were subjected to multivariate analysis. Initially, age and cough prior to admission were identified. Abdominal distension, absent or sluggish bowel sound, hypoglycaemia, bronchopneumonia, clinical anaemia, clinical sepsis, hypothermia (<36 °C), and altered consciousness on admission were thought to be probable independent risk factors. Age was included, although age-groups were not significantly associated with death, but age as a continuous variable was significant, and the strong impact of age on mortality was also proved in other studies (3,6). Clinical assessment of dehydration in severely-malnourished children is difficult. Therefore, dehydration status was not considered in the final analysis. Since breastfeeding information was inadequate,

Table 1. Clinical characteristics of *Shigella*-infected severely-malnourished children who died and who were discharged alive

Clinical characteristics	Percentage		OR (CI)
	Died (n=100)	Discharged alive (n=100)	
Male	52	52	1.0 (0.6-1.7)
Age (months)	9 (1-48)	12 (2-46)	
<6	38	26	2.2 (1.0-4.9)
6-12	31	26	1.7* (0.8-4.1)
13-24	15	24	0.9 (0.4-2.3)
25-48	16	24	1
Duration (hours) of hospital stay	45 (1-480)	144 (22-1,100)	
<96	79	34	9.3* (3.9-22.2)
>192	8	32	1*
History of			
Diarrhoea prior to admission (>10 days)	26	23	1.0 (0.6-1.9)
Vomiting prior to admission (>10 days)	7 (n=96)	7	1.1 (0.4-3.1)
Blood in stool (visible)	28	38	0.6 (0.4-1.2)
Mucus in stool (visible)	48	65	0.5* (0.3-0.9)
Cough	51	32	2.3* (1.3-4.0)
Seizure	1 (n=98)	7	3.7 (0.8-18.2)
Currently breastfed	47 (n=96)	42 (n=94)	1.2 (0.7-2.2)
Breastfeeding	75 (n=88)	78 (n=78)	0.8 (0.4-1.7)
Socioeconomic status			
Monthly income (Taka)			
>1,500	51	41	0.6 (0.2-1.6)
1,501-3,000	19	26	0.3 (0.1-0.3)
3,001-4,000	11	21	0.2* (0.1-0.8)
>4,000	13	6	1

*Significant; Median and range are given for characteristics, if applicable
CI=Confidence interval; OR=Odds ratio

Table 2. Findings, on admission, of physical examinations of *Shigella*-infected severely-malnourished children who died and who were discharged alive

Physical characteristics	Percentage		OR (CI)
	Died (n=100)	Discharged alive (n=100)	
Imperceptible/low radial pulse	63 (n=99)	31 (n=91)	3.9* (2.2-7.2)
Pulse rate <90/imperceptible	25.5	3.2	10.5* (3.0-36.0)
Hypothermia (<36 °C)	24	4	7.4* (2.4-23.0)
Clinical sepsis	59	24	4.6* (2.5-8.4)
Dehydration	69	42	3.1* (1.7-5.5)
Altered consciousness	84	57	4.2* (2.0-7.7)
Abdominal distension	29	15	1.9* (1.1-3.1)
Absent or sluggish bowel sound	20	7	3.3* (1.3-8.3)
Kwashiorkor	22	21	1.1 (0.5-2.1)
Rectal prolapse	9	12	0.7 (0.3-1.8)
Xerophthalmia	20	11	2.0 (0.9-4.5)
Clinical anaemia	45 (n=86)	28	2.1* (1.2-3.9)
Bronchopneumonia	68	40	2.8* (1.4-5.5)

*Significant
CI=Confidence interval; OR=Odds ratio

Table 3. Laboratory findings, on admission, of *Shigella*-infected severely-malnourished children who died and who were discharged alive

