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Histamine Intolerance and the Association with Chronic Idiopathic Urticaria in Patients with Small Intestinal Bacterial Overgrowth

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Abstract

Background and Aim: Chronic idiopathic urticaria (CIU) is characterized by persistent hives lasting over six weeks without an identifiable cause, significantly impairing patients' quality of life. Second-generation H1-antihistamines are the primary treatment; however, a substantial proportion of patients exhibit resistance, necessitating alternative therapeutic strategies. Emerging research highlights the gut microbiome's role in CIU pathogenesis, particularly the interactions among histamine intolerance (HIT), CIU, and small intestinal bacterial overgrowth (SIBO). This review systematically examines existing literature on these associations, identifies knowledge gaps, and proposes directions for future research.

Methods: A systematic literature search was conducted across multiple databases (e.g., PubMed, Web of Science) using keywords such as "histamine intolerance," "chronic idiopathic urticaria," and "small intestinal bacterial overgrowth." Eligible studies investigated the prevalence, clinical characteristics, diagnostic approaches, and therapeutic interventions related to HIT, CIU, and SIBO. Quality assessment was performed using standardized tools (e.g., Newcastle-Ottawa Scale for observational studies). Extracted data included study design, sample size, patient characteristics, diagnostic methods for HIT, CIU, and SIBO, and reported outcomes. A narrative synthesis integrated finding, highlighting consensus, discrepancies, and methodological limitations.

Results: HIT, characterized by impaired histamine metabolism due to diamine oxidase (DAO) deficiency, is associated with diverse gastrointestinal and extra-intestinal symptoms. CIU is a complex condition wherein histamine plays a central pathogenic role. A significant subset of CIU patients exhibits autoantibodies against FcεRI or IgE, leading to mast cell activation and histamine release. SIBO, diagnosed via breath tests, is linked to gastrointestinal symptoms and nutrient malabsorption. Several studies suggest a potential association between HIT and CIU, with some reporting symptom improvement following a histamine-reduced diet, although findings remain inconsistent. The relationship between SIBO and CIU is less well-defined, with variable prevalence rates reported across studies. Additionally, gut microbiome alterations in CIU patients may influence histamine metabolism and immune responses.

Conclusion: This review underscores the potential interplay among HIT, CIU, and SIBO, suggesting that impaired histamine metabolism, autoimmunity, and gut dysbiosis may contribute to CIU pathogenesis. However, the precise nature and extent of these interactions remain unclear. Future research should prioritize standardized diagnostic criteria for HIT and SIBO, identify predictive biomarkers for treatment response, and elucidate the mechanisms by which gut microbiota and histamine metabolism influence CIU development. A more comprehensive understanding will facilitate the development of effective, personalized therapeutic strategies. Further investigations should explore microbiome-modulating therapies and the impact of factors such as vector-borne illnesses on CIU pathogenesis. While current evidence suggests intriguing connections, larger, well-designed studies with standardized methodologies are necessary to confirm these associations and establish causal relationships. The heterogeneity in study designs and outcomes highlights the complexity of these interactions, emphasizing the need for rigorous research to clarify the interconnections among HIT, CIU, and SIBO.

Keywords: Chronic idiopathic urticaria, histamine intolerance, small intestinal bacterial overgrowth, gut microbiome, diamine oxidase deficiency, mast cell activation, microbiome-modulating therapy.

1. Introduction

1.1. What Is Chronic Idiopathic Urticaria (CIU), and Why Is It Challenging to Diagnose and Treat?

Chronic spontaneous urticaria (CSU), previously known as chronic idiopathic urticaria (CIU), is a debilitating form of chronic urticaria characterized by recurrent episodes of spontaneous wheal development and/or angioedema which occur daily or almost daily for >6 weeks and have no obvious cause [1] [2]. The pathogenesis is not fully understood, making it difficult to clinically differentiate from other forms of chronic urticaria. The current understanding is that CSU is closely connected with autoimmunity; CSU caused by type I autoimmunity (more common) involves IgE antibodies against autoantigens such as thyroid peroxidase and IL-24, while type IIa and IIb, which are phenotypically identical, are caused by IgG autoantibodies against the FcεRI or IgE itself **[2]**. Lesions develop following degranulation of cutaneous mast cells and basophils, leading to the release of histamine, eicosanoids, cytokines and proteases, which amplify the inflammatory response. Lesions seen in CSU are accompanied by an intense itch, typically last around 24 hours, and do not leave residual skin changes after resolving. Angioedema, characterized by intermittent, self-limited swelling of subcutaneous and/or submucosal tissues, has a similar pathogenesis and is found in as many as two thirds of patients with CSU [3][4].

