

## ORIGINAL ARTICLE

# Management of childhood acute diarrhea with Probiotics in Ambulatory Care (MIRACLE)

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## ABSTRACT

**Background:** Probiotics are widely regarded as effective in the management of acute diarrhea.**Aim:** To document usage of probiotics in children presenting with acute diarrhea at outpatient clinics across Pakistan, while also evaluating caregiver satisfaction with various aspects of their use.**Methods:** This national, observational, multicentre study was conducted in outpatient settings as a non-interventional analysis of therapeutic practices. A prospective design with a single follow-up was used and general practitioners and paediatricians were randomly selected to participate. The study included children aged  $\geq 1$  month to under  $\leq 5$  years who presented with acute diarrhea in ambulatory care.**Results:** Of the 1,130 children enrolled at the initial visit, 1,072 returned for follow-up. Probiotics were prescribed to 98.6% of these children. The most commonly recommended probiotics were *Bacillus clausii* (73%), followed by *Saccharomyces boulardii* (17%) and *Lactobacillus* species (6%). Caregiver satisfaction was high, with 94.3% (n=1,011) expressing approval of the prescribed treatment. Physicians observed that probiotics were primarily effective in reducing the loose consistency of stools.**Practical Implication:** The use of ORS is widespread though not universal and should be further promoted. Probiotic use is widely prevalent. However, there is the room for increasing awareness on usage of probiotics both at primary health care level and at caregiver level. In this study the prescribed probiotics reduced diarrheal symptoms within 3.3 days and improved stool consistency in more than 86% of the cases.**Conclusion** The exact proportion of probiotic prescriptions alongside other antidiarrheal treatments for children with acute diarrhea remains unclear. However, findings from this registry highlight that a significant rate of probiotic prescriptions is closely linked to high caregiver satisfaction with the treatment. The MIRACLE study represents an important step toward fostering awareness and building confidence in the use of probiotics for managing acute diarrhea in the general paediatric population of Pakistan.**Keywords:** Acute diarrhea, Probiotics, Modified Vesikari Score, *Bacillus clausii*, caregiver Satisfaction

## INTRODUCTION

Acute watery diarrhea is characterized by the passage of three or more loose or liquid stools per day, or stools occurring more frequently than normal for the individual, lasting less than 14 days<sup>1</sup>. It is the second leading global cause of death among children under the age of five. Diarrhoea accounts for approximately 2 billion cases and 1.5 million deaths annually in this age group<sup>2</sup>. In Pakistan, where over 20 million individuals are under <5 years old, 50% mortality rate in this age group was reported each year. It is estimated that 550,000 children in Pakistan lose their lives annually to illnesses such as diarrhea, pneumonia, and measles<sup>3</sup>. Among these, diarrhea remains the second most significant cause of childhood mortality, surpassed only by pneumonia<sup>4</sup>.

Probiotics are microorganisms which colonize the gut and provide health benefits to the host. They have been shown to be effective in treating diarrhea caused by suspected viral infections<sup>7</sup>, as well as antibiotic-associated diarrhea<sup>8,9</sup>, by reducing both the duration of the illness and, as highlighted in recent systematic reviews, the frequency of stools. While the evidence is less robust, some randomized clinical trials indicate that probiotics might also help prevent hospital-acquired infections<sup>10,11</sup>. Probiotics are increasingly recognized as a safe and effective intervention for managing acute infectious diarrhea in children, helping to lessen both the severity and duration of the illness<sup>12-14</sup>.

However, the evidence of using probiotics in acute diarrhea is scant in developing countries where the burden of this illness is high<sup>15</sup>. Moreover, there is no available scientific literature on how satisfied caregivers are after administering probiotic(s) to their children. For children under 5 years of age, the caregiver (usually the mother) is a crucial part of the health seeking process. The caregiver profile in Pakistan is evolving. Various studies conducted across Pakistan have explored mothers' knowledge about diarrhea, the use of ORS, and how maternal awareness influences the management of the condition. However, there remains a gap in understanding the level of caregiver satisfaction with the use of probiotics in treating childhood diarrhea.

