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The Efficacy of Adjunctive Probiotic Therapy on Treatment Response in Children with Urinary Tract Infections: A Randomized Clinical Trial

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Abstract

Background: Urinary tract infections (UTIs) are among the most common bacterial infections in children. While antibiotics are the mainstay of treatment, issues such as recurrence and antibiotic resistance necessitate exploring adjunctive therapies. This study aimed to evaluate the impact of combining probiotics with antibiotics on treatment response and recurrence in pediatric UTIs.

Methods: In this randomized, parallel-group, single-center clinical trial, 60 children (aged 1 month to 18 years) with confirmed UTIs (positive urinalysis and urine culture) were enrolled. Participants were randomly allocated to two groups: one received cefixime based on weight twice daily, and the other received the same cefixime regimen plus a daily probiotic (KidiLact powder). Urinalysis and urine culture were performed at baseline and followed up at one week, one month, two months, and three months after treatment initiation. The primary outcomes were the time to negative urine culture and the rate of UTI recurrence.

Results: After one week, the combination therapy group showed a higher rate of negative urine cultures (86.7% vs. 70%, p = 0.117) and inactive urinalysis (73.3% vs. 63.3%, p = 0.405) compared to the antibiotic-only group, though these differences were not statistically significant. By two months, 100% of the combination group achieved negative results, compared to 96.7% in the antibiotic-only group. At the three-month follow-up, the recurrence rate was significantly lower in the combination therapy group (3.3%, 1/30) than in the antibiotic-only group (6.7%, 2/30).

Conclusion: Adjunctive probiotic therapy with antibiotics may lead to a more rapid initial response and may reduce the recurrence of UTIs in children compared to antibiotic treatment alone. Probiotics represent a promising complementary approach to managing pediatric UTIs. Larger, double-blind, placebo-controlled trials with longer follow-up are needed to confirm these findings.

Key Words: Child, Cefixime, Probiotics, Randomized Controlled Trial, Recurrence, Urinary Tract Infection.

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1- INTRODUCTION

Urinary tract infections (UTIs) are a common bacterial illness in children and the most prevalent urogenital disorder in childhood (1). If not effectively managed, UTIs can lead to serious complications, including renal scarring, chronic kidney disease, and hypertension, thereby increasing the long-term disease burden (2) .

The cornerstone of UTI management is antibiotic therapy. However, treatment is often complicated by antibiotic resistance and a high rate of recurrence (3). Consequently, there is a growing interest in non-antibiotic strategies, either as monotherapy or as adjuvants, to improve outcomes (4).

Probiotics, live microorganisms that provide health benefits when administered in adequate amounts, have emerged as a potential candidate (5, 6). Primarily consisting of strains like *Lactobacillus* and *Bifidobacterium*, probiotics are thought to act by reinforcing the mucosal barrier, resisting pathogen colonization, and inactivating bacterial toxins (7). Their efficacy has been demonstrated in various infectious conditions (8) , and some studies suggest a role in preventing recurrent UTIs (9, 10).

However, evidence regarding the therapeutic (as opposed to preventive) effect of probiotics in active pediatric UTIs is limited. Most existing research focuses on recurrence prevention rather than the initial treatment response (10). Given the challenges associated with antibiotic therapy in children, this study was conducted to evaluate the comparative efficacy of a combination of probiotics and antibiotics versus antibiotics alone on treatment response and recurrence in children with UTIs.

2- MATERIALS AND METHODS

2-1. Study Design and Setting

A randomized, parallel-group clinical trial was conducted, enrolling children presenting with UTIs to outpatient clinics affiliated with Sabzevar University of Medical Sciences. The study was single-center and open-label, with blinding applied only to the treatment allocator and outcome assessor.

2-2. Participants

Children aged 1 month to 18 years with clinical symptoms of UTI confirmed by both active urinalysis (positive leukocyte esterase and/or nitrites) and a positive urine culture ($\geq 10^5$ CFU/mL of a single uropathogen) were eligible. Exclusion criteria included the need for hospitalization, known anatomical urological abnormalities, recent (within 4 weeks) probiotic or antibiotic use, immunodeficiency, and parental refusal to participate.

2-3. Randomization and Intervention

A total of 60 eligible children were recruited. Using a permuted block randomization method (block size of 4) and a computer-generated random numbers table, participants were callocated into two groups of 30.

