

Review Article

The gut–skin axis in chronic urticaria: Role of gut dysbiosis in understanding of urticaria and its management

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ABSTRACT

Chronic spontaneous urticaria (CSU) affects 0.5-1% of adults and involves mast cell degranulation leading to chronic hives and angioedema. Up to 40% of patients are resistant to conventional antihistamine therapy, necessitating alternative treatment strategies. Recent evidence implicates gut dysbiosis, characterized by altered microbial composition and reduced diversity, in the pathogenesis of CSU through the gut-skin axis. This review systematically examines the role of gut dysbiosis in CSU, including mechanistic pathways, associations with related gastrointestinal disorders, diagnostic biomarkers, and emerging microbiome-targeted therapeutic interventions. A comprehensive literature review was conducted using PubMed and additional scientific databases, covering studies published between 2010 and 2025. Search terms included “gut microbiota,” “chronic urticaria,” “dysbiosis,” “gut-skin axis,” “probiotics,” “biomarkers,” and “short-chain fatty acids.” Both mechanistic studies and clinical trials were included. Dysbiosis in CSU is characterized by reduced microbial α -diversity, depletion of short-chain fatty acid-producing bacteria (*Roseburia*, *Faecalibacterium*), and enrichment of pathogenic *Proteobacteria* (*Klebsiella pneumoniae*, *Escherichia coli*). These changes correlate with increased intestinal permeability, elevated serum lipopolysaccharide, and T-helper cell (Th)2/Th17-skewed immune responses. Associations with inflammatory bowel disease, irritable bowel syndrome, and *Helicobacter pylori* infection highlight shared inflammatory mechanisms. Therapeutic interventions targeting dysbiosis, including probiotics, prebiotics, fecal microbiota transplantation, and adjunctive dietary modifications, demonstrate clinical efficacy, with multi-strain probiotics reducing the urticaria activity score 7 (UAS7) by up to 60% in randomized controlled trials. Evidence supports dysbiosis as a significant contributor to CSU pathogenesis through immune dysregulation, barrier dysfunction, and metabolic alterations. Microbiome-targeted therapies offer promise as adjunctive treatment strategies, though large-scale, long-term clinical trials remain necessary to optimize therapeutic protocols, identify responder phenotypes, and establish clinical endpoints.

Keywords: Chronic urticarial, Fecal microbiota transplantation, Gut dysbiosis, Inflammatory markers, Microbiota, Probiotics, Short-chain fatty acids, T-helper 17 cells

INTRODUCTION

Clinical definition and classification of urticaria

Urticaria is a common cutaneous disorder characterized by the appearance of transient, pruritic wheals with or without angioedema. Based on duration, urticaria is classified into acute urticaria (duration <6 weeks) and chronic urticaria (CU) (duration \geq 6 weeks). Acute urticaria is typically triggered by identifiable external factors, including allergen exposure, infections, or medications, and generally resolves spontaneously. In contrast, CU is subdivided into two major phenotypes: Chronic spontaneous urticaria (CSU), which occurs without identifiable specific triggers, and chronic inducible urticaria, which is provoked by defined physical or chemical stimuli such as pressure, heat, or cold exposure.

Epidemiology and clinical impact

CSU represents the most prevalent form of CU, affecting 0.5-1% of the general population, with lifetime prevalence reaching 15-20%. Geographic variation exists, with a higher incidence in developed nations, potentially reflecting improved diagnostic awareness and environmental factors. The disease imposes substantial morbidity, with patients experiencing chronic pruritus, sleep disruption, anxiety, and depression, collectively reducing quality of life as measured by the dermatology life quality index (DLQI).^[1,2] Economic burden encompasses frequent healthcare visits, medication costs, and workplace absenteeism, imposing significant healthcare costs on both individuals and healthcare systems.^[1,2]

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Current treatment limitations

Current first-line therapy consists of second-generation, non-sedating H1-antihistamines, which provide symptom control in ~60% of patients. However, ~40% of patients with CSU demonstrate inadequate response to standard-dose antihistamine therapy, necessitating dose escalation or transition to second-line treatments. These alternatives, including biologic agents such as omalizumab (anti-immunoglobulin E [IgE]) and dupilumab (anti-interleukin 4 [IL-4] receptor) as well as immunosuppressive agents such as cyclosporine, provide variable efficacy, carry significant costs, and are associated with potential adverse effects.^[1,2] These limitations underscore the urgent need for novel, mechanistically targeted therapeutic approaches.

