

## PAPER DETAILS

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# Reappraisal of the role of *Helicobacter pylori* in chronic spontaneous urticaria

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## ABSTRACT

**Aims:** Chronic spontaneous urticaria (CSU) is one of the most prevalent skin disorders. *Helicobacter pylori* (HP) infection has been linked to CSU, and HP eradication therapy has been questioned as a viable treatment option. However, studies have produced contradictory results. In addition, recent studies suggest that gastritis, rather than HP bacteria, may be responsible for CSU symptoms. Herein, we aimed to ascertain the prevalence of HP infection in CSU, explore associations between HP infection, gastritis, and CSU severity or treatment response in CSU, and investigate the impact of HP eradication therapy on the CSU course.

**Methods:** We retrospectively analyzed CSU patients who were investigated for HP infection. Patient characteristics, in-clinic urticaria activity scores (ic-UAS) and urticaria control test (UCT) scores, and CSU treatment responses were compared across different patient groups.

**Results:** The study included 325 CSU patients, of whom 57.2% were HP-positive and 60.9% had gastritis. The mean baseline ic-UAS showed no difference between HP-positive and HP-negative patients ( $2.55 \pm 2$  vs  $2.45 \pm 1.98$ ,  $p > 0.05$ ) or between patients with and without gastritis ( $2.33 \pm 2$  vs  $2.51 \pm 2$ ,  $p > 0.05$ ). HP-positive patients had higher rates of elevated CRP levels (45% vs 29.9%,  $p = 0.023$ ) and ASST positivity (54.8% vs 29.8%,  $p < 0.001$ ). The AH response exhibited a statistically significant increase in HP-positive patients compared to HP-negative patients (78.4% vs 61.2%,  $p = 0.006$ ) and in patients with gastritis compared to patients with no gastritis (76.8% vs 61.3%,  $p = 0.013$ ). There was no difference in response to omalizumab treatment between HP-positive and HP-negative patients (90% vs 86.5%,  $p = 0.528$ ) or between patients with gastritis and patients with no gastritis (91.3% vs 85.3%,  $p = 0.404$ ). No significant difference was observed in response rates to antihistamines or omalizumab between HP-positive patients who had not received eradication therapy and those who had received such therapy ( $p > 0.05$ ).

**Conclusion:** Over half of CSU patients have been found to be infected with HP. However, the HP bacterium itself, the eradication of HP, or gastritis have no significant effect on CSU severity or treatment response.

**Keywords:** Disease severity, eradication, gastritis, *Helicobacter pylori*, treatment response, urticaria

## INTRODUCTION

Chronic urticaria is a dermatological condition characterized by the recurring presence of pruritic wheals and/or angioedema lasting for a duration exceeding six weeks. It has two subtypes based on the presence of a specific stimulus that causes the appearance of lesions: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU).<sup>1</sup> The clinical manifestations of these conditions are caused by the stimulation of cutaneous mast cells and the subsequent discharge of their mediators. While it is widely accepted that autoimmunity is the fundamental mechanism involved in mast cell activation, stress, infections, foods, and

medications are implicated as modulators or exacerbators of the disease.<sup>1-3</sup> One of the infections that is suggested to contribute to CSU disease activity is the *Helicobacter pylori* (HP) infection.<sup>1</sup>

*Helicobacter pylori* is a gram-negative, spiral-shaped microaerophilic bacterium, and more than 50% of the population is afflicted with its infection, with strong differences between geographical areas.<sup>4,5</sup> It invades the gastric mucosa and triggers the release of cytotoxic substances from both the bacterium itself and the host organism, leading to the development of a pronounced inflammatory response. Approximately 80% of patients

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who are infected with HP do not exhibit symptoms, but all develop gastritis.<sup>6</sup> The etiopathogenetic role of HP in gastrointestinal disorders, including peptic ulcer, gastric cancer, and lymphoma, is also widely recognized.<sup>6,7</sup>