Characteristics	Percentage		OR (CI)
	Died	Discharged alive	
Stool			
Shigella species	n=100	n=100	
S. dysenteriae type 1	18	20	0.9 (0.4-1.7)
S. flexneri	82	80	
Blood			
Glucose (<3 mmol/L)	48 (n=99)	12 (n=66)	6.5* (2.8-15.1)
Haematocrit (<30%)	40 (n=96)	47 (n=92)	1.3 (0.8-2.4)
Total WBC count (>40,000 per mm³)	3 (n=96)	3 (n=92)	1.0 (0.2-4.9)
Platelets (<90,000 per mm³)	64 (n=14)	40 (n=10)	2.7 (0.5-14.4)
Pathogen found in blood	17 (n=89)	12 (n=87)	1.3 (0.78-2.5)
Serum			
Na (mmol/L)	n=96	n=88	
<130	62	55	1.4 (0.8-2.5)
>150	3	2	1.7 (0.26-10.6)
K (mmol/L)	n=94	n=88	
<3.5	40	46	1.1 (0.6-2.0)
>5.5	25	13	2.3 (1.0-5.5)
Cl (mmol/L)	n=96	n=88	
<95	35	36	1.1 (0.57-2.2)
>106	30	24	1.5 (0.7-3.1)
TCO_2 (mmol/L)	n=95	n=85	
<14	41	22	1.6 (0.7-3.7)
>18	37	59	0.5 (0.2-1.2)
Creatinine (μmol/L)	n=52	n=30	
>150	29	3	1.2* (1.5-4.3)

*Significant
CI=Confidence interval; OR=Odds ratio; WBC=White blood cell

it was not considered for multiple logistic regression. Results of multiple regression analysis showed that hypothermia, altered consciousness, hypoglycaemia, and bronchopneumonia were significantly associated with death (Table 4). The number of patients included in the analysis was 139; data for 61 patients were missing. The initial number of variables for which the analysis was done was 11. Age, history of cough, absent or sluggish bowel sound, abdominal distension, clinical sepsis, hyperkalaemia, and clinical anaemia were removed from analysis after they were proved not to be significant. The variables which were not included were: age (adjusted p value 0.60), cough on admission (adjusted p value 0.54), absent or sluggish bowel sound (adjusted p value 0.91), abdominal distension (adjusted p value 0.93), clinical anaemia (adjusted p value 0.11), clinical sepsis (adjusted p value 0.55), and hyperkalaemia (adjusted p value 0.64).

DISCUSSION

Both malnutrition and shigellosis are major causes of deaths of children in developing countries (1,11,12). The risk factors identified in this study would be useful for the treatment of severely-malnourished children with *S. dysenteriae* type 1 or *S. flexneri*. Assertive earlier

Table 4. Characteristics associated with death of malnourished patients with shigellosis in multiple logistic regression analysis

Characteristics (on admission)	OR (CI)
Hypothermia (<36 °C)	5.7* (1.5-22.1)
Altered consciousness	2.6* (1.0-6.8)
Hypoglycaemia (<3.0 mmol/L)	7.8* (2.9-19.6)
Bronchopneumonia	2.5* (1.1-5.5)

*Significant
CI=Confidence interval; OR=Odds ratio

management with appropriate antibiotics, provision of adequate nutritional therapy, close monitoring of temperature, blood glucose, and mental status could prevent complications or secondary infections in these patients.

Infection, such as bronchopneumonia, appears to be more predictive for death than severity of colitis. Death of patients with shigellosis in general is most often due to a superimposed infection (4). In addition, malnutrition worsens the prognosis due to reduced immunity (13). In our study, clinical septicaemia as manifested with altered consciousness, low-volume pulse, bradycardia, and hypothermia was significantly more frequent in the fatal cases. Blood and mucus in stool, duration of diarrhoea and vomiting, and severe colitis were more frequent in cases than in controls.

Hypothermia and hypoglycaemia were important risk factors for death in children with shigellosis (6) and in children with severe protein-energy malnutrition (13). In previous studies, altered consciousness and unconsciousness were shown to be associated with higher mortality (6,14), and further bronchopneumonia was also recognized as a risk factor (4,6).

Four factors have been identified in our study, i.e. hypothermia, hypoglycaemia, bronchopneumonia, and altered consciousness were predictive for death, which confirms results of some earlier studies (6,7).

Although *S. dysenteriae* type 1 is characteristically associated with the highest case-fatality rate compared to other *Shigella* species, in this study, infection due to *S. dysenteriae* type 1 was detected in 18 of the 100 cases who died in the hospital and this was detected in 20 patients in the control group. As the patients infected with *S. dysenteriae* type 1 are more severely ill (6,11), they are often referred to other hospitals for the treatment of complications and are more often likely to be discharged against medical advice. The other reasons might be that its alarming features trigger caretakers to seek medical care at an early stage of the disease, which prevents the development of lethal complications (6,11). *S. dysenteriae* type 2-20 have less clinical severity than type 1 and account for 8% of all *S. dysenteriae* types (10).

