Journal of
Basic & Clinical Medical Sciences

*Original Article*

# Effectiveness of folic acid supplementation in children under five years of age with acute watery diarrhea: a randomized placebo-controlled trial

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**Citation:** Jamil R, Pracha HS, Jamil H, Shabbir S, Paracha UA. Effectiveness of folic acid supplementation in children under five years of age with acute watery diarrhea: a randomized placebo-controlled trial. J Basic Clin Med Sci. 2025;4(2):77-84.

**Received:** 01 September 2025
**Revised:** 07 December 2025
**Accepted:** 19 December 2025
**Published:** 22 December 2025

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**Abstract**

Diarrhea is caused by bacteria, viruses, or parasites, a major contributor to morbidity and mortality in children below 5 years of age. This randomized placebo-controlled trial evaluated effectiveness of folic acid supplementation for acute watery diarrhea (AWD) in children below 5 years of age. The study was conducted at the Department of Pediatric Medicine, Mayo Hospital, Lahore, and enrolled and randomized 324 pediatric patients in a 1:1 ratio to two groups. Children in Group A were given folic acid for 5 days while children in Group B were administered distilled water as a placebo for the same period. Clinical proformas were used to record and monitor the frequency of loose stools and stool consistency across both groups, on daily basis. Results of the study revealed that, compared with placebo group, folic acid supplementation did not significantly decrease frequency of loose stools, improve stool consistency, or shorten the duration of diarrhea. The average change in the number of loose stools from presentation to day 5 was similar in both groups [Group A: median = 7 (IQR = 4) versus Group B: Median = 7 (IQR = 4); $p = 0.704$]. The average duration of diarrhea was not significantly different between Group A [median = 4 (IQR = 2)] and Group B [median = 5 (IQR = 3)] ($p = 0.530$). The maximum duration of diarrhea was 11 days in Group A and 10 days in Group B. The study concluded that folic acid supplementation in AWD was not effective in reducing the frequency of loose stools, improving stool consistency, or decreasing the duration of illness among children under 5 years of age. Future studies should explore additional adjunctive therapies to help reduce diarrhea-related complications and mortality.

**Keywords**

Acute watery diarrhea; Child, preschool; Diarrhea; Dietary supplements; Folic acid; Randomized controlled trial

## 1. Introduction

Diarrhea is an intestinal disease caused by bacteria, viruses, or parasites, with viruses being the most common etiologic agents in children [1]. In children under the age of 5 years, diarrhea remains a major cause of morbidity as well as mortality. Every year, diarrheal disease accounts for more than 801,000 child deaths around the globe and is associated with growth retardation in 10 to 80% of affected children [2]. High incidence of diarrhea is due to a unsafe water supply, a lack of breastfeeding, and delayed seeking of medical care [3]. Currently, management of acute watery diarrhea (AWD) mainly relies on oral rehydration therapy (ORS). It not only corrects the patient's hydration status but is also safe, cost effective, easily available, and a major life-saving remedy. However, in underdeveloped and developing countries, appropriate rehydration therapy is often not given owing to a lack of caregiver education and a limited understanding of the prep-

aration and administration of fluids, leading to a greater number of deaths from diarrhea and dehydration [4]. Furthermore, rehydration therapies do not significantly affect disease duration, resulting in increased parental concern regarding the course of disease, which may lead to the inappropriate use of antibiotics and/or alternative medications for rapid recovery [5].

Any drug that would reduce the frequency of loose stools or disease duration would be a useful addition to ORS, for example, zinc [6,7]. Moreover, a variety of drugs, including probiotics, dioctahedral *smectite*, racecadotril, and oral immunoglobulins of bovine origin, have been studied for their role in reducing the duration of diarrhea [8,9]. However, none of these are routinely recommended because of their potential side effects, high cost, or poor palatability. Folic acid is a synthetically produced form of vitamin B9 [10]. Amino acid metabolism, as well as the synthesis and repair of DNA and RNA, depends on the adequate presence of folic acid [11]. Diarrhea may result in potential damage to the intestinal mucosal lining; therefore, folic acid has been studied as an adjuvant therapy because of its role in DNA synthesis, especially in rapidly regenerating cells.

