

Role of *Helicobacter pylori* Infection in the Treatment and Outcome of Chronic Urticaria

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Abstract

Introduction: Chronic urticaria is thought to have numerous causative factors including a large variety of infectious conditions, food intake, and drugs. The impact of *Helicobacter pylori* infection has been studied with ambiguous results. The aim of this study was to investigate the course of chronic urticaria in *H. pylori*-positive patients undergoing eradication compared to *H. pylori*-negative urticaria patients.

Patients and Methods: We included 74 urticaria patients with positive *H. pylori* breath test and 74 age- and sex-matched *H. pylori*-negative controls. All urticaria patients underwent an extensive diagnostic work-up to search for trigger foci. *H. pylori*-infected patients were submitted to eradication therapy. Mean follow-up time was 58 months.

Results: Neither the prevalence of *H. pylori* nor the eradication therapy had an influence on the clinical course of chronic urticaria. In 81.1% of *H. pylori*-infected patients at least one additional infectious focus was found. Nevertheless, it could be shown that individuals that described any kind of symptom relief presented with higher serum IgE levels at diagnosis (198.1 vs 115.7 kU/L, $p = .027$) but this effect was independent of *H. pylori* infection.

Conclusions: In conclusion there is no evidence that eradication of *H. pylori* improves the outcome in patients with chronic urticaria. The high rate of spontaneous remission and the coexistence of multiple foci will always obscure the evaluation of any specific antimicrobial therapy.

Urticaria is characterized by the rapid appearance of wheals and/or angioedema. Chronic urticaria is defined as chronic recurrent wheals for more than 6 weeks together with a significant disturbance of the daily life [1]. About 20–25% of the general population will experience an episode of acute urticaria once in their life and one fourth of these cases will transform to a chronic disease [2]. In the case of coexisting angioedema, 75% of the patients will develop chronic urticaria for more than 5 years. The natural course will lead to a spontaneous healing in 6% of the cases if the symptoms persisted for more than 6 months. Other studies revealed even higher rates of spontaneous healing up to 50% [3].

Chronic urticaria may have numerous causative factors but in one third of the cases the origin remains unclear. A large variety of infectious conditions were found to coexist with chronic urticaria. *H. pylori* infection is the most

frequent bacterial infection affecting more than half of the world's population [4]. The bacterium is the main cause of gastroduodenal ulcer disease and plays an important role in gastric carcinogenesis and the development of primary gastric B-cell lymphoma. Besides gastroenterologic diseases *H. pylori* may be involved in extraintestinal diseases especially diseases of the skin-like rosacea [5], Sjögren's syndrome [6], purpura Schönlein Hennoch [7], and chronic recurrent urticaria [8].

In this content it is obvious that *H. pylori* infection has to be taken into consideration as a trigger factor.

The aim of this study was to investigate the role of *H. pylori* infection in the treatment and course of chronic urticaria. In detail the question should be answered if the course of chronic urticaria is different in *H. pylori*-positive patients undergoing eradication compared to *H. pylori*-negative patients.

