

Effect of Probiotic on Clinical Outcomes in Children with Pneumonia: A Randomized Double-Blind Trial

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Abstract

Background: Pneumonia remains a major cause of morbidity and mortality among children worldwide. Evidence suggests that probiotics may modulate immune responses and potentially improve respiratory infections. This study aimed to evaluate the effect of probiotic supplementation on clinical outcomes in children aged 3 months to 12 years hospitalized with pneumonia.

Methods: In this double-blind randomized clinical trial, 108 children diagnosed with pneumonia were allocated into two groups: 54 received a daily 1-gram sachet of Protexin probiotic (containing 1×10^9 CFU), and 54 received a placebo matched in appearance. Clinical signs and symptoms, including fever, lethargy, tachypnea, cough, retraction, wheezing, rales, hypoxia, and length of hospital stay, were monitored at baseline and at scheduled follow-up intervals. Data analysis was performed using SPSS; t-tests were applied for normally distributed quantitative variables and Mann-Whitney tests for non-normal variables, with a significance level of $P < 0.05$.

Results: No significant differences were found between the probiotic and placebo groups regarding gender, age, baseline symptoms, or length of hospital stay ($P > 0.05$ for all). However, the frequency of fever at 36 and 60 hours after admission was significantly lower in the probiotic group ($P = 0.037$, $P = 0.034$), and lethargy at 36 hours after admission was significantly less common compared to the placebo group ($P = 0.009$).

Conclusions: While most clinical parameters did not differ between groups, probiotic supplementation was associated with a significant reduction in fever and lethargy during hospitalization. Probiotics may serve as a beneficial adjunct therapy in pediatric pneumonia, although further studies with larger sample sizes and detailed clinical endpoints are recommended.

Key Words: Children, Clinical trial, Pneumonia, Probiotics, Respiratory infection.

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1- INTRODUCTION

According to the World Health Organization, pneumonia causes over 150 million cases annually in children under 5, including around 20 million hospitalizations, with most morbidity and mortality occurring in low- and middle-income countries (1). Because childhood pneumonia is a common reason for hospitalization and a leading cause of morbidity and mortality, identifying effective adjunctive therapies that can reduce disease severity, hospitalization duration, and ultimately mortality would be highly beneficial for the healthcare system (2).

Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits to the host (3). Some studies have evaluated the effects of probiotics in several conditions, including gastroenteritis and respiratory tract infections (4,5).

The overall objective of the present study is to evaluate the effect of probiotics on reducing clinical symptoms and the length of hospitalization in children aged 3 months to 12 years with pneumonia admitted to the pediatric wards of Qa'em Hospital in Mashhad. Specific outcomes assessed include duration of fever, respiratory rate, improvement of cough, retractions, rales and lethargy, as well as differences in these variables based on age and gender.

2-METHODS

2-1. Study Design and Setting

This double-blind, placebo-controlled, non-randomized clinical trial was conducted in the pediatric wards of Qa'em Hospital, Mashhad, Iran. The study included children aged 3 months to 12 years hospitalized with pneumonia. The diagnosis of pneumonia was established by a pediatrician based on clinical findings

and chest radiography, in accordance with the Nelson Textbook of Pediatrics (6).

2-2. Ethical Approval

Written informed consent was obtained from the parents or legal guardians of all participants prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki and the ethical standards for research involving human participants.

2-3. Eligibility Criteria

Inclusion criteria: Children aged 3 months to 12 years with a confirmed diagnosis of pneumonia based on clinical and radiologic evaluation.

Exclusion criteria: Refusal to participate; presence of underlying diseases (e.g., severe malnutrition, chronic kidney disease, diabetes mellitus, asthma, or acute bronchiolitis); poor general condition requiring mechanical ventilation; hospitalization within the preceding 3 weeks; or probiotic use within the previous 2 weeks.

2-4. Allocation and Blinding

Participants were assigned to one of two study groups using a quasi-experimental allocation method. At the beginning of each day, a predetermined sequence was used: odd numbers were allocated to Treatment Group A, and even numbers to Treatment Group B. While this method is non-randomized, it was implemented to ensure balanced allocation throughout the study period.