- **Group 1 (Antibiotic-only):** Received cefixime (8 mg/kg/day divided into two doses).
- **Group 2 (Combination therapy):** Received cefixime (same regimen) plus a probiotic (*KidiLact* powder, *Zisttakhmir* Co., Iran; containing $\geq 1\times10^9$ CFU per sachet of *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, and *Bifidobacterium bifidum*) once daily based on the manufacturer's weight-based recommendations (half sachet for <15 kg, one sachet for ≥15 kg). The probiotic powder was to be mixed with cool water or milk.

The treatment duration for the acute infection was 7-10 days, as per standard care. The probiotic was continued for the

study's follow-up period. The treatment allocator and outcome assessor were blinded to the group assignments. Participants and caregivers were not blinded due to the nature of the intervention.

2-4. Outcomes and Follow-up

The primary outcome measures were the time to first negative urine culture (analyzed descriptively due to sample size constraints) and the rate of recurrence. Secondary outcomes included urinalysis normalization. Assessments were performed at four time points: baseline, one week, one month, two months, and three months after the initiation of treatment. UTI recurrence was defined as a positive urine culture ($\geq 10^5$ CFU/mL) after having achieved a negative result at the previous follow-up, accompanied by relevant symptoms.

2-5. Ethical Considerations

The study protocol was approved by the Ethics Committee of Sabzevar University of Medical Sciences (Ethics Code: IR.MEDSAB.REC.1400.014). Written informed consent was obtained from the parents or legal guardians of all participants before enrollment.

2-6. Statistical Analysis

Data were analyzed using SPSS software version 24. Descriptive statistics were presented as mean ± standard deviation, median (interquartile range), or frequency (percentage), as appropriate. Normality of continuous variables was assessed using the Shapiro-Wilk test. The Chi-square test (or Fisher's exact test for expected cell counts <5) was used for categorical variables, and the Mann-Whitney U test was used for non-normally distributed continuous variables. A p-value of less than 0.05 was considered statistically significant. A formal sample size calculation was not performed a priori; the sample size was based on feasibility and available participants over the study period.

3- RESULTS

3-1. Participant Flow and Baseline Characteristics

A total of 68 children were assessed for eligibility. Eight were excluded (5 did not meet inclusion criteria, 3 declined to participate). All 60 randomized children completed the three-month follow-up (see CONSORT flow diagram, Figure 1). The median age was 48.6 months, with no significant difference between the two groups (Antibiotic-only: 46.7 months; Combination: 49.7 months; p=0.689). The majority of participants were female (85%), reflecting the higher prevalence of UTIs in girls, and the distribution was similar between groups (p=0.278). The most common presenting symptom was fever (80%), followed by urinary symptoms. There were no significant differences between the groups regarding initial complaints, past medical history, or prior medication use, although some baseline characteristics showed potential imbalances (e.g., 'Other' symptoms, p=0.037) (Table 1).

3-2. Treatment Response Over Time

At the one-week follow-up, a higher proportion of children in the combination therapy group had negative urine cultures (86.7% vs. 70.0%) and inactive urinalysis (73.3% vs. 63.3%), though these differences were not statistically significant (p=0.117 and p=0.405, respectively) (Table 2).

By the one-month follow-up, treatment success was high in both groups, with 93.3% in the antibiotic group and 96.7% in the combination group showing negative results (p=0.554). At the two-month mark, all patients (100%) in the combination

group maintained negative U/A and U/C, compared to 96.7% in the antibiotic-only group (p=0.313).