Previous scientific evidence regarding role of folic acid in acute diarrhea has reported inconsistent findings. Multiple studies have reported that folic acid supplementation was linked with reduction in duration as well as severity of diarrheal episodes, whereas other studies failed to observe any significant therapeutic advantage of supplementation [12,13,14]. These conflicting results limit the current scientific evidence base and leave clinical utility of folic acid in management of acute diarrhea uncertain. Furthermore, few similar studies have been conducted in South Asian populations, where disease burden, nutritional status, and environmental factors may influence treatment outcomes.

Folic acid is an inexpensive, easily available, and generally safe micronutrient with a favorable tolerability profile in children and adults [15]. Though its biologically active metabolite, L-methylfolate, is often preferred because it bypasses metabolic activation and can be directly consumed in cellular processes, and it is most accessible form in many resource-limited settings. However, targeted, safe, and cost-effective pharmacological interventions capable of reducing stool frequency, improving stool consistency, or shortening the duration of acute diarrheal illness are lacking. Therefore, evaluating the therapeutic efficacy of folic acid in children with acute diarrhea is warranted, given its proposed role in intestinal mucosal repair, cellular regeneration, and immune modulation. Therefore, our study assessed effectiveness of folic acid supplementation in children under the age of five years with AWD by determining its effects on stool frequency, stool consistency, and illness duration compared with those of a placebo.

## 2. Methods

### *2.1. Study design, duration and setting*

This randomized placebo-controlled trial was conducted between November 2020 and August 2021 in the Department of Paediatrics Medicine at Mayo Hospital, Lahore, Pakistan.

### *2.2. Sample size calculation*

The sample size was calculated to detect a difference of 23.8 hours in the average length of diarrhea between groups (expected means 123.6 ± 32.90 versus 147.4 ± 33.06 hours) [16]. Using a two-sided two-sample test with $\alpha = 0.05$ and 90% power, the pooled variance formula yielded 41 participants per group (82 total). Allowing for 10% attrition, the recruitment target was set at 46 per group (92 total). Calculations were verified using OpenEPI (two-means module) and G*Power software. Although the minimum required

sample size was 92 participants, all eligible participants who presented during the study period were enrolled, resulting in a final sample of 324 children.

### *2.3. Study population and sampling technique*

Of the 358 children assessed for eligibility, 324 eligible participants were enrolled consecutively and subsequently randomized using a simple randomization method. Children aged 2 months to 5 years of either gender presenting with AWD, defined as the passage of ≥ 3 loose stools/day, and with a duration of diarrhea of less than 7 days, were eligible for enrollment. Severely malnourished children; those with bloody or chronic diarrhea; patients who had received folic acid within the preceding two weeks; and those with comorbid conditions such as pneumonia, sepsis, and meningitis were excluded from the study.

### *2.4. Ethical considerations*

Formal ethical clearance and institutional approval for this investigation were granted by Advanced Studies and Research Board (ASRB) and Institutional Review Board (IRB) of King Edward Medical University, Lahore (No. 321/RC/KEMU). The study was also registered with ClinicalTrials.gov (Identifier: NCT04782037). Written informed consent was obtained from parents as well as guardians of all eligible pediatric patients before enrollment. No personal identifiers were recorded to maintain confidentiality, and the data was used only for research purposes.

### *2.5. Randomization and allocation*

Participants were randomized using the lottery method, and group allocation was concealed until enrollment to minimize selection bias. Eligible patients were randomly allocated to either folic acid group or placebo group following a single-blind design in which participants as well as their parents or guardians were unaware of assigned intervention. A CONSORT flow diagram summarizing participant screening, randomization, allocation, follow-up, and analysis is provided in Supplementary Figure S1.