To ensure rigorous blinding, the probiotic and placebo formulations were manufactured by Niktech [Mashhad, Iran] and labeled as "A" and "B." The placebo was designed to be indistinguishable from the probiotic in terms of color, taste, texture, packaging, and sachet size. A third-party pharmacist, who was not involved in patient care or data collection, managed the allocation. The investigators,

clinical staff, participants, and their families remained blinded to the group assignments. Furthermore, the statistical analysts were also blinded to the treatment groups until the completion of the analysis.

2-5. Intervention

All participants received standardized pneumonia treatment, including identical antibiotic regimens. Participants were maintained on a uniform hospital diet to minimize confounding factors. Patients were prescribed one sachet daily.

The probiotic intervention consisted of a 1-g sachet of “Protexin,” containing a standardized dose of 1×10^9 Colony Forming Units (CFU) per species of the following microorganisms:

- *Lactobacillus casei*
- *Lactobacillus rhamnosus*
- *Streptococcus thermophilus*
- *Bifidobacterium breve*
- *Lactobacillus bulgaricus*
- *Bifidobacterium infantis*

2-6. Assessment Schedule

Clinical outcomes, including respiratory rate (to monitor tachypnea), presence of cough, chest retractions, and auscultatory findings (e.g., rales), were systematically assessed at baseline (upon admission) and at subsequent time points of 36 and 60 hours post-admission to track clinical progression.

2-7. Sample Size

A total of 108 children were enrolled in the study, with 54 participants assigned to the probiotic group and 54 participants assigned to the placebo group.

2-8. Safety and Compliance

To ensure participant safety, clinical monitoring for potential adverse

events, such as diarrhea, abdominal pain, or skin rashes, was performed daily by the nursing staff. Compliance with the intervention was evaluated through daily caregiver logs/clinical observation, ensuring that the prescribed dose was administered accurately. No treatment-related adverse events were identified during the study period.

2-9. Statistical Analysis

Data were coded and analyzed using SPSS software. To maintain the integrity of the results, an intention-to-treat (ITT) analysis was performed, ensuring that all randomized participants were included in the final analysis regardless of protocol adherence. Descriptive statistics were reported using appropriate measures of central tendency and dispersion. For inferential analysis, the independent-samples t-test was used for normally distributed quantitative variables, whereas the Mann–Whitney U test was applied to non-normally distributed quantitative variables. A P-value < 0.05 was considered statistically significant.

3-RESULT

3-1. Demographic and Baseline Characteristics

A total of 108 children were enrolled in the study, with 54 patients randomized to the probiotic group and 54 to the placebo group. The study population consisted of 62 (57.5%) females and 46 (42.5%) males. There was no statistically significant difference in gender distribution between the two groups ($P=0.085$) (Table 1).

The mean age of the participants was 24.47 ± 17.36 months (range: 4 to 74 months). No significant difference was observed in the mean age between the probiotic (23.27 ± 17.24 months) and placebo (25.72 ± 17.55 months) groups ($P=0.316$) (Table 1).

Table-1. Age and gender distribution of children in the two study groups.

Variable		Probiotic (N=54)	Placebo (N=54)	Total (N=108)	P-value
Age (months), mean $\pm$ SD		23.27 $\pm$ 17.24	25.72 $\pm$ 17.55	24.47 $\pm$ 17.36	0.316
Sex, n (%)	Female	36 (65.5%)	26 (49%)	62 (57.5%)	0.085
	Male	19 (34.5%)	27 (51%)	46 (42.5%)	

3-2. Duration of Hospitalization

The overall mean duration of hospital stay was 3.67 $\pm$ 0.82 days. As shown in Table 2, no significant difference was found in the length of stay between

the probiotic and placebo groups (P=0.155).

Furthermore, age-stratified analysis revealed no significant differences in hospitalization duration for children <24 months (P=0.412) or $\geq$ 24 months (P=0.529).

Table-2. Hospitalization duration (Days).

Group	Overall	Age < 24 months	Age $\geq$ 24 months
Probiotic	3.55 $\pm$ 0.78	3.87 $\pm$ 1.89	3.54 $\pm$ 0.73
Placebo	3.79 $\pm$ 0.85	4.01 $\pm$ 1.74	3.79 $\pm$ 0.84
P-value	0.155	0.412	0.529

3-3. Clinical Outcomes

The clinical progression of symptoms is summarized in Table 3. While most respiratory signs—including tachypnea, cough, chest retractions, and rales—showed a trend toward faster resolution in the probiotic group, these differences did not reach statistical significance (P>0.05).

and lethargy. The prevalence of fever was significantly lower in the probiotic group compared to the placebo group at 36 hours (P=0.037) and 60 hours (P=0.034). By 60 hours, all children in the probiotic group were afebrile. Similarly, lethargy resolved significantly faster in the probiotic group and was completely absent by 36 hours post-admission (P=0.009).