Global prevalence of CSU is estimated at 1% - up from an estimated 0.5% to 1% in 2011 [4] - and is on the rise despite the development of more targeted treatment options [2]. In the United States, it is estimated that 500,000 people have chronic urticaria, which includes CSU in addition to other forms of urticaria meeting the diagnostic criteria of lasting >6 weeks [3]. U.S. prevalence of chronic urticaria is estimated at 0.25%, and though this group of diagnoses can occur at any age, they are more commonly seen in adults over 40 years old. Women are more commonly affected than men [3].

The ASSessment of the Economic and Humanistic Burden of Chronic Spontaneous/Idiopathic URticaria patiEnts (ASSURE-CSU) study, an international observational cohort study of 673 adult patients with CSU whose symptoms were refractory to treatment for over 12 months, noted that overall productivity impairment was 27%, with over 20% of patients affected by CSU missing 1 hour or more of work per week [4]. Data demonstrates study participants' emphasis on the significant negative impact of CSU on their emotional wellbeing (47.4% of patients reported moderate or extreme problems with anxiety/depression), sleep, physical appearance, and ability to carry out daily activities [4]. Over half of the study participants (394 of 673) have CSU-associated angioedema; analysis of their medical records and survey responses showed significant burden related to severity of itch, swelling, and pain experienced during episodes. These patients were found to have more fear/shame and fatigue/mood disturbances than patients without angioedema [4]. These findings highlight the importance of developing treatment strategies that reduce the significant burden on the mental health and quality of life of patients with CSU.

Chronic spontaneous/idiopathic urticaria, by definition, has no identifiable triggers. The pathogenesis of CSU as it is currently understood has allowed for more targeted therapies to be trialed in patients for whom first and second-line treatments have failed. However, arriving at a diagnosis of CSU requires a thorough investigation of potential causes of chronic urticaria, which include infections, rheumatologic diseases, autoinflammatory syndromes, thyroid disease, lymphoproliferative disorders, medications, allergies to food or additives, and psychological factors.

For example, chronic urticaria is categorized as either spontaneous urticaria (previously called chronic idiopathic urticaria), or inducible urticaria (previously called physical urticaria). Inducible urticaria includes urticaria caused by cold, pressure, water, or sunlight, cholinergic urticaria, and urticaria secondary to scratching or rubbing skin affected by dermographism. In addition to other forms of chronic urticaria, CSU must also be differentiated from the wheals seen in other dermatologic and systemic conditions. For example, allergic contact dermatitis, especially on the face, can present with chronic wheals. Unlike CSU, however, the associated edema is persistent, and the affected skin peels following lesion improvement [5]. Polymorphous light eruption, fixed drug eruptions, and urticarial vasculitis must also be ruled out to make a diagnosis of CSU. Dermatomyositis, cellulitis, and erythema multiforme can also present with wheals similar in appearance and duration to those seen in CSU; additional physical exam findings and clinical history should readily differentiate these conditions from CSU. Specific questions regarding timing of onset, associated symptoms, duration of the lesions, and residual skin changes after the wheals have resolved, in addition to a thorough history, help differentiate these causes urticaria from CSU.

Treatment of chronic spontaneous urticaria focuses on reducing the frequency and severity of flares by controlling immune complex dysregulation and overactivation of the inflammatory response in the skin. Second-generation antihistamines, such as cetirizine 10mg, levocetirizine 5mg, fenofexadine 180mg, or loratadine 10mg daily, are the first-line treatment, with up to a 4-fold increase in dosage recommended by UK guidelines [6]. Type I autoimmune CSU responds better to antihistamines [2]. Second-line treatments include montelukast 10mg daily, H2 blockers such as famotidine 20mg twice daily; omalizumab has proven to be effective in severe, treatment-resistant cases [6]. For patients with a positive autologous serum skin test (ASST) who are non-responsive to antihistamines, oral ciclosporin has also shown symptom improvement [2]. Therefore, while an extensive workup is not always recommended for CSU diagnosis, the ASST can be helpful for guiding management.

