

Causes of death in diarrhoeal diseases after rehydration therapy: an autopsy study of 140 patients in Bangladesh

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The cause of death (besides dehydration) for 140 diarrhoeal patients who died in hospital following rehydration was determined by autopsy examination. Children under 5 years comprised 74% of the patients. Diarrhoeal pathogens were identified as Shigella spp. in 27%, enterotoxigenic Escherichia coli in 17%, Entamoeba histolytica in 16%, Campylobacter jejuni in 12%, Salmonella spp. in 4%, Vibrio cholerae in 4%, and Giardia lamblia in 4% of cases. The most frequent underlying causes of death were colitis in 44% and pneumonia in 38%. The most frequent immediate causes of death were septicaemia in 27%, hypoglycaemia in 9%, and hypokalaemia in 9%; multiple causes of death were present in 89% of cases. Kwashiorkor or marasmus was present in 59% and fatty degeneration of the liver was detected in 61% of cases. It is concluded that, in susceptible children, diarrhoeal pathogens produce destructive inflammation in the intestine and cause death or contribute to it by provoking disease in other tissues, especially septicaemia and fatty liver, or by combining these effects with antecedent or concomitant conditions, especially pneumonia and malnutrition.

In rural Bangladesh, Chen et al. (1) identified diarrhoea as the leading cause of death in children aged 0-4 years. The worldwide mortality due to diarrhoeal diseases was estimated to be 4.6 million in 1980, with a case-fatality rate of 0.6 deaths per 100 illnesses in children under 5 years of age (2).

Although dehydration is considered to be the most important cause of death in diarrhoeal patients, physicians who manage tropical diarrhoeal cases recognize that there is considerable mortality among these patients even after adequate rehydration. The results of autopsies performed in Bangladesh by Nalin (3) and Hirschhorn et al. (4) indicated that pneumonia, marasmus, and hypoglycaemia were important complications in fatal diarrhoeal cases. For the reduction of mortality among diarrhoeal patients after the correction of dehydration, physicians and health administrators need to know more about the

causes of such deaths. These causes of death in our hospital for diarrhoeal illnesses were determined by carrying out autopsies.

PATIENTS AND METHODS

Selection of patients

Patients who were admitted with diarrhoea to the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) from May 1982 to May 1985 and died in the hospital after rehydration were eligible for the study. This hospital serves an urban population of about 4 million people, who live largely without treated water supplies or piped sewage disposal. During the period of the study, approximately 224 000 diarrhoeal patients visited the hospital of whom 1053 (0.47%) died. Initial rehydration had been carried out with intravenous fluid (containing sodium 133 mmol/l, potassium 13 mmol/l, chloride 98 mmol/l, and acetate 44 mmol/l) or with oral rehydration solution (containing sodium 90 mmol/l, potassium 20 mmol/l, chloride 80 mmol/l, bicarbonate 30 mmol/l, and sucrose 40 g/l) in amounts of approximately 5-10% of the body weight. Effort was made to maintain

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good hydration in all patients in hospital by replacing the stool losses quantitatively with intravenous or orally administered fluids. Patients were selected who had histories of dysentery (blood and/or mucus in the stool) or reported 3 or more stools a day that were watery or loose in character. Routine laboratory tests at this hospital for seriously ill patients included microscopic examination of stool for leukocytes and parasites, stool culture for *Salmonella*, *Shigella* and *Vibrio* species, and blood examinations for erythrocyte volume fraction (haematocrit), white blood cell count, serum electrolytes, and tests of renal function. Patients who were suspected to have sepsis had blood drawn for culture and those with tachypnoea or pulmonary râles had chest roentgenograms taken. Most patients from the day of admission received antibiotics, which were most commonly ampicillin and gentamicin. The families of eligible deceased patients were asked for written informed consent before autopsy, which was also carried out on unclaimed bodies after 48 h in the cold room; 140 patients underwent post-mortem examination, 128 from families who gave consent and 12 unclaimed bodies.

