

# *Helicobacter pylori* infection and skin disorders

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## ABSTRACT

*Helicobacter pylori* is a Gram-negative bacterium that has been linked to peptic ulcer disease, gastric lymphoma, and gastric carcinoma. Apart from its well-demonstrated role in gastroduodenal diseases, some authors have suggested a potential role of *Helicobacter pylori* infection in several extra-intestinal pathologies including haematological, cardiovascular, neurological, metabolic, autoimmune, and dermatological diseases. Some studies suggest an association between *Helicobacter pylori* infection and skin diseases such as chronic idiopathic urticaria and rosacea. There have also been few case reports documenting association between *Helicobacter pylori* and psoriasis vulgaris, Behçet's disease, alopecia areata, Henoch-Schönlein purpura, and Sweet's syndrome. However, more systematic studies are required to clarify the proposed association between *Helicobacter pylori* and skin diseases; most of the studies do not show relevant relationships of these diseases with

*Helicobacter pylori* infections. This review discusses skin diseases that are believed to be associated with *Helicobacter pylori*.

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## Introduction

*Helicobacter pylori* (HP) is a frequent gastro-intestinal infectious agent having worldwide distribution. It is a Gram-negative, microaerophilic, spiral bacterium that shows particular tropism for the gastric mucosa, and induces a strong inflammatory response with release of various bacterial and host-dependent cytotoxic substances. In 1984, Marshall and Warren<sup>1</sup> first described HP. At first, they named the bacterium as *Campylobacter pyloridis*. Later, it was renamed as *Helicobacter pylori*.<sup>1-4</sup> *Helicobacter pylori* has been linked to different forms of gastritis, peptic ulcer disease, low-grade gastric lymphoma arising from mucosa-associated lymphoid tissue, and gastric adenocarcinoma.<sup>5</sup> The host, and environmental and bacterial factors are important in the clinical manifestations of infections with this bacillus.<sup>6</sup> Apart from its well-demonstrated role in gastroduodenal diseases, some authors have suggested a potential role of HP infection in several extra-intestinal pathologies including haematological, cardiovascular, neurological, metabolic, autoimmune, and skin diseases.<sup>2,7,8</sup> The immunological response caused by this bacterium is oriented locally as well as systemically. This immunological response may cause local damage as well as influence the clinical course of other

diseases, including those outside the stomach, thus, opening the field of extragastric manifestations of HP infection.<sup>9</sup>

Gastric colonisation by HP is accompanied by production of large quantities of various pro-inflammatory substances such as cytokines, eicosanoids, and acute-phase proteins. This inflammatory response may lead to the development of antigen-antibody complexes or cross-reactive antibodies (by molecular mimicry) resulting in damage to other organs. In addition, increased permeability of the gastric and intestinal mucosa in infected patients may result in increased exposure to alimentary antigens. The key pathophysiological events in HP infection include initiation and continuance of an inflammatory response.<sup>4,6,10</sup> *Helicobacter pylori* strains have been divided into types I and II. Type I strains express cytotoxin-associated antigen (CagA) and vacuolating cytotoxin antigen (VacA), whereas type II strains do not express any antigens.<sup>7</sup> *Helicobacter pylori* infection is associated with mucosal inflammation due to infiltration by neutrophils and monocytes in the gastric mucosa. Urease, catalase, protease, lipase, and phospholipase are produced by HP, and these enzymes may be involved in the pathogenesis of gastric inflammation.<sup>11</sup> Translocation of CagA into

## 幽門螺桿菌感染與皮膚病

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幽門螺桿菌 (*Helicobacter pylori*) 已被證實與消化性潰瘍病、胃淋巴瘤和胃癌的革蘭氏陰性細菌相關。除了引致胃十二指腸病，文獻亦記載了幽門螺桿菌感染可能引發其他幾種腸外病狀，包括血液、心血管、神經系統、代謝、自身免疫和皮膚的疾病。一些研究顯示幽門螺桿菌感染和皮膚病有關，如慢性特發性蕁麻疹和酒渣鼻。此外，也有少數病例報告記錄幽門螺桿菌與尋常型銀屑病、白塞氏病、斑禿、過敏性紫癍和Sweet綜合徵之間的關聯。然而，須進行系統性研究來闡明幽門螺桿菌和皮膚病的關係。事實上，大多數研究並無顯示這些疾病與幽門螺桿菌感染相關。本文綜述了被認為與幽門螺桿菌有關的皮膚疾病。