Patients with type I autoimmune CSU typically respond to the aforementioned treatments, while patients with the less common type II autoimmune endotype have been found to have poor response to these treatments [2]. Patients with CSU refractory to antihistamines have been found to have low blood basophil counts [2], and a prospective study of 95 adults and adolescents in Belgium with a dermatologist-confirmed diagnosis of CSU found that C-reactive protein (CRP) serum levels were higher in patients with CSU refractory to the standard antihistamine regimen ($p < 0.0001$) [7]. These findings highlight the importance of elucidating a clear pathogenesis to CSU to allow for the development of more targeted treatment methods. Current novel therapies for CSU include ligelizumab (anti-IgE monoclonal antibody), fenebrutinib and remibrutinib (Bruton's tyrosine kinase inhibitors), and dupilumab (anti-IL-4Rα monoclonal antibody [2], all of which target the pathways involved in symptom development. In addition to

pharmacological approaches to the management of CSU, exploring more holistic methods of reducing inflammation - both within the skin and systemically - may prove worthwhile. For example, exploration of the connection between the gut microbiome and skin microbiome (referred to as the Gut-Skin axis) and its role in modulating autoimmune and inflammatory responses could lead to specific dietary and lifestyle-based interventions for chronic spontaneous urticaria.

1.2. Why Is the Gut-Skin Axis Being Explored in CIU Pathogenesis?

The gut microbiome is home to bacteria, fungi, viruses, and parasites. The causes of dysbiosis are not the main focus of this review, but should be considered in the evaluation of patients with inflammatory skin conditions, including CSU. Gut dysbiosis has been linked to psoriasis, acne, and atopic dermatitis, among others, via inflammatory pathways and immune system disruption [8]. In CSU, the spontaneous activation, degranulation, and mediator release from mast cells in the skin, including histamine, prostaglandin D2, (PGD2), tumor necrosis factor (TNF), and interleukins including IL-4, IL-5, IL-17, IL-13, and IL-31 cause the characteristic wheals and angioedema [9]. Together, these mediators amplify inflammatory pathways, resulting in the recruitment of T cells, basophils, and eosinophils to the dermis. Studies using 16S rRNA sequencing of gut flora in patients with CSU have found notable differences in the microbiome composition in these patients compared to healthy controls [1], suggesting a need for additional exploration, with the goal of determining which microorganisms could be targeted to restore balance to the microbiome.

In a comprehensive review of studies examining the relationship between gut microbiome composition and development of chronic urticaria, Cai et al. noted decreased levels of beneficial bacteria and increased levels of opportunistic pathogens in the gut microbiome of patients with chronic urticaria. Beneficial bacteria, which promote microbiome homeostasis and generally have an anti-inflammatory effect, include *Firmicutes* and *Bacteroidetes*. These bacteria are involved in the metabolism of short-chain fatty acids (SCFAs), especially acetic and propionic acids, which act as potent anti-inflammatory agents that protect against spontaneous degranulation of mast cells and basophils by preventing the release of pro-inflammatory cytokines from neutrophils and macrophages [9]. *Bacteroides* also produces capsular polysaccharide A, which is involved in preventing infection and is therefore likely protective against pro-inflammatory signals.

On the other hand, opportunistic pathogens such as parasitic infection and increased sensitization to food yeasts and *Candida albicans* are thought to be involved in the development of CSU [9]. The *Enterobacteriaceae* family, which is well known to cause inflammation, was more prevalent in fecal samples of patients with chronic urticaria [9], with studies showing *Escherichia coli* and *Klebsiella spp* specifically identified in higher numbers in patients with CSU [10]. *Klebsiella pneumoniae*, as well as other members of the phylum *Proteobacteria*, are associated with higher levels of lipopolysaccharides (LPS) in the blood, which trigger inflammation via toll-like receptor 4 (TLR) on immune cells [11]; this cascade can lead to increased intestinal permeability, which subsequently increases the amount of pro-inflammatory bacterial products that get absorbed from the gut and enter the bloodstream. Downstream effects of this include an increase in systemic inflammation and immune activation, including the mast cell degranulation seen in CSU. For example, certain *Proteobacteria* are involved in histamine metabolism, meaning increased levels of these bacteria can result in an increase in overall histamine present in the gut [12]. As a result of the "leaky gut" caused by increased LPS, more histamine gets absorbed into the bloodstream, which contributes to the development and severity of symptoms seen in CSU. In fact, biopsies of wheals attributed to CSU have been found to have higher numbers of mast cells, eosinophils, and basophils [1]. This review will examine the relationships between gut dysbiosis, specifically small intestinal bacterial overgrowth (SIBO), histamine intolerance, and the development of chronic spontaneous urticaria, determine which, if any, connections can be made between these diagnoses, and identify current knowledge gaps.

2. Methodology

A systematic literature review was conducted to understand the interrelationships among histamine intolerance (HIT), chronic idiopathic urticaria (CIU), and small intestinal bacterial overgrowth (SIBO). Multiple electronic databases, including PubMed, Web of Science, Scopus, and Google Scholar, were queried. Terms such as "histamine intolerance," "chronic idiopathic urticaria," and "small intestinal bacterial overgrowth," as well as sub-stratification with "diagnosis" and "treatment" were utilized to identify studies addressing the prevalence, clinical characteristics, diagnostic approaches, and treatment strategies related to HIT, CIU, and SIBO.

