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Original Article

Combined Antihistamine and Probiotic Therapy Improves Clinical Outcomes and Reduces Inflammatory Biomarkers in Chronic Spontaneous Urticaria

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Abstract

Chronic spontaneous urticaria (CSU) is a mast cell-driven skin disease often associated with systemic inflammation and gut microbial dysbiosis. While probiotics show promise as an adjunct therapy, their impact on inflammatory biomarkers alongside clinical symptoms remains underexplored. To evaluate the efficacy of combined antihistamine and probiotic therapy on both clinical outcomes and systemic inflammatory markers in CSU patients over an 8-week period. In this randomized, double-blind, controlled trial, 42 CSU patients were assigned to either a control group (antihistamine only) or an intervention group (antihistamine plus a multistrain synbiotic probiotic). The Urticaria Activity Score over 7 days (UAS7) and inflammatory biomarkers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], neutrophil counts) were assessed at baseline and week 8. After 8 weeks, the intervention group demonstrated significantly greater reductions in UAS7 scores and all measured inflammatory markers compared to the control group (CRP: 3.5 ± 1.2 vs. 5.2 ± 1.5 mg/L, $p<0.01$; Neutrophils: 4900 ± 500 vs. 6300 ± 550 cells/μL, $p<0.01$). Spearman correlation analysis revealed significant positive correlations between UAS7 scores and CRP (rho=0.56, p=0.004), ESR (rho=0.52, p=0.007), and neutrophil counts (rho=0.49, p=0.011). Adjunct probiotic therapy with antihistamines provides superior clinical and anti-inflammatory benefits in CSU compared to antihistamines alone, supporting a role for gut microbiome modulation in managing this condition.

Keywords: Chronic Urticaria; Probiotics; Histamine H1 Antagonists; C-Reactive Protein; Neutrophils.

Introduction

Chronic spontaneous urticaria (CSU) is a mast cell–driven disorder characterized by recurrent wheals and/or angioedema for at least six weeks, and a clinically relevant subset exhibits systemic inflammatory activity reflected in elevated indices such as C-reactive protein (CRP) [1-3]. Beyond cutaneous manifestations, observational and metabolomic studies identify gut microbial dysbiosis and altered metabolic profiles in CSU, with compositional shifts correlating with clinical phenotype [1, 4, 5]. Translational work implicates a gut–barrier–immune axis—marked by increased intestinal permeability, higher circulating lipopolysaccharide (LPS), and diminished short-chain fatty acids (SCFAs)—that amplifies mast-cell–mediated skin inflammation and provides a biologic

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rationale for microbiome-directed interventions [4, 6, 7]. These convergent lines of evidence motivate evaluation of adjunct strategies that modulate the gut microbiota to influence both symptoms and systemic inflammatory tone in CSU [4, 8].

Randomized trials of multistrain probiotic or synbiotic add-ons to second-generation H1-antihistamines have reported modest but statistically significant improvements in validated symptom measures over approximately eight weeks [9, 10]. For instance, blinded studies using LactoCare or twice-daily synbiotics with standardized cetirizine have shown lower week-8 urticaria activity scores compared with antihistamine alone or placebo, while a separate double-blind trial reported superior Urticaria Control Test outcomes with a multi-strain probiotic on a levocetirizine background [9, 11]. However, heterogeneity in strain identity, dosing, prebiotic content, and trial conduct limits interpretability across studies, underscoring the need for rigorously controlled, strain-defined evaluations [12]. Notably, most adult randomized trials have been symptom-focused and have not integrated systemic inflammatory biomarkers alongside UAS7/UCT, constraining mechanistic inference from observed clinical gains [9, 10].

In response to these gaps, we conducted a randomized add-on study to test whether combining a defined probiotic with a fixed second-generation H1-antihistamine yields greater improvement than antihistamine alone when assessed jointly on validated symptoms and systemic inflammatory readouts over an eight-week horizon [1, 12]. The primary objective was to compare changes in CRP, erythrocyte sedimentation rate (ESR), absolute neutrophil counts, and Urticaria Activity Score over 7 days (UAS7) between treatment arms, and the secondary objective was to determine whether biomarker changes correlate with clinical improvement.