The aim of this disease registry was therefore to document the use of probiotics in pediatric population (<5 years where morbidity and mortality from diarrhea is the highest) presenting with acute diarrhea in outpatient setting and to measure the satisfaction of its usage by caregivers on various parameters including symptoms resolution, ease of administration, availability and affordability.

## METHODOLOGY

This study was an observational, national, multicenter, non-interventional investigation into therapeutic strategies, with a one-time, prospective follow-up disease registry conducted in outpatient settings. Fifty randomly selected general practitioners and pediatricians across Pakistan participated, each recruiting 24 consecutive patients. Children  $\geq 1$  month to <5 years who presented with acute diarrhea in an ambulatory setting were enrolled in the study. Caregiver consent was taken before enrollment. Hospitalized children were excluded from the study. A paper-based Case Report Form (CRF) was designed to facilitate systematic data collection on two visits: first visit (V1) at baseline and a follow up visit (V2) or telephonic contact after one week of first visit. A 3<sup>rd</sup> party call center was engaged to minimize loss to follow up by calling caregivers after 7 days. The severity of diarrhea was evaluated using the Modified Vesikari Score (MVS), a validated scoring system that effectively measures the overall severity of acute gastroenteritis (AGE) in children<sup>15</sup>. This is a history and symptom-based scoring system not requiring clinical assessments. The scoring system can be utilized by the practitioners to treat patients in accordance to the WHO IMCI Dehydration Treatment criteria.

The main objective of the study is to document the frequency of probiotic prescription in the management of acute diarrhea among the selected population. Secondary objectives were to determine type, dose, and strength and mean duration of probiotic administration by the caregiver to the child with acute diarrhea. The study also assessed caregiver satisfaction with the

use of probiotic in acute diarrhea, reasons for prescribing probiotic and record other therapeutic measures and reason for prescribing antibiotic by physicians in acute diarrhea.

**Statistics:** Information on the use of probiotics in Pakistani children was not available. Recent IMS data indicated that probiotics were prescribed in 70% children with diarrhea. The sample size required for this study was 900 considering a confidence level of 95% and margin of error to be 3%. Accounting for a 25% loss to follow up (required for satisfaction survey) in acute illnesses like diarrhea, the study proposed to recruit 1200 children in order to achieve the required sample size.

The main evaluation criteria were to assess the number of probiotic prescriptions for diarrhea in study population and to document the proportion of probiotic prescriptions amongst all therapies prescribed for acute diarrhea (number of probiotic prescriptions/total number of therapies prescribed for acute diarrhea). The number of probiotic prescriptions in the study population were recorded as frequency and percentage. The proportion of probiotic prescriptions amongst all therapies prescribed for acute diarrhea were described as percentages.

Secondary endpoints based on secondary objectives were: distribution of number of days for which probiotics were administered, satisfaction (measured in percentages based on binomial distribution of following variables such as symptom resolution, adverse events, availability by proximity, affordability, ease of administration, palatability by the child, & ease of storage). Overall satisfaction was measured as proportion of caregivers expressing satisfaction (Highly dissatisfied/ Highly Satisfied) on Likert Scale and reported as frequencies and percentages.

Percentages were reported as categorical variables while Standard Deviations with means are reported as continuous variables. Caregiver satisfaction on usage of probiotics in terms of affordability, ease of usage and proximity are assessed on Likert scale (Range from 1-5).

## RESULTS

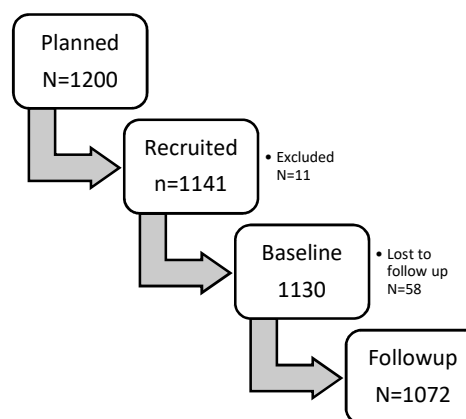
Data collection for 1200 patients involving 50 Investigators/sites was planned. Forty-eight Investigators/sites could recruit 1141 patients during the specified study timelines. Of the 1141 patients, 11 were excluded because their age was more than 5 years. Therefore, a total of 1130 patients were included at base line visit (V1). At follow up visit (V2), 1072 patients returned. (Figure 1). The study was conducted between September 2015 to September 2016.

