

Episode-specific risk factors for progression of acute diarrhoea to persistent diarrhoea in West African children

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Abstract

The aim of the present study, carried out in Guinea-Bissau, West Africa, was to identify episode-specific risk factors for persistent diarrhoea (PD) related to clinical observations and management efforts. We followed 319 episodes of childhood diarrhoea by repeated household interviews until the episode stopped or after 14 days with diarrhoea. Children who still had diarrhoea after 14 days ($n=40$, 12.5% of episodes) were regarded as suffering from PD. Clinical signs, perceived by the mother, were recorded together with care-seeking behaviour and management actions. Tired and rapid breathing prior (OR=6.52 (95% CI 1.69–25.1)), mother had to force breast feeding (OR=8.01 (2.99–21.5)) and current infection with *Cryptosporidium* (OR=5.53 (2.10–14.6)) were the most important independent risk factors for the development of PD. Late consultation (>48 h) was associated with PD, reflecting that these episodes initially were less acute. Use of oral rehydration salts did not have an impact on development of PD, whereas home medication tended to increase the risk of PD. Our study confirms the close association between systemic illness and PD as well as the importance of cryptosporidiosis as a cause of PD. We were unable to identify management factors with a significant influence on the risk of developing PD.

Keywords: persistent diarrhoea, risk factors, case management, maternal perception, oral rehydration salts, *Cryptosporidium*, Guinea-Bissau

Introduction

As oral rehydration therapy programmes achieve success in controlling deaths from acute diarrhoea, deaths from persistent diarrhoea (PD) become more prominent, accounting for about 65% of all diarrhoea-associated deaths (SACHDEV *et al.*, 1991; BHANDARI *et al.*, 1992; LIMA *et al.*, 1992; MØLBAEK *et al.*, 1992). From a public health point of view, persistent episodes are a frustrating problem for care-takers as well as health professionals, resulting in mis-management including adverse drug therapy in an attempt to terminate the illness. PD is part of a continuum in the clinical spectrum of diarrhoeal episodes, most of which stop within a few days or a week whereas 3–20% of acute episodes last for more than 14 days (ANONYMOUS, 1988; DUTTA *et al.*, 1991; LIMA & GUERRANT, 1992; BLACK, 1993; GRACEY, 1993). The limit at 14 days is arbitrary though some investigators have reported a significant rise in mortality in episodes lasting more than 14 days (BHAN *et al.*, 1986). The aetiology and pathogenesis are usually considered to be multifactorial and factors such as nutritional status, sequential infections, and immunological factors could be responsible for the continuation of the vicious cycle of malnutrition and diarrhoea (ANONYMOUS, 1988; LIMA & GUERRANT, 1992; BLACK, 1993). A number of risk factors have been associated with PD, including young age, unhygienic environment, no maternal education, not breast feeding, recent episode of diarrhoea, malnutrition, vitamin-A deficiency, cell-mediated immune deficiency, bloody or mucoid stools, and a few specific pathogens (*Cryptosporidium* and entero-aggregative *Escherichia coli*) (SHAHID *et al.*, 1988; MAHALANABIS *et al.*, 1991; BAQUI *et al.*, 1992; VICTORA *et al.*, 1992; MØLBAEK *et al.*, 1993; BHUTTA & HENDRICKS, 1996). However, knowledge of early management and reported symptoms in the initial phase of an episode as predictors for PD is limited (ANONYMOUS, 1988; VICTORA *et al.*, 1992; BLACK, 1993). We conducted the present community study in a West African suburb with the aim of identifying episode-specific determinants for the progression of an acute episode of diarrhoea to PD, with particular emphasis on the role of early management and reported signs and symptoms.

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Materials and Methods

Study area

The study was conducted in Bandim, a suburban area of the capital of Guinea-Bissau. The population, about 26000, is served by 1 health centre. A mother-and-child health clinic and a paediatric ward at the Central Hospital are available in the centre of the city, 1.5–3 km from the study area. A demographic health surveillance system has been functioning in the area since 1978. The epidemiology and aetiology of childhood diarrhoea in the study area has been described elsewhere (MØLBAEK *et al.*, 1994a, 1994b). The children with acute diarrhoea were identified by a weekly household morbidity survey for children under 5 years of age (SODEMANN *et al.*, 1996). Data on hospitalization were obtained through the routine monitoring of admissions to the national hospital of all children from the study area.