Study Design and Methodology

This randomized, double-blind, controlled clinical trial enrolled 42 patients aged 18 to 45 years diagnosed with chronic spontaneous urticaria (CSU) persisting for at least 6 weeks. Patients with significant comorbid systemic diseases, concurrent immunosuppressive treatments, or recent use of probiotics or antibiotics within 4 weeks prior to enrollment were excluded.

Participants were randomly assigned to one of two groups:

- *Control group*: Received standard antihistamine therapy (Cetirizine 10 mg, Desloratadine 5 mg, or Fexofenadine 180 mg) administered twice daily according to clinical judgment.
- *Intervention group*: Received the same antihistamine regimen plus a symbiotic probiotic capsule (*LactoCare*), containing multiple *Lactobacillus* and *Bifidobacterium* strains along with *Fructooligosaccharides* (FOS) as prebiotics, taken twice daily for 8 weeks.

Randomization was performed using a computer-generated sequence, and allocation was concealed. Both patients and clinicians were blinded to group assignments.

Clinical and Laboratory Assessments

Patients underwent comprehensive clinical evaluations at baseline and after 8 weeks of treatment.

- *Clinical outcomes*: Disease activity was measured using the validated Urticaria Activity Score over 7 days (UAS7), and quality of life was assessed with the Dermatology Life Quality Index (DLQI).
- *Laboratory markers*: Venous blood samples were collected at baseline and week 8 to measure systemic inflammatory markers and immune cell counts:
    - C-reactive protein (CRP) levels were quantified using immunoturbidimetric assays.

- Erythrocyte sedimentation rate (ESR) was measured by the Westergren method.
- Complete blood count (CBC) including differential counts (lymphocytes, neutrophils) was performed using automated hematology analyzers.

Statistical Analysis

All statistical analyses were conducted on an intention-to-treat basis. Data were analyzed using IBM SPSS Statistics (version 26) and GraphPad Prism (version 8). Continuous variables are presented as mean ± standard deviation (SD). Normality of distribution was assessed by the Shapiro-Wilk test. Comparisons within groups (baseline vs. week 8) were performed using paired t-tests or Wilcoxon signed-rank tests as appropriate. Between-group comparisons were assessed using independent t-tests or Mann-Whitney U tests. Correlations between clinical scores (UAS7) and laboratory parameters (CRP, ESR, neutrophil counts) were evaluated using Spearman's rank correlation coefficient. A p-value < 0.05 was considered statistically significant.

Results

Previous study by the authors demonstrated the therapeutic efficacy of combined antihistamine and probiotic treatment in patients with CSU, showing a significant reduction in clinical symptoms measured by UAS7 after 8 weeks of intervention [9]. Building upon these findings, the present study aimed to evaluate systemic inflammatory biomarkers and neutrophil counts as potential correlates of disease activity and clinical response.

Inflammatory Markers and Neutrophil Counts

At baseline, patients in both treatment groups exhibited elevated systemic inflammatory markers consistent with CSU. Mean serum CRP levels were 7.2 ± 1.8 mg/L in the intervention group (antihistamine + probiotic) and 7.5 ± 2.0 mg/L in the control group (antihistamine only), both exceeding the normal reference range (<3 mg/L). Similarly, ESR values were elevated at 28.1 ± 5.4 mm/hr and 27.5 ± 6.0 mm/hr, respectively (normal <20 mm/hr). Baseline neutrophil counts were at the upper physiological limits, averaging 7800 ± 600 cells/μL in the intervention group and 7900 ± 650 cells/μL in the control group. There were no statistically significant differences between groups at baseline ($p > 0.05$ for all parameters).