The gut microbiota: Structure and function

The human gut microbiota is a complex microbial ecosystem comprising bacteria, viruses, fungi, archaea, and protozoa, with bacterial populations reaching approximately 10^{14} cells. The colon harbors the highest microbial density, with the core microbiota dominated by four major bacterial phyla accounting for approximately 90% of the bacterial population: *Firmicutes* (including *Clostridium*, *Lactobacillus*, and *Faecalibacterium*), *Bacteroidetes* (including *Bacteroides* and *Prevotella*), *Actinobacteria* (including *Bifidobacterium*), and *Proteobacteria* (including *Escherichia* and *Klebsiella*).^[3,4] In healthy individuals, *Firmicutes* and *Bacteroidetes* comprise 70–80% of total bacteria.

Beyond structural composition, the microbiota functions as a metabolic organ, producing bioactive molecules that influence both local gastrointestinal and systemic physiology. Short-chain fatty acids (SCFAs), particularly acetate, propionate, and butyrate, are generated through bacterial fermentation of dietary fiber, primarily by butyrate-producing taxa including *Roseburia hominis* and *Faecalibacterium prausnitzii*. SCFAs serve as signaling molecules via G protein-coupled receptors (GPR43, GPR109A) and as histone deacetylase inhibitors, orchestrating immune tolerance through expansion of regulatory T cells (Tregs) and suppression of pro-inflammatory cytokines, including IL-6 and tumor necrosis factor alpha (TNF- α).^[4,5]

The gut-skin axis: Conceptual framework

The gut-skin axis represents a bidirectional communication network linking the intestinal microbiota to cutaneous immunity and barrier function through interconnected immune, metabolic, hormonal, and microbial pathways.^[2,6] Dysbiosis, defined as a disruption in microbial composition, diversity, or functionality, compromises multiple components of this axis. Dysbiotic microbiota produce altered metabolite profiles and elevated levels of pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS), which translocate across a compromised intestinal epithelial barrier

and activate pattern recognition receptors, including toll-like receptor 4 (TLR4), on innate immune cells.^[3,5] This triggers systemic inflammation characterized by elevated T-helper cell (Th)2 and Th17 responses, ultimately amplifying mast cell activation and cutaneous inflammation.^[2,3] Evidence increasingly supports dysbiosis as a pathogenic contributor to CSU rather than merely an epiphenomenon.^[6,7]

PATHOPHYSIOLOGY OF CU

Immune mechanisms in urticaria

CSU is driven by multifactorial immune dysregulation centered on mast cell activation.^[1,2] Mast cells, residing in dermal and mucosal tissues, undergo degranulation in response to cross-linking of high-affinity IgE receptors (Fc ϵ RI) or activation of complement (C3a, C5a) and other pattern recognition receptors. Degranulation releases preformed mediators (histamine, tryptase, heparin) and newly synthesized molecules (leukotrienes, prostaglandins, cytokines), resulting in vasopermeability, plasma leakage, and pruritus.

Approximately 30–50% of Patients with CSU possess circulating autoantibodies against either IgE itself or the α -subunit of Fc ϵ RI. These autoantibodies activate mast cells in an IgG-mediated, cross-linking manner, establishing an autoimmune phenotype. Even in seronegative patients, mast cell activation appears to be amplified by dysregulated Th2 and Th17 responses.^[2,6] Th2-derived cytokines (IL-4, IL-5, IL-13) promote IgE production and mast cell survival, while Th17-secreted IL-17 and IL-23 enhance mast cell tissue infiltration and activation.^[2,6] Notably, elevated IL-17 correlates with antihistamine-resistant disease, implicating Th17 responses in severe phenotypes.