**Patients Characteristics:** The mean age of all (n=1130) patients was  $18.4 \pm 13.6$  months with a range of 1 month to 59 months. Majority (60.2%) of patients were children between 7 to 24 months (Table II). There were 58% (n=651) females in the group. The mean ranking of children amongst their siblings was 2+1. The mean height was  $74.2 \pm 16.2$  cm, while average weight was  $9.5 \pm 3.3$  kg. Mean body temperature recorded at base line visit was  $37.4 \pm 0.7^\circ\text{C}$ . Mean pulse rate was  $101.2 \pm 18.7$  beats/min. The mean duration of current episode of diarrheal illness was  $3.2 \pm 2.2$  days (Table I). In 533(50%) children, the primary caregiver was the mother. Care giver took the child for consultation at base line visit, gave consent for same and also gave an opinion on satisfaction with probiotics at follow up visit. In 501(47%) cases the caregiver was the child's father.

Table I. Baseline Characteristics

Characteristics (n=1130)	N (%)
Age (months) Mean ( $\pm$ SD)	18.4 ( $\pm 13.6$ )
1 to 12	529 (46.8)
13 to 24	340 (30.1)
25 to 48	217 (19.2)
49 to 59	44 (3.9)
Gender	

Figure I. Study Flow Chart



Concomitant medical illnesses were reported in 35% (n=395) patients. Probiotics are available in the form of sachets with powder, prefilled liquid bottles and capsules in the local market. In this study 65% probiotics prescribed were prefilled liquid bottles, while in 28% cases it was powdered probiotic in sachet form. The three most common ailments along with diarrhea were: Infections of upper respiratory tract (20.4%), Infections of lower respiratory tract (7.4%), and malnutrition (3.8%).

Severity of Acute Gastroenteritis (AGE) measured by Modified Vesikari Score (MVS), showed that 51% patients had AGE of moderate severity while 26% patients had mild AGE and remaining 23% presented with a severe episode of AGE to the outpatient clinic (Table 2). Analysis of individual symptoms of AGE as per MVS had shown that out of 1130 enrolled patients, 79% (n=897) patients had diarrhea of duration ranging from 1-4 days. Forty four percent (n=499) children presented with 4 to 5 episodes of diarrhea in last 24 hrs. Among these 499 patients, 79.2% (n=395) are those who had diarrheal episodes for 1 to 4 days, 14% (n=69) are those with complaint of diarrhea for 5 days and remaining 35(7%) had complaint of diarrhea for more than 6 days (Table II).

Table II. Comparison of duration of diarrhea by number of diarrheal stools in last 24 hours

Last 24 hours		
Male		479 (42.4)
Female		651 (57.6)
Number of siblings		2(±1)
Ranking of child among siblings		2(±1)
Examination		
Height (cm) Mean (± SD)		74.2 (±16.2)
Weight (kg) Mean (± SD)		9.5 (±3.3)
Temperature (°C) Mean (± SD)		37.4 (±0.7)
Pulse Rate (beats/min) Mean (± SD)		101.2 (±18.7)
Duration of current episode of diarrhea (days) Mean (± SD)		3.2 (±2.2)
Category of AGE Severity	Mild	295(26.1%)
	Moderate	578(51.2%)
	Severe	257(22.7%)
Primary Care Giver	Mother	533(50%)
	Father	501(47%)

In outpatient settings, probiotics were prescribed to 1115 (98.6%) of children aged 1 to 59 months who were experiencing an acute episode of diarrhea. The proportion of probiotic prescription amongst all therapies prescribed at base line visit was 16% (1115 /7018). At consultation (baseline visit), physicians prescribed rehydration agent(s) in 972(86%) children including commercially available ORS in 516(45.7%), low osmolarity ORS in 483(42.7%) and homemade ORS in 137(12.1%) children (Table III). Most of

the patients 483(43%) were given a combination of commercial and low osmolarity ORS.