### *2.6. Intervention and study procedures*

A baseline assessment including demographic and clinical parameters was performed for all enrolled patients. Participants in Group A received oral folic acid, with children aged < 1 year receiving 3 drops daily and those aged ≥ 1 year receiving 5 drops daily for five days, whereas participants in Group B received an equal volume of placebo preparation (distilled water) according to age category. All patients received standard treatment, including breastfeeding support, nutritional counseling, zinc sulfate supplementation, and oral rehydration therapy, in accordance with World Health Organization (WHO) guidelines.

### *2.7. Outcome assessment and follow-up*

Clinical outcomes were assessed daily using a predesigned proforma and included stool frequency, consistency according to WHO grading, and duration of diarrhea. Patients showing clinical improvement were discharged and followed daily through hospital visits or telephone communication for completion of outcome data over a five-day period.

*2.8. Statistical analysis*

The data were analyzed using SPSS version 26.0. On the basis of the results of the normality test, continuous variables were tabulated as medians (IQRs) and compared between groups using the Mann–Whitney U test, whereas, categorical variables, including stool consistency grades, are tabulated as frequencies and percentages and were compared using the chi-square test. A two-sided $p$ value < 0.05 indicated statistical significance.

## 3. Results

The study population included 202 (62.35%) males and 122 (37.65%) females. Group A included 100 (61.73%) males and 62 (38.27%) females, whereas Group B included 102 (62.96%) males and 60 (37.04%) females. Table 1 shows that the median ages of patients in the folic acid (Group A) and placebo (Group B) groups were 14 (20.20) months and 15 (18.50) months, respectively. Similarly, the median weights of patients are presented in Table 1.

**Table 1.** Comparisons of age and weight across treatment groups.

| Variables | Treatment Groups | | *p* Value |
|---|---|---|---|
| | Group A | Group B | |
| | Median (IQR) | Median (IQR) | |
| Age (months) | 14.00 (20.20) | 15.00 (18.50) | 0.417 |
| Weight (kg) | 9.00 (7.00) | 9.85 (5.00) | 0.426 |

Table 2 depicts that the median number of loose stools tended to decrease in both groups from presentation to day 5. No statistically significant differences in stool consistency grades were observed between the groups on days I–V.

**Table 2.** Comparison of the number of loose stools on days 1–5 between the study groups.

| Number of Loose Stool | Treatment Groups | | *p* Value |
|---|---|---|---|
| | Group A | Group B | |
| | Median (IQR) | Median (IQR) | |
| On day 1 | 6.00 (3.00) | 6.00 (4.00) | 0.236 |
| On day 2 | 3.50 (2.00) | 3.00 (1.00) | 0.084 |
| On day 3 | 2.00 (1.00) | 2.00 (1.00) | 0.121 |
| On day 4 | 2.00 (1.00) | 2.00 (1.00) | 0.144 |
| On day 5 | 1.00 (1.00) | 1.00 (1.00) | 0.540 |

Table 3 presents the distribution of stool consistency grades among children receiving folic acid and placebo during the five-day follow-up period. Both groups demonstrated progressive improvement in stool consistency over time; however, no statistically significant differences were observed between the treatment groups at any follow-up day ($p$ > 0.05), suggesting that folic acid supplementation had no significant effect on stool consistency.

