Original Article

Persistent Diarrhea: Risk Factors and Outcome

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ABSTRACT

Objective. To identify risk factors associated with Persistent diarrhea (PD) and deaths due to PD.

Methods. This prospective case control study included 60 children with PD (cases) and 60 children (controls) with acute diarrhoea (AD). Detailed history, examination and appropriate investigations were done for all children. Crude Odds ratio was calculated for each risk factor by univariate analysis and adjusted odds ratio was calculated by multivariate logistic regression.

Results. Prior antibiotic use, steroid use, anemia, vitamin A deficiency, malnutrition, LRI, UTI, oral candidiasis, and hyponatremia, were statistically significant risk factors by univariate analysis. Prior antibiotic use, vitamin A deficiency, malnutrition and LRI were independently associated with PD by multivariate logistic regression analysis. The risk factors for mortality were stool frequency more than 10 times per day, severe malnutrition, oral candidiasis, hypoalbuminemia and HIV positivity.

Conclusions. The presence of these risk factors should alert the clinician to take appropriate measures, to decrease the mortality. **[Indian J Pediatr 2010; 77 (8): 885-888]** *E-mail: drnbiswal@yahoo.com*

Key words: *Persistent diarrhea; Malnutrition; Hyponatremia, LRI*

Nearly 2 million children die in a year due to diarrhoea or diarrhea related illness.[1] Deaths due to AD has been reduced substantially due to the usage of ORS. Though PD accounts for 2-20% of total diarrhea cases, it accounts for 23-62% of all diarrhea related deaths. Hence, PD is a challenge to the pediatrician.[1,2] Since 1980, WHO has recognized PD as an area of research priority.[3] Studies focusing on identification of risk factors for mortality in PD are likely to improve the management and referral strategies and subsequently reduce the mortality and hence this study was conducted to identify the risk factors associated with PD and deaths due to PD.

MATERIAL AND METHODS

This prospective case control study was conducted in the department of Pediatrics, JIPMER, Pondicherry from November 2000 to April 2002. It included 60 children between one month to ten yr of age with persistent diarrhea (cases) and 60 children (controls) with acute diarrhea (AD). Diarrhea lasting in a child for more than 14 days was considered persistent. A detailed history regarding the duration of diarrhea, nature of stools, prior antibiotic use, previous history of immunodeficiency states (like measles, pertussis, chronic steroid therapy, malignancy), feeding practices, use of ORS, history of contact with TB and immunisation details were elicited and documented in a proforma. Anthropometric measurements including height, weight, mid arm circumference and head circumference, were done. Percentage for 'weight for age' and Z score for 'weight for height' were calculated, based on NCHS reference values. Systemic examination, assessment of dehydration and vitamin A deficiency were done in all children. Conjuctival xerosis, Bitot's spots, corneal xerosis and corneal ulcers were the signs of vitamin A deficiency looked for. In addition, associated illness like septicemia, urinary tract infection (UTI) and Lower respiratory tract infection (LRI) were specifically looked for. Lower respiratory tract infection (LRI) was defined as cough with increased respiratory rate for age.

Stool and urine samples of all children were cultured and examined microscopically. Workup for tuberculosis (TB) including Mantoux test, Chest radiograph, gastric aspirate and sputum AFB staining and culture were done

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in both the cases and controls. Associated illness like septicaemia, pneumonia and UTI were confirmed by blood culture, Chest radiograph and urine culture respectively. HIV screening by ELISA, and hemogram were done in addition to liver and renal function tests. Children were hospitalized for treatment whenever necessary and children with PD were followed up for 3 months after recovery. Risk factors were analysed in two stages. Crude Odds ratio was calculated for each risk factor by univariate analysis using chi square or Fishers test and adjusted odds ratio was calculated by multivariate logistic regression using SPSS PC+. A p value < 0.05 was considered statistically significant.