Autopsy procedures

Standard autopsy procedures were employed, except that the thoracic viscera were removed through an incision in the diaphragm in order to avoid extension of the abdominal incision. The brain was examined in only 4 cases. The following fluids were obtained for bacteriological culture: blood from the subclavian vein, spinal fluid, fluid from the small intestine and large intestine, and swabs from the cut surfaces of the spleen, lung, and mesenteric lymph nodes. The swabs from the intestine and mesenteric lymph nodes were also cultured for *Yersinia* and *Campylobacter*. In selected children with histories of watery diarrhoea the intestinal contents were tested for rotavirus by an ELISA test and for enterotoxigenic *Escherichia coli* (5). Gross inspection of organs was carried out and they were weighed to the nearest gram. Tissues were placed in 10% formalin and blocks were prepared for sectioning and staining with haematoxylin and eosin. In cases in which the slides showed evidence of infection, the tissues were stained with periodic-acid Schiff stain for amoebae, Ziehl-Nielsen stain for *Mycobacterium tuberculosis*, methenamine silver stain for fungi and protozoa, and a tissue Gram stain for bacteria.

Definitions of diseases

Causes of death were selected from categories on the mortality list of the International Classification of Diseases (ICD) (6). One underlying cause of death

was selected for each patient, which was based on the pathologist's judgement of the autopsy findings and the clinical record. This underlying cause of death was the primary disease that initiated the events leading to the patient's death and without this the patient would have survived (7). Anatomical diseases were given priority if they were widespread or severe in degree. In addition, we sought to identify one immediate cause of death for each patient which was usually a complication of the underlying cause such as septicaemia or hypoglycaemia. Septicaemia was defined as a positive culture of blood before death or a positive culture of blood or spleen at the time of autopsy if the autopsy was performed less than 6 hours after death. Those cases with positive post-mortem cultures were only included if they had terminal clinical courses suggestive of septicaemia by the presence of fever, hypothermia, or shock. Hypoglycaemia was defined as an ante-mortem blood sugar value < 36 mg/100 ml (2mmol/l). Hypokalaemia was defined as an ante-mortem serum potassium concentration of ≤ 2.0 mol/l. Anaemia was defined as an ante-mortem haematocrit of less than 25%. Multiple causes of death were dealt with by assigning one associated cause of death for a patient if a condition other than the underlying and immediate causes was judged to have contributed directly to death together with the underlying cause or immediate cause (8, 9). In this study, up to three causes of death were assigned to each patient.

Table 1. Age and sex distribution of 140 patients with fatal diarrhoeal diseases who underwent autopsies compared with all the patients who died in the same hospital in the same period

Age (years)	Percentage of autopsy cases	Percentage of all deaths ^a
< 1	31	38
1-4	43	43
5-9	10	7
10-19	4	3
20-29	1	1
30-39	4	1
40-49	2	2
≥ 50	5	4
Males	45	59
Females	55 ^b	41

^a A total of 647 consecutive hospital deaths from May 1982 to January 1984 were included.

^b Proportion of females was significantly greater in autopsy cases than in all deaths ($P < 0.05$).

Table 2. Pathogens identified in 140 patients with fatal diarrhoeal diseases

Pathogens	No. identified	Percentage of patients tested
<i>Shigella</i> spp.	38	27
<i>S. dysenteriae</i>	10	7
<i>S. flexneri</i>	23	16
<i>S. boydii</i>	5	4
<i>S. sonnei</i>	2	1
<i>E. coli</i> (ETEC)	4	17
<i>Entamoeba histolytica</i>	22	16
<i>Campylobacter jejuni</i>	17	12
<i>Salmonella</i> spp.	6	4
<i>Vibrio cholerae</i>	6	4
<i>Giardia lamblia</i>	5	4
Rotavirus	1	4
Cytomegalovirus	3	2
<i>Yersinia enterocolitica</i>	2	1
<i>Cryptosporidium</i>	1	1
Patients with pathogens	85	61
Patients with mixed infections	20	14

Accompanying diseases were also diagnosed by the ICD but were not assigned roles in the cause of death. In this study, kwashiorkor or marasmus was diagnosed in children aged less than 10 years on the basis of severe wasting with or without oedema, respectively. These nutritional conditions were not assigned as causes of death but were listed as accompanying diseases.