Significant improvements were specifically noted in the resolution of fever

Table-3. Clinical outcomes over time (significant findings).

Symptom	Group	Baseline	36 Hours	60 Hours
Fever n (%)	Probiotic	55 (98.2%)	16 (28.5%)	0 (0%)
	Placebo	52 (100%)	25 (48%)	4 (7.6%)
	P-value	0.333	0.037*	0.034
Lethargy n (%)	Probiotic	25 (44.6%)	0 (0%)	0 (0%)
	Placebo	27 (51.9%)	6 (11.5%)	0 (0%)
	P-value	0.568	0.009*	—
Tachypnea n (%)	Probiotic	32 (57.1%)	14 (25%)	3 (5.3%)
	Placebo	33 (63.4%)	21 (40.3%)	2 (3.8%)
	P-value	0.576	0.088	0.709
Cough n (%)	Probiotic	29 (51.7%)	26 (46.4%)	7 (12.5%)
	Placebo	27 (51.9%)	25 (48%)	9 (17.3%)
	P-value	0.989	0.864	0.482
Retraction n (%)	Probiotic	14 (25%)	3 (5.3%)	0 (0%)
	Placebo	19 (36.5%)	7 (13.4%)	0 (0%)
	P-value	0.193	0.147	—
Ral n (%)	Probiotic	40 (71.4%)	14 (25%)	2 (3.5%)
	Placebo	42 (80.7%)	19 (36.5%)	1 (1.9%)
	P-value	0.257	0.193	0.602

* Indicates statistical significance (P<0.05)

4- DISCUSSION

Pneumonia remains one of the most important infectious diseases affecting children worldwide and continues to be a major cause of morbidity and hospitalization, particularly in younger age groups. Although many cases can be managed on an outpatient basis, a considerable proportion of children with respiratory infections still require hospital admission for monitoring and treatment (7). In recent years, attention has increasingly focused on supportive therapeutic strategies that may enhance host immunity and improve clinical outcomes. Among these, probiotics have been suggested as a potential adjunct therapy due to their immunomodulatory, antioxidant, and anti-inflammatory properties (8).

Clinical manifestations such as fever, tachypnea, retraction, hypoxia, and abnormal lung sounds are key indicators in the evaluation of pediatric respiratory infections. Fever is a common manifestation of the inflammatory response to infection, while tachypnea is considered a universal diagnostic criterion for pneumonia and is recommended by the World Health Organization as an important indicator of serious pulmonary infection (9). Additionally, signs such as retraction and hypoxia are recognized indicators of disease severity and have been associated with poor clinical outcomes in children with respiratory diseases (10, 11). Abnormal lung sounds, including crackles or rales, typically reflect inflammation and secretion accumulation in the lower respiratory tract and may indicate increased disease severity (12). Therefore, evaluating changes in these clinical parameters is essential when assessing therapeutic interventions in pediatric pneumonia.

In the present study, 108 children with pneumonia were evaluated, including 62 females (57.5%) and 46 males (42.5%).

There was no statistically significant difference in sex distribution between the probiotic and placebo groups ($P = 0.085$), indicating an appropriate balance between the two study groups. The age of participants ranged from 4 to 74 months, and most children (64.8%) were younger than two years. The mean age was 24.47 ± 17.36 months, and there was no significant difference between the probiotic and placebo groups in terms of age ($P = 0.316$). These findings demonstrate that the baseline demographic characteristics of the two groups were comparable.

The mean length of hospital stay among all participants was 3.67 ± 0.82 days. Although the hospitalization duration was slightly shorter in the probiotic group compared with the placebo group, this difference was not statistically significant ($P = 0.155$). Similarly, age-stratified analysis showed no significant difference in the duration of hospitalization between the probiotic and placebo groups among children younger than two years ($P = 0.412$) or those older than two years ($P = 0.529$).

