

***Helicobacter pylori* Infection in Idiopathic Chronic Urticaria**

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ABSTRACT

Helicobacter pylori (Hp) infection is the most common chronic bacterial infection in human. The role of Hp infection in various GI disorders had been widely accepted. However, further studies have found new extragastrointestinal involvement such as urticaria. Chronic urticaria is a common disorder that has complex pathophysiologic mechanism. As matter of fact, etiology remains unclear in most of the cases. This condition is called Idiopathic Chronic Urticaria. Several studies had shown high prevalence of Hp infection in patients with ICU and improved symptoms after eradication therapy of Hp. This observation had suggested that Hp has important role as etiologic factor in some cases of ICU. The presence of Hp infection and its role in ICU should be proven before initiating eradication therapy, so that irrational used of drugs and antibiotics resistance can be prevented.

Keywords: *Helicobacter pylori*, Idiopathic Chronic Urticaria

INTRODUCTION

To date, *Helicobacter pylori* (Hp) infection is considered as the most frequent chronic bacterial infection in human.¹ The role of Hp infection as the etiology of various gastrointestinal diseases had been widely accepted. Gastrointestinal disorders that frequently associated with Hp infection are active chronic gastritis, peptic ulcer, gastric malignancy and gastric mucosa-associated lymphoid tissue (MALT) lymphoma.¹ Further studies had found Hp involvement in various extra gastrointestinal disorders.^{2,3}

Chronic urticaria (CU) is a common disorder and involves complex pathophysiological mechanism. Infections (bacterial, viral, fungal and protozoa), psychological factors, neoplasm, and food additives had been reported as initiating factor. However, it needs furthers studies to confirm this.^{1,4} In fact, etiology remains unclear in most of cases of CU and this condition is called idiopathic chronic urticaria (ICU).¹ Recently, ICU has become an enigma in dermatology field.

Several studies had shown high prevalence of Hp infection in patients with ICU and improved symptoms after eradication therapy of Hp. This observation had

suggested that Hp has important role as the etiology in some cases of ICU.¹ The presence of Hp infection and its role in ICU must be confirmed before initiating eradication therapy, so that irrational therapy and antibiotics resistance can be avoided.

EPIDEMIOLOGY

Helicobacter pylori are gram negative bacteria, microaerophilic, spiral shaped, length of 2.5-4.0 µm and width of 0.5-1.0 µm, and having 4-6 flagella in one of its tip.^{2,5-7} It always gives positive result on peroxide, catalase, and urease test.² At first, Hp was considered as one species of genus *Campylobacter*, but since 1989 *Helicobacter* was classified into its own genus and *Helicobacter pylori* was one of the species.^{6,8} There are two phenotypes of Hp: Type 1 which expresses cytotoxin-associated gene antigen (CagA) and vacuolating cytotoxin-associated gene antigen (VacA), and type 2 which does not express gene antigen.^{2,9} Type 1 bacteria is much more pathogenic and results more severe inflammatory response than bacteria type 2.^{2,8} Most of Hp infection involve bacteria type 1.⁹

Helicobacter pylori infection is widely found all over the world with various prevalence figures.^{2,9} Prevalence is higher in accordance to higher age and low socio-economic condition.^{2,8,9-11} Prevalence in young adult in developing countries was approximately 80% while in developed countries it was only 20-50%.^{9,10} In developing countries, Hp infection occurred in younger people compare to those in developed countries.² Infection in adults is usually chronic condition and non responsive to therapy, while in children spontaneous resolve is common.⁹

IDENTIFICATION

Mode of transmission of infection is through fecal-oral route and is more frequent in children.⁹ Transmissions may be through body fluid such as vomit substance, saliva, feces, drinking water, or food.⁸⁻¹⁰ Self and environment hygiene factor are influenced by bacterial transmission.^{2,9} Transmission from animals has never been proven yet.⁹

Hp infection can be detected through invasive and non invasive examinations (specimen can be obtained from endoscopic biopsy procedure) such as culture, histologic examination, rapid urease test (CLO test[®], pronto dry, MIU), and polymerase chain reaction (PCR).^{2,5,12} Non invasive examinations include urea breath test (UBT), serologic test, *Helicobacter pylori* stool antigen (HpSA) and urine-HpELISA.^{5,7,13-22}

