

Helicobacter pylori infection in patients with chronic urticaria and dyspepsia, experience from a developing country

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Abstract *Objective* To determine *Helicobacter pylori* infection using stool antigen assays and *H pylori* IgM antibodies in patients having chronic urticaria and dyspepsia.

Methods This descriptive, cross-sectional study was conducted at Department of Dermatology and Department of Pathology, Fauji Foundation Hospital, Rawalpindi from May 2014 to April 2015. By non-probability purposive sampling technique, 87 patients diagnosed as having chronic urticaria and each patient having symptoms of gastritis were tested for *H pylori* infection using the monoclonal *H pylori* fecal antigen assay (Biotec®, Spain) and serological test for presence of IgM antibodies (acute infection). Patients infected with HP were given triple regimen comprising of omeprazole 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, twice daily for 10 days. HP eradication was assessed by monoclonal fecal antigen assay after 4 weeks. Beneficial effect was determined by subjective response to treatment and improvement in urticarial symptoms by using chronic urticaria quality-of-life questionnaire (CU-Q2oL) while objective response to treatment was judged by need for antihistamine medication post eradication.

Results Stool antigen was positive for *H pylori* in 52 (59.8 %) and IgM antibodies were present in 63 (72.4%) of patients with chronic urticaria and dyspepsia. After antibacterial therapy, there were 40 of 52 stool samples became negative, among them the remission of urticaria and dyspepsia was observed in 39 (75%). There were 50/63 (79.4%) *H pylori* IgM positive patients who responded to triple regimen therapy, when eradication was considered by objective improvement in urticaria and gastritis symptoms. However, when stool antigen along with serum IgM were considered simultaneously, there was 80% (52/65) remission response after the treatment ($P = 0.0001$). CU-Q2oL for patients who received specific treatment revealed significant improvement ($P = 0.0001$) while patients without specific treatment revealed no change ($P=0.1$).

Conclusion Urticaria and dyspepsia are associated with *H. pylori* infection and presence of this organism in such cases can be detected with confidence by using non invasive, sensitive, specific and cheaper techniques like stool *H. pylori* antigen and serum *H. pylori* IgM antibodies. This is particularly true in developing countries like ours where because of financial constraints, invasive techniques like gastric antral biopsy, biopsy urease test and costly noninvasive urea breath test are difficult to perform. The response of HP eradication therapy in infected patients of CU is significant and HP detection should be included in the diagnostic work up of all patients with CU and dyspepsia. However, due to intermittent shedding of the microorganism in feces, HpSA declared negative, before eradication treatment in patients with strong suspicion of H pylori should be repeated again to be certain of the diagnosis.

Key words

Helicobacter pylori infection, chronic urticaria, *H. pylori* IgM antibodies, *H. pylori* stool antigen.

Introduction

The chronic urticaria (CU) is a condition characterized by the spontaneous appearance of hives and/or angioedema for at least 6 weeks, which has impact on the patient's quality of life.¹ Possible eliciting factors of CU revealed focal infection as the etiology of urticaria in 43% of the patients, out of which *Helicobacter pylori* (HP) was responsible for 60%.² Recent observations have suggested a possible causative role of HP in few cases of CU.³ A possible association between HP gastritis and chronic urticaria currently remains to be confirmed by double-blind studies of eradication therapy. An indirect role for *H. pylori* by evoking autoantibody production through molecular mimicry has been proposed lately.⁴

At present, there are no studies on the prevalence of HP infection in patients with CU and gastritis symptoms compared with the non-urticaria control group in the Pakistani population in general.⁵ At the same time there are no local studies to determine the use of noninvasive HpSA test and IgM antibodies in patients of chronic urticaria with gastritis symptoms before and after eradication therapy. The present study was undertaken to ascertain the correlation between *H. pylori* and CU by using HpSA assays and to assess the response to treatment.