RESULTS

The general characteristics of the children in the two groups are shown in table 1. In both the groups majority were infants. Prior antibiotic use, steroid use, anemia, vitamin A deficiency, malnutrition, LRI, UTI, oral candidiasis, and hyponatremia were identified as statistically significant risk factors by univariate analysis (Table 2). Prior antibiotic use, vitamin A deficiency, malnutrition and LRI were independently associated with PD by multivariate logistic regression analysis (Table 3). Microbiological examination of stool, including microscopy and culture revealed the causative organism in only 13 (21.7%) cases and 6 (10%) controls. E.coli was isolated from stool culture in 4 (6.6%) children with PD while shigella was isolated in only 2 (3.3%). Giardia lamblia and Entamoeba trophozoites were documented in 2 (3.3%) and 4 (6.6%), cases respectively. Associated infection was found in 33 (55%) cases and 16(26%) controls. Among the cases, 16 (26.6%) had more than one infection. LRI and UTI were noted in 30 (50%) and 12 (20%) cases, respectively. Microbes isolated from urine included E.coli (2 cases), Klebsiella (2 cases) and candida (1 case). Urine culture was sterile in the other seven children. Bacteria isolated from blood included Group B Salmonella (1 case), Klebsiella (1 case), and Enterococcus (1 case). A diagnosis of Tuberculosis was established in 4 (6.7%) cases.

Table 1. General Characteristics of Children with Persistent Diarrhea and Acute Diarrhea

General characteristics	Persistent diarrhea n=60 (%)	Acute diarrhea n=60 (%)
Age		
<1 yr	30 (50)	37 (61.7)
1-5 yr	29 (48.4)	22 (36.7)
>5 yr	1 (1.6)	1 (1.6)
Sex		
Males	38 (63.3)	38 (63.3)
Females	22 (36.7)	22 (36.7)
M:F Ratio	1.7:1	1.7:1
Mean duration of diarrhea in days	31.2	4.04
Malnutrition		
Weight for height (Z < -2)	35 (58.3)	15 (25)
Weight for age (< 80%)	50 (83.3)	28 (46.8)
Associated infection	33 (55)	16 (26.6)
Mortality	5 (8.3)	0

In this study, five children (8.3%) with PD died. Among them, four were between one to five yr of age while one was an infant. Stool frequency more than 10 episodes per day, severe malnutrition, oral candidiasis, hypoalbuminemia and HIV positivity were the statistically significant risk factors for mortality by Fishers exact test (2 tailed). However, hypoalbuminemia and HIV positivity were the only risk factors which were statistically significant for mortality by multivariate logistic regression analysis.

DISCUSSION

In this study, 30 (50%) children were infants. Among them 13(21.7%) were within 6 months of age, while 17(28.3%) were between 6 to 12 months. Similar observations have been reported from Bangladesh.[4, 5] The male female ratio noted in the present study was 1.7:1. A similar ratio of 2:1and 2.6:1 has been reported in literature.[6-9] Malnutrition expressed as Z-score, for weight for height less than - 2 was identified as a risk factor for PD by both univariate and multivariate analysis (Table 2, 3). Use of Z- score to diagnose malnutrition has the advantage that unlike percentage of median, the interpretation is consistent across all ages.[10] Close association between diarrhea and malnutrition has been well recognized and PD had been rightly considered as a nutritional disorder.[9, 11] The apparent association of malnutrition with PD could have been biased if children who were malnourished had an inherently increased risk for PD because of other risk factors. This possibility was opposed by the fact that association of malnutrition and PD were unaffected by analytical adjustment for several potential confounders. Hospital based cross sectional studies, such as this, cannot provide sufficient data on antecedent nutritional status and consequently, do not permit evaluation whether malnutrition is cause or consequence of PD.

In this study, vitamin A deficiency and anemia were found to be risk factors for PD by univariate analysis but not significant by multivariate analysis. Only children with clinical vitamin A deficiency were considered and hence the less number of cases. However, both clinical and sub clinical cases have been implicated as risk factors for PD.[9, 12, 13] Anemia has been noted in 92% cases of PD in an Indian study.[14] Anemia could be a part of malnutrition contributing to PD.

