

Helicobacter pylori: A significant and treatable cause of chronic urticaria and angioedema

Abstract: *Two outpatient medical offices evaluated 204 patients with chronic urticaria during 2012. This article presents a retrospective study showing that 10% of patients with chronic urticaria may be infected with H. pylori. Furthermore, eradication of infection can be followed by remission of urticaria, reduced morbidity from gastric ulcers, and cancer.*

By Marjohn M. Rasooly, MSN, CRNP; Nancy A. Moye, MSN, CRNP; and Arnold S. Kirshenbaum, MD

The sudden appearance of urticaria, angioedema, or both may occur in all age groups.¹ The diagnosis of urticaria is common, with nearly 20% of the population experiencing episodes of urticaria in their lifetime.¹ Urticaria lasting less than 6 weeks is termed acute and is common in infants and young children, particularly in atopic individuals. Causes include acute viral infections or ingestion of foods, such as milk, eggs, or peanuts, to which the infant or child is sensitized.¹ Chronic or recurring urticaria lasting 6 or more weeks is common in older children and adults. The prevalence of chronic urticaria in the general population ranges from 0.5% to 5%.²

Since urticaria is common, always pruritic, and easy to recognize, patients often make the correct diagnosis and treat themselves with antihistamines. Raised, circular, or oval-shaped wheals may vary in size from small to large and appear as solitary or multiple lesions (see *Urticaria*). Individual lesions seldom last longer than 24 to 48 hours, although new lesions commonly arise as older ones fade away. Angioedema develops in the subcutaneous tissues where there are fewer sensory nerve endings, giving rise sometimes to pain and little or no pruritus. Resolution of

angioedema is slower than that for urticaria and can take up to 72 hours. Angioedema is especially likely to develop in areas such as the eyelids and lips. Urticaria and angioedema occur oftentimes bilaterally but can be asymmetrical.

■ Pathophysiology

Despite active research to identify causes of chronic urticaria, a majority of patients have no known cause identified, and the hives are considered idiopathic.² Histologically, what is known is that urticaria is a mast cell-driven disease.¹ After the binding of immunoglobulin E (IgE) to the skin mast cells, potent chemical mediators such as histamine, platelet-activating factor, and cytokines are released from activated mast cells to cause wheals and angioedema. Skin affected by wheals has a mixed inflammatory perivascular infiltrate of neutrophils and/or eosinophils, macrophages, and T cells but without vessel-wall necrosis or damage.

Approximately 30% to 50% of patients with chronic urticaria produce specific IgG antibodies against the alpha subunit of the mast cell IgE receptor, and approximately 5% to 10% produce IgG antibodies against IgE itself.² The mast

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Urticaria

The photo below shows a patient with urticaria with wheals present in varying sizes.



Source: Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.

cell activating signals, however, are not well defined and are likely to be complex, considering chronic urticaria subtypes, such as physical urticaria.² Physical urticaria includes mast cell activation following skin exposure to cold, pressure (delayed-pressure urticaria/angioedema), sun (solar urticaria), heat (cholinergic urticaria), exercise (cholinergic urticaria or exercise-induced anaphylaxis), vibration (vibratory angioedema), and water (aquagenic urticaria).²

■ Causes

One is more likely to find a cause for acute rather than chronic urticaria. But in some instances, the history and physical exam may suggest a cause. For example, lesions limited to exposed areas suggest solar urticaria. In most cases of chronic urticaria, however, the appearance of raised, circular, or oval-shaped urticaria gives no clue as to origin or cause. The most common reported causes of chronic urticaria include viral infections, autoimmune diseases, which include connective tissue disorders, endocrine (thyroid, pancreatic) disorders, neoplasms (lymphoreticular and lymphoproliferative disorders), and urticarial vasculitis (with low or normal complement levels). (See *Chronic urticaria and angioedema: Reported causes*.)² Rarely, IgE-mediated reactions from foods, drugs, or other allergens may result in chronic urticaria.

■ Evaluation and management

The evaluation and management of patients with chronic urticaria begins with a history and physical exam and tar-

geted, specific lab tests to exclude important underlying causes, including complete blood cell count with differential, comprehensive metabolic panel, urinalysis, thyroid function studies with antibodies, antinuclear antibody titer (ANA), and serology. Since a specific cause is not found in many cases, it is best to control the lesions until remission occurs, which may take several months or more. Management involves both nonpharmacologic and pharmacologic approaches; therefore, NSAIDs, heat, and tight clothing might exacerbate chronic urticaria and should be avoided.² Avoidance of pseudoallergens, such as food additives, fruits, vegetables, or spices without supporting history may not effectively control urticaria.

Second-generation nonsedating histamine-1 receptor antagonists (H1RA) alone, such as fexofenadine and desloratadine, are effective in the majority of patients and are considered first-line agents. Patients needing more complete control should be started on mildly-sedating antihistamines, such as cetirizine or levocetirizine taken at night to avoid driving impairment or work during the daytime. Doses up to four times conventional doses have been used for difficult-to-treat urticaria.^{3,4} Liquid suspensions are available for children and calculated according to weight.