RESULTS

Patients

The ages of the 140 patients who died ranged from 9 days to 80 years. The majority were young children, with 31% less than 1 year old, 43% between 1 and 4 years old, and 10% between 5 and 9 years old. Males comprised 45% and females 55% (Table 1). A comparison of these autopsied patients with 647 consecutive deaths at the same hospital during the same period revealed nearly the same age distribution but a significantly higher proportion of females in the autopsy group ($\chi^2 = 9.0$, $P < 0.05$).

All the patients had diarrhoea as a presenting complaint, the duration of which before admission ranged from 1 day to 1 year; 51% of them had diarrhoea lasting for more than 6 days. Their histories revealed further that 53% had complained

of blood or mucus in the stools and 41% had exclusively watery stools; 42% of the patients had given histories of fever, and 41% had temperatures greater than 38.3 °C recorded. Histories of abdominal pain or signs of abdominal tenderness had been elicited from 19% of patients.

The time of death after admission ranged from less than one hour to 24 days, with a median time of 2 days. The interval between death and autopsy ranged from 1 hour to 96 hours, with a median of 9 hours.

Diarrhoeal pathogens

As a result of ante-mortem and post-mortem stool examinations by culture, microscopy and ELISA, diarrhoeal pathogens were detected in 61% of the patients (Table 2). *Shigella* species, the most commonly detected pathogens, were present in 38 patients (27%). Stools of 23 patients were tested for enterotoxigenic *E. coli* and 4 (17%) were positive. *Entamoeba histolytica*, which was identified by motile trophozoites in the stool or trophozoites in tissue, was present in 22 patients (16%). *Campylobacter jejuni* was isolated in 17 cases (12%). Five cases of *Salmonella typhi* infection and one of *S. enteritidis* were detected by blood culture. Rotavirus was detected in the stool of one of 28 patients examined by the ELISA test for rotavirus antigen. *Vibrio cholerae* was isolated from stools of 6 patients. The 105 identifications of pathogens were greater than the number of patients with these pathogens (85) because two or more pathogens were detected in 20 patients.

Causes of death

Each patient was assigned one underlying cause of death (Table 3), the most common being colitis and pneumonia. These underlying diseases were typically severe and widespread. The colitis consisted of pancolitis or deep ulcers in most cases, and the pneumonias were widespread, affecting multiple lobes. Immediate causes of death were identified in 79 patients and were most commonly found to be septicaemia, hypoglycaemia, and hypokalaemia. Dehydration was the immediate cause of death in only one patient, a one-year-old child with cholera who became dehydrated again despite the attempts of nursing staff to maintain fluid balance. Associated causes of death were assigned to 87 patients in whom multiple diseases coexisted with competing degrees of severity to contribute to the deaths of the patients (Table 3); 89% of the patients were assigned immediate and/or associated causes of death.

The organisms responsible for more than one case of septicaemia included *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*,

Table 3. Causes of death in 140 cases of fatal diarrhoeal illnesses

Underlying causes ^a	Percentage	Immediate causes ^b	Percentage	Combined underlying, immediate and associated causes ^c	Percentage
Colitis	44	Septicaemia	27	Bronchopneumonia	31
Shigella	22	Hypoglycaemia	9	Septicaemia	30
Amoebic	13	Hypokalaemia	9	Shigella colitis	26
Not specified	9	Pulmonary oedema	5	Colitis not specified	16
Pneumonias	38	Haemorrhage	4	Amoebic colitis	15
Bronchopneumonia	20	Anaemia	1	Necrotizing pneumonia	11
Necrotizing	8	Dehydration	1	Hypoglycaemia	11
Interstitial	4			Hypokalaemia	10
Tuberculosis	4			Interstitial pneumonia	9
Bronchiolitis/bronchitis	1			Pulmonary oedema	7
Typhoid fever	3			Haemorrhagic necrosis of intestine	6
Haemorrhagic necrosis of intestine	3			Enteritis not specified	5
Gastroenteritis	3				
Cholera	2				
Meningitis	2				

^a Each patient was assigned one underlying cause of death; those that were present in at least 2% of patients are listed.