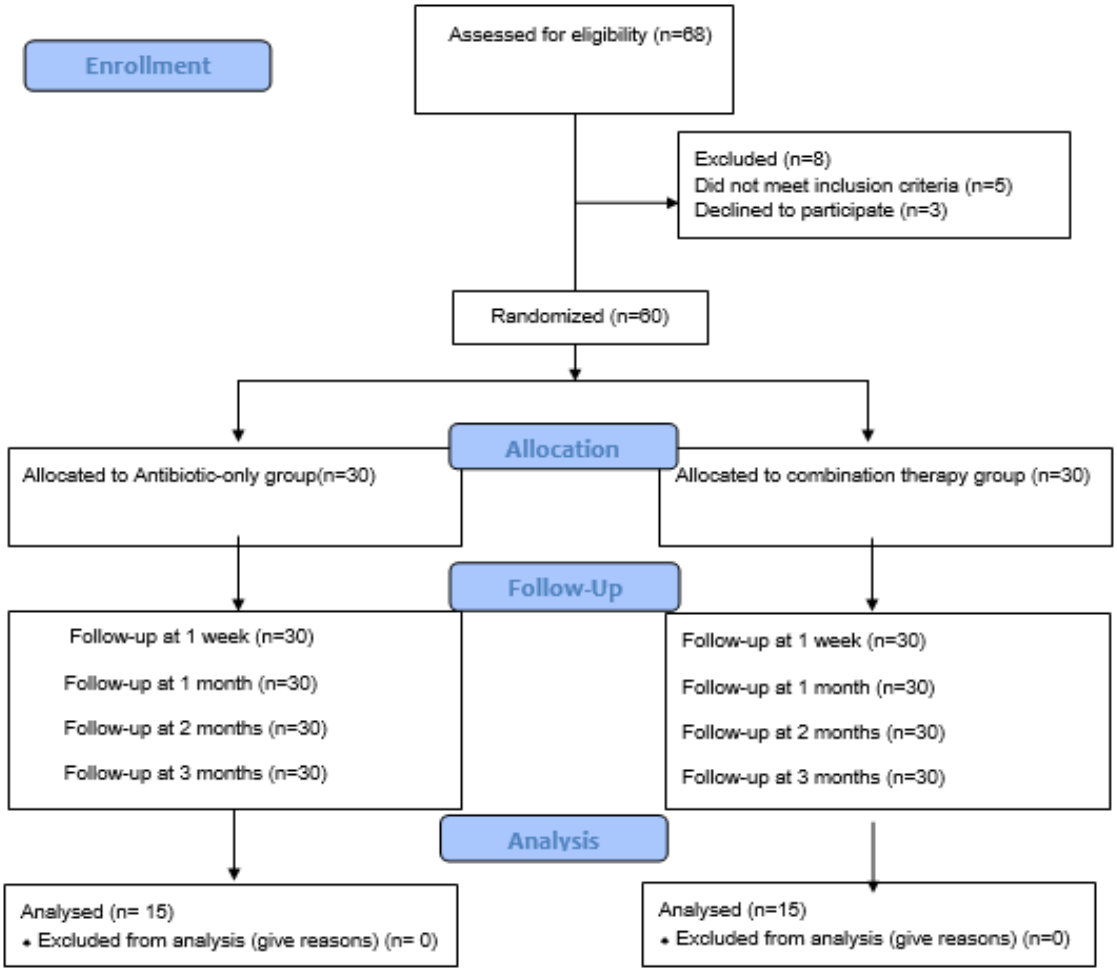

Figure-1: CONSORT flow diagram of participant enrollment, allocation, and follow-up.

Table-1. Baseline demographic and clinical characteristics of the study participants.

Variables	Groups		P-Value
	Antibiotic only N(%)	Combination therapy N(%)	
Gender **Male** **Female**	 6 (20.0) 24 (80.0)	 3 (10.0) 27 (90.0)	0.278
Age(months) Median (IQR)	48 (16.7-67.5)	33 (12-72)	0.689
Presenting Symptom			
Fever	27 (90.0)	21 (70.0)	0.053
Urinary Symptoms	14 (46.7)	15 (50.0)	0.796
Irritability/Colic	6 (20.0)	8 (26.7)	0.542
Other	11 (36.7)	4 (13.3)	0.037
Past Medical History	8 (26.7)	4 (13.3)	0.197
Prior Medication Use	0 (0.0)	1 (3.3)	0.313

Table-2. Treatment response based on urine culture and urinalysis at follow-up intervals.

Variables	Groups		P-Value
	Antibiotic only N(%)	Combination therapy N(%)	
One Week			
Negative Urine Culture	21 (70.0%)	26 (86.7%)	0.117
Inactive Urinalysis	28 (93.3%)	29 (96.7%)	0.554
Two Months			
Negative Urine Culture	29 (96.7%)	30 (100%)	0.313
Inactive Urinalysis	29 (96.7%)	30 (100%)	0.313
Three Months			
Negative Urine Culture	27 (90.0%)	29 (96.7%)	0.301
Inactive Urinalysis	27 (90.0%)	29 (96.7%)	0.301
Recurrence (by 3 months)	2 (6.7%)	1 (3.3%)	0.554

3-3. Recurrence Rate

During the three-month follow-up, UTI recurrence was observed in 2 children (6.7%) in the antibiotic-only group and 1 child (3.3%) in the combination therapy group. This suggests a slightly lower recurrence rate in the group receiving adjunctive probiotics, although the difference was not statistically significant (p=0.554, Fisher's exact test). Data on recurrence have now been incorporated into Table 2.

