

Effects of *Helicobacter pylori* Eradication in Chronic Spontaneous Urticaria: Results from a Retrospective Cohort Study

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Published online: 3 September 2015
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Abstract

Background and Objective *Helicobacter pylori* (Hp) infection has been hypothesised to play a major role in the pathogenesis of chronic spontaneous urticaria (CSU). Despite only weak evidence from Hp eradication studies, screening for Hp infection is still recommended in several CSU guidelines. The aim of this study was to investigate the effect of Hp eradication in combination with standard CSU treatment in Hp-positive compared with Hp-negative patients, applying the latest guidelines for both diseases. **Methods** 138 consecutive patients with CSU were enrolled in this retrospective cohort study. All patients underwent gastroscopy and Hp status was determined by urease testing and histologic examination. Seventy-five patients were diagnosed as Hp negative and 47 patients fulfilled criteria for

definite Hp infection, 45 of whom received eradication therapy. Sixteen patients who received eradication therapy without an appropriate indication served as the medication control. All patients received symptomatic treatment with antihistamines and/or glucocorticoids regardless of Hp status. Partial response (PR) was defined as subjective amelioration of CSU symptoms; patients returning for further CSU treatment within 6 months were considered non-responders/relapsers (NRs). **Results** The prevalence of Hp infection was comparable with Hp seroprevalence data reported for healthy western populations. Standard treatment of CSU led to relief of symptoms independent of Hp status. Hp eradication by standard triple therapy had no additional effect on PR ($p = 0.32$) or NR ($p = 0.50$). **Conclusions** Hp eradication has no discernible effect on CSU beyond that of standard CSU therapy. Therefore, Hp eradication should only be initiated in accordance with currently accepted indications of Hp treatment guidelines.

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Key Points

Treatment with antihistamines and/or glucocorticoids led to an amelioration of chronic spontaneous urticaria (CSU) symptoms in nearly all patients.

CSU patients with proven *Helicobacter pylori* (Hp) infection did not benefit from eradication therapy in terms of symptom relief.

A general screening for Hp infection in CSU patients cannot be recommended and Hp eradication in infected patients with CSU symptoms as the sole indication should be abandoned.

1 Introduction

The term urticaria has been used for a heterogeneous group of diseases presenting with the appearance of angioedema and development of wheals. Mast cell activation and subsequent release of vasoactive mediators (e.g. histamine, leukotrienes and cytokines) could be identified as underlying mechanisms, yet the pathophysiologic processes leading to mast cell activation are poorly understood. Acute urticaria is defined as the spontaneous occurrence of wheals, angioedema, or both lasting for less than 6 weeks. Chronic urticaria describes the symptoms of an urticarial skin reaction that is present for more than 6 weeks, regardless of the cause [1]. To separate the inducible and often exogenous urticaria with known triggering factors (such as physical urticaria, cholinergic urticaria or aquagenic urticaria) from endogenous urticaria, the term chronic spontaneous urticaria (CSU) has been suggested [2], replacing the term chronic idiopathic urticaria to emphasise the spontaneous and non-reproducible nature of CSU. Furthermore, CSU accentuates the clinical behaviour of the disease rather than etiology and can be applied even to patients with a known or at least assumed cause. In up to 45 % of patients, CSU is associated with autoimmunity [3, 4], especially of the thyroid gland [5]. Furthermore, autoantibodies have been identified that are directed against the extracellular fragment of the high-affinity IgE receptor (FcεRI) α subunit (FcεRIα) and can result in mast cell activation and histamine release after binding [3]. A simple and generally available test to screen for autoreactivity involved in CSU is provided by the autologous serum skin test (ASST), as reported by Grattan et al. in 1986 [6]. The immunomodulatory effects observed during *Helicobacter pylori* (Hp) infection suggest that Hp participates in this autoantibody formation, e.g. growth and proliferation of CD5+ B cells is markedly increased during Hp infection and is associated with the production of autoreactive IgM and IgG3 antibodies as well as with a reduction of immune tolerance [7, 8]. A number of studies have therefore suggested that Hp infection plays a causal role in CSU and that treatment of Hp infection may induce remission [9–13]. Nevertheless, the role of Hp infection in CSU remains a matter of debate.

The aim of this study was to examine the prevalence of Hp infection and the therapeutic effect of Hp eradication in a group of German patients with CSU. To our knowledge, this is the first study applying the latest international guidelines for the diagnosis and treatment of Hp infection in patients with CSU.

