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ANALYZING THE ROLE OF MULTI-STRAIN PROBIOTICS IN MANAGING ALLERGIC RHINITIS IN CHILDREN : A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Abstract

Background: Allergic rhinitis (AR) is a widely spread chronic illness of childhood, and it is linked with the high morbidity and poor quality of life. The conventional methods may relieve the symptoms of a disease but cannot treat, or modify it. This paper established the effectiveness of multistrain probiotic preparation on the AR symptoms of children within the age bracket of 6-15 years.

*Methods In this randomized, double-blind, placebo-controlled trial, randomly, 130 children with moderate-to-severe AR were allocated to a 12-week trial of a multistrain probiotic (Bifidobacterium longum, Lactobacillus acidophilus, Streptococcus thermophilus; 1*107 cfu/g) or placebo (micro crystals of cellulose and maltodextrin) every day at Abbasi Shaheed hospital, Karachi. Total Nasal Symptom Score (TNSS) was the primary outcome. Serum total IgE and absolute eosinophil count were the secondary outcomes. Assessed were baseline, week 6 and week 12.*

Findings: TNSS of the probiotics was reduced significantly (mean difference: -4.2 +1.1 vs -0.8 +0.9 in control; P =0.001). Similar to the amount of eosinophils decreased, serum IgE reduced in probiotic (P < 0.01) and 28% in placebo and equivalent counts of eosinophils decreased (P < 0.001) and 1% in placebo. The compliance rates were above 90 and there were no significant negative incidents.

Conclusions: Multistrain probiotics have a dramatic positive response to AR symptoms and immunological evidence of children, is a safe and cost-effective adjunctive treatment, especially in low-resource facilities. The results suggest the medicinal effects of microbiota-based intervention in the treatment of child allergies inflammation.

INTRODUCTION

AR is a frequently occurring disease having a prevalence of up to 40 percent of children worldwide and is categorized by inflammation of the nasal mucosa that is brought by environmental allergens and leads to sneezing, rhinorrhea, nasal congestion, and itching (Bousquet et al., 2008). They have adverse effects on the quality of sleep, school performance, and the quality of life and are highly

prevalent in low- and middle-income countries where they have limited access to specialist care and long-term pharmacotherapy (Hasnain et al., 2009; Rahman et al., 2024). Symptoms are alleviated using routine treatment, including antihistamines and intranasal corticosteroids, yet they do not address the immune regulation issue, which may necessitate chronic therapy with side effects in pediatrics (Scadding, 2015).

The hygiene hypothesis claims that one of the factors that contribute to the Th2-based immune responses and the allergic sensitization is the reduced exposure to microbes during the early life (Strachan, 1989; Datta and Parry, 2019). It is exacerbated by dysbiosis of gut microbiota that disturbs the functions of regulatory T-cell (Treg) and promotes the effects of pro-inflammatory cytokines (IL-4, IL-5, IL-13) that boost the production of allergen-specific IgE and the entry of eosinophils (Plaza-Diaz et al., 2019; Varsha et al., 2021). Modulators of the gut-lung axis, including short-chain fatty acid production, strengthening the epithelial barrier, and Tregs induction, are produced by the probiotics, which are live microorganisms with health-positive effects when taken in adequate quantities (FAO/WHO, 2002).

It is a possibility that multistrain probiotics may work synergistically in immunomodulatory activities compared to single strains due to the possibility to act on multiple pathways (Bergmann et al., 2021; Shemeki et al., 2023). South Asian low-resource settings of pediatric AR are not well evidenced, but past studies have shown the reduction of symptoms and benefits in biomarkers (Luo et al., 2024; Bernstein et al., 2024). The gap in this paper has been bridged by assessing a commercially viable and low-cost multistrain probiotic in children in a state-owned hospital in Karachi, Pakistan, using a practical clinical and laboratory outcome.

The primary objective was to test the impact on TNSS. The secondary goals were serum IgE and eosinophil count. We hypothesized that probiotics ought to improve the symptoms and markers remarkably compared with placebo.

Methods

Study Design and Participants

The trial was a randomized, placebo-controlled, and double-blind trial, which took place between January and June 2024 at Department of Pediatrics and Neonatology, Abbasi Shaheed Hospital, Karachi. The institutional review board (Protocol No. ASH-2023-045) was used to get ethical approval following the Declaration of Helsinki. Parents/guardians were obtained to provide written informed consent, and children ≥7 years did so. Children who met the following criteria qualified to participate in the study: children between 6 and 15 years; ARIA-defined moderate-to-severe persistent AR (>4 days/week the whole 4 weeks, confirmed by history and physical examination); and able to give informed consent. The exclusion criteria were the use of antibiotics/probiotics/steroids recently and immunotherapy, presence of chronic comorbidities (e.g., immunodeficiency, cystic fibrosis), and acute infections. The power of the study (n=130; 65/group) was computed to achieve 80% significance of a difference in TNSS of 20% (SD=2.5) including 10% attrition (Field, 2013).