To date, Urea Breath Test (UBT) examination is the most widely used test because it is very simple to perform, non invasive and has high reliability with high sensitivity of 90-98% and specificity of 92-100%.^{2,12,16} UBT may be used to detect active infection and diagnose early infection and monitor eradication therapy.^{2,9,14-16} Urine-Hp ELISA introduces new technique and recommended for children.¹⁷ This test has

sensitivity of 94.4%, and specificity of 96.9%, simple to perform, not expensive and can give fast result.¹⁷

ETIOLOGY

The role of *Helicobacter pylori* as etiology of gastrointestinal disorder has been widely accepted. Gastrointestinal disorders frequently associated with Hp infection are active chronic gastritis, peptic ulcer, gastric malignancy, and gastric mucosa-associated lymphoid tissue lymphoma.^{1,2,5,6,8-12} Recent studies had found relation between Hp infection and various extragastrintestinal disorders such as cardiovascular disease (arteriosclerosis, myocardial infarct, Henoch-Schonlein purpura, autoimmune thyroiditis, idiopathic arrhythmia, Parkinson's disease), dermatologic disorder (idiopathic chronic urticaria, rosacea, alopecia areata, numularis dermatitis) and other diseases like iron deficient anemia, growth retardation, extragastric MALT-lymphoma, diabetes mellitus, hepatic encephalopathy and late menarche.^{2,23} The Hp bacteria produces some toxins (exotoxins) which not only destroy gaster and duodenum but also interact with extragastrintestinal tissue.³

TREATMENT

The mainstay of eradication therapy of Hp infection is total elimination of organism. If the condition is obtained, then the possibility of re-infection is rarely occurred.⁹ Eradication regimen should reach cure rate of $\geq 80\%$, minimal side effect and low drug induced resistance.⁹ Gastric acid may influence effectiveness of some antimicrobial agents and usually is combined with proton pump inhibitor (PPI) or ranitidine-bismuth citrate.^{9,24,25} Nowadays, there are 8 regimens of eradication therapy which had been recommended by Food and Drug Administration (FDA).^{5,9}

Table 1. Exotoxins Produced by *Helicobacter pylori* and Work in Extragastrintestinal Tissue.³

Factor Produced	Source	Toxic effect/s
Ammonia	<i>H. pylori</i> urease	Inhibition of protein degradation and vacuolation of lysosomes
Lysolecithin	<i>H. pylori</i> phospholipases	Cytotoxic compound leading to ulceration
Acetaldehyde	<i>H. pylori</i> alcohol dehydrogenase	Denaturation of proteins and induction of lipid peroxidation
Vacuolating cytotoxin	50% of <i>H. pylori</i> organism	Vacuolation of eukaryotic cells via unknown mechanism
Haemolysin	<i>H. pylori</i> phospholipase ?	Haemolysis
Platelet activating factor	Unknown	Potent inflammatory mediator in various organs
Mucolytic factor	Unknown	Degradation of mucin
Lypopolysaccharide	<i>H. pylori</i> cell wall	Low biological activity but could inhibit mucin glycosylation

Table 2. Choice of Therapeutic Regimen of *Helicobacter pylori* Eradication Recommended by FDA⁵

Omeprazole 40 mg QD + Clarithromycin 500 mg TID x 2 weeks, then omeprazole 20 mg QD x 2 weeks;
or
Ranitidine bismuth citrate (RBC) 400 mg BID + clarithromycin 500 mg TID x2 weeks, then RBC 400 mg BID x 2 weeks
or
Bismuth subsalicylate (Pepto Bismol [®]) 525 mg QID + metronidazole 250 mg QID + tetracycline 500 mg QID x 2 weeks + H ₂ receptor antagonist therapy as directed x 4 weeks
or
Lansoprazole 30 mg BID + amoxicillin 1 g BID + clarithromycin 500 mg TID x 10 days
or
Lansoprazole 30 mg TID + amoxicillin 1 g TID x 2 weeks
or
RBC 400 mg BID + clarithromycin 500 mg BID x 2 weeks, then RBC 400 mg BID x 2 weeks
or
Omeprazole 20 mg BID + clarithromycin 500 mg BID + amoxicillin 1 g BID x 10 days
or
Lansoprazole 30 mg BID + clarithromycin 500 mg BID + amoxicillin 1 g BID x 10 days