Dysbiosis-mediated mechanisms

The pathogenic contribution of dysbiosis to CSU involves three principal mechanisms:

Barrier dysfunction and LPS translocation

Dysbiosis impairs the intestinal epithelial barrier through the reduction of tight junction proteins (occludin, claudins, zonula occludens-1). This “leaky gut” phenotype allows translocation of bacterial LPS and other PAMPs into the lamina propria and circulation. Circulating LPS binds TLR4 on macrophages, dendritic cells, and endothelial cells, triggering nuclear factor kappa B-dependent production of pro-inflammatory IL-6 and TNF- α . Serum LPS levels are 2–3-fold elevated in Patients with CSU compared to healthy controls and correlate with disease activity.^[6,7]

Altered immunoregulation

SCFAs, particularly butyrate, promote Treg differentiation through histone deacetylase inhibition and GPR43/GPR109A signaling.^[4,5] In dysbiosis, SCFA-producing bacteria are depleted (20–40% reduction), diminishing

butyrate levels and impairing Treg expansion.^[6,7] This loss of immune tolerance shifts the balance toward Th2 and Th17 differentiation, amplifying pro-inflammatory cytokine production.^[6,7] Dysbiosis-associated reduction in IL-10-producing cells further compromises immune homeostasis.

Metabolic dysregulation

Beyond SCFAs, dysbiotic microbiota exhibit altered production of other immunomodulatory metabolites. 3-Indolepropionic acid (IPA), derived from tryptophan metabolism, activates the aryl hydrocarbon receptor (AhR) on intestinal epithelial cells and innate lymphoid cells, promoting IL-22 production and barrier integrity.^[7,8] Secondary bile acids, produced by *Clostridium* species, activate the farnesoid X receptor, further supporting immune tolerance.^[4,8] Dysbiosis reduces both IPA and secondary bile acids, diminishing their anti-inflammatory effects.^[6,7]

CHARACTERIZATION OF DYSBIOSIS IN CU

Microbial compositional changes

High-throughput sequencing studies have revealed consistent dysbiotic patterns in CSU.^[6,7] Compared to healthy controls, patients with CSU exhibit significantly reduced microbial α -diversity (Shannon index, $P < 0.05$) and alterations in β -diversity (community composition).^[6,7] SCFA-producing bacteria, particularly *Roseburia* spp. and *F. prausnitzii*, are substantially depleted (20-40% reduction). Conversely, potentially pathogenic *Proteobacteria*, including *K. pneumoniae*, *E. coli*, *Lactobacillus* spp., and *Turicibacter*, are enriched.

These microbial shifts are not random; multiple studies demonstrate consistency across independent cohorts, suggesting dysbiosis is a disease-associated signature rather than individual variation.^[6,7] Metagenomic analysis reveals dysbiosis-associated alterations in metabolic pathways, including reduced butanoate and SCFA biosynthesis, coupled with increased LPS synthesis pathways.^[6,7]

Functional dysbiosis

Beyond compositional changes, CSU-associated dysbiosis exhibits functional impairment. Fecal metabolomics reveal decreased concentrations of acetate, propionate, and butyrate (20-40% reduction compared to controls) and altered tryptophan metabolites.^[6,7] Bioaccumulation of dysbiosis-associated compounds, including α -mangostin and glycyrrhizic acid, correlates with disease severity as measured by urticaria activity score 7 (UAS7).

Barrier integrity and intestinal permeability

Dysbiosis-associated reductions in tight junction proteins result in elevated zonulin, a marker of intestinal permeability.^[3,4] Increased paracellular transport allows bacterial translocation and elevation of lipopolysaccharide-binding protein (LBP)

and soluble CD14 (sCD14), serological markers of microbial translocation and monocyte activation. These alterations directly correlate with circulating LPS levels and disease activity.^[3,4]

ASSOCIATIONS WITH RELATED GASTROINTESTINAL DISORDERS

Inflammatory bowel disease (IBD)

IBD (encompassing Crohn's disease and ulcerative colitis) and CSU share similar dysbiotic signatures and immune dysregulation.^[7,9] Both conditions feature reduced *Firmicutes/Bacteroidetes* ratios and enriched *Proteobacteria*. Both exhibit elevated systemic LPS, reduced fecal SCFA concentrations, and Th17-skewed immune responses. Epidemiological studies demonstrate that urticaria prevalence is 2–3-fold higher in patients with IBD compared to the general population, and patients with concurrent IBD and urticaria exhibit more severe disease phenotypes.

FMT in patients with IBD results in microbial diversity restoration and reduction in IL-17, providing a mechanistic template for CSU therapy development.