**Table 3.** Comparison of stool consistency grades on days I–V between the study groups.

| Days | Grade of Stools | Treatment Groups | | $\chi^2$ | *p* Value |
|---|---|---|---|---|---|
| | | Group A (n = 162) | Group B (n = 162) | | |
| | | Frequency (%) | Frequency (%) | | |
| Day 1 | II | 1 (0.62) | 1 (0.62) | 6.178 | 0.103 |
| | III | 3 (18.52) | 45 (27.78) | | |
| | IV | 7 (43.21) | 73 (45.06) | | |
| | V | 61 (37.65) | 43 (26.54) | | |
| Day 2 | I | 1 (0.62) | 0 (0.00) | 7.397 | 0.116 |
| | II | 18 (11.11) | 22 (13.58) | | |
| | III | 76 (46.91) | 92 (56.79) | | |
| | IV | 53 (32.72) | 42 (25.93) | | |
| | V | 14 (8.64) | 6 (3.70) | | |
| Day 3 | I | 3 (1.85) | 9 (5.56) | 8.146 | 0.086 |
| | II | 60 (37.04) | 63 (38.89) | | |
| | III | 70 (43.21) | 75 (46.30) | | |
| | IV | 27 (16.67) | 13 (8.02) | | |
| | V | 2 (1.23) | 2 (1.23) | | |
| Day 4 | I | 29 (17.90) | 23 (14.20) | 6.158 | 0.104 |
| | II | 87 (53.70) | 104 (64.20) | | |
| | III | 38 (23.46) | 33 (20.37) | | |
| | IV | 8 (4.94) | 2 (1.23) | | |
| Day 5 | I | 54 (33.33) | 58 (35.80) | 4.608 | 0.203 |
| | II | 92 (56.79) | 97 (59.88) | | |
| | III | 14 (8.64) | 7 (4.32) | | |
| | IV | 2 (1.23) | 0 (0.00) | | |

The maximum duration of diarrhea was 11 days in Group A and 10 days in Group B. In Group A, 53 (32.71%) patients had a diarrhea duration exceeding 5 days, whereas in Group B, 49 (30.25%) had a duration of diarrhea of 4.00 (2.00) days and 5.00 (3.00) days, respectively, with no significant difference between the groups ($p = 0.530$).

## 4. Discussion

This randomized placebo-controlled trial revealed that folic acid supplementation did not significantly reduce stool frequency, improve stool consistency, or shorten the duration of AWD in children under five years of age. Both groups showed gradual clinical improvement from day 1 to day 5, but the pattern of recovery was comparable between the folic acid group and the placebo group. The average length of diarrhea was slightly lower in the folic acid group; however, this difference was not statistically significant.

Childhood diarrhea is a major global health problem despite declines in mortality due to this disease. Recent global studies have shown a high burden of diarrhea among children under the age of five years, especially in low- and middle-income regions [17]. Rahmat et al. highlighted persistent diarrhea-related morbidity among Pakistani children and linked it to unsafe water consumption, poor water sanitation, and health system-related challenges [2]. Another case–control study from Pakistan revealed that breastfeeding, maternal age, paternal education, and household income were the primary factors associated with childhood diarrhea [18].

Recent scientific literature emphasizes the assessment of dehydration among patients, the administration of oral rehydration solution, continued feeding, and the selec-

tive use of adjunct therapies as the key components of diarrhea management [19,20]. Florez et al. reported that several interventions have been clinically assessed for a reduction in diarrhea duration, but only zinc and supportive care have proven to be more effective, while many other adjunct therapies are supported by low-certainty evidence [19]. Similarly, Leung et al. reported that viral gastroenteritis is generally managed supportively and that most children improve over time with adequate hydration and oral feeding [20]. A 2024 systematic review and meta-analysis of 38 randomized controlled trials revealed that zinc supplementation increased recovery at the last follow-up and reduced diarrhea duration by approximately 13 hours in children with acute diarrhea, although vomiting was more frequent in zinc-treated children [21].