The data used in this study were obtained from admitted patients in the ICDDR,B hospital which is specialized in the management of diarrhoea and, as such, do not fully represent the whole population of severely-malnourished children in Bangladesh. Therefore, the data are likely to differ from those of the average population of the country who suffer from shigellosis. The patients who were referred to other hospitals might have some positive impact by aversion in this study. For cultural reasons, parents prefer that their children die at home rather than outside, and many patients who left against medical advice were critically ill. Similarly, the patients whose complications were not treatable in this hospital were referred to other hospitals. Their condition was critical at the time they were transferred to other hospitals. Results of a previous study suggest that the clinical features of those patients more closely resembled patients who died than those who were discharged alive (6).

The results of our study suggest that early diagnosis of shigellosis in severely-malnourished children and assertive therapy for proper management to prevent and treat hypothermia, hypoglycaemia, bronchopneumonia, or altered consciousness are likely to reduce *Shigella*-related mortality in severely-malnourished children.

ACKNOWLEDGEMENTS

This research was funded by ICDDR,B: Centre for Health and Population Research and its donors which provide unrestricted support to the Centre for its operations and research. Current donors providing unrestricted support include: Australian International Development Agency (AusAID), Canadian International Development Agency (CIDA), Department for International Development (DFID), UK, Government of Bangladesh, Government of Japan, Government of Sri Lanka, Government of the Netherlands, Swedish International Development Cooperative Agency (SIDA), The Kingdom of Saudi Arabia, and Swiss Development Cooperation (SDC). The authors gratefully acknowledge these donors for their support and commitment to the Centre's research efforts.

REFERENCES

1. Kotloff KL, Winickoff JP, Ivanoff B, Clemens JD, Swerdlow DL, Sansonetti PJ *et al*. Global burden of *Shigella* infections: implications for vaccine development and implementation of control strategies. *Bull World Health Organ* 1999;77:651-66.

2. Bennish ML, Wojtyniak BJ. Mortality due to shigellosis: community and hospital data. *Rev Infect Dis* 1991;13(Suppl 4):S245-51.

3. Chopra M, Wilkinson D, Stirling S. Epidemic *Shigella* dysentery in children in northern KwaZulu-Natal. *S Afr Med J* 1997;87:48-51.

4. Rahman MM, Kabir I, Mahalanabis D, Malek MA. Decreased food intake in children with severe dysentery due to *Shigella dysenteriae* 1 infection. *Eur J Clin Nutr* 1992;46:833-8.

5. Bennish ML, Salam MA, Wahed MA. Enteric protein loss during shigellosis. *Am J Gastroenterol* 1993;88:53-7.

6. Bennish ML, Harris JR, Wojtyniak BJ, Struelens M. Death in shigellosis: incidence and risk factors in hospitalized patients. *J Infect Dis* 1990;161:500-6.

7. Butler T, Dunn D, Dahms B, Islam M. Causes of death and the histopathologic findings in fatal shigellosis. *Pediatr Infect Dis J* 1989;8:767-72.

8. Salam MA, Dhar U, Khan WA, Bennish ML. Randomised comparison of ciprofloxacin suspension and pivmecillinam for childhood shigellosis. *Lancet* 1998;352:522-7.

9. Mitra AK, Engleberg NC, Glass RI, Chowdhury MK. Fatal dysentery in rural Bangladesh. *J Diarrhoeal Dis Res* 1990;8:12-7.

10. Ahmed F, Clemens JD, Rao MR, Ansaruzzaman M, Haque E. Epidemiology of shigellosis among children exposed to cases of *Shigella* dysentery: a multivariate assessment. *Am J Trop Med Hyg* 1997; 56:258-64.

11. Faruque AS, Teka T, Fuchs GJ. Shigellosis in children: a clinico-epidemiological comparison between *Shigella dysenteriae* type 1 and *Shigella flexneri*. *Ann Trop Paediatr* 1998;18:197-201.

12. Proportions: binomial distribution. *In*: Kirkwood B. Essentials of medical statistics. Oxford: Blackwell Scientific Publications, 1988:76-86.

13. Keusch GT. Malnutrition, infection, and immune function. *In*: Suskind RM, Lewinter-Suskind L, editors. The malnourished child. New York: Raven Press, 1988:37-59. (Nestlé Nutrition workshop series no. 19).

14. Khan WA, Dhar U, Salam MA, Griffiths JK, Rand W, Bennish ML. Central nervous system manifestations of childhood shigellosis: prevalence, risk factors, and outcome (abstract). *Pediatrics* 1999; 103:488-9.