Regarding clinical manifestations, fever was the most common symptom observed among patients in both groups and across all subgroups, including both sexes and both age categories. Most respiratory symptoms—including tachypnea, cough, retraction, wheezing, hypoxia, and rales—showed gradual improvement during hospitalization in both groups, but no statistically significant differences were observed between the probiotic and placebo groups for these symptoms during the first 72 hours after admission ($P > 0.05$).

However, significant improvements were observed in the probiotic group in relation to fever and lethargy. Fever resolved more rapidly in children receiving probiotics, with a significantly lower frequency at 36 hours after admission compared with the placebo group ($P = 0.037$). Furthermore,

by 60 hours after admission, fever had completely resolved in the probiotic group, while 7.6% of children in the placebo group remained febrile ($P = 0.034$). Similarly, lethargy improved more rapidly in the probiotic group, disappearing completely within 36 hours after admission, which was significantly different from the placebo group ($P = 0.009$).

In this study, the probiotic group showed improvements in some clinical parameters, including fever and lethargy. However, further large-scale randomized controlled trials with a pre-specified primary outcome are required to confirm these findings.

The findings of the present study are consistent with previous research examining the role of probiotics in respiratory infections. Angurana SK et al. reported that probiotic administration in critically ill ICU patients reduced the length of hospital stay and decreased the incidence of nosocomial pneumonia, although no significant effect on mortality was observed (13). Liu's study in 2025 also showed that the probiotic *Lactocaseibacillus rhamnosus* GG can reduce the incidence and severity of respiratory tract infections, improve cystic fibrosis symptoms, and increase quality of life in children. However, the evidence for its benefits in asthma remains inconclusive and requires future research (4).

Similarly, a study conducted in Barcelona involving 251 children demonstrated that continuous consumption of *Lactobacillus casei* reduced both the incidence and duration of lower respiratory tract infections (14). In another study conducted in Croatia involving 742 children, administration of *Lactobacillus* GG (LGG) significantly reduced the risk of lower respiratory tract infections (15). Additionally, Smiian and colleagues reported that probiotic supplementation in young children was safe and led to significant clinical and microbiological

improvements (16). A study conducted in Shanghai on 326 children also demonstrated that long-term probiotic use reduced the incidence and duration of respiratory symptoms such as rhinorrhea and cough (17).

Despite these promising findings, probiotics should be used cautiously in certain populations. Although generally considered safe, concerns have been raised regarding potential alterations in microbial balance and possible complications in very young infants, particularly those younger than six months. Therefore, further research is required to better understand the long-term safety profile of probiotic supplementation in pediatric populations.

4-1. Strengths and Limitations

This study has several strengths. First, it addresses an emerging topic in pediatric infectious diseases, as the clinical effects of probiotics in respiratory infections have not been extensively investigated. Second, focusing on children—a population with relatively immature immune systems and a higher susceptibility to respiratory infections—enhances the clinical relevance and epidemiological importance of the findings. Third, the use of a controlled design with both intervention and placebo groups provides a structured approach to comparing the outcomes. Finally, the study offers potential practical implications for supportive treatment strategies in pediatric pneumonia.

However, some limitations should be acknowledged. First, the study utilized a quasi-experimental allocation method rather than true randomization, which may introduce selection bias. Second, the clinical outcomes were assessed through multiple secondary endpoints without formal multiplicity adjustment (e.g., Bonferroni correction), which increases the possibility of Type I errors. Consequently, the observed improvements

should be interpreted as potential trends rather than definitive evidence. Additionally, the study did not evaluate potential adverse effects associated with probiotic administration. Future studies with larger sample sizes, true randomization, and a pre-specified primary outcome are recommended to confirm both the efficacy and safety of probiotic supplementation in pediatric respiratory infections.

5- CONCLUSION

The findings of this study indicate that fever is the most common clinical manifestation of pneumonia in children. Although probiotic supplementation did not significantly affect most respiratory symptoms or the duration of hospitalization, it was associated with a significantly faster resolution of fever and lethargy. These results suggest that probiotics may serve as a beneficial adjunct therapy in the management of pediatric pneumonia. Further large-scale clinical trials are recommended to confirm these findings and to clarify the role of probiotics in improving clinical outcomes in children with respiratory infections.

6- ACKNOWLEDGMENT

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