the gastric epithelial cells leads to increased levels of pro-inflammatory cytokines such as tumour necrosis factor- $\alpha$ , interleukin (IL)-6, IL-10, and IL-8. The VacA protein interacts with macrophages, B- and T-lymphocytes and causes reduced IL-2 production with resultant suppression of IL-2-mediated T-lymphocyte proliferation. The interaction between HP and B-lymphocytes results in uncontrolled growth and proliferation of predominantly CD5+ B-cells that produce polyreactive and autoreactive immunoglobulin (Ig) M and IgG3 antibodies. The antibodies produced do not result in clearance of the pathogen and may result in further production of autoreactive antibodies, such as anti-H/K-ATPase antibodies. These autoantibodies have been implicated in the development of gastric atrophy.<sup>12</sup> Franceschi et al<sup>13</sup> found an epidemiological link between CagA- and VacA-positive HP strains and idiopathic dysrhythmias in a study with 54 dysrhythmic patients.

*Helicobacter pylori* infection has been considered a potential inducer of several immune-mediated skin disorders. A considerable number of reports have attempted to link HP infection with the development of skin disorders, with numerous studies showing either negative or positive results. Most animal models of diseases do not provide data to support the role of HP in skin disease development. Most of the mechanisms discussed in the literature remain as hypotheses that require more extensive investigation. We need to emphasise that these studies investigating the role of HP, speculate, rather than demonstrate, a pathogenic role for this pathogen. These disorders can be manifestations of systemic vasculitides (Behçet's disease [BD]) or may be related to skin disorders with presumed autoimmune origin (urticaria, psoriasis, alopecia areata [AA], lichen planus, etc).<sup>4</sup>

The results of studies investigating HP seropositivity in skin diseases and the effect of

eradication therapy (amoxicillin and clarithromycin in triple therapy) are conflicting. *Helicobacter pylori* infection triggers a marked local inflammatory response and a chronic systemic immune response. It is possible that inflammatory mediators released during the immune response to HP infection may play a role in the pathogenesis of skin diseases. *Helicobacter pylori* eradication may result in total or partial remission of clinical symptoms in at least some cases of skin diseases with itching. There are also some studies in which certain patients achieved complete remission after successful eradication with appropriate treatment. *Helicobacter pylori* eradication has no effect on psoriasis, and there is no exact evidence of an association between HP infection and psoriasis. In addition to this, eradication therapy is not always effective for treating chronic urticaria.<sup>7,14</sup> Thus, long-term, randomised, placebo-controlled systematic studies on the potential effects of HP eradication in patients with skin diseases are needed.

In this review, skin diseases that are thought to be associated with HP and the results of eradication therapies will be discussed.

### *Helicobacter pylori* and chronic urticaria

Approximately, 15% to 25% of the population will experience at least one episode of urticaria in their lifetime, and an estimated one fourth of these people will have chronic urticaria.<sup>14,15</sup> Chronic urticaria is a skin disorder characterised by recurrent, transitory, itchy wheals, which occur daily or almost daily, and persist for longer than 6 weeks in the absence of a physical cause. The clinical symptoms are caused by the release of histamine and other vasoactive mediators induced by the binding of an allergen to the specific receptor on mast cells.<sup>16</sup> The factors that have been identified as possibly being important in the pathogenesis of chronic urticaria include infections, food additives, medications, malignancy, physical factors, and vasculitis.<sup>14,17</sup> The aetiology of chronic urticaria is unknown in 50% to 60% of cases, and this group is defined as chronic idiopathic urticaria (CIU). Patients having demonstrable histamine-releasing autoantibodies are classified as CIU and they have very strong association with autoimmune diseases such as thyroiditis, vitiligo, insulin-dependent diabetes mellitus, rheumatoid arthritis, and pernicious anaemia.<sup>18</sup> An association between HP and CIU has been proposed. One of the suggested pathogenic mechanisms is an increase in gastric vascular permeability during infection resulting in increased exposure of the host to alimentary allergens. The other one is immunological stimulation by chronic infection leading to, through mediator release, a non-specific increase in sensitivity of the cutaneous vasculature to vasopermeability-