HP infection has been implicated as having a causative role in CU and although their association has not been definitely established, eradication of *H. pylori* treatment mostly leads to symptom resolution. This may be due to the different tests used for detection of HP infection or recurrences shortly after successful therapy.^{6,7}

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Laboratory tests available to confirm presence of *H. pylori* include invasive and expensive tests like endoscopic biopsy of gastric mucosa for histologic staining, culture and rapid urease test.⁴ The non-invasive tests include radiolabeled 13C-urea breath test, detection of serum antibodies against *H. pylori* and an enzyme immunoassay (EIA) based HpSA assay. Although identification of this Gram-negative, microaerophilic bacterium from gastric biopsy specimens and 13C-urea breath test has higher sensitivities and specificities, these test require direct observation, trained staff and expensive instruments. This is because in our set-up due to financial constraints, invasive and expensive techniques like gastric biopsy and biopsy urease test and noninvasive urea breath test are difficult to perform.

Since most patients with CU and gastritis are dealt with initially by a general practitioner or a dermatologist, valid and reliable noninvasive tests with logistic ease are of prime importance for diagnosing *H. pylori* infection. This is also important as prevalence of *H. pylori* is higher in developing countries.^{4,5}

The Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) is an instrument that was specifically developed to assess quality of life in patients with CU.^{8,9} It is a self-administered 23-item questionnaire, where patients have to indicate, on a Likert scale with multiple options (1 means not at all; whereas 5 means very much) as to how much each problem has troubled them, with higher scores indicating worse quality of life. The CU-Q2 oL can be used in routine clinical practice to measure quality of life in patients with CU.^{10,11}

The detection of *H. pylori* in stools highlighted the possibility of stool-based diagnostic assays.¹² A direct antigen test can differentiate between an active, as well as, latent infection; whereas,

serology only detects exposure. The HpSAg is FDA-approved for diagnosis of active infection in symptomatic patients and monitoring effectiveness of antibiotic therapy during the 14 days of treatment.^{13,14} Several studies have recently shown that the HpSA test is comparable to other noninvasive tests for initial diagnosis of *H. pylori* infection.¹³⁻¹⁵ However, as far as monitoring the efficacy of eradication treatment is concerned, the results were equivocal.^{16,17} A negative end result would indicate that the therapy has eliminated or reduced infection below the level of detection, although eradication cannot be confirmed (at this point).¹⁸ By comparing HpSA test results to IgM antibodies, we attempted to confirm the validity of each for diagnosis and posttreatment follow-up in patients in an area having a high prevalence of *H. pylori*. The aim of the present study was to ascertain the diagnostic value of the *H. pylori* stool antigen (HpSA) test and IgM antibodies in patients of chronic urticaria with gastritis symptoms before and after eradication therapy.

Methods

This descriptive, cross-sectional study was conducted at Department of Dermatology in collaboration with Department of Pathology, Fauji Foundation Hospital, Rawalpindi from May 2014 to April 2015.

Eighty-seven patients of CU (urticaria of >6 weeks duration) and symptoms of gastritis attending the dermatology outpatient were enrolled by using non-probability convenient sampling technique. No discrimination was made on the basis of age and sex of the patients. The patients suffering from physical urticaria, pregnant females, patients less than 14 and greater than 65 years of age, patients who had taken proton pump inhibitors or antibiotics within the last 4 weeks or bismuth containing

compounds during previous four weeks or patients with history of gastric surgery were excluded from the study.

All the patients (n=87) diagnosed as having chronic urticaria with symptoms of gastritis (nausea and vomiting, a feeling of fullness in upper abdomen/ bloating, abdominal pain or indigestion) were tested for *H. pylori* infection. This was done by using the monoclonal *H. pylori* fecal antigen assay (CerTest HpSA kit, Biotec®, Spain) was used for stool antigen detection as per the manufacturer instructions, which has a sensitivity of 94% and specificity of 100% and is an effective alternative to urea breath test¹⁹ and serological test for presence of IgM antibodies (acute infection).