Zinc supplements were given to 817(72.3%) children and Antibiotics were prescribed to 571(50.5%) children. Other therapeutic measures advised by physicians were increased fluid intake in 676(59.8%), and antipyretics in 538(47.6%) (Table III).

Physicians advised caregivers to give extra meal(s) to 914(80.9%) children. Most commonly advised meals were: banana in 844(74.7%), yogurt in 836(74%) and rice with lentils (khichdi) in 782(69.2%) (Table III).

Table III. Treatment provided at the time of consultation by physician

Duration of diarrhea (days)	# of stools in last 24 hr.				
	0 n (%)	1-3n%	4-5 n%	≥6 n%	Total
0	0	0	0	0	0
1-4	25(80.6)	255(87.5)	395(79.2)	252(73.5)	897
5	4(12.9)	18 (7)	69(13.8)	36(10.5)	127
6	2(6.5)	14(5.5)	35(7.0)	56(16.0)	106
Total	31	257	499	343	1130

At baseline, the most Children were prescribed *Bacillus clausii* in a mean dose of 4.9(±0.3) ml for a mean duration of 4.6(±1.4) days. Investigators prescribed *Bacillus clausii* once daily to 41.6% and twice daily to 56.3%. *Saccharomyces boulardii* was prescribed at a mean dose of 250.7 (±44.9) mg for a mean duration of 5.0 (±1.7) days. *Saccharomyces boulardii* was prescribed predominantly in once daily dosage (55%). *Lactobacillus* was prescribed at a mean

Probiotics	Baseline n=1130				Follow up N=1072			
	n (%)	Strength range	Mean strength (±SD)	Mean duration (±SD) days	n (%)	Strength range	Mean strength (±SD)	Mean duration (±SD) days
<i>Bacillus clausii</i>	811(72.7)	2.5 - 5.0 ml	4.9(±0.3)	4.6 (±1.4)	780(72.6)	2.5-5.0 ml	4.9(±0.4)	4.4 (±1.6)
<i>Saccharomyces boulardii</i>	179(16.0)	125 - 500 mg	250.7(±44.9)	5.0 (±1.7)	183(17.1)	125-500 mg	244.5(±342)	4.4 (±1.5)
<i>Lactobacillus</i>	61 (5.4)	5.0 - 10.0 ml	5.1(±0.6)	5.5 (±1.3)	58 (5.4)	5.0-10.0 ml	5.1 (±0.7)	5.5 (±1.5)

Table V. Assessment of caregiver satisfaction with probiotic use in acute diarrhea

Satisfaction Variables	Overall satisfaction (Strongly agreed + agreed) (%)
Probiotic has improved the consistency of stools	924 (86.2)
It is easy to administer the probiotic	913 (85.2)
It is easy for the child to take the probiotic	884 (82.5)
Probiotic is easy to store	879 (81.9)
Probiotic has helped in reducing diarrheal episodes	873 (81.4)
Probiotic is easily available close to patients' home	859 (80.1)
Probiotic prescribed is affordable	755 (70.4)

**Caregiver Satisfaction with Probiotic use:** At follow-up, caregiver satisfaction with the use of probiotics was assessed on following variables including symptom resolution, ease of administration, affordability, storage, availability in proximity and improvement in stool consistency. All these variables were measured on Likert scale ranging from 1-5 where 1 was 'strongly disagree' and 5 was 'strongly agree'. Of these 86% caregivers indicated that stool consistency has shown improvement with the administration of probiotics. Eighty five percent (85%) indicated that prescribed probiotic was easy to administer probiotic by the caregiver. Eighty Three Percent (83%) caregivers were of the opinion that it was easy for the child to take the prescribed probiotic. Overall number of caregivers satisfied with the prescribed probiotics are, 1011(94.3%). At follow up, caregivers reported that the child's diarrheal symptoms resolved in 3.3 (±1.4) days. The child reverted back to normal activity in 3.8 (±1.7) days and started taking normal meals in 3.4 (±1.6) days (Table V).

dose of 5.1 (±0.6) ml for a mean duration of 5.5 (±1.3) days. It was prescribed once daily to 72% of patients (Table IV).