The addition of histamine-2 receptor antagonists (H2RA), such as famotidine or ranitidine, may be considered initially or for patients with unsatisfactory responses to monotherapy.² H2RA agents work synergistically with H1RA agents to block histamine-induced urticaria and angioedema. A third agent, such as the leukotriene modifier montelukast, can also be considered (use of montelukast is FDA-off label use). In some patients, a short course (1 to 3 weeks' duration) of prednisone may be necessary to gain control of chronic urticaria, but long-term use of corticosteroids should be avoided because of the risk of adverse reactions.² One recent advance in the treatment of chronic idiopathic urticaria is the FDA approval of omalizumab for patients unresponsive to H1RA and H2RA who are 12 years of age and older. Studies suggest that by binding unbound IgE, the use of omalizumab leads to reduction of mast cell IgE receptor numbers, reduction in mast cell activation, and clinical improvement.^{5,6} Omalizumab has a black box warning for bronchospasm, hypotension, syncope, urticaria, and/or angioedema. All patients should be observed after receiving this medication, and anaphylaxis treatment should be readily available.

■ Retrospective study

From 2012 to 2013, the two medical offices evaluated and treated 204 patients for chronic urticaria. The initial



workup was unrevealing. Published accounts suggested that examining for *Helicobacter pylori* (*H. pylori*) as a cause for urticaria may be helpful.⁷ However, evidence is conflicting, with published studies for the most part being performed outside of the United States. One recent review addressing the effectiveness of *H. pylori* eradication in

chronic urticaria recommended additional studies be performed, although resolution of urticaria appeared more likely when *H. pylori* gastritis was eradicated.^{7,8} Some guidelines suggested a “test and treat” strategy for patients rather than invasive endoscopy.⁹ Of note is that the risk of gastric cancer increases three- to sixfold in untreated *H.*

pylori-infected patients.¹⁰ Therefore, it was decided to review the office-based practice results to determine if the experience supported the evaluation and treatment of *H. pylori* in patients presenting with persistent chronic urticaria.

Chronic urticaria and angioedema: Reported causes²

Causes	Diagnostic testing
Infections	
Viral:	
Hepatitis B, C	Hepatitis B, C serology
Epstein-Barr virus (EBV)	EBV/mononucleosis serology
Herpes simplex	Herpes serology
Bacterial:	
Sinusitis	Sinus CT
Urinary tract infection	Urinalysis, urine culture
<i>Helicobacter pylori</i>	UBT
Autoimmune	
Connective tissue disorders:	
Systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, dermatomyositis	ANA titer, rheumatoid arthritis diagnostic panel
Endocrine disorders:	
Diabetes	Fasting blood glucose, hemoglobin A1c
Hypothyroidism, hyperthyroidism, thyroiditis	Thyroid-stimulating hormone Free thyroxine (FT4) Triiodothyronine resin uptake (T3RU) Thyroid peroxidase antibody Thyroglobulin antibody Thyroid-stimulating hormone receptor antibody Ultrasound
Neoplasms	
Lymphoreticular malignancy, lymphoproliferative disorders	CBC with differential, referral for bone marrow biopsy
Urticarial vasculitis	
	Human complement protein C1Q Complement component C3 Complement component C4 Referral for skin biopsy
Physical urticarias	
Cold, delayed pressure, solar, cholinergic, vibratory, aquagenic, exercise-induced anaphylaxis	Referral to allergist
Miscellaneous	
Foods, drugs, additives	Skin testing, radioallergosorbent test (RAST) Referral to allergist

Note: Angioedema alone without urticaria may be a complement disorder and requires referral for evaluation

Materials and methods: Diagnosis of *H. pylori*

Serology (IgG, IgM, and IgA) for *H. pylori* is inconclusive for acute infection.⁹ Urea breath testing (UBT) has been shown to accurately measure acute *H. pylori* gastritis in a 20-minute office test, with sensitivity (95%) and specificity (90%) higher than serology (sensitivity 85%, specificity 79%).¹¹ Therefore, the UBT was the most accurate and convenient test for the practice and without delaying treatment. Consultation with community gastroenterologists confirmed UBT to be the preferred, noninvasive test in lieu of endoscopy. This approach was begun in the practice beginning March 2012.

Patients studied and treatment

Patients' charts for office visits between 2012 and 2013 were reviewed retrospectively to determine chief complaints and histories of chronic urticaria. IRB approval was not needed, as this was a retrospective chart review. Patients presenting with a history of urticaria for greater than 6 weeks with/without gastritis or reflux were offered to have UBT performed as office standard of practice. Most patients had received antihistamines and possibly a tapering course of prednisone prescribed by an urgent care or emergency medicine provider without resolution of urticaria prior to the initial evaluation within the practice. Manufacturer guidelines advise



that patients discontinue proton pump inhibitors (PPIs) and oral antibiotics for 2 weeks and to not eat for 1 hour prior to urea breath test.