enhancing agents. Another hypothesis is that infection with HP may induce production of pathogenetic antibodies, possibly, by molecular mimicry.<sup>3,6,7</sup> *Helicobacter pylori* infection might be a source of circulating immune complexes and these immune complexes may trigger urticaria.<sup>5,19,20</sup>

The results of studies investigating HP prevalence in patients with chronic urticaria and the effect of eradication are conflicting. Fukuda et al<sup>21</sup> performed a study to assess the prevalence of HP infection and effect of bacterial eradication on skin lesions in patients with CIU (n=50). They found that 52% of the patients (n=26) with CIU were HP-seropositive, while 48% of the control subjects were HP-seropositive (statistically non-significant). Of the 26 patients with CIU infected with HP, 19 received eradication therapy, and eradication was successful in 17 of them. Of these 17 patients, six (35%) had complete remission and 11 (65%) had partial remission. On the other hand, of the nine patients without HP eradication, only two (22%) showed partial remission and seven (78%) had no improvement.<sup>21</sup> According to this study, eradication of HP would be a valid choice for the treatment of CIU if patients were infected with HP.

Wedi et al<sup>22</sup> studied prevalence of HP-associated gastritis in chronic urticaria. A potential infectious trigger could be identified in 43 (43%) of 100 patients with chronic urticaria. Of patients with focal lesions, 26 (60%) had HP-associated gastritis. Elevated HP IgA and/or IgG antibodies were found in 47 (47%) patients. Of the 47 seropositive subjects, 25 underwent endoscopy with biopsies. Gastritis of antrum (100%) and/or corpus (46%) was confirmed histologically in all these patients. In 91% of subjects, urticaria disappeared or improved after eradication treatment, whereas only 50% of untreated HP-seropositive subjects improved spontaneously. The reported association between HP and urticaria is consistent with an aetiological role of HP but does not prove it. However, the disappearance or improvement of urticaria in almost all subjects (91%) after HP eradication provides strong evidence for a causal relationship between HP gastritis and urticaria.<sup>22</sup>

Schnyder et al<sup>23</sup> identified 46 patients with CIU. Infected patients were treated in a double-blind placebo-controlled crossover study with amoxicillin and lansoprazol. They assessed HP status by enzyme-linked immunosorbent assay (ELISA) IgG and <sup>13</sup>C urea breath test (<sup>13</sup>C-UBT). Of the 50 patients, 14 (28%) had a positive serology for HP and 12 (24%) had active HP infection, as demonstrated by <sup>13</sup>C-UBT. Of the 46 (92%) patients with CIU followed up for 6 months, 19 (41%) had CIU resolved within 6 months without any or only symptomatic treatment (mainly non-sedating antihistamines). Eleven of 12 patients with active HP infection participated in the

double-blind crossover study. Eradication could be achieved in three (27%) subjects and in four (36%) individuals a resolution of the chronic urticaria was observed. Urticaria resolved in only one patient after successful eradication treatment, whereas the urticaria disappeared without eradication of HP in three patients. Thus, in this study, neither the frequency of HP infection nor the response to treatment indicated a causal relationship between chronic urticaria and HP infection.<sup>23</sup>

Moreira et al<sup>24</sup> evaluated 21 patients with CIU using <sup>13</sup>C-UBT. Triple therapy (amoxicillin, clarithromycin, and omeprazole) were given to infected patients for 7 days. The results of therapy were assessed by <sup>13</sup>C-UBT 1 month after therapy. Urticaria and gastro-intestinal symptoms were assessed on enrolment and for 6 months after eradication. Prevalence of HP infection was 71% (15/21); HP eradication rate was 86% (12/14). Three patients had clinical improvement with total resolution of urticaria, starting immediately after eradication therapy.