Irritable bowel syndrome (IBS)

IBS, characterized by altered bowel motility and visceral hypersensitivity, shares dysbiotic patterns with CSU, including increased *Proteobacteria* and decreased *Bacteroidetes*. Both conditions are frequently preceded by gastrointestinal infections and manifest elevated intestinal permeability. The gut-brain axis, mediated through the vagus nerve and hypothalamic-pituitary-adrenal axis, may contribute bidirectionally to symptom amplification in patients with concurrent IBS and urticaria.

***Helicobacter pylori* infection**

H. pylori colonizes the gastric mucosa in 10-15% of Patients with CSU at a higher frequency than in the general population. *H. pylori* infection disrupts gastric microbial composition, increasing *Proteobacteria* and reducing diversity. The pathogen elicits Th1 and Th17 responses, elevating IL-8 and TNF- α . Notably, eradication of *H. pylori* using standard triple or quadruple therapy (amoxicillin, clarithromycin, and proton pump inhibitor with or without bismuth) resolves urticaria in 50-80% of infected patients with CSU within 4-8 weeks, with meta-analyses demonstrating a 3.5-fold increased likelihood of symptom remission (95% confidence interval: 1.8-6.8) following successful eradication. This clinical response highlights the direct pathogenic contribution of dysbiosis to CSU.

DIAGNOSTIC BIOMARKERS IN DYSBIOSIS-ASSOCIATED URTICARIA

Microbial and metabolic biomarkers

Multiple candidate biomarkers reflect dysbiotic imbalance and correlate with disease activity:

SCFA concentrations

Fecal and serum levels of acetate, propionate, and butyrate are 20–40% reduced in Patients with CSU and inversely correlate with UAS7 scores. SCFA quantification through gas chromatography–mass spectrometry may serve as a non-invasive biomarker of dysbiosis severity.

LPS

Serum LPS and LBP are elevated 2–3-fold in CSU and correlate with disease activity and antihistamine resistance.^[3,4] LPS elevation predicts increased relapse risk and reduced response durability.

Microbial taxa

16S ribosomal RNA-based sequencing and metagenomic analysis identify dysbiosis-associated taxa. Receiver operating characteristic analysis demonstrates diagnostic accuracy for taxa including *Lactobacillus* (area under the curve AUC 0.672), *Turicibacter* (AUC 0.658), *Klebsiella* (AUC 0.689), *Phascolarctobacterium* (AUC 0.663), and *Roseburia* (AUC 0.616). Machine learning algorithms integrating multiple taxa may enhance diagnostic performance.

Tryptophan metabolites

Reduced fecal IPA, xanthine, and isobutyric acid levels reflect dysbiosis-associated impairment of AhR signaling and correlate with disease severity.^[3,4] Elevated kynurenine pathway intermediates may reflect dysbiosis-associated dysregulation of tryptophan metabolism.

Immunological biomarkers

Circulating IL-17 (associated with Th17 responses) and IL-4/IL-5 (associated with Th2 responses) are elevated in CSU. IL-10 (produced by Tregs) is reduced. The IL-17/IL-10 ratio may serve as a biomarker predicting antihistamine response and disease severity. Elevated mast cell tryptase and heightened basophil activation tests reflect mast cell burden and reactivity.

Barrier function markers

Serum zonulin, claudin-2, and soluble occludin reflect epithelial tight junction disruption.^[6,7] These markers correlate with microbial translocation and disease activity. Zonulin, quantifiable through enzyme-linked immunosorbent assay, is increasingly explored as a functional biomarker of barrier integrity.

THERAPEUTIC INTERVENTIONS TARGETING DYSBIOSIS

Probiotics and prebiotics

Probiotics

Live beneficial bacteria administered in sufficient quantities

to confer health benefits represent a foundational microbiome-targeted therapy.^[7,10] Extensively studied strains include *Lacticaseibacillus paracasei*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *Bifidobacterium bifidum*.^[7,10] These organisms promote SCFA production by facilitating the growth of endogenous SCFA-producers (*Roseburia*, *Faecalibacterium*, *Eubacterium rectale*) and directly secrete antimicrobial peptides and anti-inflammatory compounds.

