Chronic idiopathic urticaria (CIU) is defined by the almost daily occurrence of urticarial lesions: wheals and/or angioedema. One-half of the patients demonstrate wheals beyond 6 months but one-fifth of patients persist with considerable disability is similar to that of patients with awaiting surgery for severe coronary artery disease.

Approximately 1-25% of the population will experience at least one episode of urticaria in their lifetime, while one fourth of these people will develop chronic urticaria (4). Chronic idiopathic urticaria (CU) affects between 0.1% and 3% of the United States and Europe population. CIU is characterized by the spontaneous appearance of widespread edematous pruritic wheals that are surrounded by a bright red flare: the condition lasts 6 weeks and is often recurrent.

According to Champion, chronic urticaria is a skin disorder characterized by recurrent, transitory, itchy wheals, which occur daily or almost daily (two or more times per week) for at least three months. One-half of the patients demonstrate wheals beyond 6 months but one-fifth of patients persist with considerable disability and reduction of quality of life beyond 10 years (5). In the case of coexisting angioedema, 75% of the patients will develop CU for at least 6 weeks without an identifiable cause. Symptoms include short-lived wheals, itching and erythema.

Chronic urticaria is a 6-week or longer history of daily or almost daily (two or more times per week) for at least three months. One-half of the patients demonstrate wheals beyond 6 months but one-fifth of patients persist with considerable disability and reduction of quality of life beyond 10 years (5). In the case of coexisting angioedema, 75% of the patients will develop CU for at least 6 weeks without an identifiable cause. Symptoms include short-lived wheals, itching and erythema.

Chronic urticaria, Infection, Helicobacter pylori
PHYSICIANS: 60.4%, PHYSICIAN: 39.6%

Occupations: 49.6% of patients were physiologists, 25.7% of patients were physicians, and 14.5% of patients were nurses. The remaining occupations included teachers (4.4%), lawyers (4.4%), and other professions (2.8%).

Infections:

Overt or hidden bacterial, viral, fungal as well as protozoa infections have been reported among the most frequent possible triggering factors in the development of chronic urticaria (Table 4) (7,9,10,12,13). Moreover, Wedi et al. reported a strikingly high prevalence of Helicobacter pylori gastritis, which accounted for 60% of all focal infections in their study (Table 4) (9). In contrast, other focal infections were less frequent. Among patients with focal infections other than Helicobacter pylori, after treatment of the focal infection, 70% showed healing of CU (9).

HELICOBAHER PYLORI INFECTION

At the present, Helicobacter pylori (Hp) infection is probably the most common chronic bacterial infection in humans, affecting more than a half of the world population. It represents the main cause of gastroduodenal ulcer disease, plays an etiologic role in the
development of chronic active gastritis, gastric carcinogenesis and low-grade gastric mucosa-associated lymphoid tissue lymphoma. The prevalence is high especially in the developing world (14,15).

The heterogeneous clinical presentation of the infection which depends on different interactions between Hp strains and host genetic differences as well as recent findings, suggest an association with some extraintestinal diseases ranging from rosacea to scleroderma (16,17). The role of Hp infection in the pathogenesis of chronic UC has been assessed for more than 18 years. Most recently, the possible role of Hp as a triggering factor for at least some cases of CIU has become the reality (18-24).

By producing inflammation in gastrointestinal tract, Hp can facilitate absorption of antigens or unmask existing antigens (25). Once this occurs, the production of IgE antibodies responsible for urticarial symptoms might continue even after eradication of symptoms (25). Thus, Hp infection may perpetuate the urticarial tendency of an infected person.

**COLONIZATION AND MUCOSAL INFLAMMATION**

Helicobacter pylori is a Gram-negative spiral microaerophilic bacterium which can infect gastric mucosa. Hp was shown to have a toxic effect on the mucosa cells, where the pathogen is able to induce interleukin 8 (IL-8) mRNA expression. Furthermore, IL-8 as well as urease and lipopolysaccharide, both secreted by Hp, may induce attraction of neutrophilic granulocytes, which are able to destroy the mucosa barrier via oxidative stress and proteolytic enzymes. Penetration of food allergens/pseudoallergens may be facilitated by this toxic cell damage. This hypothesis is supported by the fact that Hp infection is not an occult infection in patients with CU; it led to symptoms of chronic gastritis in all patients in one series (13).