Study population

Three hundred and nineteen episodes of diarrhoea in children below 5 years were investigated by repeated home visits and interviews with the mothers until diarrhoea disappeared. The methodology has been described in detail elsewhere (SODEMANN *et al.*, 1996). The prevalence of human immunodeficiency virus (HIV)-2 among children in the area was 0.6% (POULSEN *et al.*, 1993). In short, children with ≥ 3 stools in the preceding 24 h were eligible for the study and each child could participate only with 1 episode. Interviews were carried out at intervals of 2 days, beginning at the second day of the episode and ending when the mother stated that the diarrhoea had stopped, the child had been hospitalized, or after 14 days with diarrhoea. The interview focused on perceived morbidity, experience with oral rehydration as well as management and care-seeking practices. Stools were examined for eggs and cysts in the case of diarrhoea as described elsewhere but only *Cryptosporidium* infection was considered in the present study (MØLBAEK *et al.*, 1994b). Amount of oral rehydration salt (ORS) administered to the child was categorized into none, low, medium or high according to number of cups of ORS solution. A cup was defined as the standard plastic cup sold at local market places.

Statistical methods

Perceived symptoms, socioeconomic and care-related factors associated with PD at the 10% level were tested by logistic regression with PD as outcome, and a

reduced model was created by step-wise elimination. A significance level of 5% was used for the elimination of variables from the multivariate model.

Results

None of the episodes stopped in the first 4 days, while 192 of 319 (60%) stopped on days 5 or 6, 72 of 319

(22.6%) stopped on days 7 or 8 and 15 of 319 (4.7%) stopped on days 9 or 10. Forty of the 319 children (12.5%) still had diarrhoea when the interviews stopped after 14 days and these episodes were regarded as episodes of PD, while the rest (279) were considered to be acute episodes of diarrhoea. Table 1 shows the variables that were significant at the 10% level.

Table 1. Determinants of progression from acute diarrhoea to persistent diarrhoea in 319 episodes of acute diarrhoea

Determinant	No. of children	No. of children with persistent diarrhoea (%)	Risk of persistent diarrhoea ^a (odds ratio (95% CI))
Clinical history and nutrition			
Current or previous infection with <i>Cryptosporidium</i>			
No	260	24 (9.2)	1
Yes	59	16 (27.1)	3.66 (1.68–7.94)
Other episode of diarrhoea within 30 days prior to current episode			
No	201	23 (11.4)	1
Yes	85	11 (12.9)	1.15 (0.53–2.48)
Absent or hospitalized ^b	33	6 (18.2)	1.72 (0.64–4.61)
Breastfed at onset of episode			
No	46	2 (4.4)	1
Yes	255	37 (14.5)	0.30 (0.12–1.15)
No information	18	1 (5.6)	0.40 (0.10–2.68)
Measles vaccination			
No	192	17 (8.9)	1
Yes	127	23 (18.1)	2.28 (1.16–4.46)
Maternal reporting of symptoms			
Sunken eyes			
No	218	21 (9.6)	1
Yes	101	19 (18.8)	2.17 (1.11–4.26)
Weak and uninterested child			
No	260	26 (10.0)	1
Yes	59	14 (23.7)	2.80 (1.36–5.78)
Mother had to force breast feeding			
No	224	18 (8.0)	1
Yes	50	20 (40.0)	7.69 (3.33–16.7)
Not breast fed	45	2 (4.4)	0.75 (0.18–2.44)
Tired and rapid breathing			
No	292	30 (10.3)	1
Yes	27	10 (37.0)	5.14 (2.16–12.2)
Management of diarrhoea			
Received drugs at home without prior consultation			
No	290	31 (10.7)	1
Yes	29	9 (31.0)	3.76 (1.57–8.99)
Child received ORS			
No	133	10 (7.5)	1
Yes	186	30 (16.1)	2.37 (1.11–5.03)
Timing of consultation			
Early (within 48 h)	84	9 (10.7)	1
Late (later than 48 h)	22	9 (40.9)	5.77 (1.93–17.3)
No consultation	213	22 (10.3)	0.96 (0.42–2.18)
Child received traditional treatment			
No	180	17 (9.4)	1
Yes	139	23 (16.5)	1.90 (0.97–3.72)
Previous use of ORS			
No	161	25 (15.5)	1
Yes	158	15 (9.5)	0.57 (0.29–1.13)
Background factors			
Mother's school education			
No	124	24 (19.4)	1
Yes	195	14 (7.4)	0.37 (0.19–0.73)
Age of child (months)			
0–5	83	4 (4.8)	1
6–11	88	19 (21.6)	5.44 (1.77–16.8)
≥12	148	17 (11.5)	2.56 (0.83–7.89)