In another study,<sup>25</sup> 78 patients with chronic urticaria were checked for the positivity of autologous serum skin test (ASST) and <sup>13</sup>C-UBT; 21 patients had both positive ASST and positive <sup>13</sup>C-UBT (group A), and 24 patients had negative ASST and positive <sup>13</sup>C-UBT (group B). All patients with positive <sup>13</sup>C-UBT received eradication treatment. The effect of HP eradication on chronic urticaria was evaluated by urticaria activity score (UAS), measured at study entry, and at 8 and 16 weeks. At week 8, baseline UAS reduced from 4.7 ± 1.1 to 2.4 ± 1.4 (P=0.027) in group A and from 4.3 ± 1.5 to 2.3 ± 1.2 (P=0.008) in group B, but there was no statistical significance between the two groups. In control group and in six patients with HP eradication failure, no changes in UAS were noted. The authors concluded that an improvement in UAS was related to HP eradication, irrespective of ASST positivity.<sup>25</sup>

In a cohort of 42 patients with CIU, Di Campli et al<sup>16</sup> found that 55% were infected by HP; 88% of infected patients, in whom the bacterium was eradicated after therapy, showed a total or partial remission of urticaria symptoms. Conversely, symptoms remained unchanged in all uninfected patients. According to this study, HP eradication was associated with remission of urticaria symptoms, suggesting a possible role of HP in the pathogenesis of this skin disorder.

Daudé et al<sup>26</sup> evaluated 25 patients with chronic urticaria using <sup>13</sup>C-UBT to find a 68% prevalence of HP infection; this value did not differ from that in the general population. After eradication therapy, only one patient showed complete remission of urticaria and two patients showed partial remission. These results support a lack of relationship between HP infection and the course of CIU.

There are many studies in the literature showing the interactions between HP and chronic urticaria. However, the results of studies investigating HP prevalence in patients with urticaria and the effect of eradication are conflicting. For this reason, more randomised and case-control studies are necessary to prove an association between HP and CIU.

### ***Helicobacter pylori* and rosacea**

Rosacea is a common chronic facial dermatosis in adults which primarily affects those aged 30 to 60 years, with women being more often affected than men, especially in the early disease stages.<sup>27,28</sup> It is characterised by transient or persistent central facial erythema, visible blood vessels, and often, papules and pustules.<sup>4,29</sup> The skin manifestations progress in stages. The disease lasts for years, with episodes of improvement or exacerbation. Alcohol, sun exposure, and consumption of coffee and other products containing caffeine, as well as hot or spicy food, may precipitate exacerbation. Four subtypes of the disease have been recognised: erythematotelangiectatic, papulopustular, phymatous, and ocular rosacea.<sup>28</sup> Although rosacea is a common disease, its cause remains a mystery. Endocrinological, pharmacological, immunological, infectious, climatic, thermal, and alimentary factors are implicated as triggers in its aetiology.<sup>27,30</sup> There is no laboratory benchmark test and aetiopathogenesis and physiology of the condition are not exactly understood. The role of microorganisms in the development of rosacea has been addressed in a variety of studies, but clear evidence for their pathogenic role has not been demonstrated. The relationship between rosacea and HP infection has previously been investigated by a number of researchers. Rosacea has often been related to hypochlorhydria, gastritis, and abnormalities in jejunal mucosa. The seasonal behaviour of peptic ulcer and of rosacea is similar. Moreover, metronidazole benefits both rosacea and peptic ulcer; in the latter case, the effects are due to its activity on HP. It is proposed that the bacterium, through the production of specific cytotoxins and the release of vascular mediators like histamines, might be the triggering factor for the development of rosacea. These clues suggest that HP may be actively involved in the pathogenesis of rosacea.<sup>31,32</sup>