Pretreatment screening tests for every patient included complete history, physical examination and laboratory workup: complete blood count, total eosinophil count, complete urine exam, liver function test, renal function test, serum test for hepatitis B and C, and thyroid stimulating hormone (TSH). In addition we examined the therapeutic efficacy of antibacterial therapy for eradication of *H. pylori* infection who had positive tests for either stool antigen or IgM antibodies or both. All patients of CU who accepted treatment based on informed consent were enrolled for the study.

IgM antibodies were determined using the ELISA test kit (Tishta-TEB®, Germany). The stool sample from each patient was stored at 2-8°C for up to 24 hours or at -70°C if prolonged storage was required till the completion of given test batch. The thawing of the specimens was done by keeping them at 37°C for 1 hour. Patients infected with HP were given triple regimen comprising of omeprazole 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, twice daily for 10 days. HP eradication was assessed by monoclonal fecal antigen assay. If

HP infection persisted after first-line treatment, patients were offered second-line therapy, comprising of amoxicillin 1000 mg, omeprazole 20 mg and metronidazole 500 mg, twice a day for another 7 days. Noninfected patients were treated with antihistamines only and as and when required. During the study duration of 3 months, all patients were kept in follow-up. An impact of urticaria on quality of life of each patient was judged by (CU-Q2 oL) questionnaire before and after therapy, and the results were compared statistically.

HP eradication was assessed by monoclonal fecal antigen assay after 4 weeks of completion of eradication therapy and by observing beneficial effect by subjective improvement in urticarial symptoms and gastritis and decrease in dependency on antihistamines post eradication.

SPSS 21 was used for statistical analysis.

Results

Out of 87 chronic urticaria patients, 73 (83.9%) were females and 14 (16.1 %) were males with a male to female ratio of 1:3. Mean age of patients was 34.94±14.95 years and ranged between 14-65 years while duration of disease ranged from 2 to 120 months with a mean of 19 ± 26 months. Stool antigen was positive in 52 (59.8%) and IgM antibodies were present in 63 (72.4%) of CU patients with dyspepsia. There were two patients with positive stool antigen but IgM antibodies were negative showing statistically insignificant difference ($P=0.731$) for CU patients presenting with symptoms of gastritis.

After antibacterial therapy, 40 out of 52 stool samples were negative, among them the remission of urticaria and dyspepsia was observed in 39 (75%). Among the rest of 12, there were 5 patients whose symptoms did not improve. However, in 7 patients, where stool

Table 1 Diagnosis and response to treatment of patients with *Helicobacter pylori* infection associated with urticaria and gastritis (n=87).

<i>Helicobacter pylori</i> detection procedure	Number of patients showing positive results	Number of patients responded* to treatment**
Stool Antigen Assay	52 (59.8%)	39 (75%)
IgM antibodies	63 (72.4%)	50 (79.4%)
Stool Antigen + IgM antibodies	65 (74.7%)	52 (80%)

*Eradication response was considered by cure of the urticaria and gastritis symptoms.

**First-line triple regimen comprising of omeprazole 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, twice a day for 10 days or second line regimen comprising of omeprazole 20 mg, amoxicillin 1000 mg, metronidazole 500 mg, twice a day for another 7 days

Table 2 Contingency table to calculate sensitivity (true positive rate) and specificity (true negative rate) of HpSA* test in relation to remission of urticaria and dyspepsia after therapy.

<i>HpSA</i> * test after therapy	Objective therapeutic response		Total
	Present	Not Present	
Negative	39	1	40
Positive	7	5	12
Total	46	6	52

* HpSA *Helicobacter pylori* stool antigen.

tests were positive for HP after completion of eradication therapy symptoms of urticaria did improve. Thus true positive rate was 84.8% and true negative rate was 83.3% and Matthew's correlation coefficient was 0.5165 (**Table 2**). There were 50 (79.3%) *H. pylori* IgM positive patients who responded with improvement of urticaria and dyspepsia symptoms to triple regimen out of total 63 HP IgM antibodies positive cases. When stool antigen and serum IgM were considered simultaneously there was 80% (52/65) objective remission rate in urticaria and gastritis in post eradication period - **Table 1** (2 patients were those who had HpSA positive but Hp IgM was negative). When data from both the tests was combined, true positive rate was