^aThe following variables were not significant at the 10% level: previous infection with measles, child has fever, number of reported symptoms, at least 1 sign of dehydration, mother: child is severely affected, nurse: child is severely affected, mother had ORS sachets at onset of diarrhoea, specific drugs given (none, antimalarial, antibiotic), quantity of ORS administered, timing of ORS administration, mother is primary care-taker, age of mother, sex of child, socioeconomic group, season and perceived cause of diarrhoea (teething).

^bOf the 33 children, 9 were hospitalized (2 with diarrhoea). Absent means absent at at least 1 home visit during the preceding 30 days.

Clinical history and nutrition

Infection with *Cryptosporidium* was a significant determinant for PD. The 21 children who were infected with *Cryptosporidium* during the episode had an odds ratio (OR) of 2.31 (95% CI 0.72–7.44) of progression to PD while the 38 children who had previously experienced the infection had an OR of 4.54 (95% CI 2.03–10.1) of progression to PD. Children who experienced infection with *Cryptosporidium* in the age-group 6–11 months had the highest risk of developing PD (data not shown). Lack of breast feeding was not a significant predictor of PD.

Maternal reporting of symptoms and management of diarrhoea

Systemic factors such as weak and uninterested child, rapid and tired breathing, and mother having to force her child to breast feed were strongly associated with PD. Symptoms of dehydration were less strongly associated or negatively associated with PD. Severity rating by the mother and the nurse was not related at all with PD.

The administration of standard ORS solution did not appear to protect against the development of PD since children receiving ORS were more likely to develop PD (OR=2.37, 95% CI 1.11–5.03). Neither timing nor quantity of administered ORS was associated with the development of PD.

Home medication with antibiotics without prior consultation and consultation later than 48 h after onset of diarrhoea were strongly associated with PD.

Background factors

Children aged more than 5 months and children whose mothers had no school education had an increased risk of developing PD.

Multivariate analysis of risk factors

Significant factors were modelled by stepwise multiple logistic regression with all background factors. Among the clinical factors, rapid breathing and mother having to force breast feeding enclosed most of the clinical information in the other clinical factors. The resulting model is shown in Table 2.

Table 2. Multivariate analysis of determinants for development of persistent episode of diarrhoea in 319 episodes of acute diarrhoea

Determinant	No. of children	Persistent diarrhoea (odds ratio (95% CI))
Mother had to force child to breast feed		
No	224	1
Yes	50	8.01 (2.99–21.5)
Not breast fed	45	0.45 (0.10–2.20)
Tired and rapid breathing		
No	292	1
Yes	27	6.52 (1.69–25.1)
Consultation		
Early (within 48 h)	84	1
Late (later than 48 h)	22	11.6 (2.19–61.0)
No consultation	213	2.07 (0.55–7.79)
Previous use of ORS		
No	161	1
Yes	158	0.35 (0.13–0.92)
Infection with <i>Cryptosporidium</i>		
No	260	1
Yes	59	5.53 (2.10–14.6)
Other episode of diarrhoea within 30 days prior to current episode		
No	201	1
Yes	85	1.76 (0.66–4.67)
Absent, travelling or hospitalized	33	4.01 (1.01–14.2)
Child's age (months)		
0–5	83	1
6–11	88	4.67 (1.18–18.5)
≥12	148	4.01 (1.00–16.0)

Discussion

The aim of the present study was to identify episode-specific determinants for acute diarrhoea progressing to PD. The results should be interpreted with some caution, owing to the relatively small size of the cohort and the low number of outcomes. Some of the variables that were significantly associated with PD in univariate analyses (Table 2) may be related to confounding or interaction with age. These include breast feeding, measles vaccine, and previous use of ORS. Nevertheless, 7 factors were identified as independent determinants for development of PD (Table 2).