**CUTANEOUS PATHOLOGY**

Regarding structural components (flagella, adhesions, membrane lipopolysaccharides) or products of Hp (urease, protease, phospholipase, cytotoxin), several relationships between Hp colonization and mucosal inflammation have to be discussed. Generally, Hp may cause immunomodulation in infected persons, which may also involve the skin. Different strains of Hp may elicit different pathogenetic responses, depending not only on the virulence of Hp (e.g., type I bacteria express the vacuolating cytotoxin in Vac A and the cytotoxin-associated gen Cag A and are recognized to be more virulent producing a more severe inflammatory response), but also on the diverse host and environmental factors (26,27,28). Recently a modulatory action of Hp on histamine release from mast cells and basophils was demonstrated in vitro (29).

The other possibility is that Hp may induce some unknown IgE-mediated or non-IgE-mediated immunomechanism, which leads to urticarial disease. Experimental evidence supporting this concept demonstrated the presence of specific IgE detected against Hp on basophils and in sera (30).

When IgA-, IgG-, and IgE-mediated immune response against Hp antigens were analyzed, some bacterial immunoresponsive proteins were identified in cases of CU (16).

Immunoblot analysis identified a specific serum IgM and IgA response to a 19-kDa outer membrane protein Hp-associated lipoprotein 20 (lpp20) in Hp-positive patients. The prevalence of anti Hp-associated lpp20 antibodies was significantly higher in Hp-positive patients with urticaria than in patients with severe Hp-associated gastritis without urticaria (21). This phenomenon may play a protective role against or lpp20 IgG antibodies since the 19-kDa lpp20 may act as a protective antigen. This protective antibody response may have a functional role in prevention or mitigation of gastritis associated with Hp infection. However, the protection depends on the magnitude and subclass of the response; for example, an IgG1 subclass monoclonal antibody raised against Hp lpp20 can reduce or even prevent Hp colonization (31). Patients with CU who exhibited the high level of anti-lpp 20 had no dyspetic symptoms in their history and only a mild gastritis that was seen on endoscopy (21). On the other hand, people may develop a severe gastritis with overt dyspeptic symptoms if harboring Hp with zero or low levels of anti-lpp20 as it has been detected in the selected dyspeptic control group (21). Thus, in addition to their putative gastroprotective effect, IgG and partly IgA antibodies against Hp associated lpp-20 could act as a source of autoimmunity, via cross reactivity between the bacterial lpp20 and some skin antigen components (21). The anti- FcεRII antibodies in chronic urticaria are related predominantly to the complement fixing subtypes IgG1 and IgG3. In this context, there is growing evidence that the phenomenon of parasite-host mimicry might initiate or maintain autoimmunity. A great number of cross-reacting (auto) antibodies may interact with the stomach and duodenal alterations caused by Hp.

### Table 3. POSSIBLE ELICITING FACTORS OF CHRONIC URTICARIA BASED ON PATIENT'S HISTORY AND EXTENSIVE DIAGNOSTIC APPROACH (n=100)*

<table>
<thead>
<tr>
<th>ELICITING FACTOR</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOCAL INFECTION</td>
<td>43%</td>
</tr>
<tr>
<td>PSEUDOALLERGIC REACTIONS</td>
<td>15%</td>
</tr>
<tr>
<td>ANTIBODIES TO THYROID</td>
<td>5%</td>
</tr>
<tr>
<td>MALIGNANT DISEASE</td>
<td>2%</td>
</tr>
<tr>
<td>IDIOPATHIC ORIGIN</td>
<td>35%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100%</td>
</tr>
</tbody>
</table>


One-third of patients with CU have circulating functional antibodies against the high-affinity IgE receptors FcεRI, or IgE, and this forms the basis for a positive autologous serum skin test. The prevalence of positive ASST in patients with CU and Hp infection is significantly higher than in patients with CU but without Hp infection (8), indicating that the presence of Hp might predispose to the development of other associated autoimmune phenomena (8). Many drug-induced autoimmune diseases continue to progress even after drug withdrawal (e.g., pemphigus). Once induced or triggered by a drug, the biological behavior and course of the disease do not differ from those of an idiopathic disease (8).