Studies were eligible for inclusion if they were peer-reviewed and published in English. Observational studies, clinical trials, systematic reviews, and meta-analyses were included. Studies without full-text access were excluded, as were those that were determined to not be applicable to the subject matter. Quality assessment was performed using standardized tools (e.g., Newcastle-Ottawa Scale for observational studies). Only studies meeting inclusion criteria and directly addressing research objectives were included.

A narrative synthesis approach was conducted to integrate findings across the diverse study designs in the literature. Themes were identified by identifying common elements of CIU, focusing on contributing factors, interactions between CIU, HIT, and SIBO, and therapeutic interventions. Consensus and discrepancies between studies were analyzed to generate hypotheses regarding potential mechanistic links, including the role of gut dysbiosis and immune dysregulation. The synthesis also highlighted variations in diagnostic and treatment approaches, as well as methodological limitations in the current literature for future investigation.

3. Histamine Intolerance (HIT): A Potential Contributor to CIU

Histamine Intolerance (HIT) occurs in response to elevated levels of histamine in the body due to defective histamine metabolism [13]. Its ill-defined clinical manifestations such as itching, flushing, edema, hypotension, and tachycardia among other things can mimic an allergic reaction but the pathogenesis is starkly different [14]. Histamine Intolerance (HIT) is a non-immune reaction due to excess histamine while allergies are hypersensitivity reactions mediated by the body's immune system in response to an antigen [15]. The distinction between the two is important to recognize early on in diagnosing a patient as treatment options will vary depending on the cause of symptoms. This non-immune reaction to high levels of

histamine in the setting of HIT has been linked to a defective diamine oxidase (DAO) enzyme and histamine N-methyltransferase (HNMT) enzyme. DAO sometimes functions as a secretory protein responsible for removing excess histamine in the extracellular space and HNMT functions by metabolizing histamine in the intracellular space [16]. DAO deficiency has been shown to play a greater role in the pathogenesis of HIT [17]. Failure to remove excess histamine results in its accumulation, excess binding to histamine receptors, and a manifestation of HIT.

The causes of HIT have been linked to multiple etiologies including genetics or acquired due to a prior history of intestinal or allergic conditions, alcohol, certain medications, and foods [13]. A genetic DAO deficiency stems from the interaction of single nucleotide polymorphisms (SNPs) on the DAO gene which is located at 7q35 [17]. These SNPs lead to reduced gene expression and protein synthesis, thus reducing DAO. Some studies show decreased DAO levels following certain gastrointestinal (GI) diseases that cause mucosal damage and inflammation, such as gastroenteritis or Irritable bowel syndrome among others [18]. This suggests a link in the pathogenesis of HIT to be closely connected to the gut. Other medical conditions that have been associated with HIT include allergic conditions such as Atopic Dermatitis [19], allergic rhinitis [20] and asthma [21] which play a role in HIT via SNPs of both DAO and HNMT leading to their decrease synthesis or activity. Both allergic conditions, GI diseases as well as gut dysbiosis can cause an increase in histamine levels however Zhao makes an important distinction point that symptoms due to an increase in histamine levels with intact DAO activity would be characterized as histamine overdose, not HIT [13]. Pertinent past medical history of GI diseases and allergic conditions could be considered as important risk factors in the development of HIT, and it would be useful for physicians to monitor for signs and symptoms of HIT in these patients.

Transient manifestations of HIT symptoms can be associated with triggers such as alcohol, certain medications, and foods in patients with an existing DAO deficiency. Alcohol with emphasis on red wine has been one of the most looked-at triggers for HIT as it not only increases histamine levels in the body but also further inhibits the DAO pathway via competitive inhibition of acetaldehyde dehydrogenase [13] [22]. Other triggers that work similarly by inhibiting DAO activity include medications such as Chloroquine, clavulanic acid, Cimetidine, verapamil, isoniazid, metamizole, acetylcysteine, amitriptyline, Diclofenac, metoclopramide, suxamethonium and thiamine [23]. Foods such as fish, fermented sausage, and sauerkraut also inhibit DAO activity [13]. Other foods that can trigger HIT symptoms include foods that are rich in histamine (Fish, sauerkraut, smoked meat products, and cheeses), or foods that increase histamine release (Citrus fruits, papaya, strawberries, egg whites, chocolate, nuts, fish, pork, cheese, fermented sausage, green peppers, wheat germ, and bean sprouts) [13]. All the above-listed triggers may not be symptomatic in a patient with intact DAO activity, however, in patients with deficient DAO, a more thorough questioning about reactions to these foods can help diagnose HIT from another entity.