Diaz et al<sup>33</sup> examined a series of 49 patients to assess the potential association between the severity of rosacea and direct and serological evidences of HP infection. Patients with rosacea were classified by severity into non-inflammatory/erythematotelangiectatic or inflammatory/papulopustular rosacea, and were tested for current HP infection and evidence of previous exposure by using <sup>13</sup>C-UBT and ELISA test for IgG antibodies to the 120 kDa (CagA) antigen of HP. Positive <sup>13</sup>C-UBT

and ELISA tests were more likely to be observed in patients with inflammatory rosacea, although not statistically significant (odds ratio [OR]=3.0; P=0.15 and OR=2.9, P=0.16, respectively). However, when the two assays were interpreted in series, patients with inflammatory/papulopustular rosacea were 4.5 times more likely to exhibit positive test results on both <sup>13</sup>C-UBT and ELISA versus at least one negative result (OR=4.5; P=0.06). This study provides sufficient evidence suggestive of a positive association between the severity of rosacea and the presence of HP to warrant further research.<sup>33</sup>

Utaş et al<sup>31</sup> evaluated 25 rosacea patients and 87 age- and sex-matched healthy controls to investigate the effect of HP eradication therapy in patients with rosacea. They detected IgG and IgA antibodies against HP in both groups. An upper gastro-intestinal endoscopy and a rapid urease test were performed on the 13 patients with rosacea. Amoxicillin 500 mg 3 times daily, metronidazole 500 mg 3 times daily, and bismuth subcitrate 300 mg 4 times daily were administered to patients positive for HP. There was no statistical difference in seropositivity between the two groups. In HP-positive rosacea patients, there was a significant decrease in the severity of rosacea after eradication. These findings suggest that HP may be involved in rosacea, and that eradication treatment may be beneficial.<sup>31</sup>

Bamford et al<sup>34</sup> evaluated 320 patients with rosacea using the rapid whole blood test and the UBT in a randomised, double-blind, placebo-controlled clinical trial. A total of 145 patients were seropositive for HP; 50 patients had a positive UBT for HP and 44 patients were enrolled in the study (the rest did not complete the study or had side-effects). The treatment group received a 14-day therapy including clarithromycin 500 mg orally 3 times a day, and omeprazole 40 mg orally once a day. There was no statistical difference when the results of active treatment were compared with those of placebo. It was concluded that treating HP infection had no short-term beneficial effect on the symptoms of rosacea to support the suggested causal association between HP infection and rosacea.<sup>34</sup>

In a prospective study, Boixeda de Miquel et al<sup>35</sup> studied 44 patients diagnosed with rosacea; HP infection was determined, and infected patients were treated with eradication therapy. A subgroup of 29 infected patients in whom eradication had been achieved was followed up for a mean ( $\pm$  standard deviation [SD]) duration of 16.8  $\pm$  17.8 months. Complete improvement was observed in 10 (34.5%) patients, relevant improvement in nine (31.0%), poor improvement in five (17.2%), and absence of improvement in five (17.2%) cases. Regarding subtype of rosacea, there was a relevant improvement in 83.3% of cases with papulopustular type as opposed to 36.5% of cases with erythematous predominance (P=0.02). This study suggests a

correlation between HP and rosacea, and that it is worthwhile to investigate for HP infections as an appreciable percentage of patients diagnosed with rosacea and HP infection benefited from eradication therapy, predominantly in the papulopustular subtype.<sup>35</sup>

Argenziano et al<sup>36</sup> evaluated serum IgG, IgA anti-HP and anti-CagA antibodies by means of ELISA and immunoenzymatic method (RADIM) in a group of 48 patients with rosacea. They found IgG antibodies in 81% of the rosacea patients with dyspepsia and 16% of the rosacea patients without dyspeptic symptoms. The IgA anti-HP antibodies were present in 62% of patients with dyspepsia and in 6% of patients with no upper gastro-intestinal symptoms. Anti-CagA antibodies were seen to be present in 75% of patients with both rosacea and gastric symptomatology, and were prevalent in patients affected by rosacea with papular symptoms versus rosacea with erythematous symptoms. This study, thus, suggested a correlation between rosacea and HP infection.<sup>36</sup>