Additionally, there is an increasing amount of evidence supporting the hypothesis that HP infection has systemic implications, potentially contributing to the development of extragastrointestinal conditions including vascular, autoimmune, and dermatological disorders. The link between HP infection and CSU has been the subject of extensive research for over three decades. However, the findings from these studies have presented contradictory outcomes.<sup>1,7</sup> Multiple studies have found a positive link between the presence of HP and the development of CU, and the commencement of HP eradication therapy has been shown to be beneficial in reducing symptoms in certain patients.<sup>8-13</sup> On the other hand, a number of additional studies have been unable to establish a statistically significant correlation between HP infection and CSU, and the complete eradication of HP has not consistently resulted in the resolution of CSU in all individuals.<sup>14-16</sup> Also, a recent meta-analysis reported that CSU patients who received antibiotic therapy for the eradication of HP demonstrated a notably higher rate of CSU remission, regardless of whether HP eradication was achieved or not.<sup>17</sup>

In addition to infectious diseases, chronic inflammatory processes from a variety of other diseases have been identified as potential causes of CSU.<sup>1</sup> Some authors suggest that the development of CU may be attributed to inflammation from gastritis rather than HP bacteria, based on the high prevalence of CU in patients with peptic ulcer disease (PUD) in the absence of HP and the positive correlation between healing of gastritis and erosions and improvement in CU symptoms.<sup>18-21</sup>

Still, although the association between HP and urticaria is not clear on an individual level and evidence from eradication studies is limited, the International Guideline for the Management of Urticaria suggests performing diagnostic tests for HP and commencing eradication therapy if the results are positive because HP is linked to the development of cancer. According to the guideline, the recommended first-line therapy for the treatment of urticaria involves the initial administration of a standard dose of second-generation H1-antihistamine (sgAH). In cases where there is no response to this initial dose, it is advised to increase the dosage of sgAHs up to fourfold. As a second-line therapy, the guideline suggests combining antihistamines with omalizumab for patients who are resistant to antihistamines.<sup>1</sup>

In this study, we aimed to ascertain the prevalence of HP infection in CSU, investigate the potential associations between HP infection and/or gastritis and CSU disease

severity or resistance to CSU treatment, and determine if HP eradication therapy led to a decrease in disease activity or an increase in control of CSU. We also aimed to address the discrepancies about the association between HP and CSU in the existing literature.

## METHODS

The study was carried out with the permission of İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Researches Ethics Committee (Date: 19.04.2021, Decision No: 163-2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We conducted a retrospective analysis of CSU patients who were referred to UCARE (Urticaria Center of Reference and Excellence) Center of Okmeydanı Training and Research Hospital during the period from January 2013 to July 2019. CSU patients who were investigated for the presence of HP were included in the study. The patients who had CIndU without CSU and those who had a known diagnosis of gastritis without HP investigation were excluded.

Patient features such as age, gender, duration of disease, presence of angioedema, concurrent CIndU, family history of CU, emergency referrals, short-term systemic corticosteroid (CS) use, non-steroidal anti-inflammatory drug (NSAID) intolerance, atopic disorders and chronic infections (e.g. within the oral cavity, nasal sinuses, gastrointestinal tract, and urogenital system), presence of stress, presence of endoscopic diagnosis of gastritis, total IgE, anti-thyroid peroxidase antibody (anti-TPO), anti-thyroglobulin antibody (anti-TG), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) amounts, eosinophil counts, skin prick test (SPT) results and autologous serum skin test (ASST), HP stool antigen test (SAT) results, baseline in-clinic urticaria activity scores (ic-UAS), baseline and follow-up urticaria control test (UCT) scores, CU treatments, HP eradication therapies (for 14 days, regimen 1: clarithromycin, amoxicillin, and lansoprazole; or regimen 2: bismuth, metronidazole, tetracycline/doxycycline, and proton pump inhibitor), and gastritis treatments (H<sub>2</sub> antagonists and/or proton-pump inhibitors) were retrieved from patients' files. Patients with positive SAT results have been defined as 'HP-positive', whereas patients with negative SAT results have been defined as 'HP-negative'. All HP-positive patients and those whose files indicated an endoscopic diagnosis of gastritis were considered to have gastritis.<sup>6</sup>

Baseline disease severity in CSU patients was assessed using the ic-UAS, which incorporates the assessment of pruritus intensity and wheal counts.<sup>22</sup> The assessment quantifies the quantity of wheals and the severity of pruritus using

a four-point scale.<sup>23</sup> Treatment responses were evaluated with UCT, where a score of 12 or higher denoted effective management of urticaria, while a score of 11 or lower indicated inadequate control of the disease.<sup>24,25</sup> If UCT scores  $\geq 12$  were achieved using a treatment, this was considered a 'response to that treatment'. 'Antihistamine refractoriness' was used as a reference term for patients who do not respond to updosed/combined antihistamines. The patients used only second-generation H1-antihistamine; no H2 receptor blockers were employed.

