Risk factors for persistent diarrhoea

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Abstract

With a systematically sampled population of children aged under 5 attending this centre for diarrhoeal disease research during 1983-5 a retrospective analysis of persistent diarrhoea (defined as >14 days' duration) was performed to identify the possible risk factors for this syndrome. Of the 4155 children included in the analysis, 410 (10%) gave a history of persistent diarrhoea. A comparison with children with acute diarrhoea matched for age showed that 11 factors were correlated with persistent diarrhoea, and strongly associated factors were stools with blood or mucus, or both, lower respiratory tract infection, malnutrition, vitamin A deficiency, and antibiotic use before presentation. The peak age was 2 years, and there was no sex difference. Deaths occurred more often in the group with persistent diarrhoea. Although *Shigella* spp, *Campylobacter jejuni*, and *Giardia lamblia* were frequently identified, their rates of isolation were not significantly higher among patients with persistent diarrhoea. No seasonal variation was observed in the rates of persistent diarrhoea. Although the introduction of family food to the diet was associated with higher rates, this factor was difficult to separate from the age dependent risks.

Introduction

Diarrhoeal diseases have been recognised as an important public health problem, particularly in children in developing countries. Although these diseases have been extensively studied over the past two decades, most of the research has focused on acute episodes of diarrhoea. With the advent of oral rehydration treatment as a breakthrough in the treatment of dehydration due to acute diarrhoea the problems of persistent, chronic, and non-dehydrating diarrhoeas have now gained prominence.

Although there is no consensus on the definition of persistent diarrhoea, most investigators use a working definition of diarrhoea that lasts for more than two or three weeks.[1] It may be defined clinically as an acute episode continuing beyond its usual course because of complications of the primary illness or a synergism between the infection and an underlying condition, such as malnutrition. From 1982 onwards reports from Matlab have suggested that about one fifth of deaths in children under 5 were associated with diarrhoea and that more than half of all the deaths due to diarrhoea were attributed to chronic diarrhoea.[2] Similar findings have been reported by Black *et al* from studies conducted in Peru.[3]

In an attempt to describe the experience with persistent diarrhoea in Bangladesh we reviewed patients attending our clinical research centre to determine the clinical features of the syndrome.

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Methods

At the clinical research centre patients are initially screened at entry according to the degree of dehydration and the presence or absence of complications. Patients are first examined by nurses to distinguish between complicated and uncomplicated diarrhoea. If there are complications patients are referred to a physician for consultation and if necessary for admission to the medical ward. For patients with uncomplicated diarrhoea the nurse screens for dehydration and categorises the diarrhoea by the degree of dehydration according to methods recommended by the World Health Organisation.[4] Patients with no visible signs of dehydration are given packets of oral rehydration solution and discharged with advice. Those with mild dehydration are referred to the oral rehydration pavilion for treatment, and those with moderate and severe dehydration are admitted to the treatment centre.[5]

Since a large number of patients attend with diarrhoea (>70 000 a year) a surveillance system was established in 1980 to study the characteristics of these patients, of whom over one third are children under 5. The surveillance system has been described elsewhere.[6] Every 25th patient who reports to this hospital is enrolled and a pretested questionnaire is administered to each patient to elicit demographic and clinical information, including previous drug use. The patient is then examined by a physician, and stool and rectal swabs are collected for laboratory investigations.

Stool samples are cultured for enterotoxigenic *Escherichia coli*, shigella, *Campylobacter jejuni*, *Vibrio cholerae* 01, *V cholerae* non-01, and salmonella. Rotavirus is identified by enzyme linked immunosorbent assay (ELISA). *Entamboeba histolytica*, *Giardia lamblia*, and cryptosporidium are identified by stool microscopy. The patients' length or height and weight are measured at discharge. Data are collected on precoded forms, which are stored and analysed on computer using the Statistical Analytical System package.

For this study the data collected over three consecutive years (1983-5) were analysed. As persistent diarrhoea is of most consequence in children under 5 we analysed data only from patients under 5. Data on feeding was available for the ages 0-35 months only.