Following 8 weeks of treatment, significant reductions in inflammatory markers and neutrophil counts were observed, particularly in the intervention group (Table 1). CRP levels decreased to 3.5 ± 1.2 mg/L in the intervention group compared to 5.2 ± 1.5 mg/L in controls ($p < 0.01$). ESR similarly declined to 13.6 ± 3.8 mm/hr and 18.9 ± 4.5 mm/hr, respectively ($p < 0.05$). Neutrophil counts in the intervention group decreased markedly to 4900 ± 500 cells/μL, whereas the control group showed a more modest reduction to 6300 ± 550 cells/μL ($p < 0.01$). These laboratory changes were paralleled by significant improvements in UAS7 and DLQI scores, confirming the clinical benefit of adjunct probiotic therapy.

Table 1. Mean ± SD of inflammatory markers and neutrophil counts at baseline and after 8 weeks of treatment.

Parameter	Intervention Group (Antihistamine + Probiotic)	Control Group (Antihistamine Only)	p-value (Between Groups at Week 8)	p-value (Within Group Baseline vs Week 8)
CRP (mg/L)				
Baseline	7.2 ± 1.8	7.5 ± 2.0	> 0.05	< 0.01 (Intervention) / 0.04 (Control)
Week 8	3.5 ± 1.2	5.2 ± 1.5	< 0.01	
ESR (mm/hr)				

Baseline	28.1 ± 5.4	27.5 ± 6.0	> 0.05	< 0.01 (Intervention) / 0.03 (Control)
Week 8	13.6 ± 3.8	18.9 ± 4.5	< 0.05	
Neutrophils (cells/μL)				
Baseline	7800 ± 600	7900 ± 650	> 0.05	< 0.01 (Intervention) / 0.05 (Control)
Week 8	4900 ± 500	6300 ± 550	< 0.01	

Note: *Between-group comparisons at week 8 were performed using independent t-test or Mann-Whitney test. Within-group comparisons (baseline vs week 8) were conducted using paired t-test or Wilcoxon signed-rank test.*

Correlation Between Inflammatory Markers, Neutrophil Counts, and Disease Severity

Spearman correlation analysis revealed statistically significant positive correlations between inflammatory biomarkers, neutrophil counts, and disease severity measured by UAS7 (Table 2). Specifically, CRP levels showed a moderate correlation with UAS7 (rho = 0.56, p = 0.004), ESR correlated similarly (rho = 0.52, p = 0.007), and neutrophil counts demonstrated a slightly lower but still significant correlation (rho = 0.49, p = 0.011). These results indicate that higher systemic inflammation and neutrophil activation are associated with increased urticaria severity (Figure 1).

Table 2. Spearman correlation coefficients between inflammatory markers, neutrophil counts, and disease severity (UAS7).

Parameter	Spearman's rho	p-value
CRP	0.56	0.004
ESR	0.52	0.007
Neutrophil count	0.49	0.011

Note: *Correlations were calculated using Spearman's rank correlation. Positive coefficients indicate a direct association between biomarker levels and disease severity measured by UAS7.*

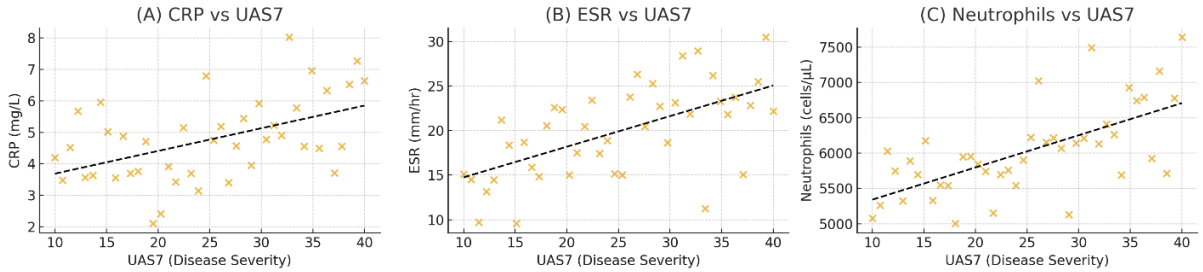


Figure 1. Scatter plots with regression lines illustrating the correlation between (A) CRP and UAS7, (B) ESR and UAS7, and (C) neutrophil counts and UAS7. The plots demonstrate the positive association between systemic inflammatory markers and disease severity.

