

Association Between Chronic Urticaria and *Helicobacter pylori* Infection Among Patients Attending Major Hospitals in Sana'a, 2025: A Case-Control Study

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Abstract

Background: Chronic urticaria (CU) is a persistent inflammatory skin disorder characterized by recurrent wheals, angioedema, or both for more than six weeks. Although many cases are considered spontaneous or idiopathic, accumulating evidence suggests that gastrointestinal inflammation and infection may contribute to disease activity in selected patients. *Helicobacter pylori* has therefore been investigated as a potentially modifiable associated factor, but findings remain heterogeneous and local evidence from Yemen has been lacking.

Objective: To determine whether *H. pylori* infection is associated with chronic urticaria among patients attending Al-Jumhuri, Al-Kuwait, and Al-Thawra hospitals in Sana'a City, Yemen.

Methods: A hospital-based case-control study was conducted from May to August 2025 among 132 participants recruited from outpatient settings, including 66 clinically diagnosed CU cases and 66 dermatology controls without urticaria. Demographic, dermatologic, gastrointestinal, and disease-related data were collected using a structured interviewer-administered questionnaire. *H. pylori* status was assessed using a stool antigen test. Group differences were assessed with chi-square tests and independent-samples comparisons as appropriate. The association between CU and *H. pylori* positivity was summarized using an odds ratio (OR) with a 95% confidence interval (CI).

Results: Cases and controls were comparable in age, sex, residence type, marital status, and education (all $p > 0.05$), although hospital distribution differed significantly ($p = 0.028$). *H. pylori* positivity was substantially higher among CU cases than controls (60.6% vs 34.8%, $p = 0.005$), corresponding to nearly threefold higher odds of infection among cases (OR 2.88, 95% CI 1.42–5.83). Gastrointestinal symptoms were common in both groups and tended to be more frequent among cases, but most between-group differences were not statistically significant. Among CU cases, disease burden was considerable, with daily symptoms in 48.5%, sleep disturbance in 53.0%, and mental health impact in 77.3%. Only 25.8% of cases reported receiving eradication therapy; among treated cases, 41.2% reported improvement in urticaria symptoms.

Conclusion: *H. pylori* infection was significantly associated with chronic urticaria in this Sana'a hospital sample. The findings support considering selective gastrointestinal evaluation and targeted *H. pylori* testing in CU patients with persistent disease or gastrointestinal complaints, while continuing guideline-based urticaria management. Prospective and interventional studies are needed to clarify temporality and the therapeutic value of confirmed eradication.

Keywords: chronic urticaria; chronic spontaneous urticaria; *Helicobacter pylori*; stool antigen; case-control study; Sana'a; Yemen

Introduction

Chronic urticaria is a common inflammatory skin disease defined by the spontaneous or inducible recurrence of pruritic wheals, angioedema, or both for longer than six weeks. It is clinically important not only because of its frequency but also because of its prolonged course, unpredictable recurrence, and major effect on daily functioning. Contemporary reviews estimate that chronic spontaneous urticaria affects roughly 0.5% to 1.0% of the population at a given time, with a higher burden among women and adults in early and middle adulthood (Gonçalo et al., 2021; Kolkhir et al., 2024; Hon et al., 2019). The condition is often accompanied by sleep disturbance, impaired work productivity, anxiety, depression, and reduced health-related quality of life, making it one of the most burdensome chronic dermatologic disorders encountered in routine practice (Staubach et al., 2011; Sánchez-Borges et al., 2021; Giménez-Arnau et al., 2022).

The clinical phenotype of chronic urticaria is heterogeneous. Some patients present predominantly with transient wheals, others with angioedema, and many experience both. Symptoms may appear daily or intermittently, may worsen at night, and may fluctuate according to environmental triggers, stress, infections, or medication exposures. Most lesions resolve within 24 hours without bruising, whereas angioedema may persist longer. The disease is now understood as a mast-cell-driven disorder in which histamine and other inflammatory mediators increase vascular permeability and induce itch, erythema, and swelling (Zuberbier et al., 2022; Seirin-Lee et al., 2024; Muñoz et al., 2024). In a substantial subgroup, autoimmune mechanisms are thought to contribute through IgG autoantibodies against IgE or the high-affinity IgE receptor FcεRI, while in other patients the precipitating pathway remains uncertain (Kolkhir et al., 2021; Zuberbier et al., 2022).

Because the etiology of CU is often multifactorial and partly unexplained, clinicians have long investigated infectious, inflammatory, endocrine, allergic, and autoimmune contributors that might influence disease onset, persistence, or severity. Gastrointestinal factors have received particular interest. Reviews on the “gut-skin” axis in urticaria suggest that disturbances in mucosal immunity, chronic infection, altered barrier function, and microbiome dysbiosis may amplify systemic inflammation and lower the threshold for mast-cell activation (Chu and Zuberbier, 2020; Cai et al., 2024). *Helicobacter pylori*, a gram-negative microaerophilic bacterium that colonizes the stomach and causes chronic gastritis, peptic ulcer disease, and other upper gastrointestinal disorders, has therefore been repeatedly evaluated as a possible associated factor in chronic urticaria (Malfertheiner et al., 2023; Wedi and Kapp, 2009).