^b One immediate cause of death was assigned to 79 patients; these causes were usually consequences of the respective underlying causes.

^c One associated cause of death was assigned to 87 patients when there was a significant diagnosis in addition to the underlying or immediate cause of death; the causes of death that were present in at least 5% of patients are listed.

Table 4. Frequency distribution of organisms isolated from septicaemic patients among the 140 fatal cases of diarrhoea

Organism ^a	No. of cases
<i>Pseudomonas aeruginosa</i>	9
<i>Klebsiella pneumoniae</i>	8
<i>Staph. aureus</i>	7
<i>Strep. pneumoniae</i>	7
<i>Escherichia coli</i>	1
<i>Salm. enteritidis</i>	1
<i>Shig. flexneri</i>	1
<i>Aeromonas hydrophila</i>	1
<i>Enterobacter</i> sp.	1
<i>Yersinia enterocolitica</i>	1
<i>Acinetobacter</i> sp.	1
Multiple isolates	4
Total	42

^a Organisms are included when they were isolated as the only pathogen in either ante-mortem (31 cases) or post-mortem (11 cases) blood culture, the latter within 6 hours of the patient's death when the clinical features were suggestive of sepsis. Five cases of typhoid fever with *Salm. typhi* isolated from blood are not included.

and *Staphylococcus aureus* (Table 4). The distribution of these bacterial species indicates that the majority originated from the intestine and/or lung. The bacteria had been isolated from ante-mortem cultures in 31 cases and from post-mortem cultures in 11 cases.

Associations between diarrhoeal etiologies and common anatomical and laboratory abnormalities

The most prevalent intestinal lesion in these patients was colitis, which was present in 62% of all cases (Table 5). Colitis was more common in patients with shigellosis, amoebiasis, and campylobacteriosis than in the other cases. Enteritis of the small intestine (present in 20%) was a less common finding than colitis, but was also more frequently observed in the cases with shigellosis, amoebiasis, and campylobacteriosis. Haemorrhagic necrosis of the intestine was detected at a similar prevalence (14–25%) in all etiological categories, except among the cholera victims who showed no cases with this lesion. Septicaemia and pneumonia occurred frequently in these patients irrespective of the specific diarrhoeal etiology.

Table 5. Associations of anatomical lesions and laboratory abnormalities with diarrhoeal etiologies in 140 cases of fatal diarrhoeal illness

Anatomical or laboratory designation	Percentages of patients in each etiologic category						No pathogen identified (n = 55)
	All cases (n = 140)	Shigellosis (n = 38)	Amoebiasis (n = 22)	<i>Campylobacter</i> (n = 17)	Cholera ^a (n = 6)	Typhoid (n = 5)	
Colitis	62	95	95	65	33	40	35
Enteritis	20	26	23	41	17	80	7
Haemorrhagic necrosis of intestine	23	24	14	24	0	20	25
Peritonitis	4	0	9	6	0	40	4
Septicaemia	36	34	36	53	17	0	40
Pneumonia	66	66	64	71	50	20	69
Bronchitis or bronchiolitis	20	13	36	29	33	20	18
Fatty Liver	61	82	55	76	50	20	60
Hypoglycaemia	13	21	9	6	33	0	13
Kwashiorkor	25	29	32	35	0	0	25
Marasmus	34	34	23	35	67	0	40
Hypokalaemia	24	29	23	35	50	0	31
Anaemia	16	16	14	18	17	0	15

^a Two of these patients were also infected with *Shigella* species.

Nutritional and metabolic conditions were also frequently detected (Table 5). Fatty degeneration of the liver, which occurred in 61% of all cases, did not correlate with the nutritional state and was especially prevalent in patients with shigellosis. Hypoglycaemia was detected in 13% of all cases and was most prevalent in cases of shigellosis and cholera. Kwashiorkor or marasmus was present in the majority of all cases with equal prevalence in all etiological categories, except that none of the cholera cases had kwashiorkor but showed a higher prevalence of marasmus.