Table IV. Most common probiotics prescribed during the study

Treatment	Baseline n=1130 (%)
Probiotics	1115 (98.6)
Rehydration agent	972 (86.0)
Commercial ORS	516 (45.7)
Homemade ORS	137 (12.1)
Low osmolarity ORS	483 (42.7)
Intravenous	110 (9.7)
Nasogastric	1 (0.1)
Zinc supplement	817 (72.3)
Increase fluid intake	676 (59.8)
Antibiotics	571 (50.5)
Antipyretic	538(47.6)
Antiparasitic	107 (9.5)
Antispasmodic	89 (7.9)
Extra meals	914 (80.9)
Yogurt	836 (74.0)
Banana	844 (74.7)
Khichdi (rice with lentils)	782 (69.2)
Others	26 (2.3)

At follow up visit, information was collected on probiotic administration only. At follow-up, the most commonly administered probiotics to children were *Bacillus clausii* (73%), *Saccharomyces boulardii* (17%), and *Lactobacillus* (6%) (Table IV).

Caregivers of 61(5.7%) of the patients were not satisfied with the prescribed probiotic at baseline visit. Reasons for dissatisfaction included: lack of efficacy in 32 cases. Among these 32 patients, 21(65.6%) were prescribed *Bacillus clausii*. Other reasons for dissatisfaction were: Lack of palatability in 15 cases and difficulty to administer probiotic in 9 cases. For these cases, adverse events (1 Serious Adverse Event [SAE] and 20 Non-Serious Adverse Events [NSAE]) were reported spontaneously by Investigators.

Table VI. Reasons for prescription of probiotics and antibiotics by Investigators

Reasons for	Probiotic Prescription n=1130 (%)	Antibiotic Prescription n=1130 (%)
Reduced loose consistency of stools	772 (68.3)	211 (18.7)
Reduced diarrheal frequency	709 (62.7)	170 (15.0)
WHO recommendation	676 (59.8)	191 (17.9)
Inadequate response to therapy at home	491 (43.5)	345 (30.5)
Worsening of symptoms	409 (36.2)	347 (30.7)
Additional symptom	175 (15.5)	203 (18.0)
Others	29 (2.6)	11 (1.0)
Accompanied fever		324 (18.7)
Other comorbidities		108 (9.6)

Investigators indicated that they had prescribed probiotics to reduce the loose consistency of stools in 68% patients and to reduce diarrheal frequency in 63% patients. Other reasons included WHO recommendation in 60% cases and inadequate response to therapies administered at home in 44% children. Investigators prescribed Antibiotics in 50.5% children. Physicians prescribed antibiotics because of worsening of symptoms (31%),

inadequate response to therapy given to child at home (30%) and accompanying fever (19%) (Table VI).

## DISCUSSION

The use of probiotics in acute infectious diarrhea assumes that they target intestinal pathogens. However, the exact mechanism by which probiotics exert their effects remains unclear. Potential mechanisms include the stimulation of antimicrobial substances<sup>16,17</sup>, competition for nutrients needed for pathogen growth<sup>18</sup>, inhibition of pathogen adhesion<sup>19,21</sup>, modification of toxins or their receptors<sup>22,23</sup> and the stimulation of both nonspecific and specific immune responses to pathogens<sup>24,25</sup>.