** Although not FDA approved, amoxicillin has been substituted for tetracycline for patients for whom tetracycline is not recommended*

*** This dual therapy regimen has restrictive labeling. It is indicated for patient who are either allergic or intolerant to clarithromycin or for infections with known or suspected resistance to clarithromycin*

The potential eradication from these 8 regimens was ranged between 61-94%.⁵ In general, triple therapy regimen (2 antibiotics + 1 antisecretory) has better eradication potential compare to dual therapy.⁵ Regimen consists of amoxicillin + clarithromycin + PPI is the first line therapy according to national consensus of management of Hp infection (2003).²⁶ Therapy is given for 1 week and considered successful if UBT/HpSA or histopathologic examination that is conducted 4 weeks post therapy is negative.²⁶

IDIOPATHIC CHRONIC URTICARIA

Idiopathic Chronic Urticaria (ICU) is chronic urticaria which etiology cannot be identified after careful anamnesis, physical examination and supporting examination.²⁷ Physics urticaria and vasculitis urticaria are not included in ICU.²⁸ Incidence and prevalence of ICU had not been very clear but estimated to be 0.1-3% of population.²⁹ Incidence in women was twice than in men.²⁷ There was 80-90% cases of chronic urticaria were found to be ICU.^{27,30} Histologically, ICU demonstrated non necrotic perivascular lymphocytic infiltrates and mast cell accumulation.^{31,32} Further studies classified ICU into two subgroup, ICU presumed to be caused by autoimmune disorder (autoimmune chronic urticaria) and chronic urticaria with unknown etiology (truly idiopathic).^{27,33}

Data had showed the association between ICU and autoimmune thyroiditis and this had encouraged studies on autoimmune disorder in ICU. Previous studies

revealed autoimmune thyroiditis prevalence in ICU was 14-20%.^{34,35}

Study on autoimmune disorder in ICU had identify successfully autoantibody to high affinity IgE receptor sub unit α (Fc ϵ RI α) in 1/3 cases of ICU.^{28,29,33-42} Hyde et al was the first researcher who reported the presence of autoantibody and concluded its role in pathogenesis of ICU.³⁸ Autoantibody to had been proven in vitro could stimulate histamine release from mast cell and basophil.^{27,28,39} The role of autoantibody to Fc ϵ RI α in the pathogenesis of ICU supported by evidence that this autoantibody was not found in healthy people. There was also clinical improvement of patients with ICU who underwent plasmapheresis therapy.³⁸

Further studies found incidence autoantibody to Fc ϵ RI α in ICU was higher (35-70%). In fact, this autoantibody was also known to be the isotype of IgG (IgG₁ and IgG₃).^{28,33,41} Autoantibody IgG₁ and IgG₃ were called functional antibody because they could activate complements (C5a) and release mediator from mast cell and basophil.^{36,38-44} Actually, this autoantibody is also found in other autoimmune diseases such as pemfigus vulgaris (39%), dermatomyositis (36%), SLE (20%), and bullous pemfigoid (13%).⁴² However, autoantibody to Fc ϵ RI α in other autoimmune diseases involves nonfunctional IgG₂ and IgG₄ which could not activate complement and release mediator from mast cell and basophil.^{36,42}

In small part of ICU cases (10%), it was also found the autoantibody to IgE molecule.^{27,37,39} The role of this autoantibody is still unknown. Autoantibody binding to IgE molecule on the surface of mast cell or basophil was presumed to stimulate the release of mediators.^{27,37,39}

Tong et al, concluded that in autoimmune chronic urticaria (ACU) there were 3 groups of patients. First was those who poses autoantibody to FcεRIα, second who poses autoantibody to IgE and third those who poses circulating factors that could stimulate mediator release from mast cell and basophil.³⁹ Study on circulating factors has been conducted until now.³⁹

Bakos et al, found antibody IgG and IgA to Hp-lipoprotein 20 in patients with chronic urticaria and Hp infection. The autoantibody was presumed to have role in the pathogenesis of chronic urticaria.⁴⁵