DISCUSSION

This study identified colitis and pneumonia as the leading underlying causes of death, besides dehydration, in patients with diarrhoeal diseases; the leading immediate causes of death were septicaemia, hypoglycaemia, and hypokalaemia. Ulcerative diseases of the colon and, sometimes, of the small intestine caused by *Shigella* spp., *Entamoeba histolytica*, or *Campylobacter* spp. were detected in the majority of these cases. Our results are consistent with recent reports which show that the leading causes of death in children worldwide are acute

respiratory infections and diarrhoea (10). Furthermore, we found that diarrhoeal diseases and pneumonia frequently occurred together and probably produced additive effects to cause death.

Most of these patients were infants and children aged 1–4 years. This age distribution of our cases is consistent with other reports of the susceptibility of young children to diarrhoeal illness and their risk of having fatal complications (2). The larger proportion of females in this study group than was expected from the sex distribution of all fatal cases at our hospital was attributed to the fact that informed consent for autopsy was obtained more frequently from families of female patients. The presence of fever in nearly half of the patients, even after rehydration, correlated with a high frequency of invasive intestinal infections, pneumonia, and septicaemia, in contrast to the usual watery diarrhoeal syndromes in which fever is often absent. Although dehydration is an important cause of death in watery diarrhoea, our cases were all rehydrated after hospital admission; dehydration was therefore rarely recorded as a cause of death in the present study.

Septicaemia was the most frequently assigned immediate cause of death in this study, because of the known effect of circulating bacteria to produce fever, shock, and death. The bacteria probably gained entry

to the blood stream in many cases through ulcers in the colon that were often caused by *Shigella* species and *E. histolytica*. Some of the septicaemias, including those caused by *Strep. pneumoniae*, originated from the lung, and others may have been nosocomially induced through the intravenous route.

Haemorrhagic necrosis of the intestine, which was detected in about a fourth of these patients, was attributed to vascular insufficiency in the intestine. This lesion developed acutely just before death as a result of decreased perfusion and/or oxygenation of the intestinal mucosa. In our patients the factors that may have been contributed to the haemorrhagic necrosis of the intestine were septicaemic shock, hypoalbuminaemia, and previous dehydration.

Pneumonia, an important disease in these patients, was detected in two-thirds of the cases. This high proportion of fatal diarrhoeal illness with concomitant pneumonia suggests that diarrhoeal disease may predispose patients to lung infection. Alternatively, the pneumonia and diarrhoeal disease may have occurred together as a result of common predisposing factors. Monto & Koopman (11) also concluded that children with diarrhoea showed a greater-than-expected frequency of respiratory symptoms, but the nature of this enteric-respiratory illness complex is poorly understood. The etiologies of pneumonia in our cases were bacterial in some patients with *Strep. pneumoniae* bacteraemia, but respiratory viruses were not looked for. Bacteraemia originating from the ulcerated intestine and seeding in the lungs is a possible mechanism for the pneumonia in some of our patients.

The presence of moderate or severe fatty degeneration of the liver was a common finding in these cases but the cause was not clarified in this study. The association of fatty liver with fatal shigellosis has been known since 1928 and was reviewed by Felsen (12). In 4 fatal cases of shigellosis in the USA, Barrett-Connor & Connor (13) reported that two showed marked fatty livers. The cause of fatty liver in shigellosis could be endotoxaemia, which Yoshino (14) showed could cause fatty livers in rabbits within 24 h after intravenous injection of *Shigella* endotoxin. Our findings of fatty liver in children with malnutrition are consistent with reports of kwashiorkor from other tropical countries (15). Malnutrition may, therefore, be a predisposing factor for the development of fatty liver preceding and during diarrhoeal diseases.

The presence of pre-existing severe malnutrition in some of our patients raises the possibility that impaired immunity contributed to susceptibility to infection and to increased severity of illness. A longitudinal study in Bangladesh by Black et al. (16) showed that malnutrition was associated with an

increase in the duration of diarrhoeal episodes but not an increase in the incidence of diarrhoea. It is likely that malnutrition predisposed some of our patients to have protracted diarrhoeal episodes which led to complications and death. On the other hand, the results of our autopsy study do not permit conclusions about how the complex interactions between nutrition and infection operated to cause deaths of the patients, because the exact sequences of pathophysiological events could not be accurately determined.