2 Patients and Methods

Clinical data of consecutive patients presenting with urticaria to the outpatient clinic of the Department of Dermatology and Venerology at the University Hospital of Cologne (Cologne, Germany) between January 1998 and June 2010 who had a documented upper gastrointestinal endoscopy were analysed retrospectively. Criteria for the diagnosis of CSU were based on the EAACI/GA²LEN/EDF/WAO (European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization) guidelines [14, 15] and patients were considered to have CSU when they experienced wheals or/and angioedema occurring two or more times per week over a continuous period of >6 weeks. Other known causes of urticaria had to be excluded and eligible patients underwent a standardised diagnostic work-up at study entry including assessment of the CSU activity score (UAS) in accordance with the guidelines mentioned above. For all patients, sets of data concerning quality and duration of CSU, history of atopic diseases and gastrointestinal symptoms (pain, reflux, diarrhoea, nausea) were retrieved from clinical records. All patients received symptomatic treatment with antihistamines and/or glucocorticoids regardless of Hp status. An insufficient number of cases with objective evaluation of UAS during follow-up could be retrieved from the clinical data files. Thus, partial response (PR) was defined as subjective amelioration of intensity, duration or frequency of the urticaria based on self-assessment by the patients. Patients returning with the need for further CSU treatment within 6 months were considered as non-responders/relapsers (NRs).

2.1 Autologous Serum Skin Test

All patients were deprived of antihistamine therapy for at least 5 days prior to the ASST. The ASST was conducted as described elsewhere [16].

2.2 Assessment of *Helicobacter pylori* Infection

Patients underwent upper gastrointestinal endoscopy. Hp infection was considered as proven (1) when the rapid urease test as well as gastric biopsies were positive for Hp; and (2) in cases of duodenal ulcer when either the rapid urease test or gastric biopsies were positive for Hp.

2.3 Triple Therapy

Patients in whom Hp infection was confirmed received a 7-day treatment course of amoxicillin 1 g twice daily, clarithromycin 500 mg twice daily and pantoprazole 40 mg

twice daily (French triple therapy), or metronidazole 400 mg twice daily instead of amoxicillin (Italian triple therapy).

2.4 Statistical Analysis

Continuous data are given as mean $\pm$ standard deviation and the Kruskal-Wallis test was applied for the analysis of inter-group differences. Discrete variables were compared using the Chi-squared (χ^2) test and Fisher's exact test, when appropriate. All p values are two-tailed and a p value <0.05 was considered significant. Analyses were carried out using SPSS® statistics 22 (IBM Corp., Armonk, NY, USA). Figure 1 was constructed using GraphPad Prism software (version 5.04; GraphPad Software, La Jolla, CA, USA).

3 Results

One hundred and thirty-eight patients with documented esophagogastroduodenoscopy (EGD) were included in this study. Of the 91 patients with unproven Hp infection according to the defined diagnostic criteria, 16 patients received eradication therapy, e.g. based on a positive rapid urease test only in conjunction with macroscopic aspects of gastritis. These patients were excluded from the Hp-negative group (group 1; $n = 75$) and served as a control group to investigate the effect of triple therapy itself on the symptoms of CSU (group 3; $n = 16$). Hp infection was diagnosed in 47 cases (34.1 %), of which 45 patients received eradication therapy (group 2; $n = 45$). Two Hp-positive patients refused eradication therapy and were therefore excluded from further

analyses. The baseline characteristics of the three groups were comparable with respect to age, sex, allergic/autoimmune predisposition, abdominal symptoms and severity of CSU (see Table 1). With the exception of Hp eradication therapy, further treatment modalities, including antihistamines and corticosteroids, were also comparable (data not shown).

Symptomatic treatment with antihistamines and/or corticosteroids led to a PR in nearly all patients, with no significant differences between groups ($p = 0.33$; see Fig. 1). Independent of the initial Hp status, no beneficial effect could be detected following eradication therapy: NR after triple therapy 71.1 % (group 2) and 80 % (group 3) versus 65.2 % (group 1; $p = 0.50$). Interestingly, eradication therapy itself appeared to have a positive effect on urticaria symptoms regardless of Hp status (PR rate of 90.0 %), which was comparable to the PR rate in Hp-infected patients (97.1 %; $p = 0.32$). Eighty-four patients returned with the need for further CSU treatment after a median of 6 weeks in groups 1 ($n = 27$) and 2 ($n = 45$), and 7 weeks in group 3 ($n = 12$) [$p = 0.66$]. Also, the presence of abdominal symptoms or the initial CSU severity did not predict PR or NR following Hp eradication (data not shown) and no worsening of symptoms was observed with either of the therapies including Hp eradication.