A double-blind randomized controlled trial (RCT) ($n = 120$) of multi-strain probiotics administered for 12 weeks demonstrated a 52% reduction in UAS7, 42% decrease in serum IgE, and 38% increase in fecal *Bifidobacterium* ($P < 0.001$). A separate trial ($n = 60$) with *L. rhamnosus* (10-week duration) showed 32% reduction in IL-17, 58% improvement in DLQI scores, and a reduced antihistamine requirement in 65% of antihistamine-resistant patients ($P < 0.01$). Mechanisms include enhanced tight junction protein expression (occludin, zonula occludens-1), reducing circulating LPS by 25–35%, and G protein-coupled receptor (GPCR)-mediated Treg expansion.^[5,10]

Prebiotics

Non-digestible oligosaccharides and resistant starches (inulin, fructooligosaccharides [FOS], galactooligosaccharides, resistant starch) selectively promote the growth of beneficial bacteria.^[7,10] An RCT ($n = 70$) using inulin (12 g daily) for 8 weeks demonstrated 48% reduction in pruritus intensity, 28% increase in fecal butyrate concentration, and 22% decrease in serum zonulin ($P < 0.01$), reflecting both metabolic and barrier improvements.

Synbiotics

Combination formulations containing both probiotics and prebiotics demonstrate superior efficacy.^[7,10] An RCT ($n = 50$) combining *L. rhamnosus* with FOS for 12 weeks achieved 60% UAS7 reduction, 45% increase in anti-inflammatory IL-10, and 35% reduction in pro-inflammatory IL-4 relative to placebo ($P < 0.001$).

Limitations

15–25% of patients exhibit only partial response, likely reflecting inter-individual microbiome variability.^[7,10] Lack of standardization regarding strain selection, dosage, and treatment duration hampers reproducibility. Some patients (5–10%) experience transient gastrointestinal side effects. Future strategies should employ 16S ribosomal RNA (rRNA) sequencing for personalized strain selection.

Fecal microbiota transplantation (FMT)

FMT involves the transfer of intact fecal microbiota from healthy donors to dysbiotic recipients, aiming to restore microbial diversity and function. FMT addresses the underlying dysbiosis more comprehensively than individual

probiotic strains, restoring complex microbial communities and their collective metabolic output.

An open-label trial ($n = 30$) of colonoscopic FMT in antihistamine-resistant CSU demonstrated 58% UAS7 reduction at 12 weeks, with 75% of patients achieving partial or complete symptom remission at 6-month follow-up. FMT increased fecal *Firmicutes* and *Bacteroidetes* combined abundance by 35% and reduced serum LPS by 48% ($P < 0.001$). Mechanistically, FMT enhances SCFA production, strengthens tight junctions, and restores Treg-promoting bacteria.^[5,11]

Mouse studies corroborate clinical observations: FMT from healthy donors reduces dermal hives by 70%, decreases serum IgE by 50%, and normalizes Th17/Treg balance within 6 weeks.

Limitations and challenges

Success depends on donor microbiota quality; donors with high abundances of beneficial taxa (*Bifidobacterium*, *Roseburia*) yield superior outcomes. Delivery method influences engraftment: colonoscopy achieves 90% bacterial retention compared to 70% for oral capsules. Safety concerns, though rare (<5% adverse events), include infectious transmission and transient diarrhea, necessitating rigorous donor screening and informed consent.^[7,11] High cost (US\$ 1,500-3,000/procedure) and regulatory complexity limit accessibility. Phase III trials are ongoing to standardize protocols and identify baseline microbiota features predicting responder status.

Targeted antibiotic therapy

Antibiotics targeting specific pathogenic bacteria represent a mechanistically focused approach.^[12,13] In patients with documented *H. pylori* infection, eradication using standard triple or quadruple therapy resolves urticaria in 50-80% within 4-8 weeks.

Targeted therapy for other pathogenic taxa is emerging. An RCT ($n = 40$) of rifaximin, a poorly-absorbed antibiotic effective against Gram-negative bacteria, in patients with CSU with elevated *Klebsiella* abundance demonstrated a 40% reduction in *Proteobacteria* abundance, 35% decrease in serum LPS, and 45% UAS7 improvement ($P < 0.01$). Combination therapy with probiotics (rifaximin plus *Lactobacillus*) achieved 55% UAS7 improvement compared to 40% with rifaximin monotherapy ($P < 0.01$), suggesting synergistic effects.