Randomization and Blinding

Computer-generated blocks were used to randomly assign the participants 1:1. The probiotic (sachet: B. longum, L. acidophilus, S. thermophilus; 1 * 107 cfu/g) and placebo (microcrystalline cellulose/maltodextrin) were packed the same way. Participants, assessors and investigators were blinded.

Intervention

The participants were given 12 weeks of 1 daily sachet (mixed in water/milk). The parents were advised not to use new medications/supplements; compliance was checked through diaries and sachet numbers.

Outcomes and Assessments

Primary: TNSS change (012: nasal sneezing, itch, rhinorrhea, obstruction; 012) in the baseline, week 6, and week 12.

Secondary: Baseline serum total IgE (IU/mL; chemiluminescense) and absolute eosinophil count (cells/ mL; automated hematology). Safety: Negative events through diaries.

Statistical Analysis

The SPSS v27.0 (IBM Corp.) was applied to analyze data. Normal test was done through Shapiro Wilk. Between-group differences: independent t-

tests/MannU. Within/time variation: repeated-measures ANOVA/mixed models. Categorical: χ^2. P < 0.05 significant. Last-observation-carried-forward intention-to-treat analysis.

Results

Participant Characteristics

Out of 150 screened 130 randomized (65/group); 125 completed (3 dropouts/group; Fig. 1, not shown). The demographics were balanced during the baseline (Table 1): the mean age of 10.2 ± 2.8 years; 52% male; the mean AR of 2.1 ± 1.0 years; 78 percent of low socioeconomic status.

Table 1. Baseline Demographics

Characteristic	Probiotic (n=65)	Placebo (n=65)	P-value
Age (years), mean ± SD	10.1 ± 2.7	10.3 ± 2.9	0.72
Male, n (%)	34 (52)	34 (52)	1.00
AR duration (years), mean ± SD	2.0 ± 1.0	2.2 ± 1.0	0.45
Low SES, n (%)	51 (78)	50 (77)	0.89

The baseline TNSS (7.8 ± 1.2 vs. 7.9 ± 1.1), IgE (245 ± 45 IU/mL vs. 248 ± 46), and eosinophils (450 ± 80 cells/ uL vs. 455 ± 82) did not differ.

Primary Outcome: TNSS

It also dropped to 3.6 (-4.2 + -1.1; P < 0.001) in probiotic group TNSS, but to 7.9 -7.1 (-0.8 + -0.9; P = 0.12) in placebo (between-group P < 0.001; Table 2). At week 6, the changes began to increase (-2.1 vs. -0.4; P < 0.01).

Table 2. TNSS Changes Over Time.

Time Point	Probiotic TNSS (mean ± SD)	Placebo TNSS (mean ± SD)	Between-Group P
Baseline	7.8 ± 1.2	7.9 ± 1.1	0.78
Week 6	5.7 ± 1.0	7.5 ± 1.0	<0.01
Week 12	3.6 ± 0.8	7.1 ± 0.9	<0.001

Secondary Outcomes

IgE of (245 to 176 IgE/mL; P < 0.01) vs. placebo (248 to 243; P = 0.65; between-group P = 0.01) IgE decreased 28 and 2 percent, respectively. There was a reduction of 35% in eosinophils (450 to 293 cells/ u L; P <0.001) compared with +1% (455 to 460 cells/ u L; P = 0.89; P <0.001 between).

Compliance 93 per cent probiotic, 91 per cent placebo (>90 per cent doses). Rescue antihistamine: 15 percent probiotic and 68 percent placebo (P < 0.001).

Safety

No serious adverse events. Self limiting Mild GI symptoms (bloating: 8% probiotic vs. 5% placebo) were self limiting.

Discussion

The results of the current Randomized and double-blind and placebo-controlled trial are positive data that a 12-week multistrain probiotics (Bifidobacterium longum, Lactobacillus acidophilus, Streptococcus thermophilus) intervention may have the capacity to work in minimizing the clinical symptoms and in the regulation of the immunological markers with the children with moderate-severe allergic rhinitis (AR) aged 6 to 15 years. This is a significant reduction of TNSS of 54% in the probiotic compared to the insignificant 10% in the placebo; significantly higher than the clinically important change (MCID) of TNSS in the AR group of pediatrics (Bousquet et al., 2008). At the same time, reduction in the overall levels of IgE in serum (28) and absolute eosinophil count (35) is also an indication of a realistic immunomodulatory response with the change in the inflammatory state biasing towards Th2 towards the tolerant state. One can correlate the reported findings with the gut-lung axis paradigm where redundant fermentation of probiotics by microorganisms is linked to production of short-chain fatty acids (SCFA), which has been reported to advantage epithelial well-being and

Foxp3+ regulatory T-cell (Treg) differentiation, which inhibits IL-4/IL-13-mediated eosinophilic recruitment and eosinophilic IgE-class class-switching (Plaza-Diaz et al., 20).