Statistical analysis was conducted using IBM SPSS Statistics for Windows v.21.0. (IBM Corp., Armonk, NY). The frequencies and percentages were used to present categorical variables, while the mean $\pm$ standard deviation or median were used to present quantitative variables. The Kolmogorov-Smirnov test was employed to assess the normality of the distribution of numeric variables. The student's t test, Mann-Whitney U test, chi-square test, and Fisher's exact test were used for independent group comparisons. The statistical significance level was considered to be  $p < 0.05$ .

## RESULTS

### The Study Population

A total of 325 CSU patients were included in the study. A total of 186 patients (57.2%) tested positive for HP, while 198 patients (60.9%) were diagnosed with gastritis. The details of patient characteristics are shown in [Tables 1](#) and [2](#).

Characteristics	N=325
HP infection, n (%)	186 (57.2)
Eradication therapy for HP, n (%) (n=323)	60 (18.6)
Gastritis, n (%)	198 (60.9)
Sex, female, n (%)	249 (76.6)
Age (y), mean $\pm$ sd; min-max	41.57 $\pm$ 13.07; 11-85
Accompanying CIndU, n (%)	42 (12.9)
Disease duration (mo), mean $\pm$ sd; median; min-max	34.17 $\pm$ 54.9; 12; 2-360
Angioedema, n (%)	178 (54.8)
Family history of CU, n (%) (n=323)	55 (17)
Emergency referral, n (%) (n=209)	157 (75.1)
Short-term systemic CS use, n (%) (n=201)	141 (70.1)
NSAID intolerance, n (%) (n=232)	22 (9.5)
Atopic disorder, n (%) (n=293)	84 (28.7)
Autoimmune thyroiditis, n (%) (n=213)	32 (15)
Stress, n (%) (n=293)	112 (38.2)
Chronic infections, n (%) (n=291)	127 (43.6)
Baseline ic-UAS score, mean $\pm$ sd; min-max (n=208)	2.4 $\pm$ 2; 0-6
Baseline UCT score, mean $\pm$ sd; min-max (n=189)	7.4 $\pm$ 4.02; 0-16
Baseline UCT score $\leq 12$ , n (%) (n=189)	164 (86.8)

CIndU: chronic inducible urticaria, CS: corticosteroid, CU: chronic urticaria, HP: *Helicobacter pylori*, NSAID: nonsteroidal anti-inflammatory drug, UAS: urticaria activity score, UCT: urticaria control test

**Table 2. Laboratory characteristics**

Characteristics	
CRP levels $> 5$ mg/L, n (%) (n=217)	83 (38.2)
ESR levels $> 20$ mm/h, n (%) (n=209)	91 (43.5)
Total IgE levels $> 100$ IU/ml, n (%) (n=256)	202 (78.9)
Total IgE levels $\leq 40$ IU/ml, n (%) (n=250)	47 (18.8)
Total IgE level, mean $\pm$ sd; min-max (n=250)	298.81 $\pm$ 604.4; 0-7158
Blood eosinopenia, n (%) (n=97)	21 (21.6)
Anti-TPO $> 34$ IU/ml, n (%) (n=254)	51 (20.1)
Anti-TG $> 34$ IU/ml, n (%) (n=192)	25 (13)
SPT positivity, n (%) (n=154)	60 (39)
ASST positivity, n (%) (n=198)	85 (42.9)

anti-TPO: anti-thyroid peroxidase antibody, anti-TG: anti-thyroglobulin antibody, ASST: autologous serum skin test, CRP: C-reactive protein, ESR: estimated sedimentation rate, SPT: skin prick test

### *Helicobacter pylori* Infection does not Increase CSU Disease Severity

The disease activity showed no difference between HP-positive and HP-negative patients with regard to mean baseline ic-UAS ( $2.55 \pm 2$  vs  $2.45 \pm 1.98$ ,  $p > 0.05$ ).