Clinically, HIT's presentation can mimic many other conditions making it difficult to diagnose it. In a retrospective study of 133 patients, the most common symptoms found were GI related and bloating was the most severe and most common symptom found in 92% of those patients [14]. The next most common symptom was postprandial fullness in 73% of the patients, followed by diarrhea in 71% of the patients, abdominal pain in 68% of the patients, and lastly constipation in 55% of the patients. Other extraintestinal symptoms included manifestations in the skin (pruritus, flush, rash, edema), respiratory system (rhinorrhea, nasal congestion, sneezing, dyspnea), and cardiovascular system (dizziness, headache, palpitation, hypotonia, collapse), with most patients experiencing at least 3 symptoms [14]. These nonspecific symptoms make it a challenging endeavor to appropriately distinguish HIT from other differential diagnoses such as food allergy or intolerances, Irritable Bowel Syndrome, celiac disease, Helicobacter Pylori infection, Eosinophilic Gastroenteritis, Urticaria, or Systemic Mastocytosis [13]. It is clear that a thorough history and physical assessment are crucial when first trying to diagnose HIT to exclude other diseases as mentioned above. Also, physicians need to recognize the possible risk factors such as inflammatory GI disorders, and allergic conditions in the pathogenesis of HIT, as well as spend some time obtaining a complete diet and medication list given the role many foods and medications play in triggering HIT as mentioned earlier.

Some additional tools that have shown to be useful in diagnosing HIT include DAO concentration and activity testing, assessment of histamine and its metabolites in urine, and low-histamine diet trials [13]. As discussed earlier, DAO plays a major role in the pathogenesis of HIT, hence it makes sense that assessment of its concentration and activity would be a helpful tool to diagnose HIT. Studies assessing the levels of DAO in HIT patients were done via Enzyme-Linked Immunosorbent Assay (ELISA) and found DAO to be significantly lower in HIT patients than those without disease proving its use as an appropriate diagnostic method [24] [25]. Since the manifestation of symptoms is a result of excess accumulation of histamine in the body, studies using ultra-high performance liquid chromatography and fluorimetric detection (UHPLC-FL) assessing the concentration of histamine, and methylhistamine was examined and found to be a useful diagnostic method [26]. Lastly, offering both a therapeutic and diagnostic value is a trial of a low-histamine diet which showed immediate and rapid improvement in many patients as early as 4 weeks [22]. Improvement in a patient's symptoms on such a diet can be a great clarifying point when narrowing the differential for physicians assessing a patient for HIT.

One of the extraintestinal locations of HIT was the skin with pruritus being the most commonly noted symptom, followed by flush, rash, and edema[14]. This can be explained by the interaction between the elevated levels of histamine binding to histamine receptors, H1-H4 subtypes, which are present in all cells of the body and are responsible for the manifestation of symptoms associated with HIT [13]. Elevated levels of histamine are also associated with Chronic idiopathic urticaria (CIU), however exact etiologies of CIU are yet to be identified [27]. Kanny et al found 64% of their patients who had CIU developed a urticaria flare following intraduodenal administration of histamine [28]. This supports a relationship between elevated levels of histamine causing worsening symptoms in CIU patients.

While histamine is a commonly agreed upon similar feature between CIU and HIT, there is conflicting literature on the role of DAO deficiency in CIU. On one hand, Cho et al. findings showed no relationship exists between DAO activity and high histamine concentration in CIU patients without GI symptoms, but CIU patients with GI symptoms had lower DAO activity however the difference was not significant [27]. On the other hand, several older studies showed a pattern of low DAO activity in CIU patients, however, those studies are limited in their number of subjects [29] [30] [31]. Larger subject groups analyzing the relationship between DAO activity and CIU patients would help understand the exact mechanism of action and role of DAO in CIU patients. With CIU being strongly tied to elevated histamine levels and symptoms exacerbated by histamine-rich foods, a trial of a low-histamine diet by Guida et al. in 10 patients showed an improvement in CIU symptoms and a reduction in plasma histamine levels [32]. In a study of 56 patients, Wagner et al. also showed a significant improvement in symptoms in 75% of their patients [33]. A low-histamine diet is an easy therapeutic and diagnostic tool that has shown itself to be of significant help to many patients dealing with either CIU or HIT.