Discussion

The present randomized add-on trial demonstrates that layering a probiotic onto a background of second-generation H1-antihistamine therapy yields greater improvement in both clinical and inflammatory domains than antihistamine alone over eight weeks. Reductions in C-reactive protein, erythrocyte sedimentation rate, and absolute neutrophil counts were significantly larger in the probiotic arm, and week-8 between-group comparisons favored the adjunctive strategy across markers. Importantly, biomarker changes tracked with symptomatic improvement: declines in CRP, ESR, and neutrophils correlated with UAS7 reductions, supporting a link between attenuation of systemic inflammation and disease control. Together, these observations extend an emerging clinical signal that microbiome-directed adjuncts can modestly improve CSU symptoms when added to antihistamines, while uniquely providing concomitant biochemical evidence of reduced inflammatory tone.

Placed alongside prior trials, our symptomatic findings are directionally consistent with randomized studies testing multistrain probiotic or synbiotic add-ons for approximately eight weeks. In our previous study using LactoCare, we reported a greater UAS7 reduction compared to antihistamine alone, although details on placebo matching and strain identity were limited [9]. A double-blind, twice-daily synbiotic added to standardized cetirizine achieved a lower week-8 UAS7 than placebo without a differential DLQI effect [10]. More recently, a double-blind study using levocetirizine, with bilastine permitted for intolerance, found superior UCT outcomes in the probiotic arm, indicating improved disease control on a validated instrument [11]. Our results reproduce the symptomatic benefit seen across these studies and complement them by integrating systemic inflammatory readouts. By contrast, nonrandomized or short-duration designs—such as a four-week single-strain Lactobacillus reuteri add-on to ebastine—suggest improvement but are less definitive for sustained adjunctive effects in CSU [13]. A large pragmatic randomized study described eight-week benefits of a "symbiotic" sachet added to antihistamines, but ambiguities in product identity, blinding, and age reporting temper cross-trial comparability [14]. Against this heterogeneous background, the present trial contributes more granular inflammatory data aligned with clinical outcomes.

The biomarker profile observed here—falling CRP, ESR, and neutrophils in parallel with UAS7 improvement—resonates with observational characterizations of an inflammatory CSU phenotype. Antihistamine-resistant patients exhibit higher CRP and IL-6, elevated ESR, and gut dysbiosis with reduced alpha-diversity and specific taxonomic shifts; inflammatory markers correlate with disease activity in these cohorts [1]. Mechanistic work further supports a gut–skin axis in CSU pathogenesis: decreased short-chain fatty acids and increased plasma lipopolysaccharide, linked to barrier dysfunction and pathobionts such as Klebsiella pneumoniae, promote mast-cell–mediated skin inflammation in translational models, while SCFA-producing taxa exert protective effects [15]. Although our study did not assay IL-6, LPS, or SCFAs, the pattern of systemic inflammatory reduction with probiotic adjunct therapy is directionally consistent with these pathways and offers a plausible biological rationale for the clinical benefits we and others have observed. In this sense, our findings bridge the gap between symptom-focused adult RCTs [9, 10] and the mechanistic literature articulating how microbiota modulation could down-regulate systemic inflammation and, indirectly, mast-cell effector activity [1, 15].

Comparative interpretation across trials must also account for formulation heterogeneity and trial conduct. The 2023 meta-analysis synthesizing probiotic interventions in urticaria concluded that effects are strain- and product-dependent, with single-strain add-ons sometimes yielding clearer signals and multi-strain mixtures showing variable results; it called for larger, strain-defined, rigorously controlled RCTs [12]. Most individual trials—including those reporting positive symptom outcomes—provided limited strain-level identifiers, CFU at end-of-shelf-life, or prebiotic content, and only one explicitly ensured a prebiotic-free placebo to avoid biologically active controls [9, 10, 12]. Background antihistamine standardization and prespecified rescue rules also varied, which can influence both symptom trajectories and inflammatory markers. Within this context, the concordant clinical and biochemical improvements observed here strengthen the inference that adjunct microbiome-targeted therapy can modulate disease biology beyond symptomatic relief, but they do not obviate the need for strain-resolved replication under tightly standardized conditions.