### *Helicobacter pylori* Infection is Linked to Increased CRP Levels and ASST Positivity

Comparing HP-negative patients, a greater proportion of HP-positive patients exhibited elevated CRP levels (45% vs 29.9%,  $p = 0.023$ ) and ASST positivity (54.8% vs 29.8%,  $p < 0.001$ ), but other laboratory parameters did not differ ( $p > 0.05$ ) ([Table 3](#)).

**Table 3. Comparison of laboratory characteristics between HP-positive and HP-negative patients**

Characteristics	HP-positive n/N (%)	HP-negative n/N (%)	P value
CRP levels $> 5$ mg/L	54/120 (45)	29/97 (29.9)	0.023
ESR levels $> 20$ mm/h	50/114 (43.9)	41/95 (43.2)	0.919
Total IgE levels $> 100$ IU/ml	113/138 (81.9)	89/118 (75.4)	0.207
Total IgE levels $\leq 40$ IU/ml	21/134 (15.7)	26/116 (22.4)	0.174
Blood eosinopenia	14/52 (26.9)	7/45 (15.6)	0.175
Anti-TPO $> 34$ IU/ml	29/143 (20.3)	22/111 (19.8)	0.928
Anti-TG $> 34$ IU/ml	13/105 (12.4)	12/87 (13.8)	0.772
SPT positivity	35/88 (39.8)	25/66 (37.9)	0.811
ASST positivity	57/104 (54.8)	28/94 (29.8)	$< 0.001$

anti-TPO: anti-thyroid peroxidase antibody, anti-TG: anti-thyroglobulin antibody, ASST: autologous serum skin test, CRP: C-reactive protein, ESR: estimated sedimentation rate, HP: *Helicobacter pylori*, SPT: skin prick test

No statistically significant differences were observed between HP-positive and HP-negative patients regarding age and sex distribution, disease duration, presence of angioedema, concurrent CIndU, emergency referrals, systemic CS use, NSAID intolerance, family history of CU, atopic disorders, autoimmune thyroiditis, chronic infections, and stress ( $p > 0.05$  for all).



### ***Helicobacter pylori* Infection is not Linked to Resistance to CSU Treatment**

While there was no difference in response to omalizumab treatment between HP-positive patients who had not received eradication therapy and HP-negative patients (90% vs 86.5%,  $p=0.528$ ), HP-positive patients who had not received eradication therapy exhibited a higher AH response compared to HP-negative patients (78.4% vs 61.2%,  $p=0.006$ ) (Table 4).

### ***Helicobacter pylori* Eradication Therapy does not Improve CSU Treatment Responses**

*Helicobacter pylori* eradication therapy was initiated in 60 HP-positive patients (32.2%). There was no difference in response rates to neither antihistamines nor omalizumab treatment between HP-positive patients who had not received eradication therapy and HP-positive patients who had received such therapy ( $p > 0.05$ ) (Table 4). Also, the rates for chronic infections other than HP were similar between these two groups (44.4% vs 51%,  $p=0.438$ ).

### **Gastritis is not Associated with CSU Disease Severity**

No difference in mean baseline ic-UAS ( $2.33 \pm 2$  vs  $2.51 \pm 2$ ,  $p=0.553$ ) was observed between patients with and without gastritis.

### **Gastritis is not Associated with Resistance to CSU Treatment Regardless of *Helicobacter pylori* Infection**

While there was no difference in response to omalizumab treatment between patients with gastritis and patients with no gastritis (91.3% vs 85.3%,  $p=0.404$ ), overall AH response was significantly higher in patients with gastritis than in patients with no gastritis (76.8% vs 61.3%,  $p=0.013$ ) (Table 5).

No difference was observed in response rates to neither antihistamines nor omalizumab treatment between patients with HP-negative gastritis and patients with no gastritis ( $p>0.05$ ) (Table 5).