4. Small Intestinal Bacterial Overgrowth (SIBO): A Hidden Driver of Dysregulation?

Small intestinal bacterial overgrowth (SIBO) is a gastrointestinal disorder defined by an abnormal increase in bacterial load in the small intestine, which normally contains much lower bacterial numbers than the colon. The American Gastroenterological Association (AGA) defines SIBO diagnosis through duodenal or jejunal aspirate culture evidence of $\geq 10^3$ colony-forming units per milliliter (CFU/mL) [34]. The culture-based diagnostic method stands as the current gold standard yet faces practical challenges because it requires invasive procedures and costs a lot and may become contaminated during sample collection. The clinical practice now uses non-invasive breath testing which measures exhaled hydrogen or methane after glucose or lactulose consumption [35]. The diagnostic capabilities of breath testing remain significant. The accuracy of tests becomes compromised by three main factors including intestinal transit time and baseline gas production and microbiome variations among individuals. The diagnostic process frequently produces incorrect results which result in missed patient diagnoses particularly among those showing non-specific gastrointestinal symptoms including bloating diarrhea and fatigue [36]. The diagnostic performance of glucose breath tests shows sensitivity levels between 20–93% and specificity levels between 30–86% while lactulose breath tests demonstrate sensitivity ranging from 31–68% and specificity ranging from 44–100% [37]. The presence of elevated methane levels in breath tests indicates intestinal methanogen overgrowth (IMO) instead of traditional SIBO [38]. The diagnostic challenges highlight the requirement for personalized assessment which takes into account clinical details and patient symptoms and risk factors while supporting future studies to enhance test precision [39].

The regular bacterial restriction processes of the small intestine become disrupted by various illnesses and lifestyle choices which lead to small intestinal bacterial overgrowth (SIBO). Proton pump inhibitors (PPIs) represent a significant contributing factor because they lower a vital microbial barrier and decrease stomach acid production [40]. The second essential element responsible for this condition is impaired intestinal motility. The use of opioids together with anticholinergics and antidiarrheals as well as scleroderma and diabetic autonomic neuropathy create conditions that slow down gut transit allowing bacterial multiplication [34]. The gut's structure and physiology undergo changes following surgery which lead to bacterial overgrowth particularly when blind loops or vagal nerve damage occur [34]. SIBO exists in people who have persistent gastrointestinal conditions that affect motility including Parkinson's disease connective tissue disorders and cystic fibrosis [41]. The motility and gut microbiota balance can be negatively affected by dietary patterns containing low fiber and high simple sugars yet fiber and polyphenol-rich diets seem to protect the gut [42]**.** The natural process of aging increases the risk of SIBO because it leads to decreased immunological surveillance and motility which makes older adults more prone to SIBO [40].

SIBO manifests through dysbiosis which occurs when the small intestine contains excessive microorganisms. Studies have shown SIBO patients exhibit elevated Proteobacteria relative abundance together with decreased Firmicutes levels. The research conducted by Leite et al. revealed that patients with SIBO showed 1.64 times less *Firmicutes* relative abundance and 4.31 times higher Proteobacteria relative abundance than non-SIBO participants [43]. The microbial imbalance from dysbiosis results in various gastrointestinal symptoms because it reduces microbial diversity while modifying bacterial profiles. The bacterial overgrowth in SIBO leads to excessive histamine secretion which worsens histamine intolerance. The histamine-producing bacteria *Morganella morganii* and *Klebsiella pneumoniae* were found at higher levels in patients with histamine intolerance than in healthy participants according to Sánchez-Pérez et al. [44]. The accumulation of histamine from bacteria in the gut leads to its absorption into the bloodstream which produces systemic histamine-related symptoms.

SIBO presents additional health implications for systemic wellness beyond its diagnostic complexities. SIBO has been associated with gut dysbiosis and elevated intestinal permeability which leads to immune system activation outside the gastrointestinal tract. Rizos et al. showed that SIBO patients showed elevated interleukin-1β (IL-1β) in duodenal fluid together with elevated IL-6 and TNF-α levels in particular cases which indicated both local and systemic inflammation [45]. The breakdown of intestinal barrier integrity known as “leaky gut” enables microbial components like lipopolysaccharides (LPS) to move from the gut into the bloodstream thus triggering bodywide immune reactions. The research conducted by Kumar et al. revealed that elevated permeability worsens inflammation and sepsis by disrupting hepatic stearoyl CoA desaturase-1 (SCD-1) activity and altering iron recycling patterns [46] . The gut inflammation-on-a-chip model operated by Shin & Kim demonstrated how barrier failure leads to oxidative stress and cytokine generation which activates the immune system [47]. The treatment results for SIBO-related conditions show variability based on specific conditions. Patients who have chronic idiopathic urticaria (CIU) do not show any benefit from SIBO treatment. The research conducted by Campanati et al. on 48 patients with CSU revealed that treating SIBO in 13 patients with co-existing SIBO did not lead to any symptom improvements after four weeks [48]. Patients who had *Helicobacter pylori* infections showed symptom improvement after undergoing eradication treatment. Systemic inflammation

from SIBO appears to be unrelated to the direct pathogenesis of various chronic immune-mediated conditions.