Limitations

Several constraints temper generalization and clarify priorities for interpretation. Our biomarker panel did not include IL-6, D-dimer, fibrinogen, basophil counts, or functional assays such as the basophil activation test, which have been variably linked to CSU activity and angioedema risk and would enhance mechanistic resolution. We did not evaluate permeability or endotoxemia surrogates, including plasma LPS, nor SCFA profiles, precluding direct testing of the gut–barrier pathway highlighted in translational studies. As with many probiotic trials in dermatology, broader external validity depends on explicit reporting of strain designations, per-dose CFU at end-of-shelf-life, prebiotic content, and placebo composition; lacking these details constrains cross-study synthesis and dose–response inference and mirrors limitations seen in prior trials. Finally, although baseline inflammatory comparability supports internal validity, neutrophil counts are sensitive to intercurrent infections and concomitant medications. Rigorous capture and control of antibiotics, proton-pump inhibitors, rescue corticosteroids, and nonstudy probiotics—factors known to alter the microbiome and inflammatory milieu—remain essential to exclude alternative explanations for biomarker shifts.

Future Comparative Work

The next phase of investigation should move beyond symptom-only end points and embed a harmonized clinical-to-mechanistic framework. Double-blind, placebo-controlled trials that are strain-resolved and dose-defined, with CFU verified at end-of-shelf-life and explicitly prebiotic-free placebos, are required to enable valid cross-study comparisons and meta-analysis. Background therapy should be fixed to a single second-generation H1-antihistamine with prespecified rescue rules, while outcomes should integrate UAS7 and UCT with responder thresholds to facilitate interpretability across trials. Biomarker suites ought to include hs-CRP and IL-6 together with coagulation indices, basophil counts or activation assays, and translational readouts of the gut–barrier–SCFA axis such as plasma LPS and targeted SCFA metabolomics to test causal mediation suggested by mechanistic studies. Prospective stratification by endotype indicators—including total IgE, basopenia, and thyroid autoimmunity—should be incorporated to determine whether patients with inflammatory signatures derive disproportionate benefit from microbiome-modulating adjuncts, thereby advancing precision adjunctive therapy in CSU.

Conclusion

The addition of a specific multistrain synbiotic probiotic to second-generation H1-antihistamine therapy in Chronic Spontaneous Urticaria (CSU) leads to significantly greater improvement in both clinical symptoms and systemic inflammatory biomarkers compared to antihistamine treatment alone. The observed correlation between reduced inflammation and lower disease activity suggests that modulating the gut microbiome may be a beneficial adjunct strategy for managing CSU by addressing underlying systemic inflammation.

Abbreviations

CSU: Chronic Spontaneous Urticaria; **CRP**: C-Reactive Protein; **ESR**: Erythrocyte Sedimentation Rate; **UAS7**: Urticaria Activity Score over 7 days; **DLQI**: Dermatology Life Quality Index; **CBC**: Complete Blood Count; **LPS**: Lipopolysaccharide; **SCFAs**: Short-Chain Fatty Acids; **FOS**: *Fructooligosaccharides*; RCT: Randomized Controlled Trial.

Ethical Approval

The study protocol was approved by the Institutional Review Board (**IR.IUMS.FMD.REC .1398.129**), and the trial was registered under **IRCT20190825044613N1**. All participants provided written informed consent prior to enrollment, and confidentiality was strictly maintained.

Availability of Data and Materials

The datasets generated and analyzed during the current study are not publicly available due to patient confidentiality agreements under the approved ethics protocol but are available from the corresponding author upon reasonable request.

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Authors' Contribution

SH.SH.: Conceptualization, Methodology, Investigation, Data Curation, Writing – Original Draft, Project Administration. **N.A**.: Methodology, Formal Analysis, Investigation, Resources, Writing – Review & Editing. **M.F**.: Formal Analysis, Writing – Review & Editing, Supervision. All authors read and approved the final manuscript.

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Consent for Publication

Written informed consent for publication was obtained from all participants included in the study.

Competing Interests

The authors declare no competing interests.

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