4 Discussion

In this study, 136 patients with the diagnosis of CSU were included who underwent EGD during diagnostic work-up for CSU. In contrast to previous studies, patients were considered Hp-positive only when diagnosis and treatment of Hp infection were in accordance with current German and international guidelines [17, 18]. This led to the identification of 45 definitely Hp-infected patients who were compared to 75 Hp-negative patients. The prevalence of Hp infection in these CSU patients (34.1 %) is comparable with the overall seroprevalence of 32.5 % that has been reported for a healthy western population [19]. To investigate effects arising from the medication used for eradication therapy itself, a third group that had been treated with triple therapy despite negative results during Hp diagnostic work-up was included in this study. Unlike previous studies [11–13, 20–22], we could not detect any positive effect of Hp eradication beyond the response rates achievable with standard CSU treatment. In addition, even in patients without confirmed Hp infection, eradication therapy was associated with a PR in 90.0 % of cases. Due to its retrospective design, firm conclusions about the contribution of a placebo effect to this phenomenon cannot be drawn from our study. Anti-inflammatory and immunomodulatory effects of macrolides have been

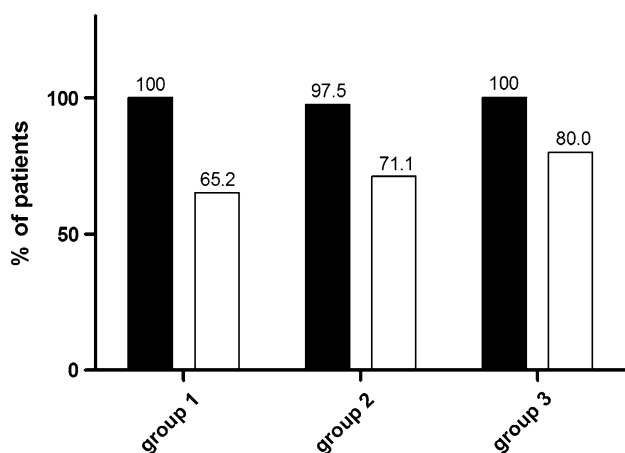


Fig. 1 Response to treatment: percentage of patients with a self-assessed partial response (black bars) and percentage of patients returning for additional treatment within 6 months (non-response/relapse; white bars) in the study groups. No significant difference in response rates could be detected following *Helicobacter pylori* eradication therapy. Group 1: *H. pylori* negative without eradication therapy; group 2: *H. pylori* positive and eradication therapy; group 3: *H. pylori* negative and eradication therapy

Table 1 Patient characteristics

Characteristics	Hp negative without eradication therapy (group 1; <i>n</i> = 75)	Hp positive and eradication therapy (group 2; <i>n</i> = 45)	Hp negative and eradication therapy (group 3; <i>n</i> = 16)	<i>p</i> value
Sex, female	48 (64.0)	23 (51.1)	12 (75.0)	0.18
Age (years); mean $\pm$ SD	46.0 $\pm$ 14.8	43.3 $\pm$ 14.3	42.0 $\pm$ 13.4	0.63
ASST positive	11 (14.7)	6 (13.3)	3 (18.8)	0.79
Overall IgE (kU/L); mean $\pm$ SD	187.4 $\pm$ 282.3	153.0 $\pm$ 124.0	143.6 $\pm$ 136.7	0.52
History of thyroid disease	16 (21.3)	5 (11.1)	1 (6.3)	0.15
Allergic disposition				
Food allergy	17 (22.7)	13 (28.9)	1 (6.3)	0.14
Allergic rhinitis	15 (20.0)	5 (11.1)	4 (25.0)	0.37
Allergic drug reaction	11 (14.7)	9 (20.0)	2 (12.5)	0.66
Angioedema	52 (69.3)	28 (62.2)	11 (68.8)	0.76
Urticaria activity score; mean (range)	3 (1–6)	3 (1–5)	4 (1–5)	0.08
Abdominal discomfort	23 (30.7)	25 (55.6)	5 (31.3)	0.29

Data are presented as *n* (%) unless otherwise stated

ASST autologous serum skin test, *Hp* *Helicobacter pylori*, SD standard deviation

described [23]; however, coincidental successful treatment of an undetected infection following *Hp* eradication therapy could be another explanation, since latent infections are considered to be a triggering factor for CSU [24].