Several biologically plausible mechanisms have been proposed for the relationship between *H. pylori* and urticaria. Chronic infection may sustain cytokine production, complement activation, nitric oxide-mediated vascular changes, and systemic inflammatory signaling that intensify skin reactivity. Molecular mimicry and immune cross-reactivity have also been hypothesized, as has facilitation of autoimmune phenomena in predisposed patients (Kasperska-Zajac, 2009; Wedi and Kapp, 2009; Cai et al., 2024). Yet the literature remains mixed. Some case-control and cohort studies have reported higher *H. pylori* prevalence among patients with chronic urticaria or chronic spontaneous urticaria and have observed symptomatic improvement after eradication therapy in selected subgroups (Dennis et al., 2020; Muhammed and Mohammed, 2016; Shakouri et al., 2010; Akashi et al., 2010; Magen et al., 2007). Other work has found weaker or no clear associations, suggesting that upper gastrointestinal inflammation more broadly, rather than *H. pylori* alone, may be relevant in at least some patients (Hook-Nikanne et al., 2000; Bülbül et al., 2005; Chen et al., 2021).

The uncertainty in international evidence has practical implications. Current urticaria guidelines appropriately prioritize second-generation H1-antihistamines, dose escalation when needed, and escalation to biologic or immunomodulatory therapy for refractory disease. At the same time, they encourage focused evaluation for comorbidities or associated conditions when clinically justified, rather than indiscriminate testing (Zuberbier et al., 2022; Zuberbier et al., 2024). In low-resource settings, where access to advanced therapies may be limited, identifying treatable associated conditions can be especially relevant. If *H. pylori* contributes to disease activity in a meaningful subset of patients, confirming and managing infection could become an adjunct to standard care rather than a replacement for evidence-based dermatologic treatment.

The diagnostic and therapeutic challenge of chronic urticaria is especially pronounced in environments where patients may present late, investigations are constrained, and continuity of care is inconsistent. In such settings, recurrent wheals and itch are often treated episodically with antihistamines or corticosteroids without a broader search for associated triggers, comorbidity, or modifiable inflammatory conditions. Yet patients with chronic urticaria frequently ask why the disease persists, whether it is “allergy” in the conventional sense, and whether treatment can be tailored to an underlying cause. The question of *H. pylori* is therefore clinically relevant not only as a scientific hypothesis but also as a response to common patient and clinician concerns about chronicity, recurrence, and incomplete response to routine therapy.

Yemen represents an important context in which to examine this question. The country faces heavy burdens of infectious disease, strained health services, and variable access to specialist care and diagnostic testing. However, local research on chronic urticaria has been limited, and the specific relationship between CU and *H. pylori* infection has not been well characterized in Sana'a hospitals. Without locally generated evidence, clinicians must rely largely on data from other populations that may differ in exposure patterns, healthcare utilization, comorbidity profiles, and antimicrobial treatment practices. Establishing local evidence is therefore valuable not only for academic purposes but also for pragmatic clinical decision-making.

The present study was designed to address this gap. It aimed to determine whether *H. pylori* infection was associated with chronic urticaria among patients attending three major hospitals in Sana'a during 2025. In addition to estimating the association between CU and *H. pylori* positivity, the study described the demographic and clinical profile of affected patients, compared selected gastrointestinal and dermatologic manifestations between cases and controls, and explored patient-reported symptom burden and treatment experience. The working hypothesis was that *H. pylori* infection would be more common among CU cases than among non-urticarial dermatology controls.

Methods

Study design and setting

This study used a hospital-based case-control design. A case-control approach was selected because the primary objective was to assess the association between a defined clinical outcome—chronic urticaria—and an exposure of interest—*H. pylori* infection—within a feasible timeframe and a routine outpatient environment. The study was conducted in Sana'a City, Yemen, in the outpatient clinics of Al-Jumhuri Hospital, Al-Kuwait Hospital, and Al-Thawra Hospital between May and August 2025.

Participants, case definition, and controls

Eligible participants were patients aged 12 years or older attending the selected clinics. Cases were defined as patients with clinically diagnosed chronic urticaria, that is, recurrent pruritic wheals, angioedema, or both persisting for more than six weeks, in keeping with international urticaria guidance (Zuberbier et al., 2022). Controls were recruited from the same outpatient settings and consisted of patients with dermatologic conditions other than urticaria and with no history or clinical evidence of urticaria. This source population strategy was intended to reduce differential referral by healthcare setting while preserving a realistic outpatient comparison group.