Table 3 Response to treatment.

	n	Subjective response to treatment (CU-Q ₂ oL)			Confidence interval	P value
		Pre-treatment (mean ± SD)	Post-treatment (mean ± SD)	Mean Change (mean ± SD)		
<i>H. pylori</i> eradication treatment given	65	72.12 ± 9.93	43.43 ± 8.00	28.68 ± 4.58	28.65, 28.72	0.0001
Antihistamine treatment given	22	70.19 ± 7.93	66.22 ± 7.766	3.97 ± 0.17	7.28, 7.70	0.1

88.1% and true negative rate was 83.3% and Matthew's correlation coefficient was 0.5332 reflecting moderate correlation (**Table 2**).

It is difficult to predict eradication of infection by *H. pylori* IgM antibodies as the antibodies may remain in blood even after the clearance of organisms (antigens) from the body. Therefore, eradication was considered by objective improvement in urticaria and gastritis symptoms. 50 (76.9%) infected patients achieved eradication with first-line therapy while 15 (23.1%) patients required second-line therapy for eradication. As far as subjective improvement was concerned, patients of CU (positive for either of the two tests or both) who received eradication treatment n=65, had a mean pretreatment CU-Q₂ oL score of 72.12 ± 9.93, mean post treatment score of 43.43 ± 8.00 (mean change 28.68 ± 4.58), which was statistically significant, *P* = 0.0001 (5% confidence interval at (28.65, 28,72). Whereas patients of CU (negative for either of the tests) who received only antihistamines n=22, had a mean pretreatment CU-Q₂ oL score of 70.19 ± 7.93, mean posttreatment score of 66.22 ± 7.766 (mean change 3.97 ± 0.17), which was statistically insignificant, *P* = 0.1, 5% confidence interval at 7.28, 7.70, **Table 3**.

Discussion

H. pylori is now known to be associated with many gastrointestinal disorders, ranging from chronic gastritis to gastric lymphoma and adenocarcinoma and chronic urticaria. *H. pylori*

infection should be considered in the differential diagnosis of patients with upper gastrointestinal problems with urticaria and can be determined by noninvasive tests using serology and carbon isotope-urea breath tests (UBT), or by endoscopic biopsy for rapid urease testing, histopathology with special stains and culture.²⁰ Serology and whole blood tests are widely available and relatively inexpensive, the UBT is more sensitive and specific, and is well-suited for monitoring the treatment response as it determines the load of active bacteria. The test, however, is more expensive and requires specialized and expensive equipment for mass spectrometry.

The *H. pylori* fecal antigen detection by enzyme immunoassay is now a well-recognized noninvasive test. The test has been approved by the U.S. Food and Drug Administration for diagnosing *H. pylori* infection before and after therapy.²¹

HP infection has a causative role in chronic urticaria and treatment often leads to symptom remission although there is discrepancy in causal association in several studies. This may be due to the different methods used for detection of HP infection or recurrences after successful treatment

Studies on the prevalence of HP infection in several countries among CU patients showed conflicting results between 10-39%²² and 47-67%.^{2,23} This was probably due to various HP infection identification methods used and

geographic differences. Most studies used serologic tests (IgG, IgA or both) to identify HP infection, which could not determine active HP infection.²⁴ But none used *H. pylori* specific IgM antibodies as in our study. Only one study was done in a developing country using UBT to identify HP infection in CU patients, by Ghazzawi *et al.*⁹ where HP infection was found in 87 (87%) patients but the control group in that study did not undergo UBT but used serologic test instead.

Federman *et al.*²⁴ reviewed ten studies where the combined data showed that the rate of remission of urticaria after *H. pylori* eradication was 30.9% compared to 21.7% when *H. pylori* was not eradicated i.e. eradication of *H. pylori* was both quantitatively and statistically associated with remission of urticarial ($P < 0.005$).

Weingart *et al.*¹² used monoclonal stool antigen test which showed diagnostic sensitivity equal to that of the UBT i.e. 96.2% prior to treatment and sensitivity 94.3% post eradication treatment. This supports our and other such studies^{18,20,25,26} advocating HpSA assays as noninvasive alternative approach to diagnose adults and children in outpatients with suspected *H. pylori* infection and to monitor the success of eradication treatment.²⁷

The stool assay is shown to be highly sensitive in our study i.e. 59.8% (n=52). However, the reason for false negative tests may be due to intermittent shedding of the bacterial antigen in the stool and in our setting, patients are frequently prescribed antimicrobials by the general practitioners. It was not possible to exclude these cases who might have used such medicines without knowledge. Moreover, false negative tests may be due to low load of *H. pylori* antigen in loose stool specimens and in stool samples mixed with blood.

As reported in literature, the *H. pylori* infection detection by the IgM antibodies against *H. pylori* is frequent in patients with chronic urticaria, which is important as it could be implied in the diagnosis and treatment.²⁸ The stool antigen and *H. pylori* IgM antibodies tests, however, should be considered, especially when urea breath testing is not available as is the case in our setup.

Experience with HpSA for the identification of *H. pylori* antigens in fecal samples is wide with use of monoclonal anti-*H. pylori* antibodies and has shown good diagnostic performance in diagnosing or evaluating the success of eradication therapy.^{17,19} However, limitations and discrepancies with respect to intertest variations, cutoff values, and lower accuracy compared to the results seen with UBT after eradication therapy have been reported.^{29,30}

Results of studies with serological diagnostic tests show relatively higher prevalence rates of HP infection (63% and 68%)^{24,27,28} which is consistent with our study i.e. 72.4% (n=63) as they persist for longer periods even after successful eradication measures. Studies documented that HP caused inflammation in gastric mucosa facilitates absorption of antigens which leads to production of IgE antibodies which persist after eradication treatment. This may be responsible for urticarial symptoms and points to lack of role of immunoglobulin estimation in posttreatment setup.³⁰ Higher levels of IgM antibody titre may be due to inclusion of only those CU patients who had dyspepsia. Out of a total of 63 IgM positive cases 50 (79.4%) improved after HP eradication treatment, which indicated that there was some indirect evidence of role of *H. pylori* IgM antibodies in diagnosis in such cases although others do not support role of IgM alone (33.3%). A combination of IgG, IgM, fecal antigen, fast test of urease, histological study (83%) can be of

help.³¹ However, role of IgM antibodies alone in diagnosis and detection of successful eradication was unconvincing in the present study.

The results of study indicate that stool antigen immunoassay and *H. pylori* IgM antibodies could be used as a routine diagnostic tool for *H. pylori* infection with association of urticaria. It has the advantage of being patient friendly, noninvasive, easy and quick to perform and cost-effective than the urea breath test. These tests can meet the requirements of dermatologists treating most patients with urticaria and infected with *H. pylori*, convenient for pretreatment diagnosis as high sensitivity and specificity are attainable.³² However, due to intermittent shedding of the microorganism in feces, HpSA declared negative before eradication treatment in patients with strong suspicion of *H. pylori* should be repeated again to ascertain the diagnosis.

There are reports of patients of CU who had gone into remission after elimination of HP and had a relapse with reinfection, which again cleared after elimination.^{3,32} Limitations of our study were: short duration of study, inability to study the natural history of chronic urticaria, and inability to study the natural history of HP infection.

Conclusion

Chronic urticaria and dyspepsia are associated with *H. pylori* infection and presence of this organism in such cases can be detected with confidence by using noninvasive, sensitive, specific and cheaper techniques like *H. pylori* stool antigen. This is particularly true in developing countries like ours where because of financial constraints, invasive techniques like gastric antral biopsy, biopsy urease test and costly non invasive urea breath test are difficult

to perform. HP detection should be included in the diagnostic work up of all patients with CU.

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