In relation to probiotics, the ESPGHAN Working Group on Probiotics and Prebiotics has issued guidelines recommending their use for the treatment of acute gastroenteritis (AGE) in infants and children<sup>26</sup>. These guidelines suggest that the active use of probiotics, alongside oral rehydration solution (ORS), is effective in reducing the duration and severity of gastroenteritis symptoms. They recommend certain probiotics for use in children with AGE (I, A) (strong recommendation, moderate-quality evidence). Recent evidence supports this, confirming that some probiotics can reduce the duration of symptoms in children with AGE (I, A) (strong recommendation, moderate-quality evidence).

The present study illustrates that moderate to severe AGE is predominant amongst patients under five presenting with acute diarrhea treated in an outpatient setting in Pakistan. Probiotics and ORS were the mainstay of therapy for acute diarrhea in outpatient clinical settings which is in line with ESPGHAN recommendations mentioned above as well as WHO recommendations. Zinc supplements are also prescribed as per WHO recommendation for routine use in diarrheal disease along with probiotics.

Caregivers were both, mothers and fathers who took the child to an outpatient clinic to seek further medical care. Thirty Six percent (86%) caregivers indicated that they were satisfied with the use of probiotics because stool consistency improved with the administration of probiotics. Overall, 94% caregivers were satisfied with the prescribed probiotic. Our study represents primary care settings in mostly urban areas of the country. Investigators were randomly selected from a list of clinicians with large pediatric practices. These results may be applicable to the presentation of acute diarrhea in primary care settings across urban Pakistan.

The findings are limited to children who presented in outpatient settings and may not be applicable to broader community contexts. Additionally, they may not represent children who are taken directly to secondary or tertiary hospitals by their caregivers.

In the MIRACLE registry, the magnitude of moderately severe gastroenteritis was 51.2% and comprised more than half of total included population. Among these patients, most of them had diarrheal episodes for past 5 days and passed 4-5 stools in last 24 hrs. before consulting physician. Not only these patients complained of diarrhea, but also had episode of vomiting for past 2 days with episodes of 2-4 vomiting in last 24 hrs before consultation. The persistently high rates of acute diarrheal episodes among Pakistani children significantly affect their survival, both through the immediate acute effects and the long-term, indirect impact on their nutritional status<sup>3</sup>.

In this study 98.6% of the cases were prescribed probiotics, however the overall proportion of probiotic prescription in clinical routine in Pakistan for acute diarrhea management in children under 5 years of age is not documented. There is need to create awareness among physicians and to educate caregivers on the early use of probiotics in diarrhea. This will save time and cost of management as well as prevent complications, mortality and morbidity due to diarrhea, which is on high toll in our country.

Caregivers who had administered probiotics as per physician instructions, were satisfied on the use of same in terms of early resolution of diarrheal symptoms, improvement in stool consistency and reversion to normal feeding habits.

## CONCLUSION

The results of this registry study show that the probiotics in acute diarrhea were mainly described to reduce the symptoms. However, this registry cannot demonstrate evidence with regards to morbidity and mortality prevention. Strong statistical clinical evidences are still required to claim these products as lifesaving medication. Currently the proportion of probiotic prescription among other antidiarrheal prescriptions is not sufficiently known, but this registry will add knowledge and give confidence for increasing usage of probiotics in acute diarrhea. We conclude that a large proportion of acute diarrhea cases brought to outpatient clinics in urban areas of Pakistan are moderate to severe in nature. The use of ORS is widespread though not universal and should be further promoted. Probiotic use is widely prevalent. However, there is the room for increasing awareness on usage of probiotics both at primary health care level and at caregiver level. In this study the prescribed probiotics reduced diarrheal symptoms within 3.3 days and improved stool consistency in more than 86% of the cases. Hence the results of the MIRACLE registry are helping to create awareness for the additional use of probiotic in holistic management of acute diarrhea in Pakistani children.

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1. Conception and design of or acquisition of data or analysis and interpretation of data.
2. Drafting the manuscript or revising it critically for important intellectual content.
3. Final approval of the version for publication.

All authors agree to be responsible for all aspects of their research work.

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