Eligibility criteria and pilot study

Participants were included if they were at least 12 years old, male or female, and willing to participate after being informed about the study. Exclusion criteria were designed to minimize major sources of misclassification or exposure distortion and included age younger than 12 years, current use of proton pump inhibitors, immunomodulatory agents, or systemic corticosteroids, drug addiction, history of hepatobiliary disease, and refusal to participate or inability to provide consent. A pilot study involving 12 chronic urticaria patients at Al-Jumhuri Hospital was undertaken before the main study to assess feasibility, timing, comprehension, and sequencing of questionnaire items, broadly consistent with common recommendations for pilot work in observational research (Hertzog, 2008).

Sample size

The final analytic sample comprised 132 participants: 66 cases and 66 controls. According to the source report, sample size estimation was performed using OpenEpi version 7 on the basis of an anticipated *H. pylori* prevalence of 72% among cases and 40% among controls, a 95% confidence level, and 95% power. This yielded a minimum requirement of 128 participants, or 64 per group. The achieved sample therefore exceeded the calculated minimum while maintaining an approximately 1:1 case-control ratio.

Data collection instrument

Data were collected through face-to-face interviews using a structured questionnaire developed for the study and refined after expert review and pilot testing. The instrument captured sociodemographic information, hospital site, residence type, education, marital status, dermatologic manifestations, gastrointestinal symptoms, chronic urticaria symptom characteristics, perceived triggers, treatment response, and the perceived effect of disease on sleep, mental health, and daily life. Content validity was reviewed by supervisors and subject specialists in community medicine and dermatology. Reliability was supported by standardized administration procedures and iterative revision of items that appeared ambiguous or redundant during piloting.

Laboratory assessment of *H. pylori*

H. pylori infection status was determined using a stool antigen test performed on stool samples analyzed in the microbiology laboratory. The stool antigen approach was operationally appropriate for a multi-hospital outpatient study because it is non-invasive, relatively accessible, and suitable for current infection detection compared with purely serologic measures. In the final dataset, all 132 enrolled participants underwent *H. pylori* testing, which helped minimize the possibility that any observed association was an artifact of differential testing uptake between cases and controls.

Clinical descriptors and variables

The questionnaire also captured several clinically useful case-only descriptors intended to characterize disease burden rather than define formal severity scores. These included duration category, symptom frequency, itch severity based on scratch-related skin changes, sleep effect, mental health effect, overall daily life impact, treatment response, and perceived triggers such as heat, cold, stress, and food.

Although these variables do not substitute for validated activity tools such as the Urticaria Activity Score, they provide a meaningful picture of disease impact in routine outpatient practice and were sufficient for the descriptive objectives of the study.

Statistical analysis

The principal outcome for the case-control comparison was *H. pylori* positivity among cases and controls. Additional descriptive outcomes included the distribution of dermatologic and gastrointestinal symptoms, the clinical burden of chronic urticaria among cases, and the frequency of reported improvement among cases who had received eradication therapy. Independent variables included age, sex, residence, education, marital status, and hospital site, as well as case status for comparative analyses of symptoms and infection. The report also described disease-related factors among cases, including symptom frequency, itch severity, sleep interference, mental health impact, and self-reported triggers.

Ethical considerations

Data were entered and analyzed in IBM SPSS Statistics version 27. Descriptive statistics were used to summarize continuous variables as means with standard deviations and categorical variables as counts and percentages. Group comparisons were performed using chi-square tests for categorical variables and independent-samples comparisons for continuous variables, with appropriate alternatives when assumptions were not met. The association between *H. pylori* positivity and chronic urticaria was summarized using an unadjusted odds ratio with a 95% confidence interval. The original report also stated that multivariable logistic regression was planned to adjust for age, sex, residence, education, and hospital site. However, the final reported results emphasized the crude association, and no adjusted coefficient was clearly presented in the final tables; accordingly, this manuscript focuses on the reported unadjusted estimate while preserving the stated analytical plan.

Results

Baseline characteristics and hospital distribution

A total of 132 participants were included in the analysis, comprising 66 chronic urticaria cases and 66 controls. Baseline comparability between groups was generally good. The mean age of the full sample was 33.0 ± 12.5 years, with no statistically significant difference between cases and controls (33.6 ± 12.6 vs 32.4 ± 12.5 years, $p=0.585$). Women accounted for 72.0% of the overall sample and were similarly represented in both groups (69.7% among cases and 74.2% among controls, $p=0.698$).

Residence type, marital status, and educational attainment also did not differ significantly between groups, supporting the internal validity of the case-control comparison. The one baseline feature that differed significantly was hospital site distribution ($p=0.028$): most participants were recruited from Al-Jumhuri Hospital, while cases were relatively more concentrated at Al-Thawra Hospital and controls were relatively more concentrated at Al-Kuwait Hospital.