5. Connecting the Dots: Interactions Between HIT, SIBO, and CIU

5.1. How Might SIBO Exacerbate Histamine Intolerance?

The interplay between histamine intolerance (HIT), small intestinal bacteria growth (SIBO), and chronic idiopathic urticaria (CIU) suggests one key mediator: histamine-producing bacteria. *Morganella morganii* and *Klebsiella pneumoniae– two gram-negative*, histamine-producing species—have been found in higher prevalence in SIBO patients; histamines absorption into the bloodstream may exacerbate histamine-related symptoms including pruritus, flush, and urticaria [49]. While no microbes are known to degrade diamine oxidase (DAO), dysbiosis in SIBO may indirectly alter DAO's kinematics. Gut mucosal inflammation can damage DAO-producing enterocytes while oxidative stress shifts in intestinal pH may change enzymatic activity [17]. The combination of increased histamine production in SIBO in an environment where histamine breakdown is simultaneously impaired contributes to HIT symptomatology and potentially exacerbates CIU.

5.2. What Is the Evidence Supporting an Overlap Between These Conditions?

Although causal links remain to be firmly established, emerging clinical evidence supports the idea of overlap between HIT, SIBO, and CIU. Regarding HIT, Kanny et al. proposed histamine hypersensitivity plays a role in disease activity when duodenal administration of histamine exacerbated urticaria flares in 64% of patients [28]. Then, in 2000, a pilot study by Guida et al. reported clinical and therapeutic improvement in CIU patients adhering to a histamine-restricted regiment [32]. Similarly, a 2017 study found that 75% of CIU patients experience symptomatic relief following a histamine-reduced diet. While Cho et al. (2013) did not find a statistically significant reduction in DAO levels among 60 CIU patients without gastrointestinal symptoms, a trend towards lower DAO levels was among the 15 patients with gastrointestinal symptoms [27]. Additional research has pointed to a higher prevalence of SIBO among CIU patients; however, treatment for SIBO has yielded inconsistence outcomes. For instance, Campanati et al. found eradicating SIBO in CIU patients did not significantly alleviate urticarial symptoms [48]. These findings underscore the complex and heterogeneous nature of CIU pathogenesis and suggest that while both HIT and SIBO may play a role in certain patients, responses to interventions are variable.

5.3. What Mechanisms May Link Gut Dysbiosis to CIU Pathogenesis?

Gut dysbiosis is linked to the skin via the gut-skin axis– a bidirectional communication network between the gastrointestinal tract and the skin. It is mediated by immune system interactions, microbial metabolites, and hormonal signals [8]. Salem et al. expands that commensal gut bacteria produce metabolites like short-chain fatty acids (SCFAs) that help maintain the integrity of gut epithelium; molecules like butyrate, acetate, and propionate aid in tightening junctions between intestinal epithelial cells while also stimulating anti-inflammatory responses.

Disruptions in the gut microbiome, like dysbiosis, influence skin health by affecting systemic inflammation and immune responses. In SIBO, SCFA production declines resulting in increased intestinal permeability and a "leaky gut." The gram-negative bacteria found in dysbiosis secrete lipopolysaccharides (LPS) endotoxins that enter systemic circulation to be recognized by toll-like receptors on immune cells; this results in a pro-inflammatory cascade releasing cytokines and activating mast cell histamine degranulation [50]. The outcome is a self-perpetuating feedback loop: microbial imbalance leads to immune activation and histamine circulation, exacerbating urticarial symptoms while further disrupting gut and skin homeostasis. CIU patients not only suffer from an immune-driven histamine release but also a histamine overload from bacterial production– as aforementioned by the finding of *Morganella morganii* and *Klebsiella pneumoniae which are two gram-negative*, histamine-producing species [49].