It is congruent as well as contextually novel to the existing literature. A meta-analysis of 12 randomized controlled trials (RCTs) of 1248 children with AR reported a standardized mean difference (SMD) of -1.45 (95% CI: -2.12 -0.78; P < 0.001) in favor of the use of probiotics interventions and that multistrain preparations have a better effect (SMD -1.67) than single-strain preparations (Wang et al., 20 Likewise, Luo et al. (202

Dissectable, mechanistically, the observed immunological changes can be reduced to the microbiota-immune crosstalk. The dysbiosis is experienced by the AR-prone children, which is the decrease in the abundance of Bifidobacterium/Lactobacillus, compromising HDAC inhibition by SCFA, which serves to maintain Th2 dominance (Varsha et al., 2021; Davoodvandi et al., 2021). It is likely that our multistrain intervention has restored eubiosis as B. longum, and L. acidophilus, provoked the activity of mucin-2 gene and tight junction protein (e.g., occludin, ZO-1) activity to counteract the action of allergen translocation and systemic sensitization in such murine models (Sharma & Im, 2018). To a greater degree, it can be also done with the help of Streptococcus thermophilus by extending TLR2/4 agonism, which simplifies the dendritic cell tolerization and peripheral Tregs creation (Abbasi-Dokht et al., 2023). Although our analysis did not include metagenomic profiling, as we were resource constrained, these IgE and eosinophil alterations are a proxy cluster of evidence regarding this re-calibration, which is in line with the findings including the epigenetic modifications (e.g., miR-146a upregulation) in probiotic-exposed atopic groups (Davoodvandi et al., 2021).

The soundness of the trial is supported with internal validity of the trial of two-blindness, intention-to-treat analysis, and more than 90 adherence, which is also criticized in the prior review in comparison with underpowered or open-label trials (Martinelli et al., 2020; Fijan et al., 2023). It is more externally relevant in the case of an LMIC setting where the prevalence of AR is more than 25 percent during urban allergen burdens (Sheikh et al., 2018; Rahman et al., 2024). In contrast to high-income designs that involve using expensive endpoints of omics (e.g., flow cytometry of Tregs; Wei et al., 2023), such biomarkers of TNSS and regular serology are readily available to us, therefore, enabling production of evidence by probiotics an accessible intervention to prevent drug therapy. Particularly, the decline in the use of rescue antihistamines (i.e., by 77 percent) does not only limit the risks of polypharmacy (i. e. the impaired cognition as the consequence of sedation; Scadding, 2015), but it also corresponds to the priority of ARIA to the integrated, patient-centered care (Bousquet et al., 2008).

Although the strengths are observed, there are a number of limitations that are questionable. The 12week horizon can modify acute symptoms and is unable to measure long-term remission or prevention of atopic march which is also found in 80 percent of pediatric probiotic RCTs (Depoorter & Vandenplas, 2022). Mechanistic granularity will not work because there will be no fecal microbiota sequencing or cytokine multiplexes (e.g. IL-10/IL-4 ratios) that could confound the association of strain-specific synergies with dose effects. The single location recruitment has led to a selection bias and the validity was only applicable to the South Asian population in urban regions and it needs to be multicenter validated (Ciprandi et al., 2023). Also, dietary confounders (i.e. fiber intake which is modular to produce SCFA end-products) and self-reported TNSS (subjective but should be conquered by scale-tested scales) are subjective but expected to be overcome by scale-tested scales. These encouraging safety data (no life-threatening events; mild GI transients in 8%), require pharmacovigilance in comorbid subgroups (e.g., asthmatics; Van den Nieuwboer et al., 2015).

It has a clinical implication because such findings indicate that probiotics should be included in the tiered AR management plans, especially in LMICs where estimates of the cost-benefit analysis are aimed at saving 40-60 percent of expenses as the outcome of the decreased clinic visits (Bernstein et al., 2024). The policy implication would involve fortification of the population health, e.g. the school-based nutrition will include probiotics which would potentially prevent the 20 percent AR incidence increase which

will occur in Asia in 2030 (Rahman et al., 2024). Longitudinal and strain-optimized RCTs and multi-omics bioinformatics (metagenomics, metabolomics) should be the focus of future research to describe responders (e.g., by structuring basal dysbiosis), and interventions in which allergen immunotherapy or environmental manipulation are used (Wei et al., 2023; Redfield, 2023). Added is some better pediatric cohorts with improved hybrid designs with it added through another digital adherence tracking.

Conclusion

In general, this trial suggests that multistrain probiotics is an effective and safe and cost effective therapy of AR in pediatrics with significant symptomatic surcease and immunological rebalance that occurs in the absence of placebo protocols. We are even over-restoring palliative symptoms through the hygienic hypothesis in the form of microbiota restoration to the level of immunomodulatory prophylaxis in precarious ontogenies. In the miseries of LMIC healthcare, in which the disease-modifying treatments are disproportionately forced on the population by allergic burdens, this modality makes the therapies equally accessible, which can have potential to reduce the socioeconomic impact of chronic rhinitis. Nevertheless, as any new line of therapy, the translational faithfulness will require a finer form of empiricism: long-term follow-up, mechanistic clarification, and circumstantial adjustment will become the key to the success of the full prophylaxis potential of the probiotics. These observations eventually are a symbiotic rendezvous point of microbiology, immunology, and population health, to create healthy immune ecologies of the future generations.

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Conflicts of Interest

None declared.

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