The hospital-site pattern is worth emphasizing because it may reflect real-world care pathways. Of all participants, 66.7% were recruited from Al-Jumhuri Hospital, 22.0% from Al-Kuwait Hospital, and 11.4% from Al-Thawra Hospital. Among controls, 68.2% came from Al-Jumhuri and 27.3% from Al-Kuwait, with only 4.5% from Al-Thawra. Among cases, the proportion from Al-Thawra rose to 18.2%, while the proportion from Al-Kuwait declined to 16.7%. Although this distribution does not directly explain the primary exposure-outcome association, it indicates that service utilization and referral patterns likely differed across facilities and should be considered when extrapolating the findings to other settings in Sana'a or beyond.

Table 1. Baseline characteristics of cases and controls

Characteristic	CU cases (n=66)	Controls (n=66)	p-value
Age, mean $\pm$ SD (years)	33.6 $\pm$ 12.6	32.4 $\pm$ 12.5	0.585
Female sex	46 (69.7%)	49 (74.2%)	0.698
Urban residence	49 (74.2%)	43 (65.2%)	0.344
Married	39 (59.1%)	36 (54.5%)	0.623
University education	15 (22.7%)	9 (13.6%)	0.384
Hospital site distribution (overall)	—	—	0.028
Al-Jumhuri Hospital	43 (65.2%)	45 (68.2%)	
Al-Kuwait Hospital	11 (16.7%)	18 (27.3%)	
Al-Thawra Hospital	12 (18.2%)	3 (4.5%)	

Dermatologic findings were consistent with accurate separation of cases and controls. Itching was by far the most prominent complaint among chronic urticaria cases, reported by 80.3% compared with 37.9% of controls ($p < 0.001$). Wheal itching was also more common among cases (12.1% vs 1.5%, $p = 0.033$). In contrast, some non-urticarial manifestations appeared only among controls, including skin rash (15.2% vs 0.0%, $p = 0.003$) and acne (12.1% vs 0.0%, $p = 0.006$). Other manifestations, such as skin dryness, erythema, pigmentary changes, warts, and hair loss, were uncommon and showed no significant between-group differences. This pattern supports the clinical validity of the case-control classification and reduces concern that the exposure association was driven by major phenotype misclassification.

Primary exposure and symptom comparison

Gastrointestinal symptoms were frequent in the study population as a whole. Any gastrointestinal symptom was reported by 84.8% of participants and was more common among cases than controls (90.9% vs 78.8%), although this difference did not meet the conventional threshold for statistical significance ($p = 0.089$). The same directional pattern was seen for several individual symptoms: stomach pain was reported by 50.0% of cases and 36.4% of controls ($p = 0.160$), loss of appetite by 50.0% and 33.3% respectively ($p = 0.077$), heartburn by 48.5% and 40.9% ($p = 0.484$), and bloating by 36.4% and 31.8% ($p = 0.713$). Thus, gastrointestinal symptom burden was substantial in both groups and tended to

be greater among chronic urticaria cases, but the study did not demonstrate statistically robust symptom-level discrimination between groups.

Table 2. Primary exposure and selected symptom comparisons

Variable	CU cases (n=66)	Controls (n=66)	p-value
<i>H. pylori</i> positive	40 (60.6%)	23 (34.8%)	0.005
Any gastrointestinal symptom	60 (90.9%)	52 (78.8%)	0.089
Stomach pain	33 (50.0%)	24 (36.4%)	0.160
Loss of appetite	33 (50.0%)	22 (33.3%)	0.077
Heartburn	32 (48.5%)	27 (40.9%)	0.484
Itching	53 (80.3%)	25 (37.9%)	<0.001
Wheal itching	8 (12.1%)	1 (1.5%)	0.033

The crude odds ratio for *H. pylori* positivity among cases versus controls was 2.88 (95% CI 1.42–5.83), indicating a statistically significant association between chronic urticaria and infection in this study population.

Clinical profile and treatment experience among cases

The primary exposure-outcome comparison showed a clear and statistically significant association. *H. pylori* testing was completed in all participants, thereby avoiding differential testing as a source of bias in the analytic sample. Overall, 47.7% of participants were *H. pylori* positive. Positivity was substantially higher among chronic urticaria cases than among controls (60.6%, 40/66 vs 34.8%, 23/66; $p=0.005$). The corresponding crude odds ratio was 2.88 (95% CI 1.42–5.83), indicating that patients with chronic urticaria had nearly three times the odds of *H. pylori* infection compared with non-urticarial dermatology controls in this setting. Because the study design was case-control, this finding should be interpreted as an association rather than evidence of temporality or causation.

Among the 66 chronic urticaria cases, the disease profile suggested frequent activity and considerable burden. Nearly half of cases reported daily symptoms (48.5%), while one third reported symptoms once per week. Itch severity was notable: 77.3% reported scratching with redness and 13.6% reported scratching severe enough to cause bleeding. Sleep was affected in 53.0% of cases, and 77.3% reported an adverse impact on mental health. When asked about effects on daily life, 48.5% described a mild impact, 25.8% a significant impact, and 9.1% a very severe impact. Hotness or heat exposure, whether alone or in combination with other triggers, was reported by 53.0% of cases, suggesting that environmental heat was an important perceived trigger in this cohort.