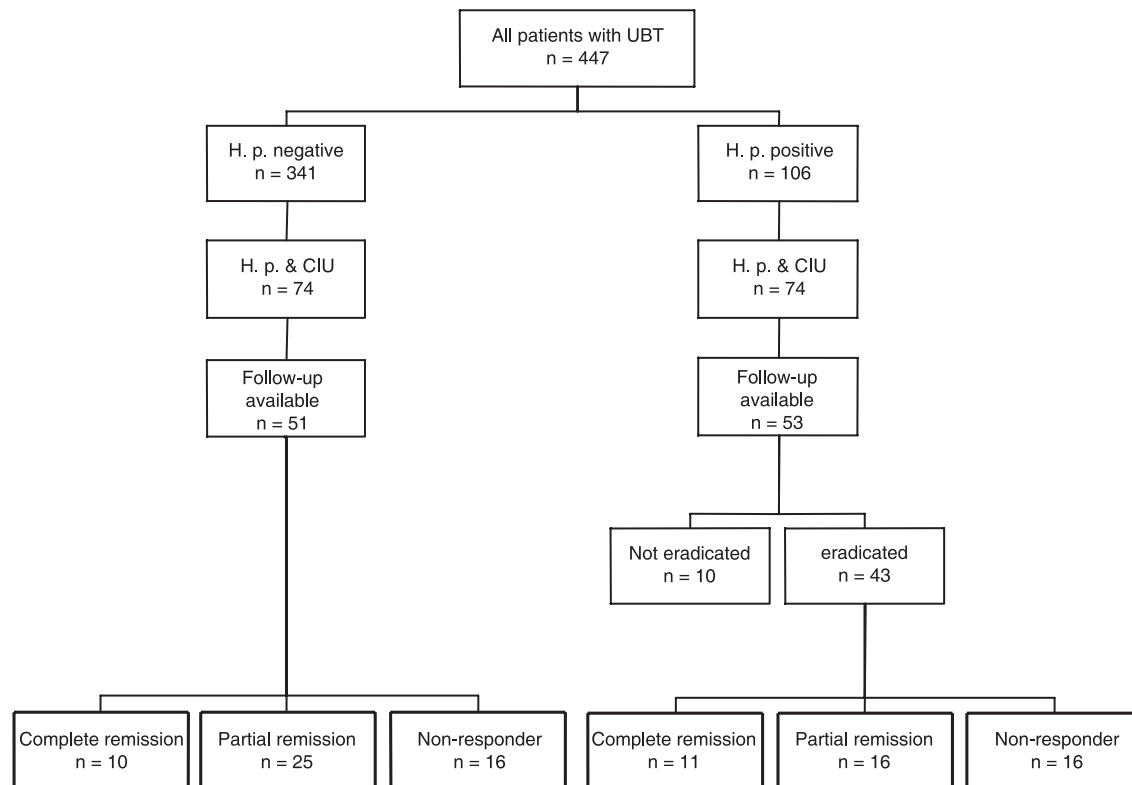


Figure 1 Patient recruitment and follow up. UBT, urease breath test; H. p., *Helicobacter pylori*; CIU, chronic idiopathic urticaria.

Patients and Methods

Patients

Patients were recruited in the Department of General Internal Medicine and the Department of Dermatology of the University Hospital of Schleswig-Holstein, Campus Kiel. The patients were hospitalized for a standardized diagnostic work-up for chronic urticaria in the Department of Dermatology. The work-up included an *H. pylori* urea breath test which was conducted in the Laboratory for Clinical Gastroenterology within the Department of General Internal Medicine. Patients were identified using the charts of the breath test laboratory (Fig. 1). Only patients with undoubtful results from January 1999 to December 2004 were included. In total, 106 *H. pylori*-positive and 341 *H. pylori*-negative patients were identified. After reviewing the patients charts in the Department of Dermatology, 74 *H. pylori*-positive patients (32% males, mean age 44 years, range 14–81 years) were identified who met the criteria for chronic urticaria as described above. In a second step an age- and sex-matched control group of 74 *H. pylori*-negative urticaria patients was selected. All patients underwent an extensive diagnostic

work-up including history, clinical, and laboratory examinations.

H. pylori Breath Test

The prevalence of *H. pylori* infection was tested using the ^{13}C urea breath test (UBT) (IRIS®, Firma Wagner, Bremen, Germany) in the laboratory of Clinical Gastroenterology in the Department of General Internal Medicine. *H. pylori* metabolizes ^{13}C labeled urea after ingestion using his enzyme urease. Subsequent ^{13}C labeled CO_2 can be detected in the breath. The change of ^{13}C concentration correlates with the presence of *H. pylori* within the gastric mucosa. Sensitivity and specificity of the ^{13}C UBT is estimated to be 90%.

After 12 h of fasting 75 mg of labeled urea dispensed in 200 mL of water is ingested. The first probe will be taken at the beginning of the test to estimate the zero value. A second probe is taken 30 minutes after the ingestion of the tracer. The $^{13}\text{C}/^{12}\text{C}$ ratio (delta value) was measured by mass spectroscopy. A change of more than 4.5‰ is defined as active *H. pylori* infection. Changes lower than 2.5‰ exclude an *H. pylori* infection. Patients with changes between 2.5 and 4.5‰ were advised to repeat the test and were not included in this study.

Follow Up

In total 50 of 74 *H. pylori*-positive patients underwent eradication therapy during their hospitalization. In 24 patients, urticaria symptoms were not present at dismissal, and eradication treatment was advised if recurrence of the symptoms occurred. Thus, all 148 patients were contacted by telephone between July 1, and August 15, 2006 to get the necessary information. The mean follow-up time for all patients was 58 months (60 months in the *H. pylori*-positive group and 53 months in the *H. pylori*-negative group)

The following questions were asked: 1, Did you receive eradication therapy after the hospital stay? 2, Did the urticaria vanish after eradication? 3, Are you completely free of symptoms, is the intensity or duration reduced or has nothing changed?