Minaz et al. reported that probiotics were associated with a clinical cure and a shorter duration of diarrhea [22]. Collinson et al. reported no clear benefit in low-risk-of-bias analyses and highlighted heterogeneity and publication bias [23]. In contrast, Yang et al. and Huang et al. reported reductions in diarrhea duration and stool frequency with probiotics or supportive care but also highlighted variability across formulations and study settings [24,25]. The ESPGHAN 2020 update stated that despite many trials, high-quality evidence for benefit was limited, and recommendations for several strains were weak [26]. The 2023 ESPGHAN position paper again emphasized that probiotic effects are strain-specific and that products without documented benefit should be discouraged [27]. Recent randomized and meta-analytic evidence for selected probiotics has reported that some interventions can be effective under specific conditions. Rerksuppaphol et al. reported that Lactobacillus reuteri (DSM 17938) shortened diarrhea duration in Thai children with acute gastroenteritis in an outpatient setting [28]. McFarland and Li reported that Saccharomyces boulardii (CNCM I-745) reduced duration of pediatric acute gastroenteritis [29]. These findings contrast with those of the present study and suggest that interventions targeting gut microbiota, inflammation, or pathogen-related mechanisms may influence diarrheal outcomes through mechanisms different from those proposed for folic acid. Recent folate literature highlights differences in the bioavailability, metabolism, and clinical interpretation of different folate forms [13]. Maruvada et al. reported that the clinical effects of folate depend on baseline folate status, dose, metabolic context, and interactions with vitamin B12 status [12].

Racecadotril provides another useful comparison. It has a direct antisecretory mechanism, yet a 2019 Cochrane review concluded that racecadotril appears safe but offers little benefit for acute diarrhea in children under five years of age, and current evidence does not support its routine use outside placebo-controlled trials [30]. This supports conclusion that even mechanism-based adjunctive therapies may fail to provide meaningful clinical benefit in routine pediatric diarrhea care and that not all low-cost adjuncts improve clinically relevant outcomes when standard care is already provided.

Our study targeted children under the age of five years with a large sample size. Furthermore, the study considered multiple clinical outcomes related to diarrhea management, which adds to the strengths of the study. However, the single site design of this study may limit the generalizability of the findings. Stool frequency and consistency were partly based on caregiver reporting, which may introduce recall or observation bias. Baseline folate, vitamin B12, zinc, and nutritional biomarkers were not measured. Stool volume, dehydration episodes, the need for intravenous fluids, and recurrence after follow-up were also not assessed.

## 5. Conclusions

It is concluded that folic acid supplementation in AWD was not effective at reducing the frequency of loose stools, improving the grades of diarrhea or decreasing the overall

duration of illness among children under 5 years of age. Future studies should explore additional adjunctive therapies that may help reduce diarrhea-related complications and mortality among children.

**Supplementary materials:** The following supporting information can be accessed through the embedded link: Supplementary Figure S1. CONSORT flow chart for recruitment of participants, allocation, and follow-up.

**Author contributions:** Conceptualization, RJ, HSP, HJ, SS, and UAP; methodology, RJ, HSP, HJ, SS, and UAP; software, RJ, HJ, and SS; validation, RJ, HJ, and SS; formal analysis, RJ, HJ, and SS; investigation, RF, HJ, and SS; resources, RF, HSP, and SS; data curation, HJ, and UAP; writing—original draft preparation, RJ, HJ, SS, and UAP; writing—review and editing, HSP; visualization, HJ, and UAP; supervision, HJ; project administration, RJ, HJ, and SS. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no specific grant from the public, commercial, or not-for-profit funding agencies.

**Ethics statement and consent to participate:** Formal ethical clearance and institutional approval for this investigation were granted by Advanced Studies and Research Board (ASRB) and Institutional Review Board (IRB) of King Edward Medical University, Lahore (No. 321/RC/KEMU). The study was also registered with ClinicalTrials.gov (Identifier: NCT04782037). Written informed consent was obtained from parents as well as guardians of all eligible pediatric patients before enrollment.

**Consent to publication:** Not applicable.

**Data availability:** The data supporting this study's findings are available from the corresponding author, Hafiza Saima Pracha, upon reasonable request.

**Acknowledgments:** None.

**Conflicts of interest:** The authors declare no conflicts of interest.

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