Treatment-related findings also illustrated the practical burden of the disease. In narrative results presented in the source report, 24.2% of cases described complete response to treatment, 69.7% partial response, and 7.6% no response. However, only 25.8% of cases reported having received *H. pylori* eradication therapy. Among those who received eradication therapy ($n=17$), 41.2% reported improvement in urticaria symptoms and 58.8% reported no improvement. These data should be

interpreted cautiously because treatment allocation was not randomized, eradication success was not independently confirmed within the results section, and the number of treated cases was small. Nevertheless, they offer a useful descriptive snapshot of current management patterns and the possibility of clinical improvement in a subset of infected patients.

Taken together, the results support three main observations. First, the case-control groups were sufficiently similar across most baseline variables to support the main comparison. Second, the central study hypothesis was supported by a statistically significant association between chronic urticaria and *H. pylori* positivity. Third, chronic urticaria cases in this sample experienced substantial symptom frequency, psychosocial burden, and incomplete response to treatment, which reinforces the clinical importance of investigating potentially modifiable associated factors in appropriate patients.

Table 3. Clinical burden and treatment-related findings among chronic urticaria cases

Characteristic	Cases (n=66)
Daily symptoms	32 (48.5%)
Sleep affected	35 (53.0%)
Mental health impact	51 (77.3%)
Hotness reported as a trigger (alone or combined)	35 (53.0%)
Complete treatment response	16 (24.2%)
Partial treatment response	46 (69.7%)
No treatment response	5 (7.6%)
Received eradication therapy	17 (25.8%)
Improvement among treated cases	7/17 (41.2%)
No improvement among treated cases	10/17 (58.8%)

Discussion

Principal findings

This hospital-based case-control study found that *H. pylori* infection was significantly more common among patients with chronic urticaria than among dermatology controls without urticaria. The magnitude of the observed association was clinically meaningful: 60.6% of cases were *H. pylori* positive compared with 34.8% of controls, and the crude odds ratio of 2.88 suggested nearly threefold higher odds of infection among cases. In a context where baseline demographics were largely comparable between groups, this finding supports the study hypothesis and provides locally relevant evidence that *H. pylori* may be an important associated factor in chronic urticaria among patients attending major hospitals in Sana'a.

Comparison with previous studies

The finding is broadly consistent with several reports from other settings. Dennis and colleagues, working in Tanzania, reported higher *H. pylori* prevalence among chronic urticaria cases than controls, while Muhammed and Mohammed described a similar association in Erbil. Evidence syntheses and interventional studies have also suggested that eradication of *H. pylori* may improve symptoms in selected patients, even though the strength and consistency of benefit vary across studies and designs (Dennis et al., 2020; Muhammed and Mohammed, 2016; Shakouri et al., 2010; Akashi et al., 2010; Guo et al., 2021). The present study does not prove that *H. pylori* causes chronic urticaria, but its results move local evidence in the same direction as that body of literature: infection appears to cluster more frequently among CU patients than among comparable dermatology controls.

Gastrointestinal context and biological plausibility

At the same time, the current findings should be interpreted within the broader debate on gastrointestinal inflammation and urticaria. Some studies have found weaker or absent direct associations between *H. pylori* and chronic urticaria, and population-based cohort evidence suggests that peptic ulcer disease and upper gastrointestinal inflammation may themselves be linked with CU independent of *H. pylori* status (Hook-Nikanne et al., 2000; Bülbül et al., 2005; Chen et al., 2021). This alternative interpretation is plausible in our dataset as well. Gastrointestinal symptoms were common in both groups and tended to be more frequent among cases, yet most individual symptom comparisons were not statistically significant. That pattern suggests that the gastrointestinal context may matter clinically even when no single symptom cleanly distinguishes cases from controls. In other words, *H. pylori* may be one contributor within a broader inflammatory gut-skin axis rather than an exclusive or universal explanation for chronic urticaria.

Mechanistic interpretation

Biological plausibility strengthens the relevance of the observed association. Chronic urticaria is fundamentally a mast-cell-mediated disease in which histamine, leukotrienes, cytokines, and other mediators drive pruritus, whealing, and tissue edema. *H. pylori* infection can induce chronic gastric mucosal inflammation, systemic immune activation, cytokine release, nitric oxide-mediated vascular effects, and changes in host immune tolerance. Molecular mimicry, complement activation, and dysregulated mucosal immunity have all been proposed as ways by which chronic infection could amplify skin reactivity or lower the threshold for urticaria recurrence (Kasperska-Zajac, 2009; Wedi and Kapp, 2009; Malfertheiner et al., 2023; Cai et al., 2024). The present results are therefore coherent with current pathophysiologic theories, even if they cannot distinguish which pathway is most relevant in the studied population.