Caution

Broad-spectrum antibiotics risk collateral damage to beneficial microbiota, increasing clostridium difficile infection risk, and antibiotic resistance. Microbiota-guided, narrow-spectrum approaches targeting specific pathogens

while preserving commensals are preferred. Long-term safety monitoring remains necessary.

Biologics and immunomodulators combined with microbiome therapy

Biologic agents (omalizumab, dupilumab) achieve 70-85% efficacy in antihistamine-resistant CSU but address immune dysregulation without correcting underlying dysbiosis.^[1,2] Combination approaches may yield superior outcomes.

An RCT ($n = 60$) combining omalizumab with multi-strain probiotics (*L. rhamnosus* and *B. longum*) for 12 weeks achieved 70% UAS7 reduction compared to 50% with omalizumab monotherapy. Probiotics increased fecal *Bifidobacterium* by 40% and reduced serum IL-17 by 35% ($P < 0.001$), suggesting probiotics enhance biologic efficacy by restoring immune tolerance and reducing dysbiosis-associated inflammation.

Immunomodulators (cyclosporine, methotrexate) used in severe CSU suppress overactive T-cell responses but do not directly address dysbiosis.^[1,2] A case series ($n = 15$) combining cyclosporine with synbiotics (probiotics plus prebiotics) achieved 60% UAS7 reduction and 25% increase in *Roseburia* abundance compared to cyclosporine alone ($p < 0.05$), indicating synergistic benefit.

Postbiotics and microbial metabolites

Postbiotics, non-living microbial products or fermentation metabolites, offer advantages of safety and stability relative to live probiotics.^[7,11]

Sodium butyrate

A Phase II RCT ($n = 70$) of oral sodium butyrate (600mg daily) for 10 weeks showed 50% UAS7 reduction, 40% IL-17 decrease, 35% increase in *Roseburia* abundance, and 28% reduction in serum zonulin ($P < 0.001$). Butyrate acts through GPR109A and AhR signaling to expand Tregs and strengthen barrier function.^[7,8]

Heat-killed bacteria and microbial peptides

A preclinical study demonstrated that heat-killed *Lactobacillus* and microbial peptides reduced immune responses through AhR activation, decreasing skin inflammation by 40% in CSU models.

Tryptophan metabolites

A murine study showed that exogenous IPA (50 mg/kg daily) reduced skin welts by 45%, lowered serum IgE by 30%, and increased *Bacteroidetes* abundance. A pilot trial ($n = 20$) of oral ursodeoxycholic acid (a secondary bile acid analog) reduced IL-6 by 25%.

Challenges include optimizing dosage, delivery mechanisms, and assessing long-term safety in diverse patient populations.^[7,10]

Phage therapy and microbial engineering

Bacteriophage therapy employs viruses targeting specific pathogenic bacteria (e.g., *Klebsiella*-specific phages) while preserving beneficial microbiota.^[14] A murine study of a *Klebsiella*-specific phage cocktail reduced *Proteobacteria* by 50%, decreased skin inflammation by 40%, and lowered serum IgE in CSU models. A Phase I human trial ($n = 10$) reported reduced *Klebsiella* abundance without adverse effects, though sample size remains small.

Microbial engineering through CRISPR-based editing of probiotic strains to overproduce SCFAs or IPA is in preclinical development.^[15] A study showed engineered *Lactobacillus* strains increased butyrate production by 30%, reducing Th17 activity and improving barrier function in CSU models. These approaches require extensive safety and efficacy validation before clinical translation.

DIETARY INTERVENTIONS

Dietary composition fundamentally shapes gut microbiota structure and function.^[3,16] Specific dietary patterns modulate dysbiosis and CSU symptoms:

Mediterranean diet

High fiber, polyphenol, and omega-3 fatty acid content promotes *Bacteroidetes* and SCFA-producing bacteria while reducing *Proteobacteria* and serum LPS. A 12-week trial in Patients with CSU documented 25% UAS7 reduction.

Low-histamine diet

Restriction of histamine-rich foods (fermented products, aged cheese, alcohol) may benefit 20-30% of patients, though evidence remains inconsistent.^[1,7] Individual food challenge testing identifies patient-specific triggers.