Statistical analysis—Eleven possible risk factors of persistent diarrhoea were identified, and the contribution of each of these was analysed in two stages. Firstly, all the factors were analysed in univariate fashion taking one at a time and comparing their occurrence in children under 5 who had persistent diarrhoea and in children whose diarrhoea was of shorter duration. The significance of all these factors in predicting persistent diarrhoea was tested by the χ^2 test (two tailed).

Definitions—Diarrhoea was defined as three or more loose stools or one episode of mucoid or bloody stool in a day. Dehydration was assessed according to the guidelines described by WHO.[4] Persistent diarrhoea was defined as diarrhoea lasting for more than 15 days before the patient attended this centre. Measles was defined as a history of rash with fever lasting for four to five days within a month of the visit to hospital. A history of night blindness was obtained from the mother. Lower respiratory tract infection was defined as the presence of crepitations on auscultation. Vitamin A deficiency was found by examining the eyes. The nature and quantity of antibiotics consumed could not be clearly identified, but mothers were asked to describe the medicine bottles and state their costs.

Results

A total of 4155 patients under 5 who visited the clinical research centre during 1983-5 comprised the study subjects in this analysis. Of these, 410 (10%)

TABLE I—*Management of 4155 children aged under 5 who attended with acute and persistent diarrhoea*

Management of patients	Acute diarrhoea No	Acute diarrhoea %	Persistent diarrhoea No	Persistent diarrhoea %
Discharged by screening nurse for oral rehydration	501	13	85	21*
Admitted for oral rehydration treatment	1522	41	165	40
Admitted to treatment centre	1369	37	81	20
Admitted to medical ward	309	8	73	18*
Serious problems other than diarrhoea. Referred to other hospital	44	1	6	1
Total	3745		410	

*<0·01.

TABLE II—*Distribution of patients (expressed as percentages) according to risk factors by duration of diarrhoea*

Risk factors	Duration of diarrhoea ≤14 days (n=3745)	Duration of diarrhoea >14 days (n=410)	Significance
Dehydration:			
None	23	39	p<0·00001
Mild	52	43	
Moderate	21	15	
Severe	4	3	
Stool characteristics:			
Watery	80	53	p<0·0001
Not watery	20	47	
Stool character:			
Mucoid	37	49	p<0·0001
Bloody	<1	<1	
Mucoid+blood	11	31	
History of cough:			
None	56	52	p<0·0001
Before diarrhoea	24	16	
After diarrhoea	20	32	
Chest:			
Clear	92	85	p<0·0001
Bronchial sound	5	7	
Crepitation	3	8	
Antibiotic use (before attending hospital)	34	57	p<0·001
History of measles (within past month)	6	9	NS
Weight/height <70%	3	8	p<0·0001
Shigella spp	10	14	NS
Campylobacter jejuni	12	10	NS
Giardia lamblia	4	4	NS
Vitamin A deficiency:			
None	94	84	p<0·0001
Night blindness	<1	5	
Conjunctival xerosis	5	13	
Death in hospital	<1	2	p=0·001

TABLE III—*Prevalence of breast feeding and consumption of family food among children with acute and persistent diarrhoea (information available only for children under 36 months)*

Age (months)	Acute diarrhoea No (n=3149)	Acute diarrhoea No (%) breast fed+family food (A) (n=2580)	Persistent diarrhoea No (n=318)	Persistent diarrhoea No (%) breast fed+family food (P) (n=198)	Odds ratio P/A
0-5	454	350 (77·1)	34	26 (76·5)	0·99
6-11	1082	943 (87·2)	89	72 (80·9)	0·93
12-17	701	634 (90·4)	57	46 (80·7)	0·89
18-23	428	359 (83·9)	51	12 (23·5)	0·28**
24-29	321	201 (62·6)	57	24 (42·1)	0·67*
30-35	163	93 (57·1)	30	15 (50·0)	0·88

**p<0·01; *p<0·05.

TABLE IV—*Prevalence of breast feeding and no family food among children with acute and persistent diarrhoea (information available only for children under 36 months)*