Disease burden and clinical phenotype

An additional strength of the study is that the clinical phenotype of chronic urticaria cases appeared internally consistent. Itching and wheal-related symptoms clustered strongly among cases, whereas acne and non-urticarial rash were largely confined to controls. This pattern supports accurate clinical classification and reduces the likelihood that the exposure association simply reflects poor case ascertainment. The high levels of daily symptoms, sleep interference, and reported mental health impact among cases are also noteworthy. International studies have repeatedly shown that chronic urticaria carries heavy psychosocial burden and disrupts sleep, concentration, daily functioning, and quality of life (Gonçalo et al., 2021; Staubach et al., 2011; Giménez-Arnau et al., 2022). The current study

reproduces that burden in a Yemeni outpatient population and highlights why even apparently “benign” skin diseases can have profound consequences for wellbeing.

Treatment implications

The substantial burden observed among cases also reinforces the importance of looking beyond symptom suppression alone. Nearly half of the cases described daily symptoms, more than half reported impaired sleep, and over three quarters reported mental health effects. Such figures suggest a disease experience that extends far beyond transient rash and itch. They also create a clinical rationale for evaluating contributory factors when standard treatment is only partly effective. Even if *H. pylori* turns out to influence only a subset of patients, that subset may still be clinically important in settings where chronic urticaria can remain under-investigated and under-controlled for long periods. In this sense, the relevance of *H. pylori* lies not only in its statistical association, but in its potential role within a more individualized and comorbidity-aware management strategy.

Hospital-site distribution and selection considerations

The results also point to an important care-gap issue. Only one quarter of cases reported receiving eradication therapy, and among those treated, fewer than half reported improvement in urticaria symptoms. These data should not be over-interpreted as an efficacy estimate, because treatment exposure was non-random, the number of treated patients was small, and eradication success was not independently documented in the results tables. Nonetheless, the finding raises practical questions. Some patients with chronic urticaria in similar settings may never be evaluated for gastrointestinal comorbidity or tested for *H. pylori* even when symptoms persist. Conversely, others may receive empiric treatment without standardized confirmation of infection or eradication. A more structured diagnostic pathway—selective rather than routine—could help rationalize testing and reduce unnecessary treatment while preserving the option of addressing infection when clinically relevant.

Strengths and limitations

Hospital site distribution differed significantly between cases and controls, and that deserves careful interpretation. Cases were relatively overrepresented at Al-Thawra Hospital, whereas controls were more concentrated at Al-Kuwait Hospital. This imbalance may reflect referral pathways, clinic specialization, differential access, or variation in disease severity rather than a true epidemiologic difference in exposure. It does not nullify the main finding, but it does mean that some selection effects may have influenced the observed prevalence of both chronic urticaria and *H. pylori* infection. The original report appropriately planned multivariable adjustment for hospital site and other factors, and future analyses with larger samples should retain that strategy and report the adjusted coefficients explicitly.

Clinical implications and future research

Several limitations should therefore be acknowledged. First, the case-control design cannot establish temporal sequence; it is impossible to determine whether *H. pylori* preceded the onset of urticaria, intensified existing disease, or was simply more prevalent in a subgroup of patients who were otherwise predisposed. Second, residual confounding is possible. Although age, sex, residence, marital status, and education were comparable between groups, unmeasured factors such as socioeconomic status, prior antibiotic use, non-steroidal anti-inflammatory drug sensitivity, autoimmune disease, thyroid status, atopy, or other infections may have influenced the association. Third, the study was hospital-based and

relatively modest in size, which limits generalizability beyond similar outpatient settings. Fourth, some case-only measures, particularly treatment response and symptom improvement after eradication therapy, were self-reported and therefore subject to recall error and expectation bias.

Overall interpretation

Despite these limitations, the study has meaningful clinical implications. It supports a selective, clinically driven approach to gastrointestinal evaluation in chronic urticaria. In patients with persistent disease, upper gastrointestinal symptoms, recurrent flares despite standard therapy, or clinical suspicion of infectious contribution, testing for *H. pylori* may be justified and could be incorporated into a broader assessment of associated conditions. This recommendation aligns with contemporary urticaria management: guideline-based treatment remains the foundation of care, but the identification of treatable comorbidity can complement standard therapy rather than compete with it (Zuberbier et al., 2022; Zuberbier et al., 2024). In lower-resource contexts, such a complementary strategy may be especially valuable when access to biologics or specialist follow-up is constrained.

Conclusion

In this case-control study conducted in three major hospitals in Sana'a, *H. pylori* infection was significantly associated with chronic urticaria. Patients with CU had markedly higher *H. pylori* positivity than dermatology controls, while also reporting substantial symptom burden, sleep disturbance, and mental health impact. Although the study design does not establish causality, the strength and direction of the association, together with its biological plausibility and consistency with several international studies, suggest that *H. pylori* may function as a contributory or aggravating factor in at least a subset of CU patients.