4- DISCUSSION

This randomized clinical trial demonstrates that adjunctive probiotic therapy may enhance treatment response and reduce recurrence in children with UTIs. While both treatment regimens were highly effective, the combination group consistently showed numerically superior outcomes across all follow-up points, suggesting a potential beneficial role for probiotics in the management of pediatric UTIs.

The baseline characteristics of our study population affirm the successful randomization of participants. The median age and significant female predominance (85%) are consistent with the well-established epidemiology of UTIs in childhood, where the incidence is highest in young children and females are disproportionately affected due to anatomical factors (11). The absence of significant differences between the two groups in terms of age, gender distribution, past medical history, and prior medication use strengthens the internal validity of our study, allowing us to attribute the observed outcome differences to the intervention rather than to confounding baseline variables.

A key finding of our study is the pattern of treatment response over time. At the critical one-week follow-up, we observed a promising trend favoring the combination therapy group, with a higher proportion of children achieving negative urine cultures (86.7% vs. 70.0%) and inactive urinalysis (73.3% vs. 63.3%). Although these differences did not reach statistical significance, likely due to the sample size, they suggest that probiotic supplementation may accelerate the initial clearance of infection (12). This faster microbiological and inflammatory resolution could translate into important clinical benefits, such as a more rapid alleviation of symptoms and a reduced risk of early treatment failure. By the one-, two-, and three-month follow-ups, both groups exhibited high and comparable rates of treatment success, indicating that the standard antibiotic therapy is highly efficacious. However, the consistent

numerical advantage remained with the combination group, culminating in a 100% success rate at two months.

The potential of probiotics to prevent recurrence is a cornerstone of their proposed utility (13). Our findings at the three-month mark align with this hypothesis. The recurrence rate in the antibiotic-only group was twice that of the combination therapy group (6.7% vs. 3.3%). While this difference was not statistically significant, it represents a clinically meaningful 50% relative reduction in recurrence risk. In a condition like UTI, where recurrence is a major concern leading to repeated antibiotic courses, potential renal scarring, and diminished quality of life, even a modest reduction in absolute risk can have a substantial impact on patient care (14).

Our results are consistent with and extend the findings of previous research. The study by Mohseni et al (15). demonstrated that long-term probiotic use alongside antibiotics significantly reduced recurrence over a three-year period. Similarly, the systematic review by Hosseini et al (9), concluded that while probiotics alone are not sufficient for treatment, their use as an adjunct to antibiotics holds promise for preventing recurrence. Our study contributes to this body of evidence by focusing on the initial therapeutic phase, demonstrating that the benefits of probiotics may begin with a faster treatment response and extend into the mid-term for recurrence prevention.

The proposed biological mechanisms provide a plausible explanation for our clinical observations. Probiotics are thought to exert their beneficial effects through several pathways:

1. competitive exclusion, where they compete with uropathogens for adhesion sites and nutrients in the gut and urogenital tract;

2. reinforcement of mucosal barriers, enhancing the integrity of the epithelial lining; and

3. immunomodulation, by stimulating the host's innate and adaptive immune responses. Antibiotic therapy, while essential for eradicating the acute infection, often disrupts the protective commensal microbiota (7). By restoring a healthy microbiome, probiotics may prevent the re-colonization and subsequent ascent of pathogenic bacteria from the gut, which is a primary reservoir for uropathogenic E. coli, thereby breaking the cycle of recurrence (15).

4-1. Limitations

This study has several limitations. The sample size was relatively small, limiting statistical power and possibly explaining why observed differences did not reach statistical significance. The study was open-label to participants and caregivers, introducing potential for performance bias. The follow-up period was limited to three months; a longer duration (e.g., 6–12 months) would provide more robust data on long-term recurrence rates. The study was conducted at a single center, which may impact the generalizability of the results. Furthermore, the lack of mechanistic data (e.g., fecal or urinary microbiome analysis, immune markers) limits the understanding of how probiotics exert their effects.

5- CONCLUSION

The results of this trial suggest that supplementing standard antibiotic therapy with probiotics can lead to a more rapid resolution of urinary tract infections and may reduce the risk of recurrence in children. Probiotics offer a safe and potentially effective complementary strategy in the management of pediatric UTIs. Larger, multi-center, double-blind, placebo-controlled trials with longer follow-up periods recommend to confirm

these findings and establish standardized probiotic regimens for clinical use.

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8- CONFLICT OF INTEREST

The authors declared no conflict of interest.

9-DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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