Complete remission was defined as no symptoms until the date of the interview. Partial remission was defined as reduced intensity, duration, or frequency of the urticaria episodes. If the patients reported no change in intensity, duration, or frequency of episodes they were classified as nonresponder. Patients who could not be contacted by telephone were contacted by mail. Thus, follow-up data of 53 *H. pylori*-positive and 51 *H. pylori*-negative patients were obtained. In total 43 of 53 (81.1%) patients tested positive received eradication therapy. All 74 *H. pylori*-positive patients were invited to a second UBT to proof the eradication. Only 20 patients were willing to undergo a second UBT. Sixteen of 18 *H. pylori*-positive patients (88.9%) who received eradication therapy were negative for *H. pylori* infection. Two *H. pylori*-positive patients, who did not undergo eradication, were tested positive again in the second UBT.

Data Collection and Management

Data were collected from the patients' charts of both Departments and merged in an Excel file. For this study the following parameters were extracted: age, gender, duration of symptoms before diagnosis, *H. pylori* and eradication status, course of the disease according to follow up, prevalence of allergies divided into drugs, food, animals, dust and hay fever, other foci than *H. pylori* infection divided into ear, nose, throat, and teeth, hepatitis, other bacterial infections, drug therapy before and after hospitalization, differential blood cell count, serum IgE levels, and C-reactive protein (CRP).

Statistical Analysis

Statistical analysis was carried out using the program Statistical Package for the Social Sciences (SPSS) Version

8.0 for Windows (SPSS GmbH Software, München, Germany). *t*-test was used for the equality of means of two independent samples after Levene's test for equality of variances was applied. Distribution of categorical variables was compared using Pearson's χ^2 test. Level of significance was set to $p < .05$.

Results

Influence of *H. pylori* Infection

Mean age of *H. pylori*-positive patients was 44.4 years (32.4% male), comparable to *H. pylori*-negative patients with a mean age of 43.6 years with the same distribution of gender.

Neither the prevalence nor the eradication therapy if active *H. pylori* infection was confirmed in UBT had an influence on the clinical course of chronic urticaria ($p > .05$) (Table 1). *H. pylori*-infected patients suffered from urticaria before diagnosis as long as *H. pylori*-negative patients did (26.3 vs 38.4 months, $p > .05$). Furthermore there was no significant difference in differentiated blood cell count (data not shown) and IgE levels (169.7 vs 164.6 kU/L, $p > .05$).

Interestingly, *H. pylori*-negative patients had higher levels of CRP (11.0 vs 6.1 mg/L, $p = .009$) and suffered more frequently from allergies (47.3 vs 31.1%, $p = .043$) compared to *H. pylori*-positive patients.

Coexistent Foci in *H. pylori*-Infected Patients

Interestingly, only in 14 of 74 *H. pylori*-positive patients no other infectious focus was found. In total, 31 patients had proof of specific antibodies against *Yersinia enterocolitica* (IgG), 25 patients had evidence for infections of ear, nose,

Table 1 Clinical course of urticaria according to *H. pylori* and eradication status

		Clinical course of urticaria			
		Complete remission	Partial remission	Nonresponder	Total
<i>H. pylori</i> status	Negative	n 10	25	16	51
	%	20%	49%	31%	49%
Positive	n 11	16	16	16	43
	%	26%	37%	37%	41%
Eradicated	n 1	6	3	10	10
	%	10%	60%	30%	10%
Not eradicated	n 22	47	35	104	104
	%	21%	45%	34%	100%

throat, and teeth; 11 patients had serologic evidence of passed through hepatitis; and 20 patients presented with other infectious foci. The mean number of infectious foci other than *H. pylori* infection was 1.24 per patient. Thus, in 81.1% of *H. pylori*-infected patients at least one additional infectious focus was found.

Influence of Gender

There were no gender-specific differences in the clinical course of urticaria, duration of symptoms before diagnosis, or prevalence of foci or allergies (data not shown). Male patients showed significant higher serum IgE level than female patients (246.0 vs 130.5 kU/L, $p = .022$).