## **DISCUSSION**

*Helicobacter pylori* is a common cause of chronic bacterial infections in humans. The reported prevalence of HP infection shows significant variation, influenced by factors including age, socioeconomic status, and geographic regions. In developed countries, the prevalence ranges from 10% to 50%, while in developing countries, it reaches as high as 80%.<sup>4,5,26</sup> Between 2014 and 2020, the prevalence of adult HP infection decreased from 50-55% to 43% worldwide. This decline is primarily linked to advancements in living standards, socioeconomic status, and hygiene, as well as a rise in the use of eradication therapies.<sup>4,6,27</sup> The prevalence of HP infection in Turkey was reported as 82.5% with the 13C-Urea Breath Test (UBT), whereas in two different studies performed in Istanbul, the prevalence of HP was determined to be 36.6% using the SAT and 41.44% using the urease test.<sup>28-30</sup>

The prevalence of HP infection in CSU patients also varies across different regions, ranging from 25% to 83%.<sup>31,32</sup> Some authors suggested a potential causal relationship between CSU and HP infection based on the high prevalence of HP in CSU.<sup>10,33</sup> A recent case-control study using SAT to diagnose HP infection claimed that HP-positive patients had a 6-fold higher risk of developing CSU than HP-negative patients.<sup>34</sup> A meta-analysis comprising 16 studies revealed a weak positive correlation between HP infection and CU.<sup>35</sup> However, the authors of the study indicated that the majority of the included studies used the serology method to detect HP-specific antibodies, and no association was observed when only the studies using the UBT were considered.<sup>35</sup> Non-invasive diagnostic methods such as the UBT and SAT allow for the identification and confirmation of an active infection with high sensitivity and specificity (95-100%). The identification of serum HP-specific IgG/IgA antibodies through serological methods cannot differentiate between a current infection and a past infection with HP; confirmation by UBT or SAT is

**Table 4.** Comparison of CU treatment response rates between HP-negative patients, HP-positive patients who had not received eradication therapy, and HP-positive patients who had received eradication therapy

Treatments	HP-negative n/N (%)	HP-positive eradication therapy (-) n/N (%)	HP-positive eradication therapy (+) n/N (%)	P value*	P value**
AH response	71/116 (61.2)	80/102 (78.4)	39/58 (67.2)	0.006a	0.119a
Omalizumab response	32/37 (86.5)	18/20 (90)	15/18 (83.3)	0.528b	0.448b

AH, antihistamine; HP, *Helicobacter pylori*. \*Comparison between 'HP-negative' and 'HP-positive, eradication therapy negative' groups, \*\*Comparison between 'HP-positive, eradication therapy negative' and 'HP-positive, eradication therapy positive' groups, aPearson chi-square test, bFisher exact test

**Table 5.** Comparison of CU treatment response rates between patients without gastritis, patients with gastritis, and HP-negative patients with gastritis

Treatments	No gastritis n/N (%)	Gastritis n/N (%)	HP-negative gastritis	P value*	P value**
AH response	65/106 (61.3)	86/112 (76.8)	6/10 (60)	0.013a	0.593b
Omalizumab response	29/34 (85.3)	21/23 (91.3)	3/3 (100)	0.404b	0.638b

AH, antihistamine; HP, *Helicobacter pylori*. \*Comparison between 'No gastritis' and 'Gastritis' groups, \*\* Comparison between 'No gastritis' and 'HP-negative gastritis' groups, aPearson chi-square test, bFisher exact test

required.<sup>6</sup> Thus, the use of the serological method to determine the presence of a causal relationship between HP infection and CU may certainly lead to misleading conclusions. Besides, many studies have shown that the prevalence of HP infection among healthy individuals and CSU patients is comparable.<sup>11,13,16,36-39</sup> In our routine clinical practice, the SAT is used for the detection of active HP infection. This test is rapid, noninvasive, cost-effective, and reliable.<sup>6</sup> The prevalence of HP infection in CSU was found to be 57.2% in our study. Despite the lack of a comparison group, our results suggest that the prevalence of HP infection among CSU patients is higher than that of the population in the same region.<sup>28,29</sup> Our study suggests that there may be a causal relationship between HP infection and CSU; however, the lack of a control group limits the strength of this statement.