Szlachcic<sup>37</sup> studied 60 patients (aged 30-70 years) with visible cutaneous rosacea symptoms and 60 age- and gender-matched controls without skin diseases but with dyspeptic symptoms similar to those of rosacea and without endoscopic changes in gastroduodenal mucosa (non-ulcer dyspepsia [NUD]) to examine the prevalence of HP infection verified by <sup>13</sup>C-UBT, *Campylobacter*-like organism test (CLO-test), HP culture, and serology (IgG and IgA). All the subjects underwent gastroscopy during which mucosal biopsy samples were taken from the stomach (antrum and corpus) and tested for rapid urease CLO-test (Jartoux-H.p.-test; Procter & Gamble Pharmaceuticals, Weiterstadt, Germany) and bacterial culture on special agar plates with the addition of 5% horse serum and antibiotics that blocked the growth of non-HP bacteria. Furthermore, the biopsy samples of antral and fundal mucosa were taken for histological evaluation using the Sydney classification. To confirm HP infection in the stomach, the <sup>13</sup>C-UBT was performed. Additionally, the levels of IgG and IgA anti-HP antibodies were measured in plasma and saliva by ELISA, CLO-tests were performed, and bacterial cultures were performed with material from the oral cavity (saliva, dental plaque, and gingival pocket fluid). The tests were conducted before and 4 weeks after anti-HP therapy. All subjects with diagnosed HP infection received 1-week triple therapy with omeprazole (2×30 mg), clarithromycin (2×500 mg), and metronidazole (2×500 mg). In the group of 60 subjects with skin lesions typical of rosacea, 53 (88.3%) were diagnosed as having HP infection in the stomach, compared with only 39 (65%) of the NUD controls, confirmed by at least two HP tests (<sup>13</sup>C-UBT, CLO-test, or culture). The overall difference in HP prevalence between rosacea patients and

NUD controls was statistically significant. A large proportion of the rosacea subjects (72%) had chronic active gastritis, involving predominantly the antral portion of the stomach (antritis). About 10% of the subjects had chronic active multifocal inflammation of the stomach (gastritis multifocalis), and the remaining 18% had both antritis and chronic inflammation of the body of the stomach (corpusitis). Only antral chronic active gastritis without involvement of the fundal gland area was histologically documented in the NUD controls. The titres of the anti-HP IgG antibodies in the plasma were significantly lower in the NUD controls than in the rosacea subjects. After application of the systemic and local therapy in the oral cavity, HP was eradicated from the stomach in 97% and from the oral cavity in 73% of treated patients. Of the 53 subjects with cutaneous rosacea symptoms and HP infection, 51 showed disappearance or improvement of skin lesions after eradication of HP, and the best results were seen in cases with mild or moderate skin symptoms. This study proposed that rosacea is a disorder with various gastro-intestinal symptoms closely related to gastritis, especially involving the antral mucosa, and that eradication of HP leads to improvement of symptoms of rosacea and reduction in related gastro-intestinal symptoms.<sup>37</sup>

Thus, many studies have suggested that HP is involved in the aetiology of rosacea, at least as a triggering factor, and that eradication treatment provides symptomatic relief.

### ***Helicobacter pylori* and psoriasis vulgaris**

Psoriasis vulgaris is a chronic, debilitating skin disease that affects millions of people worldwide. The underlying pathophysiology of psoriasis involves Th1 and Th17 cells, and most likely, their interaction with cells involved in innate immunity. It is characterised by periods of exacerbation and remission. Clinically, red plaques (due to dilatation of blood vessels) with silver- or white-coloured scales (due to rapid keratinocyte proliferation) that are clearly demarcated from adjacent, normal-appearing, non-lesional skin are usually seen. Individuals with psoriasis have areas of involved skin (lesional skin) as well as areas of normal-appearing uninvolved skin (non-lesional skin). Lesions often occur at sites of epidermal trauma, such as the elbows and knees, but can appear anywhere on the body. Psoriatic arthropathy is seen approximately in 7% to 8% of psoriatic patients. Other co-morbidities observed in individuals with psoriasis can include cardiovascular disease, diabetes mellitus (mainly type II), metabolic syndrome, obesity, impaired quality of life, and depression.<sup>38</sup> A number of bacterial and fungal pathogens have been proposed as causal for psoriasis.<sup>5</sup> Several recent reports have pointed to a