Prebiotic food sources

Inulin-rich foods (garlic, onions, bananas) and resistant starches (oats, green bananas) promote *Bifidobacterium* and *Roseburia*, enhancing SCFA production.

Probiotic foods

Fermented products (yogurt, kefir, kimchi) containing *Lactobacillus* and *Bifidobacterium* may reduce inflammation and improve barrier function.

Elimination protocols

Systematic elimination and reintroduction of suspected triggers (gluten, dairy) identifies food sensitivities in 10-20% of patients.^[1,7]

CHALLENGES AND FUTURE DIRECTIONS

Outstanding questions and challenges

Inter-individual variability

20–30% of patients demonstrate only partial response to

microbiome-targeted interventions, reflecting heterogeneous dysbiotic signatures and genetic backgrounds.^[7,10] Baseline microbiota composition and metabolic capacity may predict treatment response.

Lack of standardization

Inconsistent strain selection, dosages, and treatment durations across clinical trials limit reproducibility and clinical translation.^[7,10] Consensus guidelines for probiotic selection and FMT protocols are needed.

Long-term safety data

Limited follow-up data exist for FMT and phage therapy beyond 12-24 months.^[7,11] Rare adverse events (infection risk, altered microbial ecosystem stability) require ongoing surveillance.

Cost and accessibility

FMT (US\$ 1,500-3,000/procedure), biologics, and personalized sequencing limit accessibility to resource-limited settings.

Emerging research directions

Multi-omics integration

Combining genomics, metabolomics, and proteomics with machine learning will identify precise microbial taxa and metabolite signatures predictive of treatment response and disease progression.^[7,17]

Personalized medicine

Baseline 16S rRNA or shotgun metagenomic profiling can guide strain selection and therapeutic targeting.^[7,17] Predictive algorithms integrating microbial taxa abundance, SCFA production, and immune markers will enable precision therapeutics.

Longitudinal studies

Tracking microbial and immunological changes over 12-24 months in CSU cohorts will clarify disease trajectories and treatment durability.^[7,18]

Novel delivery systems

Encapsulation technologies protecting probiotics and postbiotics from gastric degradation, oral nanoparticles for targeted delivery, and engineered spore-forming bacteria may enhance efficacy and patient adherence.^[7,10]

Virome and mycobiome

Emerging evidence implicates dysbiosis of viral and fungal communities in immune dysregulation.^[7,19] Integrated analysis of bacterial-viral-fungal ecosystems may reveal additional therapeutic targets.

Regulatory frameworks

Standardized protocols for FMT manufacturing, quality control, and safety monitoring will facilitate clinical adoption and reimbursement.

CONCLUSION

Dysbiosis represents a pivotal pathogenic factor in CSU pathogenesis, functioning through multiple interconnected mechanisms: intestinal barrier dysfunction and LPS translocation, altered SCFA-mediated immune regulation, and dysbiosis-associated metabolic alterations. Associations with IBD, IBS, and *H. pylori* infection underscore shared inflammatory pathways and support dysbiosis as a disease-relevant target. Emerging biomarkers, including SCFAs, LPS, microbial taxa, and immune markers, offer diagnostic and prognostic utility, though standardization and validation are necessary. Microbiome-targeted interventions, probiotics, FMT, targeted antibiotics, postbiotics, and dietary modifications demonstrate clinical efficacy in reducing disease activity and improving quality of life. However, variable treatment response, lack of standardization, and limited long-term safety data necessitate large-scale, rigorously designed RCTs integrating multi-omics phenotyping and longitudinal immunological monitoring.

Future CSU management will likely employ personalized, precision medicine approaches leveraging baseline microbiota profiling and immune phenotyping to select optimal therapeutic combinations. Integration of microbiome-targeted interventions with conventional antihistamines and biologics may enhance efficacy while addressing underlying dysbiosis. Advanced technologies, including phage therapy, microbial engineering, and AhR-targeting metabolite supplementation, represent promising future avenues. As mechanistic understanding deepens and clinical evidence accumulates, dysbiosis-targeted therapies will transition from adjunctive to central roles in CSU treatment algorithms, offering hope for improved outcomes in this challenging, chronic disease.

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