Age (months)	Acute diarrhoea No (n=3149)	Acute diarrhoea No (%) breast fed only (A)	Persistent diarrhoea No (n=318)	Persistent diarrhoea No (%) breast fed only (P)	Odds ratio P/A
0-5	454	302 (66·5)	34	19 (55·9)	0·84
6-11	1082	660 (61·0)	89	44 (49·4)	0·81
12-17	701	240 (34·2)	57	17 (29·8)	0·87
18-23	428	89 (20·8)	51	6 (11·8)	0·57*
24-29	321	26 (8·1)	57	6 (10·5)	1·30**
30-35	163	7 (4·3)	30	3 (10·0)	2·33**

*p<0·05; **p<0·01.

gave histories of persistent diarrhoea (duration of diarrhoea over 14 days). Table I shows how the patients were managed. A higher percentage of children with persistent diarrhoea than with acute episodes of diarrhoea needed admission to the medical ward owing to complications but did not require rehydration. We found no seasonal pattern of admission for persistent diarrhoea.

Table II lists the factors that were considered to be related to persistent diarrhoea. Children presenting with no dehydration or only a mild degree were more likely to have persistent diarrhoea. Patients with watery stools were more likely to have acute diarrhoea, but patients with bloody or mucoid stools or both were more likely to have persistent diarrhoea. A history of previous antibiotic use, night blindness, and poor nutrition (weight/height <70% of the median of the National Centre for Health Statistics' standard)[7] were also significantly more common among patients with persistent diarrhoea, and death occurred more often among those patients.

As feeding histories were available only for children under 3 we looked at the effects of breast feeding with and without the addition of other items in the diet in 6 month age groups (tables III and IV). Lack of breast feeding appeared to be a risk factor for persistent diarrhoea. This was most apparent in children over 18 months, among whom 51 (37%) children in the persistent diarrhoea group were breast fed compared with 650 (72%) children in the group with acute diarrhoea. Rates of persistent diarrhoea increased in the third year of life among those not supplemented with family diet (table IV).

Discussion

This study has shown that persistent diarrhoea is common among children aged under 5 attending the clinical research centre. During the three years of the analysis persistent diarrhoea was identified among 10% of patients under 5 with no detectable differences in sex and season. Unlike patients with diarrhoea of less than two weeks' duration the patients with persistent diarrhoea usually had several associated conditions, notably mucus and blood in the stool, vitamin A deficiency, malnutrition, and a history of antibiotic use. Although bacterial and parasitic agents were frequently identified in stools of patients with persistent diarrhoea, the isolation rates for *Shigella* spp, *C jejuni*, and *G lamblia* were not significantly different from those for patients with acute diarrhoea.

Breast feeding and the consumption of family foods are correlated with age and all three may be important in the risk of developing persistent diarrhoea. Among six age groups a history of breast feeding was always less common in the persistent diarrhoea group, and there was a suggestion that the difference in the rate of breast feeding widened for children aged 18-23 months. After 1 year of age most of the children of both groups were receiving family food. Vitamin A deficiency and case fatality rates were both higher for persistent diarrhoea than for acute diarrhoea, though the rates were low for both.

Several limitations of the data are as follows. Firstly, we relied on the history given by the parents at the time of the visit so the duration of diarrhoea, antibiotic use, and dietary history, for example, are not known with precision. The health workers obtaining the information, however, were not aware of the hypothesis regarding persistent diarrhoea and bias is unlikely.

Secondly, from our results we cannot separate cause from effect for many of the characteristics. For example, use of an antibiotic before the visit to us might have been a result of the persistent diarrhoea

rather than a risk factor for diarrhoea. Alternatively, antibiotic use as a factor might have selected out a group of patients who failed to respond while at the same time antibiotics contributed to the disease process by suppressing normal intestinal flora. Thus a given characteristic which correlates with persistent diarrhoea could both be a result of the factor and also contribute to it. Similarly, the correlation between malnutrition and persistent diarrhoea could be both a cause and an affect. Persistent diarrhoea is associated with malabsorption and anorexia. In addition the malnourished child may be at higher risk of persistent diarrhoea.