possible relationship between HP infection of gastric mucosa and psoriasis, and have suggested that HP may be one of the organisms capable of triggering psoriasis.<sup>39</sup> Qayoom and Ahmad<sup>40</sup> detected HP antibodies in 20 (40%) psoriatic patients and five (10%) patients of control group. Healthy individuals without any gastro-intestinal complaints were taken as controls. Patients taking antibiotics or medications for upper gastro-intestinal problems were excluded from the study. *Helicobacter pylori* serology was done in both groups using ELISA test. As the number of seropositive individuals was significantly different in the two groups, the authors concluded that the data supported a causal role of HP in the pathogenesis of psoriasis.<sup>40</sup> Fabrizi et al<sup>41</sup> conducted a study with 49 patients (age range, 5-19 years): 20 patients with psoriasis and a control group of 29 patients without skin disorders. Patients who had an equivocal clinical picture or who were taking antibiotics, antacids, or other medications for their gastric complaints were excluded. All patients were tested for HP infection with <sup>13</sup>C-UBT. Of the 20 patients with psoriasis, two (10%) had a positive test result. Of the 29 patients without skin disorders, five (17%) had a positive test result. This study showed that there was low prevalence of HP infection in children and teenagers with psoriasis, and that this relationship was not different from that in children without skin disorders. These data did not support a relationship between HP infection and psoriasis, at least in childhood.<sup>41</sup> Fathy et al<sup>42</sup> compared 20 patients with chronic plaque-type psoriasis with 20 healthy, age- and sex-matched controls for HP infection by using HP IgG quantitative enzyme immunoassay (ELISA test). The mean ( $\pm$  SD) prevalence of HP IgG seropositivity in psoriatic patients was significantly higher compared with controls ( $67.7 \pm 32.5$  vs  $33.9 \pm 15.1$ ;  $P < 0.05$ ), and higher values were correlated with severe psoriasis. Based on these results, the link between HP and psoriasis might be supported. Large-scale studies and further investigation for the eradication of HP in psoriatic patients with HP seropositivity are required for a definite confirmation.<sup>42</sup> In a study by Onsun et al,<sup>43</sup> 300 patients with plaque-type psoriasis and 150 non-psoriatic healthy controls were evaluated to determine the prevalence of HP seropositivity in psoriasis, the relationship between Psoriasis Area and Severity Index (PASI) scores and HP infection, and the impact of HP infection on the response to treatment. A stool antigen test for HP was performed in both patients and controls. Severity of disease was assessed using PASI scores in all patients. Fifty patients were selected at random from 184 psoriatic patients infected with HP. These 50 were assigned to one of two groups: the first group (n=25) received HP treatment and acitretin, while the second group (n=25) received acitretin monotherapy. Additionally, 25 patients who received

only HP treatment without any systemic treatment were also compared with the two groups. Eight weeks later, the patients' PASI scores were measured and compared. The prevalence of HP infection was 61.3% in psoriatic patients (n=184) and 59.3% in controls (n=89/150;  $P > 0.05$ ). The mean PASI score was  $5.92 \pm 5.50$  in patients with psoriasis who were HP-positive while it was  $0.79 \pm 0.54$  in patients with psoriasis who were HP-negative ( $P < 0.001$ ). Patients who received acitretin and who were also treated for HP infection showed more rapid improvement than those who received acitretin alone (mean decrease in PASI score,  $3.38 \pm 1.99$ ;  $P < 0.001$  vs  $1.22 \pm 0.77$ ;  $P < 0.05$ ). Patients who received only HP treatment also showed significant improvement versus controls (decrease in mean PASI score,  $2.85 \pm 1.25$ ;  $P < 0.001$ ). This study suggests that HP infection plays a role in the severity of psoriasis, and that eradicating such infections enhances the effectiveness of psoriasis treatment.<sup>43</sup>