Patients with ACU usually have more urticaria lesions, more wide, severe itch and more systemic symptoms than patients with ICU but no autoantibody.²⁸ Other autoimmune diseases are also commonly found in ACU.²⁸ Recently, there were found HLA-DR4, DQB 0302 (DQ8), DQA0302 and DQA0301 in patients with ACU.^{29,37,46} Diagnosis of ACU was based on detection of autoantibody by serum autologue skin test, histamine release assay (HRA), ELISA, or immunoblotting analysis (western blot analysis).^{28,29,33,47,48} Patients with ACU were more resistant to therapy and had more progressive disease course compare to nonautoimmune urticaria.³³ Immunosuppressive therapy such as cyclosporine is recommended to severe form of ACU.^{33,47} Other therapy had been studied including intravenous immunoglobulin, plasmapheresis and the use of humanized monoclonal antibodies for FcεRIα or IgE.^{33,47-49}

About 40-60% cases of ICU had no etiology (truly idiopathic) and no autoantibody was found in the sera.^{27,33} Infection and food additives were suspected to be the causal factors. However, it would need further studies to confirm this.²⁷ Diagnosis of true ICU had to be considered in patients with persistent ICU who is non responsive to therapy and no antibody found on laboratory examination.³³

ASSOCIATION OF *HELICOBACTER PYLORI* AND IDIOPATHIC CHRONIC URTICARIA

Many studies had shown high prevalence of Hp infection in patients with ICU along with remission of sign and symptoms after eradication therapy of Hp. Early reports had demonstrated prevalence of Hp infection in 55-80% cases and clinical remission in 95-100% of patients who were given eradication therapy.^{1,20,50,51} This finding had suggested the role of Hp as the etiologic factor in some cases of ICU.¹ Further studies had found various prevalence and frequency of association.^{2,20,50,52}

There had been speculations and theory about mechanism involving Hp infection in chronic urticaria. One of the theory stated that chronic infection could stimulate immunologic system by release of mediators and hence, cause nonspecific increased sensitivity of vascular wall to certain substances which can increase vascular permeability.² There were also increased production of interleukin-8 (IL-8), platelet activating factor (PAF), and leucotrien B4 and C4 in gastric mucosa of patients infected by Hp. Those mediators had widely known role in skin metabolism.²

Liutu et al, Andersen et al, Aceti et al had found specific IgE antibody to Hp in patients with chronic urticaria.* Figura et al had failed to detect the antibody

Table 3. Percentage of *Helicobacter pylori* Infection in Patients with Chronic Urticaria.²

Authors and Years	Number of Cases	Percentage <i>H. pylori</i> (%)	Country
Wustlich et al, 1999	188	15.95*	Germany
Valsecchi and Pigatto, 1998	125	62.00	Italy
Liuty et al, 1998	107	39.25*	Finland
Schnyder et al, 1999	50	24.00*	Switzerland
Di Campli et al, 1998	42	54.76	Italy
Kalas et al, 1996	40	43.00*	Hungary
Ozkaya-Bayazit et al, 1998	37	77.00*	Turkey
Kolibasova et al, 1994	30	70.00	Slovakia
Wedi et al, 1998	26	47.00*	Germany
Tebbe et al, 1996	25	68.00	Germany
Bonamigo et al, 1999	18	66.70	Brazil
Bohmeyer et al, 1996	10	80.00	Germany

* Ratio not significantly different from that for the general population in that country

by Western blot technique.* However, all studies mentioned above had also showed increased release of histamine in patients with ICU and Hp infection.*

Hizal et al, concluded that Hp infection might stimulate production of IgE antibody because of cross reaction between Hp antigen and gastric parietal cell.⁵³ Other possibilities are Hp infection has caused inflammation in gastrointestinal tract and ease the absorption of antigen or unmasking antigen that had been presented before.⁵³ Once this occurred, the IgE antibody will be produced continuously and urticaria may not be resolved eventhough eradication therapy is given.⁵³

The effect of eosinophyl in Hp infection had not much been studied yet. Bacterial infection may stimulate infiltration and degranulation of eosinophil. It is presumed that toxic protein produced by eosinophil has role in inflammation process.²Bakos et al, analyzed the relation between Hp infection in ICU with or without autoimmune thyroiditis.³¹ Previous reports had shown prevalence of autoimmune thyroiditis in 14-20% cases of ICU.^{34,35} Bakos et al had demonstrated that Hp (CagA plus strain) had

important role as stimulating factor in ICU with autoimmune thyroiditis. Monoclonal antibody to Hp CagA plus strain had reacted positively with thyroid follicular cell. There is similar molecular structure between peroxide enzyme of human thyroid and peroxide enzyme of Hp so that immunologic cross reaction may occur.³⁴