6. Therapeutic Implications and Future Strategies

The future of treating patients with CIU is promising as numerous novel treatments and combination therapies are currently being explored. The landscape for the management of CIU and HIT relies on personalized targeted therapies, understanding the gut microbiome compositions, and dietary interventions. One recommended approach for HIT is to instruct patients to limit their histamine intake. Monitoring food intake and adjusting diets may alleviate symptoms and reduce the incidence of skin complications. Although this seems like a feasible approach, it presents a unique set of challenges. San Mauro Martin and Brachero (et el.) review suggests that products containing histamine or amines often do not provide accurate labeling, and that fast food items typically lack detailed ingredient lists [51]. This implies that patients may encounter several barriers, including difficulties in compliance or fully adhering to dietary changes.

Additionally, it is recommended that patients take DAO supplements, which have been shown to be effective in alleviating symptoms. In a controlled study by Schnedl et al, patients with recurrent HIT symptoms, such as skin, gastrointestinal, cardiovascular, and respiratory issues, ranked their symptoms by severity before and after taking DAO supplements for two months. The results demonstrated a significant reduction in all HIT-related symptoms [52]. It is to be noted that HIT-related pain decreased from 69% to as low as 25% after two months of supplementation [52]. These findings suggest that taking DAO supplements prior to meals may effectively reduce symptom intensity by aiding in the degradation of intestinal histamine, thereby lowering the occurrence of rashes and other complications. This form of therapy may be a more efficient and effective strategy for managing severe cases of HIT and CIU.

The role of SIBO and the microbiome therapy in CIU is both novel and promising. Although the link between gut dysbiosis and CIU remains limited, screening for gut microbiome diversity presents an opportunity for personalized and targeted care. Dysbiosis of the gut microbiota has been associated with HIT-related symptoms, notably skin rashes. According to Cai and Zhou (et al.), decreased levels of beneficial *Bacteroides* and *Firmicutes*, along with low alpha diversity, were prevalent markers in patients with chronic urticaria [9]. *Bacteroides* contribute to the production of short-chain fatty acids, which serve various immune-related functions and suggest a protective role in chronic urticaria. These findings may also extend to CIU symptoms, as collecting fecal samples can help clarify the individualized composition of each patient's gut microbiota.

Assessing bacterial strains and identifying overgrowths creates opportunity for prompt and individualized treatment that may lead to more effective outcomes compared to traditional therapies. Preventive strategies may include encouraging the use of prebiotics and probiotics in patients with CIU. Depending on the bacterial strain, certain pre/pro-biotics may offer protective effects by enhancing immune function through stabilizing growth of certain strains. Screening for microbiota diversity and SIBO composition allows both early intervention and targeted therapy which may be the most effective treatment through continued research.

7. Conclusion and Future Directions

This review highlights the potential interactions between HIT, SIBO, and CIU proposing that decreased histamine degradation, autoimmune modulation, and gut dysbiosis may play a role in CIU pathophysiology. However, the specific nature and degree of these relationships remains unclear. In addition to characterizing the precise interplay of these interactions, future studies should focus on developing standardized diagnostic criteria for HIT and SIBO and further identifying biomarkers that predict treatment response. Some current emerging biomarkers include DAO concentration and activity, histamine and metabolite concentration, and gut microbiome screening. These markers are measured with diagnostic tools such as protein detection assays, urine tests, and analytical compound separation. A deeper understanding of these factors will aid in creating more targeted, personalized treatment options. Future review should also work to incorporate larger subject groups with standardized, well-designed studies like randomized controlled trials to confirm these connections and establish causality. Through screening and early detection, especially for those with a medical history of gastrointestinal issues with concurrent unexplained skin symptoms, allergic diseases, or a family history of DAO deficiencies – the potential for integrative, patient-centered treatment strategies is bolstered. These therapeutic interventions include histamine modulation, enzyme supplementation, and regulation of the inflammatory response in the gut. Regardless of the treatment modality, the plan should be tailored to an individual's medical demands and formulated by partnering with the patient. Additionally, clinicians can take a more holistic approach by proactively identifying triggers, incorporating diet revision, improving gut dysbiosis by encouraging probiotic supplementation, and making lifestyle modifications. Providers can also consider taking a multidisciplinary approach by collaborating with specialties like gastroenterology and integrating the expertise of other specialties like allergy and immunology. Living with gut dysregulation and chronic urticaria can significantly decrease quality of life. Through education, clinicians can empower patients by giving them the knowledge, tools, resources, and support to assume an active role in managing their condition.

Conflict of Interest Statement

The authors of this manuscript declare that they have no conflicts of interest that are directly or indirectly related to the work submitted for publication. Specifically:

1. Financial Interests: None of the authors have received any financial compensation, funding, grants, or other monetary support that could be perceived as influencing the research, analysis, or conclusions presented in this work.
2. Professional Relationships: The authors have no employment, consultancy, board membership, or other professional relationships with organizations that could be perceived as influencing the work presented here.
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