### ***Helicobacter pylori* and other dermatological disorders**

Behçet disease, first described by Hulusi Behçet in 1937, is a multisystemic, chronic, relapsing vasculitis of unknown origin that affects nearly all organs and systems. Involvement of the gastro-intestinal system is called Entero-Behçet disease.<sup>44</sup> Cakmak et al<sup>45</sup> studied 40 patients with BD using fibre-optic oesophagogastroduodenoscopy and UBT. *Helicobacter pylori* was found in 26 (65%) patients with BD and in 28 (70%) controls (no statistical significance by Chi squared test,  $P > 0.05$ ). In a study by Avci et al,<sup>46</sup> anti-HP IgG was positive in 41 (83.7%) patients with BD and in 35 (71.4%) controls. The difference was not statistically significant ( $P = 0.22$ ).<sup>46</sup> Ersoy et al<sup>47</sup> evaluated 45 BD patients and 40 controls to study the prevalence of HP. They found no significant difference between the two groups in terms of prevalence of HP (73% vs 75%) and eradication rate (75% vs 70%).<sup>47</sup>

Henoch-Schönlein purpura (HSP), also known as a leukocytoclastic vasculitis of small vessels, primarily involves the skin, gastro-intestinal tract, joints, and kidneys. The pathogenesis of HSP remains unclear, but a wide variety of conditions such as bacterial or viral infections, vaccinations, drugs, and other environmental exposures may be responsible for the onset. Hoshino<sup>48</sup> reported a 33-year-old man who presented with HSP accompanied by gastric HP infection. The gastro-intestinal manifestations and purpuric rashes were dramatically resolved after HP eradication therapy.<sup>48</sup>

Mytinger et al<sup>49</sup> reported a 13-year-old boy with HSP associated with HP infection. Treatment of the HP infection was accompanied by prompt resolution of the HSP.

Alopecia areata is a disease of the hair follicles, with strong evidence supporting an autoimmune origin, although the exact pathogenesis of the disease is not clear.<sup>50</sup> It affects 1% to 2% of the population,<sup>5</sup> and occurs in all ethnic groups, ages, and both sexes.<sup>51</sup> The pattern of hair loss can vary and can affect any part of the body. Alopecia areata frequently occurs in association with other autoimmune diseases such as autoimmune thyroiditis, lichen planus, psoriasis, Sjögren syndrome, and idiopathic thrombocytopenic purpura.<sup>50</sup> Abdel-Hafez et al<sup>51</sup> compared 31 patients with AA and 24 healthy volunteers of similar gender ratio for the presence of HP surface antigen (HpSAg) in stool. Optical density values for HP infection were positive in 18 (58.1%) of all 31 patients evaluated, while these were negative in 13 (41.9%) patients. In the control group, 10 (41.7%) of 24 yielded positive results. Although the mean HpSAg level was higher in the AA group, the difference was not statistically significant. This study did not support the relationship between HP and AA.<sup>51</sup> Campuzano-Maya<sup>50</sup> reported the case of a 43-year-old man with an 8-month history of AA of the scalp and beard areas. He had a history of dyspepsia and the UBT confirmed HP infection. The patient went into remission from AA after HP eradication therapy. This association, however, must be confirmed with epidemiological studies.<sup>50</sup> Rigopoulos et al<sup>52</sup> also reported no increased prevalence of HP infection in patients with AA.

Sweet's syndrome, or acute febrile neutrophilic dermatosis, is characterised by the acute onset of fever, leukocytosis, and erythematous plaques infiltrated with neutrophils. It has been associated with inflammatory and neoplastic diseases, but most cases are idiopathic. An association between HP and Sweet's syndrome has been proposed. Kürkçüoğlu and Aksoy<sup>53</sup> reported a 42-year-old woman with Sweet's syndrome. Her endoscopic biopsy specimens from gastric mucosa disclosed chronic active gastritis and showed HP organisms. After eradication therapy, the skin lesions subsided. New case reports and clinical trials are necessary to confirm this association.

## Conclusion

Although some studies have shown that HP has a role in the pathogenesis of some dermatological diseases, it is not known whether HP is a trigger or the causative agent for the disease. The results of studies investigating HP seropositivity in skin diseases and the effect of eradication are conflicting. For this reason, systematic studies examining the relationship between dermatological entities and infection with HP, and documentation of the effect of HP eradication are needed to further our understanding on this topic.

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