Thirdly, since the faecal specimen was obtained late in the illness the pathogens recovered almost certainly were affected by the intervening events—for example, antibiotic use and clearance of bacteria. A prospective study with surveillance would be needed to identify pathogens occurring early in the episode if a given agent was to be associated with persistent diarrhoea.

Finally, the results of using patients with acute diarrhoea as a comparison group should be interpreted with caution. For risk factor analysis a group of healthy children from the community would be better; nevertheless, the comparison with other patients is helpful in formulating a hypothesis for future studies.

Follow up prospective studies are needed to define more clearly the role of breast feeding, invasive organisms, vitamin A deficiency, and use of antibiotics as risk factors and protective factors in the pathogenesis of persistent diarrhoea.

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1 Ament ME, Barclay GN. Chronic diarrhea. *Pediatr Ann* 1982;**11**:124-31.
2 Chowdhury MK, Razzaque A, Mostafa G, Sarder AM, D'souza S. *Demographic surveillance system—Matlab.* Vol 10. *Vital events and migration-tables, 1980.* Dhaka: International Centre for Diarrhoeal Disease Research, Bangladesh, 1982:61. (Scientific report No 58.)
3 Black RE, Lopez de Ramana G, Brown KH, *et al.* Development of nutritious hygienic weaning food to reduce diarrhea in Peru. *Johns Hopkins University annual report. 1982-1983.* Baltimore: Johns Hopkins, 1983.
4 World Health Organisation. *Diarrhoeal diseases control programme. A manual for the treatment of acute diarrhoea.* Geneva: WHO, 1980. (WHO/CDD/SER/80.2.)
5 Samadi AR, Islam MR, Aziz KMS. *ICDDR, B model for treatment of diarrhoeal diseases.* Dhaka: International Centre for Diarrhoeal Disease Research, Bangladesh, 1982:1-12. (Special publication No 19.)
6 Stoll BJ, Glass RI, Huq MI, Khan MU, Holt JE, Banu H. Surveillance of patients attending a diarrhoeal disease hospital in Bangladesh. *Br Med J* 1982;**285**:1185-8.
7 World Health Organisation. *A guideline for the measurement of nutritional impact of supplementary feeding programmes aimed at vulnerable groups.* Geneva: WHO, 1979. (FAP 79.1.)

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BOOKS RECEIVED

Alternative medicine

A World Without AIDS: the Controversial Holistic Health Plan. L Chaitow, S Martin. (Pp 288; £6.99 paperback.) Wellingborough: Thorsons, 1988. ISBN 0-7225-1632-0.

Anaesthesia

Controversies in Cardiovascular Anesthesia. Ed P N Fyman, A W Gotta. (Pp 208; figs; £39.50.) Boston: Kluwer, 1988. ISBN 0-89838-985-2.

Anatomy

Michael Salmon: Arteries of the Skin. Ed G I Taylor, M N Tempest. (Pp 208; figs; £39.) London: Churchill Livingstone, 1988. ISBN 0-443-03605-5.

Biochemistry

Clinical Studies in Medical Biochemistry. Ed R H Glew, S P Peters. (Pp 288; figs; £15 paperback.) New York: Oxford University Press, 1988. ISBN 0-19-503922-X.

Biology

Intraoperative Cytology. An Adjunct to Frozen Sections. J A Wilkerson, J M Bonnin. (Pp 104; colour plates; £43.) New York: Igaku-Shoin, 1987. Distributed by Williams and Wilkins. ISBN 0-89640-131-6.

Environmental and public health

IPCS International Programme on Chemical Safety. "Epichlorohydrin Health and Safety Guide." United Nations Environment Programme/International Labour Organisation/World Health Organisation. (Pp 42; $3.) Geneva: World Health Organisation, 1987. ISBN 92-4-154333-7.

IPCS International Programme on Chemical Safety. "Isobutanol Health and Safety Guide." United Nations Environment Programme/International Labour Organisation/World Health Organisation. (Pp 42; $3 paperback.) Geneva: World Health Organisation, 1987. ISBN 92-4-154665-4.