Thyroid autoimmunity has been considered an important factor in the pathogenesis of CU in Hp-infected patients. In cases of CU with and without thyroid autoimmunity, a different prevalence of Hp infection was found and the thyroid autoimmunity was connected with CagA (+) Hp strains (27). A higher prevalence of antihelobacter antibodies was found in patients with CU and positive ASST, then in patients with CU and negative ASST. Whether these antibodies have any pathogenetic role in the development of CU in Hp-infected patients is questionable, as antithyroid antibodies usually persist even after urticaria disappeared (32,33). Similarly, a higher prevalence of Hp-specific antibodies was found in patients with CU and positive ASST, then in patients with CU and negative ASST (8). Magen et al. showed that eradication of Hp infection sig-

### Table 4. FOCAL INFECTIONS AS POSSIBLE ELICITING FACTORS OF CHRONIC URTICARIA*

<table>
<thead>
<tr>
<th>FOCAL INFECTION</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HELICOBACTER PYLORI GASTRITIS</td>
<td>60%</td>
</tr>
<tr>
<td>EAR-NOSE-THROAT FOCUS</td>
<td>21%</td>
</tr>
<tr>
<td>EPSTEIN-BARR VIRUS, CYTOMEGALOVIRUS</td>
<td>9%</td>
</tr>
<tr>
<td>DENTAL</td>
<td>5%</td>
</tr>
<tr>
<td>YERSINIOSIS</td>
<td>5%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100%</td>
</tr>
</tbody>
</table>

significantly and equally improved CU in patients with and without positive ASST (33). The presence of a positive ASST response does not seem to be a predictor for a good clinical response to antihista-
mine therapy as well (34). The results of these studies do not sup-
port the hypothesis that in patients with CU, clinically recognized
autoimmunity (by ASST and plasma antithyroid antibodies) may be a factor which can modify Hp-induced immunomodulation, but other yet unknown aspects of Hp to cause some kind of immune
deviation in CU (7,33). Moreover, much more work needs to be
done before the ASST is accepted as a valuable tool for the classi-
fication of autoimmune urticaria (35,36).

PREVALENCE OF HELICOBACTER PYLORI ASSOCIATED GASTRITIS IN CHRONIC URTICARIA

Based on our current knowledge, the prevalence of Hp infec-
tion in patients with CU (24-70,58%) does not significantly differ
from that in patients without CU (25-84%) (12-14, 28,37). Thus,
Dauden et al. found the high prevalence of 68% in patients with
CU, which did not differ from the prevalence of 84% estimated in
the general population in the same geographic area (37). In a
doouble blind, placebo-controlled, crossover study, only 24% of patients
with CU had an active Hp infection which correlated with the prevalent of a comparable age population but without urticaria in
Switzerland (19% asymptomatic people, 39% in dyspeptic people)
(12). In one Finish report, 25% of the patients with CU were posi-
tive for Hp. The prevalence of Hp infection was not significantly
higher among urticaria patients compared with the normal Finish
population in any of the age groups studied. The prevalence rose
with age similarly to that of the control subjects (38). The high
prevalence of Hp infection has been reported from India. The prevalent of 70.58% among patients with CU did not differ from
the prevalence of 67.64% found in the control group without CU
(14).