Differences Between Responder and Nonresponder

Patients who experienced complete remission had a mean duration of symptoms before diagnosis of 16.5 months, patients with partial remission of 54.5 months, and nonresponders of 30.5 months. These differences did not reach statistical significance. Nevertheless, it could be shown that individuals that described any kind of symptom relief presented with higher serum IgE levels at diagnosis (198.1 vs 115.7 kU/L, $p = .027$). There were no differences in prevalence of allergies and foci or other laboratory values (data not shown).

Discussion

The role of *H. pylori* infection in the pathogenesis of chronic urticaria has been discussed for more than 18 years with ambiguous results. Initial studies reported rates of remission of nearly 100% after eradication [9,10]. To date there are only observational studies that report an effect of *H. pylori* eradication [11–13]. In these studies uncommon antibiotic therapies, small patient numbers, and missing control groups obscure the interpretation. In a double-blind placebo-controlled cross-over study, Schnyder et al. treated *H. pylori*-infected urticaria patients with amoxicillin and lansoprazole [14]. The number of *H. pylori*-infected patients included was 12 and the follow up was only 6 months. However, no association between *H. pylori* infection and chronic urticaria could be found, taking into consideration that only three patients were eradicated successfully. Gaig et al. conducted a placebo-controlled treatment trial in 20 *H. pylori*-positive urticaria patients. There were no significant differences between verum and placebo group concerning the outcome [15]. Moreover, the small number of patients included led to low power of the studies [8].

In our study, we compared an *H. pylori*-infected group of patients with chronic urticaria to an age- and sex-matched

H. pylori-negative control group. There was no significant difference concerning the outcome of the two groups.

H. pylori-infected patients showed a lower rate of concomitant allergies compared to negative patients. This data is in agreement with a cross-sectional study of the prevalence of three atopic disorders in 3244 subjects participating in a community-based, prospective, randomized, controlled trial of *H. pylori* eradication. The prevalence of asthma, eczema, and allergic rhinitis was reduced by about 30% in individuals with active *H. pylori* infection [16]. This finding could be explained by the fact that the prevalence of *H. pylori* infection is mainly dependent on the socio-economical status and the hygienic conditions. In addition it is known that a high hygienic standard is a risk factor for the development of allergies. One could speculate that *H. pylori* infection comes along with an intensive exposition to antigens in childhood, what itself may be a protective factor for an allergic predisposition [17].

In our study, *H. pylori*-infected patients presented with lower levels of CRP than *H. pylori*-negative patients. Saribas et al. investigated the role of CRP in the diagnosis and follow up of *H. pylori* infections. The authors concluded that even if CRP levels at admission were higher in *H. pylori*-positive than *H. pylori*-negative patients, CRP is not a very effective marker for *H. pylori* infection in primary diagnosis or in eradication follow up [18]. In a cross-sectional survey of a large national sample, the Third National Health and Nutrition Examination Survey, *H. pylori* infection was not correlated with serum CRP level [19]. The higher level of CRP in *H. pylori*-negative individuals in our study may be a hint towards other infectious foci in these patients.

Interestingly, in 81.1% of *H. pylori*-infected patients at least one additional infectious focus was found. Although some infectious trigger foci like pass through viral hepatitis will not be affected by antibiotic therapy, the administration of two antibiotics for 7 days for eradication will obviously eliminate most of the infectious foci that coexisted in the ear, nose, throat, and teeth. Thus, there is no way to purify the effect of antibiotic elimination of an active *H. pylori* infection on the course of chronic urticaria.

Initial IgE levels seem to have an impact on the outcome of chronic urticaria rather than *H. pylori* infection. We could show that individuals who experience a relief of symptoms during follow up present with significantly higher IgE level at diagnosis than nonresponders independent of *H. pylori* status.

Looking at our results, some facts have to be taken into consideration. Like any other interventional study in patients with chronic urticaria we have to deal with a high rate of spontaneous remission up to 50% in 6 months [20]. Time between eradication and follow up was least 12 months in our study. For follow up, we were subjected

to the personal impression of the patients concerning intensity and frequency of symptoms.

In conclusion there is no evidence that eradication of *H. pylori* improves the outcome in patients with chronic urticaria. The high rate of spontaneous remission and the coexistence of multiple foci will always obscure the evaluation of any specific antimicrobial therapy.

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