In the 319 children with diarrhoea, as many as 12.5% of the acute episodes of diarrhoea became persistent. This may be related to the design of the study. Only children with ≥3 stool passages at day 2 in the episode were eligible, thereby excluding mild episodes with only 1 or 2 days' duration. Persistent episodes are not associated with dehydration in the early phase, but are often concomitant to or associated with a progressive weight loss, often accompanied by systemic infections and an increased risk of death in a longer time perspective (BLACK, 1993). This view of the insidious nature of PD is corroborated by the present study. Thus, the variable 'mother having to force breast feeding', which was correlated with clinical signs such as weak and uninterested child, sunken eyes, and tired and rapid breathing, was a major predictor of progression to PD, whereas variables indicating signs of acute dehydration or increased thirst could not predict progression to PD. We have previously shown that a child's breast feeding behaviour as perceived by the mother during a diarrhoeal episode had important influence on maternal perception of severity and subsequent care-seeking behaviour (SODEMANN *et al.*, 1996). In particular, chest infection in relation to acute diarrhoea has repeatedly been reported by other studies as a risk factor for increased duration of a diarrhoeal episode (SHAHID *et al.*, 1988; MAHALANABIS *et al.*, 1991; BAQUI *et al.*, 1992), and our study confirms that severe systemic illness is associated with PD. Furthermore, late consultation was associated with increased risk of PD, reflecting that severity increases as time passes. Home medication before consultation tended to increase the risk of developing PD. Several studies have reported an association between use of antibiotics and increased duration of diarrhoeal episodes (SHAHID *et al.*, 1988; ARAYA *et al.*, 1991; BAQUI *et al.*, 1992). This finding may reflect initial severity, but may also be related to antibiotic-associated diarrhoea.

It is generally agreed that PD may be initiated with almost any agent from the wide array of enteric pathogens that are responsible for the high rates of diarrhoea in developing countries. In addition, studies from Guinea-Bissau suggest that *Cryptosporidium* is associated with PD (MØLBAK *et al.*, 1993). The present study supports this, but shows furthermore that even infection with *Cryptosporidium* prior to the current episode clearly increases the risk of progression to PD. Delayed mucosal injury or persistency of low-grade infections may be possible explanations of this finding. Larger studies are needed to confirm this association, and in particular to investigate long-term morbidity following cryptosporidiosis in infancy and early childhood.

A recent episode of diarrhoea is a known risk factor for PD, though this finding is a subject of debate (ARAYA *et al.*, 1991; SAZAWAL *et al.*, 1991; BLACK, 1993; KNUDSEN, 1994). In addition, children who had been absent, travelling or hospitalized during the preceding month had a higher risk of developing PD. This group probably comprised children who had repeated episodes of diarrhoea, hence they were often absent because they were brought in for consultation at hospitals, clinics, or traditional healers.

It is generally agreed that ORS has very limited effect on PD (MILLER, 1992; BEHRENS, 1993), but the role of administration in the acute phase has not been clarified

(BAQUI *et al.*, 1992). We could not demonstrate any significance of the timing of ORS administration. However, previous use of ORS was protective against PD, which may mirror better care practices including nutritional support. Hence, previous use of ORS may be a proxy for an experienced mother.

The associations between PD and factors such as signs of systemic infection, cryptosporidiosis and a previous diarrhoeal episode corroborate other studies of risk factors for PD. There are, however, also some dissimilarities between the present study and other studies. Lack of breast feeding was not a significant predictor of PD for a given acute episode of diarrhoea. The protective effect of breast feeding found in other studies may thus primarily be explained by a general protection against all types of diarrhoea rather than a specific effect against PD. Also, most episodes of PD take place in the age-groups in which children are still breast fed.

The present study showed that signs of severe systemic involvement and infection with *Cryptosporidium* were the most important factors for the progression of a given acute episode of diarrhoea to PD. This calls for a broader clinical view on PD. More emphasis should be put on integrated management of children with PD by searching for and treating concomitant infections along with the intensified feeding schemes. However, we could not demonstrate any positive effect of early treatment with ORS or early consultation on the duration of diarrhoea. This could be due to the minute amounts of ORS administered. Controlled intervention studies with early administration of correct amounts of different types of ORS are needed to determine the role of oral rehydration in the development of PD.

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