Table 5. THE EFFECT OF ANTIBIOTIC THERAPY FOR HELICOBACTER PYLORI-INFECTED PATIENTS
WITH CHRONIC URTICARIA*

<table>
<thead>
<tr>
<th>PATIENTS WITH CHRONIC URTICARIA</th>
<th>COMPLETE REMISSION OF URTICARIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>AGE (years)</td>
</tr>
<tr>
<td>266</td>
<td>10-82</td>
</tr>
</tbody>
</table>

HP, Helicobacter pylori; n, number of treated patients with chronic urticaria Helicobacter pylori infection completing study

Contrary to the data regarding active Hp infection, the Hp
serology studies revealed (almost always) the significantly higher
prevalence in patients with CU than in those without CU (7,8,13).
In one study from Germany, the circulating specific IgG-antibodies
against Hp were detected in all patients with CU, and in 78% of
patients without CU (13). In a European Mediterranean population-
based study on the prevalence of anti-Hp serology, anti Hp antibod-
ies were present in 51% of the study population (39).

Nevertheless, the assessment of Hp-specific IgG and IgA antibod-
ies (the sensitivity and specificity of the enzyme-linked
immunosorbent assay-ELISA for IgA is 88.9% and 97.1%, respec-
tively, and for IgG 96.7% and 95.5%, respectively) cannot be used for the detection and establishment of Hp infection. Since these antibodies are associated with active gastritis in only some patients, the assessment of antibodies does not indicate active disease and
titers may remain positive even after successful eradication ther-
apy. All patients should be examined for Hp infection actively, by
the urea breath test ($^{13}$C-UBT) and/or upper endoscopy with antral
biopsy for urease test and histopathology (to confirm Hp). Patients
infected with Hp (diagnosed by the $^{13}$C-UBT, and/or endoscopy
with rapid urease test or histology or both), should receive eradica-
tion therapy. The response to eradication therapy should be evalu-
ated by the $^{13}$C-UBT or the monoclonal fecal antigen assay which
has the sensitivity of 94% and specificity of 100% (40). The histol-
ogy for the diagnosis of Hp infection has the sensitivity and speci-
ficity between 53-90%; the specificity of the rapid urease test var-
ies from 95-100%, while the sensitivity varies from 85-95%.

Generally, Hp infection is frequent, but we should bear in mind
that regardless to its prevalence, it would trigger urticaria only in
some (somehow predisposed) infected patients.

EFFECT OF ANTIBIOTIC THERAPY FOR HELICOBACTER PYLORI - INFECTED PATIENTS
WITH CHRONIC URTICARIA

Recommendations to administrate antibiotic treatment for Hp
infection in patients with CU should be evidence-based. The
reported association between Hp and CU is consistent with a trig-
gering effect of Hp but does not provide strong evidence for a
causal relation between Hp-associated gastritis and CU. Results on
the effects of Hp eradication on the course of ICU are conflicting.
Eradication of Hp infection was achieved in 27-96% (12,14) and in
8-81.2% was the eradication associated with the resolution of
urticaria (14,18,37). Though representing a potential subject for
meta-analysis, available reports still differ in substantive ways. As
Patients with CIU (Table 6) (7). In one case control study, patients et al. found at least one additional focus in 81% of Hp-infected between the 2 groups (13). Furthermore, in a recent study, Helmig, infections were found, however there was no significant difference infected and in 68% of non-infected patients with CU other focal ease should be sought and treated. For example, in 45% of Hp-infected patients if antimicrobial therapy for intestinal candidi- Hp-infection was made by either serology, urea breath test, or by upper endoscopy; and metronidazole were given from 7-14 days, proton pump inhibitors (omeprazole, lansoprazole) were given concurrently for 7-28 days. There was a great variability in time of follow-up evaluation (Table 5) (23). Two analyses were performed, eradication versus unsuccessful eradication or placebo treatment, and eradication versus control persons who were not Hp-infected. It was shown that eradication of Hp was significantly associated with remission of urticaria, with an odds ratio 2.9 (95% confidence interval 1.4-6.8; P=0.005). When patients with eradica- tion of Hp were compared with control persons who were not Hp-infected, the odds ratio for remission of urticaria was 4.7 (95% con- fidence interval 2.6-17.6), p<0.001 (23).