Prior antibiotic use was significantly associated with

TABLE 2. Univariate Analysis of Risk Factors for Persistent Diarrhea

Risk factors	Persistent diarrhea n=60 (%)	Acute diarrhea n=60 (%)	p value x^2	Odds ratio (95% CI)
Prior Antibiotic use				
Yes	43 (72.7)	18 (30)	<0.0001*	5.9 (2.5-14)
No	17 (28.3)	42 (70)		
Steroid use				
Present	8 (13.3)	2 (3.3)	0.048*	4.46 (0.82-31.9)
Absent	52 (86.7)	58 (96.7)		
Anemia				
Present	48 (80)	31 (51.7)	0.002*	3.74 (1.55-9.15)
Absent	12 (20)	29 (48.3)		
Vitamin A deficiency				
Present	24 (40)	7 (11.6)	0.0008*	5.05 (1.82-14.5)
Absent	36 (60)	53 (88.4)		
Z Score(Weight for Height)				
< -2	35 (58.3)	15 (25)	0.0004*	4.2 (1.8- 9.89)
> -2	25 (41.7)	45 (75)		
Weight for age				
>80%	10	32		
70%-79%	12	16		
60%-69%	13	8	0.00005*	5.7 (2.28-14.64)
50%-59%	9	1		
<50%	16	3		
LRI				
Present	30 (50)	11 (18.3)	0.0005*	4.45 (1.81-11.12)
Absent	30 (50)	49 (81.7)		
UTI				
Present	12 (20)	0 (0)	0.003*	15 (2.05-65)
Absent	48 (80)	60 (100)		
Oral Candidiasis				
Present	8 (13.3)	2 (3.3)	0.048*	4.46 (0.82-44.9)
Absent	52 (86.7)	58 (96.7)		
Serum Sodium (meq /L)				
<135	22 (36.7)	6 (10)		
135-150	37 (61.7)	51 (85)	0.0016*	5.05 (1.74-16.5)
>150	1 (1.6)	3 (5)		

*Significant statistically (p value < 0.05)

TABLE 3. Multivariate Logistic Regression Analysis of Risk Factors for Persistent Diarrhea

Risk factors	Persistent diarrhea n=60 (%)	Acute diarrhea n=60 (%)	p value x^2	Adjusted Odds ratio (95% CI)
Prior Antibiotic use				
Present	43 (72.7)	18 (30)	0.0003*	5.28
Absent	17 (28.3)	42 (70)		(2.01–13.74)
Vitamin A deficiency				
Present	24 (40)	7 (11.6)	0.012*	4.28
Absent	36 (60)	53 (88.4)		(1.29–14.09)
Z Score (Weight for Height)				
< -2	35 (58.3)	15 (25)	0.04*	1.66
> -2	25 (41.7)	45 (75)		(1.0–2.77)
LRI				
Present	30 (50)	11 (18.3)	0.008*	3.69
Absent	30 (50)	49 (81.7)		(1.36–10.07)

* Significant statistically (p value < 0.05)

PD both by univariate and multivariate analysis. Similar association between indiscriminate use of antibiotics and PD has been reported earlier.[9, 12, 14] Unnecessary antibiotics prescribed for acute diarrhea may prolong the episode making it 'persistent'. LRI, UTI and oral candidiasis were significantly associated with PD by univariate analysis, while LRI alone was significant by multivariate analysis. This finding is similar to the previous reports.[9, 15]

The case fatality in this study was 8.3% which is similar to studies from India and Bangladesh.[16, 17] Though maximum number of PD was observed in infancy, highest mortality was in the age group of one to five yrs. This is consistent with the observation from Bangladesh[1], though higher mortality in younger age group has been reported from India and Turkey.[18, 19] Among the children who died, 80% had a stool frequency more than 10 per day. A similar observation has been noted in a study from Pakistan.[20] Severe malnutrition, oral candidiasis and hypoalbuminemia were the other statistically significant risk factors for mortality due to PD, which is similar to earlier reports.[15, 19, 20] In the present study, 3 out of the 5 fatal cases had HIV infection. According to an African study, HIV infection had a 11-fold increase in death from

persistent diarrhea.[21] HIV can cause PD indirectly through immunodeficiency and infection although, its direct role is less certain.

CONCLUSIONS

Protein energy malnutrition, vitamin A deficiency, lower respiratory tract infection and prior antibiotic use were the risk factors for PD. The yield of microbiological organism is low in PD. No specific organism was found to be associated with PD. TB was not a significant contributory factor in PD statistically. The presence of risk factors like severe malnutrition, oral candidiasis, HIV positivity, low serum albumin or high purge rate (>10 per day) in children with PD should alert the clinician to take appropriate measures to decrease the mortality. Hence, proper nutritional support, Vitamin A supplementation, diligent search for secondary infection and its treatment is of utmost importance in management of PD.

Contributions: BU; collected and analysed data. BA; drafted the manuscript. NB; supervised the study and will act as guarantor for the manuscript. SCP and SS; participated in critical review.

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