Epidemiology

The Challenge of Epidemiology: Issues and Selected Readings. Scientific Publication No 505. Ed C Buck, A Llopis, E Nájera, M Terris. (Pp 1008; figs; $30 paperback.) Washington DC: Pan American Health Organization, 1988. ISBN 92-75-11505-2.

Haematology

Essentials of Haemostasis and Thrombosis. L A Kay. (Pp 300; figs; £11.95 paperback.) Edinburgh: Churchill Livingstone, 1988. ISBN 0-443-03686-1.

Health care issues

Health Planning for Effective Management. Ed W A Reinke. (Pp 304; £19.50.) New York: Oxford University Press, 1988. ISBN 0-19-505337-0.

Laboratory medicine

Dictionary of Medical Laboratory Sciences. Ed A D Farr. (Pp 328; £15.95.) Oxford: Blackwell Scientific, 1988. ISBN 0-632-01762-7.

Safety in Clinical and Biomedical Laboratories. Ed C H Collins. (Pp 176; £11.50 paperback.) London: Chapman and Hall, 1988. ISBN 0-412-28370-0.

Medical education

Heinemann Medical: Student Reviews. "Primary Care." Ed B Jarman. Series editor P Richards. (Pp 208; £7.95 paperback.) London: Heinemann Medical, 1988. ISBN 0-433-00028-7.

Learning Physiology Through MCQ. A Comprehensive Text. M L Forsling. (Pp 232; £8.95 paperback.) Chichester: Wiley, 1988. ISBN 0-471-91026-0.

Learning Psychiatry Through MCQ. A Comprehensive Text. Ed T Sensky. (Pp 272; £9.95 paperback.) Chichester: Wiley, 1988. ISBN 0-471-91896-2.

MCQs and Short Notes in Psychiatry. A S Burns, A S David, M Farrell. (Pp 144; £6.95 paperback.) London: Wright, 1988. Distributed by Butterworth. ISBN 0-7236-0938-1.

MCQs for Psychiatric Studies. C Freeman. (Pp 164; £6.95 paperback.) Edinburgh: Churchill Livingstone, 1988. ISBN 0-443-03230-0.

Neurology

Butterworths International Medical Reviews: Neurology 9. "The Molecular Biology of Neurological Disease." Ed R N Rosenberg, A E Harding. (Pp 274; figs; £35.) London: Butterworth, 1988. ISBN 0-407-02400-X.

Major Problems in Neurology. Vol 16. "Neurological Infections." M Wood, M Anderson. Consulting editor Sir John Walton. (Pp 680; figs; £60.) Toronto: Saunders, 1988. Distributed by Harcourt Brace Jovanovich. ISBN 0-7020-1324-2.

Obstetrics and gynaecology

Genital Tract Infection in Women. Ed M J Hare. (Pp 392; figs and colour plates; £50.) Edinburgh: Churchill Livingstone, 1988. ISBN 0-443-03485-0.

Illustrated Textbook of Obstetrics. G Chamberlain, C R Gibbings, Sir John Dewhurst. (Pp 272; figs; £13.50 paperback.) London: Gower Medical Publishing, 1988. ISBN 0-397-44580-6.

The Malformed Fetus and Stillbirth. A Diagnostic Approach. R M Winter, S A S Knowles, F R Bieber, M Baraitser. (Pp 328; figs; £75.) Chichester: Wiley, 1988. ISBN 0-471-90946-7.

Medical Counselling Before Pregnancy. Ed D R Hollingsworth, R Resnik. (Pp 576; figs; £50.) New York: Churchill Livingstone, 1988. ISBN 0-443-08517-X.

Oncology

Cambridge Monographs on Cancer Resarch. "The Chemistry and Biology of Benz[a]anthracenes." M S Newman, B Tierney, S Veeraraghavan. (Pp 244; £35.) Cambridge: Cambridge University Press, 1988. ISBN 0-521-30544-6.

Cancer Treatment and Research. "Immunotoxins." Ed A E Frankel. Series editor W L McGuire. (Pp 592; figs; £93.25.) Boston: Kluwer, 1988. ISBN 0-89838-984-4.