There is no difference in age, gender, the presence of angioedema, or disease duration between HP-positive and HP-negative CSU patients in the literature, as observed in our study.<sup>9,11,15,16,37,40-43</sup> As we also found, accompanying CIndU rates were comparable between these two groups.<sup>11</sup> Infection with HP has been reported to be associated with a chronic increase in circulating inflammatory markers, especially CRP, which was also higher in HP-positive patients in our study compared to HP-negative patients.<sup>44</sup> In previously published studies, CU disease activity was evaluated with UAS. In three of these studies, no difference between the groups regarding disease severity was observed.<sup>9,40,41</sup> In one study, however, HP-positive patients experienced a more severe disease, whereas in another, HP-negative patients did.<sup>37,45</sup> In addition, the authors reporting higher disease severity in HP-positive patients noted that gastric inflammation and bacterial colonization were also higher in these patients.<sup>37</sup> In our study, we evaluated CSU disease activity using baseline ic-UAS, which did not differ between HP-positive and HP-negative patients. Our research indicates that HP infection does not cause more severe disease. In addition, in our study, parameters such as emergency referrals, short-term CS use, and the presence of angioedema, which have been linked to a more severe disease, did not differ between the two groups.<sup>46,47</sup>

Atopic disorders, such as asthma, allergic rhinitis, and atopic dermatitis, are frequently observed as comorbid conditions in patients with CU.<sup>20</sup> HP-positive patients have previously been reported to have a lower rate of concomitant atopic disorders compared to HP-negative patients.<sup>42,48</sup> This result can be explained by the fact that the HP infection is mainly associated with low socioeconomic status and poor hygiene conditions, whereas high hygiene standards are a risk factor for the development of allergic conditions.<sup>49</sup> However, in our study, there was no difference between the two groups

regarding atopic disorders or total IgE elevation, the latter of which was found to be similar in another study.<sup>11</sup>

Autoimmune CSU (type 2b autoimmunity) is one of the most prevalent CSU endotypes and is characterized by circulating autoantibodies against IgE (IgG anti-IgE) and/or the  $\alpha$  subunit of the high-affinity IgE receptor (IgG anti-Fc $\epsilon$ RI).<sup>50</sup> Autoimmune CSU is frequently associated with other autoimmune disorders, elevated anti-TPO levels, and lower total IgE levels.<sup>50,51</sup> The present clinical assessment of patients exhibiting autoimmune antibodies involves the use of ASST. A positive test result supports the possibility of an autoimmune etiology, but it does not definitively establish the diagnosis.<sup>51,52</sup> One of the proposed pathogenetic mechanisms for the link between HP infection and CSU is the induction of autoimmune reactions, possibly as a result of an abnormal immune response to HP-specific antibodies through molecular mimicry.<sup>21,53</sup> Concerns regarding the role of HP infection in the formation of autoantibodies drove studies on the relationship between ASST and HP infection. While two separate analyses concluded that ASST positivity rates did not differ between HP-positive and HP-negative patients, another study found a notable increase in ASST positivity among HP-positive patients.<sup>54-56</sup> In our study, we also observed a higher prevalence of ASST positivity among HP-positive patients. However, there were no significant differences in the rates of autoimmune thyroiditis, thyroid autoantibody, or low total IgE between the two groups. However, the low predictive value of the ASST and the lack of predominance of autoimmune CSU features in our HP-positive patients mitigate the hypothesis of a possible role of HP infection in autoimmune CSU.<sup>51</sup>

Additional evidence supporting the proposed causal relationship between CSU and HP infection is presented by several studies demonstrating clinical improvement of CU in many HP-positive patients after eradication of the bacterium.<sup>8,9,13,37,39,57</sup> However, the evidence supporting the efficacy of HP eradication in CU patients is weak and contradictory. Other research groups reached the conclusion that eradication therapy failed to provide remission in CU.<sup>11,14-16,31,36,38,42,58</sup> There are many limitations that may account for the opposing outcomes observed in previous studies. The diagnostic methods for HP infection, the eradication regimens, the methods used to define complete remission, partial remission, and improvement of CU, which were mostly subjective, and the follow-up periods for patients after eradication therapy (ranging from 4 weeks to 24 weeks) varied between studies. This widespread heterogeneity of studies casts serious doubt on the efficacy of HP eradication in CU therapy. In addition, the sample size of patients included in the studies was considerably limited. A significant proportion of these studies did not employ

statistical analysis methods for comparisons.<sup>8,9,11,15,16,31,42,57</sup> Some of the studies did not report the outcomes of patients who did not undergo eradication therapy and did not perform comparisons.<sup>14,33,37-39,41,45</sup> The results of these studies are also in question because most studies did not mention the concurrent use of antihistamines and corticosteroids, which may have improved the symptoms of CU.<sup>8,9,11,13,15,16,33,37,42,57</sup> When all of these significant factors are taken into account, the overall evidence level for or against HP eradication as a treatment for CSU is very low. In our study, we reported comparisons of response rates to antihistamines and omalizumab between patients who received eradication therapy for HP and those who did not. There was no difference observed in CSU treatment responses between the two groups. Our study showed that eradication of HP does not have a significant impact on the course of CSU or on the treatment response.