These findings support a balanced clinical message. *H. pylori* should not be treated as the sole explanation for chronic urticaria, nor should infection-focused care replace established urticaria management. However, selective *H. pylori* testing and gastrointestinal assessment may be appropriate for patients with persistent symptoms, dyspepsia, or other gastrointestinal complaints, particularly in low-resource settings where recognizing treatable associated conditions may improve care. Further Yemeni multicenter, prospective, and interventional research is warranted to determine whether eradication produces reproducible symptom benefit and to define the patients most likely to benefit from such an approach.

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Author Contributions

Conceptualization, methodology, data collection, analysis, manuscript drafting, and manuscript revision were undertaken by the student research team under the academic supervision of Dr. Abdulkareem Obadi and Associate Professor Mutaia Abuarij. All listed authors contributed to the final report on which this manuscript was based and approved the adapted manuscript version for academic use.

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Conflicts of Interest

The authors declared no conflicts of interest in the source report.

Ethical Approval and Consent to Participate

Ethical approval was obtained from the Faculty of Medicine ethical committee of 21 September University prior to data collection. Participation was voluntary, and informed consent was obtained from all participants.

Data Availability

The data supporting this manuscript are derived from the submitted final report and summarized in aggregate form. No individual-level dataset was provided with the source document.

References

Akashi, R., Ishiguro, N., Shimizu, S. and Kawashima, M. (2010) 'Clinical study of the relationship between *Helicobacter pylori* and chronic urticaria and prurigo chronica multiformis: Effectiveness of eradication therapy for *Helicobacter pylori*', *The Journal of Dermatology*, 38(8), pp. 761–766. doi: 10.1111/j.1346-8138.2010.01106.x.

- Cai, R., Zhou, C., Tang, R., Meng, Y., Zeng, J., Li, Y. and Wen, X. (2024) 'Current insights on gut microbiome and chronic urticaria: Progress in the pathogenesis and opportunities for novel therapeutic approaches', *Gut Microbes*, 16(1), p. 2382774. doi: 10.1080/19490976.2024.2382774.
- Chen, C.-M., Huang, W.-T., Chang, L.-J., Hsu, C.-C. and Hsu, Y.-H. (2021) 'Peptic ulcer disease is associated with increased risk of chronic urticaria independent of *Helicobacter pylori* infection: A population-based cohort study', *American Journal of Clinical Dermatology*, 22(1), pp. 129–137. doi: 10.1007/s40257-020-00561-9.
- Chu, C.-Y. and Zuberbier, T. (2020) 'Urticaria and the gut', *Current Opinion in Allergy and Clinical Immunology*, 20(4), pp. 381–385. doi: 10.1097/ACI.0000000000000653.
- Dennis, M.F., Mavura, D.R., Kini, L., Philemon, R. and Masenga, E.J. (2020) 'Association between chronic urticaria and *Helicobacter pylori* infection among patients attending a tertiary hospital in Tanzania', *Dermatology Research and Practice*, 2020, p. 5932038. doi: 10.1155/2020/5932038.
- Giménez-Arnau, A., Maurer, M., Bernstein, J., Staubach, P., Barbier, N., Hua, E., Severin, T., Joubert, Y., Janocha, R. and Balp, M.M. (2022) 'Ligelizumab improves sleep interference and disease burden in patients with chronic spontaneous urticaria', *Clinical and Translational Allergy*, 12(2), e12121. doi: 10.1002/clt2.12121.
- Gonçalo, M., Giménez-Arnau, A., Al-Ahmad, M., Ben-Shoshan, M., Bernstein, J.A., Ensina, L.F., Fomina, D., Galvão, C.A., Godse, K., Grattan, C., Hide, M., Katelaris, C.H., Khoshkhui, M., Kocatürk, E., Kulthanan, K., Medina, I., Nasr, I., Peter, J., Staubach, P., Wang, L. and Maurer, M. (2021) 'The global burden of chronic urticaria for the patient and society', *The British Journal of Dermatology*, 184(2), pp. 226–236. doi: 10.1111/bjd.19561.
- Guo, Y., Li, H.-M., Zhu, W.-Q. and Li, Z. (2021) 'Role of *Helicobacter pylori* eradication in chronic spontaneous urticaria: A propensity score matching analysis', *Clinical, Cosmetic and Investigational Dermatology*, 14, pp. 129–136. doi: 10.2147/CCID.S293737.
- Hertzog, M.A. (2008) 'Considerations in determining sample size for pilot studies', *Research in Nursing & Health*, 31(2), pp. 180–191.
- Hon, K.L., Leung, A.K.C., Ng, W.G.G. and Loo, S.K. (2019) 'Chronic urticaria: An overview of treatment and recent patents', *Recent Patents on Inflammation & Allergy Drug Discovery*, 13(1), pp. 27–37. doi: 10.2174/1872213X13666190328164931.
- Hook-Nikanne, J., Varjonen, E., Harvima, R.J. and Kosunen, T.U. (2000) 'Is *Helicobacter pylori* infection associated with chronic urticaria?', *Acta Dermato-Venereologica*, 80(6), pp. 425–426. doi: 10.1080/000155500300012837.
- Kasperska-Zajac, A. (2009) 'Role of infections and autoimmunity in chronic urticaria', *Current Opinion in Allergy and Clinical Immunology*, 9(5), pp. 447–453.
- Kolkhir, P., Metz, M., Altrichter, S. and Maurer, M. (2017) 'Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: A systematic review', *Allergy*, 72(10), pp. 1440–1460.
- Kolkhir, P., Munoz, M., Asero, R., Ferrer, M., Hide, M., Kaplan, A.P. and Maurer, M. (2021) 'Autoimmune chronic spontaneous urticaria detection with IgG anti-TPO and total IgE', *The Journal of Allergy and Clinical Immunology: In Practice*, 9(11), pp. 4138–4146.e8. doi: 10.1016/j.jaip.2021.07.043.
- Kolkhir, P., Bonnekoh, H., Metz, M. and Maurer, M. (2024) 'Chronic spontaneous urticaria: A review', *JAMA*, 332(17), pp. 1464–1477. doi: 10.1001/jama.2024.15568.
- Magen, E., Mishal, J., Schlesinger, M. and Scharf, S. (2007) 'Eradication of *Helicobacter pylori* infection equally improves chronic urticaria with positive and negative autologous serum skin test', *Helicobacter*, 12(6), pp. 567–571. doi: 10.1111/j.1523-5378.2007.00522.x.
- Malfertheiner, P., Camargo, M.C., El-Omar, E., Liou, J.-M., Peek, R., Schulz, C., Smith, S.I. and Suerbaum, S. (2023) '*Helicobacter pylori* infection', *Nature Reviews Disease Primers*, 9(1), p. 19. doi: 10.1038/s41572-023-00431-8.