Contemporary Biomedicine. "Leukolysins and Cancer." Ed J H Ransom, J R Ortaldo. (Pp 344; figs; $79.50.) New Jersey: Humana, 1988. ISBN 0-89603-125-X.

IARC Scientific Publications. No 88. Vol 5. "Cancer Incidence in Five Continents." Ed C Muir, J Waterhouse, T Mack, *et al.* (Pp 1012; figs; £50.) Oxford: Oxford University Press, 1988, for International Agency for Research on Cancer. ISBN 92-832-1188-X.

Thinking About Breast Cancer. J Emanuel, L Thomson, M Twomey. (Pp 30; figs; 5-100 copies £5.95 per 5, 100-500 copies £5.45 per 5, 500-1000 copies £4.95 per 5, 1000 plus copies £4.45 per 5. A 5% handling charge will be added to invoiced orders.) Cambridge: National Extension College, 1988. ISBN 1-85356-003-0.

Orthopaedics

The Crucial Ligaments: Diagnosis and Treatment of Ligamentous Injuries About the Knee. Ed J A Feagin Jr. (Pp 600; figs; £95.) New York: Churchill Livingstone, 1988. ISBN 0-443-08549-8.

Paediatrics

Disorders of Gastrointestinal Motility in Childhood. Ed P J Milla. (Pp 160; figs; £21.50.) Chichester: Wiley, 1988. ISBN 0-471-91780-X.

Pathology

Guides to Clinical Aspiration Biopsy. "Retroperitoneum and Intestine." K C Suen. Series editor T S Kline. (Pp 232; figs; £35.) New York: Igaku-Shoin, 1987. Distributed by Williams and Wilkins. ISBN 0-89640-125-1.

Psychiatry

Animal Models of Psychiatric Disorders. Vol 2. "An Inquiry into Schizophrenia and Depression." Volume and series editors P Simon, P Soubrié, D Widlocher. (Pp 220; figs; £85.90.) Basel: Karger, 1988. Distributed by John Wiley and Sons. ISBN 3-8055-4757-9.

Chronic Pain. Ed R D France, K Ranga Rama Krishnan. (Pp 584; £19.50.) Washington DC: American Psychiatric Press, 1988. Distributed by Cambridge University Press. ISBN 0-88048-206-0.

Electroconvulsive Therapy. R Abrams. (Pp 248; £25.) New York: Oxford University Press, 1988. ISBN 0-19-504536-X.

The Key to Genius. D J Hershman, J Lieb. (Pp 224; £14.95.) New York: Prometheus Books, 1988. ISBN 0-87975-437-0.

Medical Aspects of Anorexia Nervosa. S Bhanji, D Mattingly. (Pp 152; figs; £22.) London: Wright, 1988. Distributed by Butterworth. ISBN 0-7236-1115-7.

Physical Treatments in Psychiatry. L G Kiloh, J S Smith, G F Johnson. (Pp 492; £49.50.) Melbourne: Blackwell Scientific, 1988. ISBN 0-86793-112-4.

Miscellaneous

The Assertive Pregnancy. N Wesson. (Pp 272; £4.99 paperback.) Wellingborough: Grapevine, 1988. ISBN 0-7225-1782-3.

Encyclopaedia of Medical Devices and Instrumentation. Editor in chief J G Webster. (Pp 3074; figs; £325, in 4 volumes.) New York: Wiley, 1988. ISBN 0-471-82936-6.

Journey into Madness. Medical Torture and the Mind Controllers. G Thomas. (Pp 384; £12.95.) London: Bantam Press, 1988. ISBN 0-593-01142-2.

Living with Chronic Illness. The Experience of Patients and Their Families. Ed R Anderson, M Bury. (Pp 272; £28 hardback, £9.95 paperback.) London: Unwin Hyman, 1988. ISBN hardback 0-04-362066-3, paperback 0-04-362067-1.

Meditation: a Beginner's Guide. G Dawrant. (Pp 40; figs; £4.70 paperback.) Stress Management Associates Inc, Box 1030, 10665 Jasper Avenue, Edmonton, Alberta T5J 3S9, Canada. ISBN 0-921150-00-8.