One possible explanation for the observed correlation between eradication therapy for HP and CU remission in previous studies may be that the antibiotherapy may have effectively eliminated an undetected occult bacterial infection. This argument is supported by the observation that, while eradication therapy does not successfully eradicate HP in certain patients, it is still associated with rapid improvement in urticaria symptoms.<sup>31</sup> In our study, the distribution of a known chronic infection other than HP was found to be comparable among patients who received eradication therapy and those who did not. Perhaps this is the reason why a difference between the two groups could not be identified. It should also be noted that the natural course of CSU exhibiting spontaneous remission can potentially be misinterpreted and attributed to the efficacy of eradication therapy in previous studies.

In the literature, very few studies exist that assess the effect of HP bacteria itself on the CU course or on CU treatment, with conflicting results. In one small-sample study, the patients with untreated HP infection had a higher remission rate than HP-negative patients, whereas another one reported no difference between the two groups.<sup>15,42</sup> On the other hand, a recent meta-analysis stated that the HP-negative patients exhibited significantly more remission of CSU symptoms than the patients with untreated HP infection.<sup>17</sup> Also, HP positivity was found to be higher in AH-refractory patients than in AH-responsive patients in an earlier study.<sup>59</sup> However, in our study, the antihistamine response in HP-positive CSU patients was higher than that in HP-negative CSU patients. Also, there was no difference in the omalizumab response between the two groups in our study. In line with our finding, HP-positivity did not differ between omalizumab responders and non-responders in another study.<sup>60</sup> Based on our findings, we suggest that

HP infection is not associated with CSU remission or resistance to CSU treatment.

Chronic inflammatory conditions, such as gastritis and PUD, have been linked to the development of CSU.<sup>1,18,20,61</sup> The rate of patients who developed CU was observed to be higher in PUD-positive patients compared to PUD-negative patients in HP-negative patients.<sup>19</sup> Patients with healed gastric ulcers had a higher rate of CU improvement than patients with unhealed ulcers, regardless of HP infection.<sup>18</sup> Therefore, recent studies suggest that CU may be caused by gastritis-related inflammation rather than by HP bacteria. However, in our study, mean baseline ic-UAS did not differ between patients with and without gastritis. And, the overall antihistamine response in CSU patients with gastritis was higher than that in those without gastritis. Additionally, there was no difference in response rates to neither antihistamines nor omalizumab between CSU patients with HP-negative gastritis and CSU patients without gastritis. Our findings indicated that gastritis is not associated with disease severity and is not associated with resistance to CSU treatment, regardless of HP infection.

This study was subject to various limitations. This was a retrospective study, and recall bias cannot be excluded. There was no healthy control population from which the HP prevalence could be determined. Most patient files lacked information on eradication regimens, and those that did contained different HP eradication regimens. There was also no information regarding the confirmation of the success of the eradication therapy. On the other hand, our study's strengths were the use of SAT to detect active HP infection, the assessment of CSU disease activity using ic-UAS, the assessment of treatment response using UCT, and the knowledge of comorbid chronic infections.

## CONCLUSION

CSU patients have a higher HP infection rate than the general population. This observation prompts further investigation into the potential association between HP infection and the development of CSU. However, HP infection does not play a role in the development of a more severe disease. Neither the HP bacterium itself nor the eradication of HP have any significant effect on the course or treatment response of CSU. Moreover, no association existed between gastritis and disease severity or resistance to CSU treatment, regardless of HP infection. Nevertheless, in spite of the absence of a correlation between HP infection and CSU course, it is best to initiate eradication therapy for HP-positive patients as recommended by the International Guideline for the Management of Urticaria to provide complete healthcare for CSU patients.



## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Researches Ethics Committee (Date: 19.04.2021, Decision No: 163-2021).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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**Author Contributions:** All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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