For more than a decade, studies have suggested a relationship between *Hp* infection and chronic urticaria [9–13], but this connection remains an issue of considerable debate. Autoimmune mechanisms are well-accepted to be involved in the pathogenesis of CSU: at least 30 % of CSU patients have an autoimmune aetiology and peak incidence is found in the fourth decade, consistent with the epidemiology of other autoimmune disorders [25]. The pathophysiological mechanisms by which *Hp* could be capable of inducing urticaria are still unknown. It has been suggested that *Hp*-associated lipoprotein 20 (lpp20) could act as an antigen that is involved in molecular mimicry to mast cell molecules. For instance, significantly higher levels of lpp20 antibody titers have been described in patients with CSU than in *Hp*-positive patients without CSU [26]. This hypothesis is further supported by the findings of Yamanishi et al. [7] and Amedei et al. [27], who found that molecular mimicry of *Hp* is able to activate cross-reactive T cells as well as B cells, leading to autoimmunity in genetically susceptible individuals. Despite these experimental approaches, data also exist showing no correlation of *Hp* infection/*Hp* eradication and CSU [28–33], and high-quality randomised controlled trials are still lacking. In their meta-analysis, Shakouri et al. [34] emphasised the limited number of studies with clearly defined endpoints such as definitions of complete response and PR as well as *Hp* infection criteria [34]. Based on the available data, the authors could not find any evidence that

routine *Hp* eradication in patients with chronic urticaria improves the outcome. Thus, it is surprising that screening for *Hp* infection is still recommended by current guidelines [14, 24], especially since a negative effect of eradication therapy on CSU development has recently been reported [35].

This study has several limitations, mainly related to its retrospective design. To warrant valuable conclusions, only items for which >75 % of individual data were available from the clinical records were analysed. Amelioration of CSU symptoms, and hence the definition of PR, had to be based on patient self-assessment since an insufficient number of cases with objective evaluation of CSU symptoms using the UAS could be retrieved from the clinical data files. Assuming that patients who had experienced relief following the initial treatment from their CSU symptoms would have returned in the case of recurrence, the non-returning patients (within 6 months) could be considered as potential complete responders (PCRs). Of course there are other explanations for relapsing patients not returning, e.g. moving to another region, dissatisfaction with the treatment centre/staff or mild disease. However, there was no difference in initial CSU symptom severity between returning and non-returning patients. Even if all non-returning patients are considered PCRs, the rate of non-returning patient did not differ among patients with and without proven *Hp* infection or with and without *Hp* eradication therapy. Unfortunately, a control EGD to confirm eradication success was performed in only 17.8 % of the group with definite *Hp* infection; however, these patients all tested negative for *Hp* after eradication therapy. Given the low resistance rates of *Hp* against clarithromycin

of 2.5 %, as reported recently by Selgrad et al. [36], we can assume eradication therapy was successful for the vast majority of our patients even without confirmation.

5 Conclusions

Patients with CSU do not benefit from Hp eradication therapy even in cases of confirmed infection with or without abdominal symptoms. Based on our findings, screening for Hp infection in CSU patients no longer seems justified.

Compliance with Ethical Standards

Funding No sources of funding were used to assist in the preparation of this study.

Conflict of interest H.-M. Curth, J. Dinter, K. Nigemeier, F. Kuetting, N. Hunzelmann and H.-M. Steffen declare that they have no conflicts of interest relevant to the content of this manuscript

Ethical approval Written informed consent from the participants and a consent of the local ethics committee were not obtained. In accordance with German law, a votum of a local ethics committee is not required to conduct strictly retrospective studies (paragraph 15, sentence 1, Nordrhein Medical Association's professional code of conduct from 14 November 1998 as amended on 19 November 2011). There is also no need to get written informed consent from the participants if the considered data was collected and analysed retrospectively (paragraph 6, sentence 1, Health Data Protection Act of Nordrhein-Westfalen).

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