Multiple causes of death were assigned in the majority of these patients. The challenge to physicians who manage seriously ill diarrhoeal patients is that they must consider diagnoses both in the intestine and the extraintestinal problems of septicaemia, pneumonia, and hypoglycaemia. The correct treatment of these complications is problematic because the physician must be alert to both rehydration needs and antimicrobial treatment of enteric infections. As treatment is urgently needed and laboratory diagnosis may not be available, treatments must often be given empirically for presumed enteric pathogens and for extraintestinal complications.

The implications of this study are that certain public health measures may be able to reduce mortality from diarrhoeal diseases in developing countries. Although oral rehydration has been proposed as life-saving therapy for dehydrating diarrhoeas, rehydration alone would not have been sufficient to prevent death when complications are present. The high rates of shigellosis and amoebiasis in this population, who had diarrhoeal symptoms usually for more than 6 days, suggests that earlier diagnosis and treatment of these treatable infections may reduce mortality. Similarly, the high rates of pneumonia and septicaemia indicate that earlier diagnosis and selective antibiotic usage could have prevented a fatal outcome. Although the poor nutritional condition of many children in this study was believed to be secondary to the metabolic burden of infectious diseases, the underlying nutritional deficiencies doubtless contributed to the deaths of some patients by reducing the metabolic reserves required to sustain patients during the stress of infection.

The adverse living conditions associated with poverty and ignorance in developing countries are the more fundamental factors that lead to the high mortality rates from diarrhoea. Among these underlying factors that were important in our patients are low standards of personal hygiene and sanitation, lack of breastfeeding and other good nutritional practices, and limited access of the people to preventive and curative health services.

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RÉSUMÉ

LES CAUSES DE DÉCÈS APRÈS UNE MALADIE DIARRHÉIQUE TRAITÉE PAR RÉHYDRATATION:
RÉSULTATS DE L'AUTOPSIE DE 140 MALADES AU BANGLADESH

Dans la plupart des cas, les décès dus aux maladies diarrhéiques tropicales peuvent être évités grâce à la réhydratation mais il arrive que, même après celle-ci, des malades décèdent. Pour en déterminer la cause, on a pratiqué une autopsie sur 140 victimes décédées dans un hôpital pour maladies diarrhéiques au Bangladesh. Parmi ces victimes, 74% étaient des enfants de moins de 5 ans. Les agents pathogènes à l'origine de la diarrhée ont été identifiés dans 84% des cas: *Shigella* sp. (27% des cas), *Escherichia coli* entérotoxigène (17%), *Entamoeba histolytica* (16%), *Campylobacter jejuni* (12%), *Salmonella* sp. (4%), *Vibrio cholerae* (4%) et *Giardia lamblia* (4%).

A l'origine du décès, on trouvait le plus souvent une colite (44% des cas) ou une pneumopathie (38% des cas), la cause immédiate du décès étant une septicémie dans 27% des cas, une hypoglycémie dans 9% des cas et une hypokaliémie dans 9% des cas. Dans 89% des cas, le décès était dû à plusieurs causes. Des maladies nutritionnelles telles que le kwashiorkor ou le marasme étaient présentes dans 59% des

cas et une stéatose du foie dans 61% des cas. Les pneumopathies et septicémies survenaient fréquemment chez les malades, quelle que soit l'étiologie de la diarrhée, tandis que l'hypoglycémie était plus fréquemment associée à la shigellose et au choléra.

L'étude permet de conclure que, chez les enfants sensibles, les agents pathogènes intestinaux entraînent une inflammation destructrice de l'intestin et provoquent ou précipitent le décès en favorisant l'atteinte d'autres tissus (septicémie et stéatose du foie notamment) et en associant leurs effets à ceux d'un état morbide récent ou concomitant tel que pneumopathie ou malnutrition. Pour réduire la mortalité par maladie diarrhéique tropicale après une réhydratation correctement conduite, il faudra instaurer plus précocement ce traitement et/ou veiller à prévenir les infections intestinales dans la communauté; les médecins devront également être attentifs aux complications extra-intestinales des diarrhées telles que pneumopathies, septicémies et hypoglycémie.

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