Patients with CU and Hp infection should receive the therapy for eradication of Hp. However, other possible causes of the dis- ease should be sought and treated. For example, in 45% of Hp-infected and in 68% of non-infected patients with CU other focal infections were found, however there was no significant difference between the 2 groups (13). Furthermore, in a recent study, Helmig, et al. found at least one additional focus in 81% of Hp-infected patients with CU (Table 6) (7). In one case control study, patients who were not Hp-infected, reached a comparable clearance rate of Hp-infected patients if antimicrobial therapy for intestinal candidi- asis or sinusitis was successful, or diet free from nutritional and/or drug-related provocation factors was conducted (13).

Looking at these data, some facts have to be taken into account.

Firstly, after successful eradication of infection with antibiotics, only one third of patients with Hp-associated CU will be in remis- sion. Secondly, only patients who have active infection will benefit in resolution of urticaria. Thirdly, the majority of patients with the active infection will concurrently have causes unrelated to Hp.

**CONCLUSION**

At the present, it can be concluded that the reported association between Hp and CU is consistent with a triggering role of Hp. Every patient with CIU should be sent to a gastroenterologist. It should be kept in mind that recurrence shortly after successful thera- py may be the main reason for the recurrence of urticaria.

**Abstract**

Chronic idiopathic urticaria (CIU) is defined by the almost daily presence of urticaria for at least 6 weeks, without an identifiable cause. The European Academy of Allergy and Clinical Immunology (EAACI) and the Global Allergy and Asthma European Network (GA2LEN) guidelines do not dif- ferentiate between chronic urticaria (CU) and CIU, since multiple causes of CU exist. Overt or hidd- den bacterial, viral, fungal and protozoan infections have been reported as the most frequently rec- ognized triggering factors. A strikingly high prevalence of Helicobacter pylori gastritis accounted for 60% of all focal infections, was reported. Of the patients with focal infections other than Helicobacter pylori, 70% showed healing of CU after treatment of the focal infection. Helicobacter pylori (Hp) infection affects more than a half of the world population. The heteroge- neous clinical presentation which depends on different interactions between Hp strains and host genetic differences, suggests an association with some extraintestinal diseases ranging from rosacea to scleroderma. Most recently, the possible role of Hp as a triggering factor for at least some cases of CIU has become the reality. It seems that the prevalence of Hp infection in patients with CU (24-70.58%) does not significantly differ from that in patients without Cu (25-84%). Generally, Hp infection is frequent, but regardless to its prevalence, it will probably trigger urticaria only in some (somehow predisposed) infected patients.

Hp infection was not always an occult infection in patients with CU; it led to the symptoms of chronic gastritis in all patients in one series. Recommendations to administrate antibiotic treatment for Hp infection in patients with CU should be evidence-based. It was found that resolution of urticaria was more likely when antibiotic therapy was successful in eradication of Hp. Patients with CU and Hp infection should receive the therapy for eradication of Hp, however, other possible causes of the disease should be sought and treated. After successful eradication of infection, only one third of patients with H-associated CU will be in remission; only patients who have active infection will result in resolution of urticaria; the majority of patients with the active infection will have causes unrelated to Hp.

At the present, it can be concluded that the reported association between Hp and CU is consistent with a triggering role of Hp. Every patient with CIU should be sent to a gastroenterologist. It should be kept in mind that recurrence shortly after successful therapy may be the main reason for the recurrence of urticaria.

<table>
<thead>
<tr>
<th>PATIENTS WITH COEXISTING FOCI</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAR-NOSE-THROAT AND TEETH FOCUS</td>
<td>25</td>
<td>33.8</td>
</tr>
<tr>
<td>PASS THROUGH VIRAL HEPATITIS</td>
<td>11</td>
<td>14.8</td>
</tr>
<tr>
<td>YERSINIOSIS</td>
<td>31</td>
<td>41.9</td>
</tr>
<tr>
<td>OTHER FOCI</td>
<td>20</td>
<td>27.0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>60</td>
<td>81.1</td>
</tr>
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REFERENCES:


