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Association between *H. Pylori* and Urticaria or Gastritis

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Abstract

Background: Studies have established that Helicobacter pylori can cause chronic gastritis. Recent evidence suggests that Helicobacter pylori infections play a great role in the pathogenesis of a variety of skin diseases, the best evidence for such a link is found for two diseases; chronic urticaria and immune thrombocytopenic purpura.

Objectives: the current study is aiming at evaluating the relationship between *H. pylori* among patients with different cutaneous problems mainly chronic urticaria by using immunological methods. On the other hand the study is aiming at verifying the effect of treatment on the prevalence of disease.

Materials and Methods: 119 Specimens (blood and stool samples) were obtained. Serum was stored at -20°C until used. Stool was collected in clean container and tested immediately. Specimens were processed by Serum ICT (ACCURATE, diagnostic use, china) and Stool Antigen ICT KITS (CERTEST BIOTEC S.L.) for detection of *H. pylori*. Significance tests, measures of accuracy and confidence intervals were calculated using the biomedical Stats Direct Statistical Software v2.7.9 (7/9/2012). IBM SPSS Statistics v22 was used in the descriptive data analysis.

Results and discussion: *H. Pylori* infection was detected in about half of the patients who suffered from either urticaria or gastritis. The prevalence of H. Pylori was estimated in the three groups as 48.3% (CI: 35.2% to 61.6%); in the urticaria group, 51.7% (CI: 32.5% to 70.6%); in the gastritis group and 13.3% (CI: 3.8% to 30.7%) in the apparently healthy group (labelled 'Normal'). Proportions of *H. Pylori* infection in the urticaria and the gastritis groups were not

statistically significantly different. Both groups, however, had a significantly different proportion of HP infected patients when compared with the apparently healthy (Normal) group. This statistically significant difference was suggestive of an association between *H. Pylori* and both of urticaria and gastritis.

Keywords: *H. Pylori*; Urticaria; Gastritis.

INTRODUCTION:

Helicobacter pylori (H. pylori*)* is a Gram negative, spiral flagellated bacterium that infects approximately 50 percent or more of the world population (Goodman and Cockburn, 2001)**.** The bacterium was initially named Campylobacter pylori is, then renamed C. pylori to correct a Latin grammar error. When 16S rRNA gene sequencing and other research showed in 1989 that the bacterium did not belong in the genus Campylobacter, it was placed in its own genus, *Helicobacter*. *H.pylori* survive the acidic pH of the lumen and conceal into the mucus to reach its niche and moves through the stomach lumen and drills into the mucoid lining of the stomach (Chan WY. et al., 1994). The survival of *H. pylori* in the acidic stomach is dependent on urease and the ammonia along with the other products of *H.Pylori* including protease, vacuolating cytotoxin A (VacA), and certain phospholipases damage the epithelial cells (Smoot DT. 1997). Initial infection typically occurs during childhood after oral ingestion and the bacterium persists for the life of the host unless treated (Everhart, 2000).

In Sudan, information about the prevalence of *H. pylori* infection is very patchy. and there is only one study which showed high prevalence (80%) of *H. pylori* infection among patients with symptoms of gastritis, 56% with duodenal ulcer, while 60% with duodenitis and 16% apparently look normal (Elbagir M, Ahmed K, 2001). However, former epidemiologic studies of *H. pylori* infection in Sudan using serologic tests demonstrate the prevalence of *H.pylori* infection in endoscopic biopsies using rapid urease test [Campylobacter-like organism (CLO) test] and culture using Skirrow's selective supplement in 100 patients, reported that *H.pylori* was positive in 50% and 33% of them were belonged to group O (**Azim Mirghani YA. et al., 1994**). Another study in Sudan had shown that seropositivity of *H. pylori* was found in

60% of patients with gastritis, 56% of patients with duodenal ulcer, values similar to rates seen in developing countries (**Ahmed A. 2002**).

Apart from its well-demonstrated role in gastroduodenal diseases, some have suggested a potential role of *H. pylori* infection in several extra-intestinal pathologies including haematological, cardiovascular, neurological, metabolic, autoimmune, and dermatological diseases. However, more systematic studies are required to clarify the proposed association between *Helicobacter pylori* and chronic urticaria (CU) and possible skin improvement after its eradication (Y.C.Chiu, W. C. Tai *et al,* 2013*).* Several etiologic factors for CU have been described, among them the chronic infections and the parasitic infestations. The infection by H. pylori has been the subject of investigation as a possible etiologic factor for CU in the last few years (Wedi B *et al,* 2009). Several pathophysiologic mechanisms have been suggested to explain the association between CU and H. pylori. First, an IgE mediated immune response to the bacterial infection, since the patients with higher IgE levels on diagnosis show a more significant improvement of the symptoms of CU in response to treatment institution (Castillo Reguera YM *et al,* 2012). Second, the release of auto-antibodies induced by the immunogenic bacterial cell wall (Kanani A *et al,* 2011), whose molecule is similar to the thyroid antiperoxi-dase antibody (Kilic G *et al,* 2010*).* Finally; the presence of the H. pylori in the gastric mucosa stimulates the activated eosinophils to release cytotoxic proteins, which are involved in the pathophysiology of urticaria, and interfere with the production of pro-inflammatory cytokines and with the expression of epitopes of adhesion to the endothelial cells, which triggers a systemic immune response (Castillo Reguera YM *et al*, 2012). Also, substances produced by the *Helicobacter pylori*, such as urease, protease, phospholipase and cytokines, can trigger the complement response (Wedi B *et al,* 2009). *Helicobacter pylori* infection might also be a source of circulating immune complexes and these immune complexes may trigger urticaria (Ben Mahmoud L *et al,* 2011). However, as it has been shown that persistent infection caused by *H. pylori* could be a potential trigger for chronic urticaria, the infection by this organism in these patients should be identified and eradicated, as this is one of the most successful therapeutic approaches.

A reliable primary diagnosis and control of treatment success of *Helicobacter pylori* (*H. pylori*) infection is crucial for patients with a wide spectrum of *H. pylori* infection. Accurate

diagnosis of *H. pylori* infection involves the combined knowledge, effort and research of laboratories, gastroenterologists and pathologists.

Traditional diagnosis is made using a combination of tests, both invasive and noninvasive. The choice of tests usually depends on clinical circumstances, the likelihood ratio of positive and negative tests and the cost-effectiveness of the testing strategy and of the availability of the tests. Non-Invasive methods include: Serology, Urea breath test, Stool antigen test and Molecular test. Serological tests that detect anti-H pylori IgG antibodies are non-invasive, less expensive, not influenced by sampling error, and less likely to be confounded by suppression of H pylori infection by colloidal bismuth, proton pump inhibitors, or antibiotics (Dunn BE, Cohen H, Blaser MJ 1997). Serological tests are widely used (Suerbaum S, Michetti P 2002) but they cannot differentiate a current infection from a past exposure (Vaira D *et al,* 2002). Stool antigen test by immunochromatography (S-ICT) is non-invasive, cost effective, and requires less than 15 min to perform. Therefore, it is convenient for patients and can be easily performed even in small laboratories and primary outpatient clinics.

The ideal therapeutic regimen for H. pylori infection should achieve an eradication rate of ≥ 80%. Treatment may depend on the patient, treatment indication, local antibiotic-resistance profile, and whether the patient was treated previously for *H. pylori* infection. First-line therapy **c**omprising two antibiotics, amoxicillin and clarithromycin, and a proton pump inhibitor (PPI) for 1 or 2 weeks was recommended as the initial treatment of choice at several consensus conferences (Chey WD, Wong BC 2007). Eradication rates with triple therapy range between 70% and 85% (Fujioka T *et al,* 2012).

Quadruple therapy: Triple therapy regimens are becoming less effective; therefore, alternative therapies are needed. Quadruple therapy containing PPI, bismuth, metronidazole and tetracycline given for 10-14 days, is a good alternative for first line treatment of H. pylori infection (Malfertheiner P *et al,* 2012). Success rates range of this treatment is between 75% and 90%. The sequential regimen is a simple dual therapy including a PPI plus 1 g amoxicillin (both twice daily) given for the first 5 d, followed by triple therapy including a PPI, 500 mg clarithromycin, and a nitroimidazole antimicrobial (all twice daily) for the remaining 5 d. Its initial reported success rate was > 90% (Scaccianoce G *et al,* 2006). In patients who were treated for *H. pylori* infection, and did not achieve eradication, second-line therapy is required, that if triple therapy

fails, either a bismuth-containing quadruple therapy or levofloxacin-containing triple therapy can be used as second line therapy (Malfertheiner P *et al,* 2012).

Accordingly, the current study is aiming at evaluating the prevalence of *Helicobacter pylori* infection in patients with different cutaneous problems mainly chronic urticaria by using immunological methods. On the other hand the study is aiming at verifying the effect of treatment on the prevalence of disease.

Materials and Methods:

***Ethical consideration*:** Written consent was obtained from each volunteer under supervision of physician. The confidentiality of the patients was established by coding of the questionnaires and the data list by a different code from their files to ensure the anonymity of respondents. All investigations were carried out for patients free of charge.

***Study Design*:**

This was a case-control study which had been conducted in Khartoum Dermatology Teaching Hospital and Omdurman Teaching Hospital during the period from January 2014 to June 2015.

***Study population*:**

One hundred and twenty patients who had gastrointestinal symptoms (heart-burn, nausea, vomiting, pain in upper abdomen) suspected to had *H. pylori* infection and chronic idiopathic urticaria symptoms (itching, skin-rash), also patients who have no symptoms of *H. pylori* infection or CIU were included**.**

***Sampling*:**

Around 119 Specimens (blood & stool samples) were obtained. Both were collected under strict sterile condition. 3 ml of whole venous blood was collected after disinfected of skin by 70% alcohol, and then the blood was poured in plain container and centrifuged at 2000 rpm for 5 minutes to obtain the serum. Serum was stored at -20°C until used. Stool was collected in clean container and tested immediately.

Specimens were processed by Serum ICT (ACCURATE, diagnostic use, china) & Stool Antigen ICT KITS (CERTEST BIOTEC S.L.) for detection of *H. pylori*.

Statistical analysis:

In this study, the diagnostic accuracy of the serum test was investigated in the classical way by comparing its performance to a reference test, namely the stool antigen test. Significance tests, measures of accuracy and confidence intervals were calculated using the biomedical StatsDirect Statistical Software v2.7.9 (7/9/2012). IBM SPSS Statistics v22 was used in the descriptive data analysis. An R code for simultaneous comparison of multiple proportions (Marascuillo Method) was obtained from:http://www.itl.nist.gov/div898/handbook/prc/section4/prc46.htm

In all statistical tests, p-values ≤ 5% were considered significant. Unless otherwise stated, the confidence interval (**CI**) shown for any estimate is a two-sided 95% CI.

Results

The sample initially consisted of 120 individuals, 56 males and 64 females, and was composed of three groups: urticaria patients (60); gastritis patients (30); and apparently healthy individuals, labled 'Normal', (30). One male participant from the gastritis group, however, was excluded for refusing to take the stool test. The remaining individuals (119) had a mean age of 30.7 (SD: 10.3) years. Their ages ranged between 18 and 60 years. The sample characteristics of those participants are summarized in table 1.

Table 1: Baseline Sample Characteristics

				Sex				Skin Symptoms				GI Symptoms							
Group	H. Plori	N[1]	Age Mean (SD)	Male N (%)		Female N (%)		Itching N (%)		Skin Rash N (%)		Nausea N (%)		Vomiting N (%)		Pain[2] N (%)		Heart Burn N (%)	
Urticaria	+ve	29	32.6 (11.2)	13	(44.8)	16	(55.2)	29	(100)	28	(96.6)	17	(58.6)	1	(3.4)	12	(41.4)	16	(55.2)
	-ve	31	30.8 (10.0)	10	(32.3)	21	(67.7)	31	(100)	25	(80.6)	17	(54.8)	1	(3.2)	12	(38.7)	17	(54.8)
Total		60	31.5 (10.5)	23	(38.3)	37	(61.7)	60	(100)	53	(88.3)	34	(56.7)	2	(3.3)	24	(40.0)	33	(55.0)
Gastritis	+ve	14	28.2 (9.0)	6	(42.9)	8	(57.1)	1	(7.1)	1	(7.1)	14	(100)	0	(0)	12	(85.7)	11	(78.6)
	-ve	15	31.9 (12.3)	6	(40.0)	9	(60.0)	3	(20.0)	3	(20.0)	15	(100)	3	(20)	11	(73.3)	14	(93.3)
Total		29	30.3 (10.9)	12	(41.4)	17	(58.6)	4	(13.8)	4	(13.8)	29	(100)	3	(10.3)	23	(79.3)	25	(86.2)
Normal	+ve	6	29.6 (8.1)	5	(83.3)	1	(16.7)	1	(16.7)	0	(0.0)	4	(66.7)	1	(16.7)	1	(16.7)	3	(50.0)
	-ve	24	29.3 (12.8)	15	(62.5)	9	(37.5)	2	(8.3)	2	(8.3)	6	(25.0)	2	(8.3)	2	(8.3)	2	(8.3)

Total	30	29.5 (9.7)	20	(66.7)	10	(33.3)	3	(10.0)	2	(6.7)	10	(33.3)	3	(10.0)	3	(10.0)	5	(16.7)

1: N: Number of individuals; **2**: Abdominal Pain.

Participants in the urticaria group, mainly, presented with itching (100%) and skin rash (88.3%). Those in the gastritis group mainly presented with nausea (100%), heart burn (86.2%) and abdominal pain (79.3). Of the apparently healthy group, 33.3% were found to be suffering from nausea; but no other remarkable complaint.

Prevalence of H. Pylori in the Three Study Groups

H. Pylori stool test was performed at baseline for all 119 participants. The results are shown in table 2 below.

Table 2: H. Pylori stool test results in the three study groups

Group	H. Pylori		Total
	+ve	-ve	
Urticaria	29 (48.3%)	31 (51.7%)	60 (100%)
Gastritis	14 (48.3%)	15 (51.7%)	29 (100%)
Normal	6 (20.0%)	24 (80.0%)	30 (100%)
Total	49 (41.2%)	70 (58.8%)	119 (100%)

In the urticaria group, 29 out of the 60 patients tested positive for H. Pylori. The prevalence of H. Pylori infection in that group was found to be 48.3% (CI: 35.2% to 61.6%). In the gastritis group, 14 out of the 29 patients who took the test, were found to be positive for H. Pylori with an estimated prevalence of also 48.3% (CI: 29.4% to 67.5%). The apparently healthy group had only six individuals who tested positive, with an estimated prevalence of 20% (CI: 7.7% to 38.6%).

To investigate differences in the prevalence of H. Pylori in the three study groups, Pearson's χ^2 test was performed. The test indicated a statistically significant difference between at least two of the three estimates of prevalence of H. Pylori in those (p=.002). The Marascuillo procedure for comparing multiple proportions was further used to simultaneously test for differences within the three pairs. Result of that comparison is shown in table 3 below.

Table 3: Comparison of the proportions of H. Pylori infected individuals in the three groups

Pair*	value	Critical range	Significance (5%)
U vs G	0.001	0.126	No
U vs N	0.283	0.114	Yes
G vs N	0.283	0.114	Yes

*U: Urticaria group; G: Gastritis group; N: Normal (apparently healthy) group

It is evident from table 3 that the prevalence of H. Pylori infection in patients with urticaria was not significantly different from that of the gastritis patients, whereas the prevalence of H. Pylori in the apparently healthy sub-sample differed significantly from the prevalence in the two other groups suggesting an association between H. Pylori and both urticaria and gastritis.

Diagnostic test analysis

At baseline, participants were subjected to both stool test and a serum test. The stool test was used as the reference test for detecting the presence or absence of H. Pylori infection. Participants were then classified according to the results of the two tests in each group, as shown in table 4 below.

Table 4: Cross classification of participants by group and type of test

Test		Group											
		Urticaria			Gastritis			Normal			All		
		Stool Test			Stool Test			Stool Test			Stool Test		
		+ve	-ve	Total	+ve	-ve	Total	+ve	-ve	Total	+ve	-ve	Total
Serum Test	+ve	8	9	17	4	6	10	0	5	5	12	20	32
	-ve	21	22	43	10	9	19	6	19	25	37	50	87
Total		29	31	60	14	15	29	6	24	30	49	70	119

Diagnostic accuracy of the serum test was investigated in the three study groups, separately. Result obtained is shown in table 5.

Table 5: Comparison of the serum test performance in the three study groups

	Urticaria	Gastritis	Normal
Prevalence	48.3% (35.2% to 61.6%)	48.3% (29.5% to 67.5%)	20% (7.7% to 38.6%)
Sensitivity	27.6% (12.7% to 47.2%)	28.6% (8.4% to 58.1%)	0% (97.5% one-sided CI: 0% to 45.9%)
Specificity	71.0% (52.0% to 85.8%)	60% (32.3% to 83.7%)	79.2% (57.9% to 92.9%)
Predictive value of +ve test (post-test likelihood of disease)	47.1% (23.0% to 72.2%) {change = -1%}	40% (12.2% to 73.8%) {change = -8%}	0% (97.5% one-sided CI: 0% to 52.2%) {change = -20%}
Predictive values of -ve test			
(post-test likelihood of no disease)	51.2% (35.5% to 66.7%) {change = -1%}	47.4% (24.5% to 71.1%) {change = -5%}	76% (54.9% to 90.6%) {change = -4%}
(post-test disease likelihood despite -ve test)	48.8% (33.3% to 64.5%) {change = 1%}	52.6% (28.9% to 75.6%) {change = 5%}	24% (9.4% to 45.1%) {change = 4%}
Likelihood Ratio			
LR (positive test)	0.950 (0.428 to 2.090)	0.714 (0.254 to 1.911)	0 (0 to 2.222)
LR (negative test)	1.020 (0.726 to 1.428)	1.190 (0.68 to 2.127)	1.263 (0.667 to 1.589)

From table 5 above, both urticaria and gastritis patients had the same point estimate of prevalence of H. Pylori infection (48.3%); but the 95% CI was wider in the gastritis group due to the smaller sample size of that group compared with the urticaria group. Prevalence in the

apparently healthy group (20%) was less than half the prevalence found in each of the two other groups.

The sensitivity (true positive rate) of the serum test in the urticaria group was only 27.6% (CI: 12.7% to 47.2%). The 95% CI indicated that the true sensitivity of the serum test could be as low as 12.7% where the false negative fraction would have reached a high of 87.3%, while the upper limit of the confidence interval of 47.2% indicated that the serum test, at its best, would miss a minimum of 52.8% of those truly infected with H. Pylori.

In the gastritis group of patients, the sensitivity of the serum test was also low at 28.6% (CI: 8.4% to 58.1%). Again, the 95% CI indicated that the true sensitivity of the serum test could be even lower at 8.4%, where the false negative proportion could have reached a high of 91.6%, whereas the upper limit of the confidence interval of 58.1% indicated that the serum test, at its best, would miss a minimum of 41.9% of those truly infected with H. Pylori.

In the apparently healthy group of patients, the serum test failed to pick out any of the infected individuals, resulting in a sensitivity of 0% (97.5% one-sided CI: 0% to 45.9%). The upper limit of the CI, however, indicated that a sensitivity of 45.9% could also be as plausible – resulting in a false negative fraction of 54.1%.
Compared to its sensitivity, the specificity (true negative rate) of the serum test was generally higher. It was at its highest level in the apparently healthy group 79.2% (CI: 57.9% to 92.9%); less high in the urticaria group 71.0% (CI: 52.0% to 85.8%); and at its lowest level in the gastritis group at only 60% (CI: 32.3% to 83.7%). The test would have incorrectly identified 20.8%, 29% and 40% of the non-infected participants in the three groups, respectively, as being HP infected (false positives).

The predictive value of the positive test (post-test likelihood of H. Pylori infection) at 47.1%, 40% and 0% in the urticaria, gastritis and the apparently healthy groups was 1%, 8% and 20%, respectively, less than the pre-test likelihood of H. Pylori infection. Being lower than the pre-test likelihood, the post-test likelihood obtained in the three groups indicated that the serum test was worse than the mere judgement that could have been made depending only on the prevalence of the infection in those groups (48.3% in both urticaria and gastritis groups; and 20% in the apparently healthy group). It was rather clinically useless when applied to the urticaria patients and misleading, to a varying extent, in the gastritis group and in the apparently healthy individuals, having had a change over pre-test likelihood of the infection of (-8%) and (-20%), respectively.

The predictive value of the negative test (post-test likelihood of no H. Pylori infection) was found to be 51. 2% (CI: 35.5% to 66.7%) in the urticaria patients; 47.4% (CI: 24.5% to 71.1%) in the gastritis patients; and 76% (CI: 54.9% to 90.6%) in the apparently healthy group, which was rather uninformative (change of -1% to -4% over the pre-test likelihood of no HP infection).

.From table 5, it is also evident that the likelihood ratio (LR) for a positive test was less than unity (<1) in the three study groups, whereas a sensible test is supposed to have a value >1; and the likelihood ratio for a negative test was >1 contrary to what is also expected from a sensible test. This indicates that the serum test seems to have worked in the reverse direction: a positive

test result suggested absence of HP infection, while a negative test result suggested the presence of an infection - contrary to expectations.

Treatment Outcome

Of the 29 patients who initially tested positive for H. Pylori in the urticaria group, 22 were treated with treatment A; one patient was treated with B; and 3 patients were treated with A followed by B. The remaining three patients were lost to follow up. One month after completion of treatment, all 26 patients had a stool retest carried out and the treatment outcome assessed. Data on stool retest and treatment outcome (presence/absence of itching) were cross classified as is shown in table 6 below.

Table 6: Outcome classified by Therapy and the stool re-test result

Therapy	Stool Re-test	Itching		Total
		Disappeared	Persisted	
A	H. Pylori +ve	0	**2**	2
	H. Pylori -ve	11	9	20
Total		11	11	22
B	H. Pylori +ve	0	**1**	1
	H. Pylori -ve	0	0	0
Total		0	**1**	1
A,B	H. Pylori +ve	0	**1**	1
	H. Pylori -ve	0	2	2

	Total		0	3	3
Total		H. Pylori +ve	0	**4**	4
		H. Pylori -ve	11	11	22
	Total		11	15	26

It can be seen from table 6 that out of the 22 patients who were treated with therapy A alone, 11 (50%, CI: 28.2% to 71.8%) did not attain relief from baseline symptoms, namely itching, together with the single patient who was treated with treatment B only and all of the three patients who were treated with A followed by B.

The eradication rate of treatment A (20/22) amounted to 90.1% (CI: 70.8% to 98.9%). Treatment B alone and the combination (A,B), however, were tested in a too small number of patients that didn't warrant a meaningful analysis.

Overall, persistence of skin symptoms, namely itching was reported for 15 out of the 26 patients (57.7%), of whom only 4 had a positive stool retest while the remaining 11 were found to be H. Pylori free after receiving treatment A only.

Assuming no difference between the baseline proportion of those who suffered from itching and their proportion after complete eradication of H. Pylori was attained (100% vs 45%, respectively), a paired proportion test was performed. The difference between the two proportions (55%, Score based (Newcombe) 95% CI: 28.7% to 74.2%) was found to be statistically significantly different from zero (Exact two sided P = 0.001). With 95% confidence it can be said that the true population value for the proportion difference lies somewhere between 28.7% and 74.2%. This shows that eradication with treatment A produced a significant reduction in itching suffered by urticaria patients and provides some evidence about the association between H. Pylori and urticaria.

Discussion

The current study confirms and extends the data obtained in other studies (Wedi etal., 1998; Fukuda et al., 2004). Proportions of *H. Pylori* infection in the urticaria and the gastritis groups were not statistically significantly different. However, the present study revealed a significantly different proportion of HP infected patients when compared with the apparently healthy (Normal) group. This statistically significant difference was suggestive of an association between H. Pylori and both of urticaria and gastritis. In 43 cases out of 100 gastritis associated chronic urticaria patients studied by Wedi etal., a potential infectious trigger could be identified, high

prevalence of H. pylori gastritis was found since 47% of patients showed elevated H. pylori-specific IgA and/or IgG antibodies. 27 patients underwent endoscopy and in all but 1 (96%) antral H. pylori infection was found. In contrast, a prevalence rate of 47% among asymptomatic adults has been published (Wedi etal., 1998). Fukuda et al on the other hand found that 52% of the chronic urticaria patients, he studied were H.pylori seropositive, while 48% of the control subjects were H. pylori-seropositive which was statistically insignificant (Fukuda et al., 2004).

In accordance with other studies, *H.pylori* eradication was associated with remission of urticaria symptoms, suggesting a possible role of *H.pylori* in the pathogenesis of chronic uticaria. This was clearly demonstrated by Di Campli and others among 45 chronic idiopathic urticaria patients. It was found that 55% were *H. pylori* infected; 88% of infected patients, in whom the bacterium was eradicated after therapy, showed a total or partial remission of urticaria symptoms while urticarial symptoms remained unchanged in all uninfected patients (Di Campliet al., 1998).

Association between *H. Pylori* and urticaria was further investigated in those who tested positive for H. Pylori (26). Although they were all given the appropriate treatment, only data from those who received treatment A and attained complete eradication (20 patients) were analyzed. A statistically significant reduction of 55% in the itching symptom (from 100% to 45%) was found (Exact two sided P = 0.001). The 95% CI indicated that the true difference between the pre-treatment and the post-treatment proportion of urticaria patients with itching symptom was likely to be in range of 28.7% to 74.2% which obviously does not include one at its upper end; again indicating a statistically significant reduction in the proportion of those with itching. Schnyder et al studied 46 patients with chronic idiopathic urticaria, *H.pylori* positive patients were treated in a crossover double-blind placebo-controlled study with amoxycillin and lansoprazol. 14 (28%) had a positive serology for H.pylori and 12 (24%) had active HP infection, as demonstrated by 13C-UBT. Of the 46 (92%) patients with chronic idiopathic urticaria followed up for 6 months, in 19 (41%) the urticarial symptoms disappeared within 6 months with only symptomatic treatment such as non-sedating antihistamines. Eleven of 12 patients with active HP infection participated in the crossover double-blind study; eradication was achieved in three (27%) subjects and in four (36%) a complete resolution of the chronic urticaria was observed. Urticaria resolved in only one patient after successful eradication treatment, on the other hand; the urticaria resolved without eradication of *H.pylori* in three patients. In this study,

neither the frequency of *H.pylori* infection nor the response to treatment indicated an underlying relationship between chronic urticaria and *H.pylori* infection (Schnyder et al., 1999). Similarly in a study by Daudén & et al; only one patient showed complete remission of urticaria and two patients showed partial remission thus supporting lack of relationship between H.pylori infection and the course of chronic urticaria.

In another study, all *H.pylori* positivepatients received eradication treatment and the effect of eradication on chronic urticaria was evaluated by urticaria activity score, the authors concluded that there was significant improvement in urticaria symptoms in relation to *H.pylori* eradication (Magenet & al., 2007). Moreira & et al treated 21 patients with chronic idiopathic urticaria with Triple therapy (amoxycillin, clarithromycin, and omeprazole) for 7 days. The results of therapy were assessed by ^{13}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 (Moreira et al., 2003).

Positive autologous serum skin tests have been associated with *H. pylori* infection in chronic urticaria (Lazaridouet al., 2011). Interestingly, in most patients with chronic urticaria, autologous serum skin tests became negative after *H. pylori* eradication (Wedi et al., 2009).

However; in spite of the controversial evidence from several studies, it has been reported that the remission and improvement rates of symptoms in patients with chronic urticaria nearly doubled when successfully treated for *H. pylori* infection compared to the untreated *H. pylori* -positive or *H. pylori*-negative controls (Wedi et al., 2009).

In 11 out of the 15 patients with persisting symptoms, the stool retest was negative for H. Pylori after treatment suggesting that their symptoms could be unrelated to H. Pylori infection. Treatment A successfully eradicated *H. Pylori* in 20 out of 22 patients. The eradication rate amounted to 90.1% (CI: 70.8% to 98.9%).

In patients treated with therapy A alone, 11 of 22 (50%, CI: 28.2% to 71.8%) did not attain relief from the itching symptom. The CI shows that the true rate of itching persistence was most likely to be no lower than 28.2% and no higher than 71.8%. A reduction of the proportion

of patients with itching symptom (from 100% to 45%) was observed in those who had attained a complete eradication of HP following treatment with regimen A. The difference between the two proportions (55%, Score based (Newcombe) 95% CI: 28.7% to 74.2%) was statistically significantly different from zero (Exact two sided P = 0.001). This shows that eradication with treatment A produced a significant reduction in itching suffered by urticaria patients and provides some evidence about the association between *H. Pylori* and itching.

According to Wedietal, disappearance (67%) or improvement of urticaria (24%) occurred in most patients receiving antimicrobial treatment after 3-12 weeks. In contrast, only 50% of the untreated H. pylori-seropositive patients with chronic urticaria showed spontaneous remission or improvement within 12 weeks (Wedietal. 1998). Also Daniel et al found that resolution of urticaria was more likely when antibiotic therapy was successful in eradication of *H pylori* infection than when patients who were infected did not achieve eradication (Daniel et al 2003). A study by Nadir et al; found a significant difference in eradication rates between the traditional triple therapy (30 mg lansoprazole bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid for 14 days) and modified sequential therapy groups (lansoprazole 30 mg bid and amoxicillin 1 g bid for seven days, followed by metronidazole 500 mg bid, tetracycline 500 mg qid, and lansoprazole 30 mg bid for an additional seven days), thereby showing that sequential therapy promise a better alternative treatment (Nadir et al., 2011).

In conclusion, in the current study, the serum test showed that it was practically useless in detecting *H. Pylori*, due to its very low sensitivity in all three groups (urticaria: 27.6%: gastritis: 28.6%; 'Normal': 0%). The specificity (true negative rate) of the kit was moderate at 71%, 60% and 79.2%, respectively. It may be used as an alternative in the absence of other accurate *H. Pylori* test kits – with the risk of incorrectly classifying 29%, 40% and 20.8% non-infected persons as positive in the three groups, respectively. In agreement with this study, the accuracy of these tests is no longer adequate to justify their clinical use on clinical or economic grounds (Junko eta al., 2014). Accordingly; the current study recommends that a large randomized controlled trial is needed for an acceptable strong evidence of association between *H. Pylori* and urticaria or gastritis.

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