New study by Atta et al, had tried to detect auto antibody to thyroid, autoantibody IgE and autoantibody to C1 INH in patient with and without Hp infection.⁵⁴ Studies demonstrated titer of autoantibody to thyroid was low in both group and there was no significant difference of level of IgE antibody in both groups. There was increased circulating immune complex from autoantibody C1 INH in patients with CU and Hp infection. The role of immune complex remains unclear, but it was presumed it was produced caused by phagocytosis disorder during Hp infection. In general, Atta et al concluded that there was no association between Hp infection and autoantibody production in patients with ICU.

Table 4. Studies on Effects of *Helicobacter pylori* Eradication Therapy in Patients with Chronic Urticaria.⁵¹

Study reference	No. of treated patients with urticaria and Hp infection completing study	Reported age of patients with Hp (y)	Follow up evaluation (mo)	Eradication regimen	Complete remission of urticaria when eradication of Hp achieved	Complete remission of urticaria when eradication of Hp not achieved	Remission of urticaria when patients with Hp infection were treated with placebo or not treated with antibiotics	Remission of urticaria in patients without Hp infection
Schnyder et al	11	15 - 78	6	LA	1/3	2/7	1/9	
Erel et al	29	37.5 (median)	not stated	OAC	1/25	0/4		
Wustlich et al	30	21- 61 (mean 45)	6	OA	6/24	0/6		
Valsecchi & Pigatto	31	24 - 61	8	OCM	3/29	0/2		1/25
Ozkaya-Bayazit et al	23	18 - 72 (mean 38.6)	6	OAC	4/17	2/6		3/8
Wedi et al	39	17 - 82 (mean 44.4)	6-9	OAC	14/21		5/18	6/14
Di Campi et al	18	46 (mean)	3	LAC	13/16	0/2		0/19
Tebbe et al	17	10 - 65	1.5-2.5	A or C or T and MBO	8/14	0/3		0/8
Dauden et al	15	22 - 67 (mean 42.2)	12	OAC	1/12	0/3		
Hook-Nikanne et al	53	14 - 70 (mean 41.1)	5	LM and A or T	8/30	3/5	5/18	
TOTAL	266				59/191	7/38	11/45	10/74

A: amoxicillin, B: bismuth subs alicylate, C: clarithromycin, L: lansoprazole, M: metronidazole, O: omeprazole, T: tetracycline

Eradication therapy in ICU with Hp infection

Many studies had been conducted to evaluate effectiveness of eradication therapy in ICU with Hp infection. The results were varied and might be caused by different diagnostic methods, therapeutic regimen, and period of post therapy observation.¹

From table 4 above, it showed that remission rate was 30.9% in patients with urticaria and Hp infection who were given eradication therapy, 21.7% in group of patients who did not get eradication therapy and 13.5% in control group who had no Hp infection. Low successful rate was probably caused by antibiotics resistance and many studies used serologic test as eradication therapy effectiveness parameter.^{1,53} Serologic test could not indicate active Hp infection. On the other hand, eradication therapy can only result in resolution of urticaria in patients with active Hp infection. Clinicians should monitor therapeutic effectiveness using Urea Breath Test (UBT).¹

CONCLUSION

ICU is still an enigma in dermatology field. Several studies had shown high prevalence of Hp infection in patients with ICU and improved symptoms after eradication treatment of Hp. Some experts had recommended Hp infection screening test in management of ICU. However, it needs further studies to confirm Hp as the etiology of ICU. Remission of urticaria after eradication therapy of Hp could not ascertain causal relationship because combination of antimicrobial agents used in eradication treatment of Hp might also eradicate other source of infection that induced urticaria. To prevent irrational therapy, adverse effects of drugs, and the risk of antibiotics resistance, it is recommended that eradication therapy is indicated only in patients with ICU and has been proven to have Hp infection. Effectiveness of eradication therapy should be monitored using Urea Breath Test (UBT).

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