- Muhammed, F.R. and Mohammed, K.B. (2016) 'Association of chronic urticaria with *Helicobacter pylori* infection in Erbil: A case-control study', *Zanco Journal of Medical Sciences*, 20(2), pp. 1376–1384.
- Muñoz, M., Kiefer, L.A., Pereira, M.P., Bizjak, M. and Maurer, M. (2024) 'New insights into chronic inducible urticaria', *Current Allergy and Asthma Reports*, 24(8), pp. 457–469. doi: 10.1007/s11882-024-01160-y.
- Saini, S., Shams, M., Bernstein, J.A. and Maurer, M. (2020) 'Urticaria and angioedema across the ages', *The Journal of Allergy and Clinical Immunology: In Practice*, 8(6), pp. 1866–1874. doi: 10.1016/j.jaip.2020.03.030.
- Sánchez-Borges, M., Ansotegui, I.J., Baiardini, I., Bernstein, J., Canonica, G.W., Ebisawa, M., Gomez, M., Gonzalez-Diaz, S.N., Martin, B., Morais-Almeida, M. and Ortega Martell, J.A. (2021) 'The challenges of chronic urticaria part 1: Epidemiology, immunopathogenesis, comorbidities, quality of life, and management', *World Allergy Organization Journal*, 14(6), p. 100533. doi: 10.1016/j.waojou.2021.100533.
- Seirin-Lee, S., Takahagi, S. and Hide, M. (2024) 'Pathophysiological mechanisms of the onset, development, and disappearance phases of skin eruptions in chronic spontaneous urticaria', *Bulletin of Mathematical Biology*, 87(1), p. 1. doi: 10.1007/s11538-024-01380-3.
- Shakouri, A., Compalati, E., Lang, D.M. and Khan, D.A. (2010) 'Effectiveness of *Helicobacter pylori* eradication in chronic urticaria: Evidence-based analysis using the GRADE system', *Current Opinion in Allergy and Clinical Immunology*, 10, pp. 362–369. doi: 10.1097/ACI.0b013e32833c79d7.
- Staubach, P., Dechene, M., Metz, M. et al. (2011) 'High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria', *Acta Dermato-Venereologica*, 91, pp. 557–561.
- Wedi, B. and Kapp, A. (2009) 'Chronic urticaria and infections', *Current Opinion in Allergy and Clinical Immunology*, 9(5), pp. 438–444.
- Zuberbier, T., Aberer, W., Asero, R., Abdul Latiff, A.H., Baker, D., Ballmer-Weber, B.K., Bernstein, J.A., Bindslev-Jensen, C., Brzoza, Z. et al. (2022) 'The EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria', *Allergy*, 77(3), pp. 734–766. doi: 10.1111/all.15090.
- Zuberbier, T., Ensina, L.F., Giménez-Arnau, A., Grattan, C., Kocatürk, E., Kulthanan, K., Kolkhir, P., and Maurer, M. (2024) 'Chronic urticaria: Unmet needs, emerging drugs, and new perspectives on personalised treatment', *The Lancet*, 404(10450), pp. 393–404. doi: 10.1016/S0140-6736(24)00852-3.