Clinical staff administered the UBT and operated the Breathtek Analyzer in each office as standard of care for all patients that met the aforementioned criteria for chronic urticaria. UBT kits were directly purchased from Otsuka Pharmaceuticals, with each analyzer and insurance coded using 83013 (administration) and 83014 (analysis). Patients having Blue Choice, United Health Care (commercial), and BC/BS National Capitol Area required UBT kits from Labcorp, which were provided upon request and insurance coded only with 83013. For treatment of UBT-positive individuals, guidelines were designed and employed with community gastroenterologists for *H. pylori* eradication, considering antibiotic resistance (30%), which were as follows: Prevpac (PPI+ clarithromycin+amoxicillin) (eradication 85%) or Helidac (bismuth+tetracycline+metronidazole) (eradication 87%) for penicillin-allergic patients for 14 days.¹⁵ Quadruple therapy (Helidac+H2RA or PPI) was used if the repeat UBT test of cure (TOC) remained positive after 4 weeks. Individuals were referred for endoscopy after two unsuccessful treatments.

■ Results

The prevalence of positive UBT testing (n=20) among all individuals diagnosed with chronic urticaria was 9.8% (n=204). (See *Demographics of H. pylori-positive patients.*) Seventeen were female and three were male, and ages ranged from 27 to 76 with a mean of 47.5 years. In addition to urticaria, other presenting symptoms (n=14) included excessive belching (45%), clearing of throat (35%), nausea (30%), hoarseness (20%), loss of voice (15%), and coughing (15%), with 30% (n=6) having no symptoms. A majority of individuals (n=13; 65%) denied having a previous diagnosis of reflux. Consistent with this finding was the absence of PPI or H2RA use by most patients prior to our evaluation (n=19; 95%).

The majority of individuals (n=17; 85%) had no comorbid conditions known to cause or exacerbate chronic urticaria, although three individuals had either systemic lupus erythematosus or diabetes mellitus, which was reportedly stable or in remission. Of the patients who returned for the TOC at least 4 weeks following treatment (n=11), eradication of *H. pylori* was 82%, with 100% resolution of urticaria. Two patients had positive TOC following initial treatment and failed to return following a second course of treatment. One of those patients, in addition to the remaining patients

who failed to return, reported that the urticaria had completely resolved following treatment.

■ Discussion

Evaluation and treatment is essential to eliminate nausea, pruritus, dermatitis, and to restore everyday quality of life for patients presenting with chronic urticaria and gastritis. It is well known that the majority of patients with chronic urticaria have no underlying cause identified and require prolonged treatment with H1RA/H2RA, leukotriene modifiers, omalizumab injections, or other treatments.¹² The work herein documents that acute *H. pylori* within the practice accounts for approximately 10% of patients presenting with chronic urticaria.

This was a retrospective review and real life experience. Therefore, charts for patients initially presenting with chronic urticaria and positive UBT were reviewed to determine if treatment of *H. pylori* resulted in resolution of chronic urticaria and improvement in quality of life. The small population size was another limitation of the study. The results, however, clearly suggest that eradication of *H. pylori* gastritis can result in complete resolution of chronic urticaria when the two conditions occur simultaneously.

In contrast, the association of *H. pylori* with gastritis is well known. According to the CDC, approximately two thirds of the world's population is infected with *H. pylori*, making it the most widespread infection in the world.¹³ *H. pylori* is contagious, spread from person to person through direct contact via saliva, vomit, or fecal matter, and may even spread from contaminated food and water. There is a high incidence rate in areas where living conditions and hygiene are poor, and close contact occurs with someone infected with *H. pylori*.¹³ Developing countries have a higher incidence of *H. pylori* than developed countries.

■ Prevalence

Here in the United States, prevalence of *H. pylori* may be closer to 20% to 30%, with 50% adults infected over the age of 60 and a higher prevalence in Blacks, Hispanics, and older adults. Approximately 80% of those infected may be asymptomatic, although common clinical symptoms include nausea, belching, bloating, epigastric discomfort, and pain.¹³ If infection is associated with acid reflux, additional symptoms may include throat clearing, coughing, loss of voice, and hoarseness. Occasionally, patients may have more serious symptoms, including: anemia, dysphagia, rectal bleeding, melena, vomiting, and weight loss.



H. pylori can easily penetrate the gastric protective mucous lining, avoiding the acidic pH of the stomach and moving toward a less acidic environment where it produces a significant amount of urease, an enzyme that converts the urea in the stomach into carbon dioxide, and ammonia.¹⁴ This is the basis for the C13/C14 urea breath test. The ammonia is then converted to ammonium, which leads to neutralization of gastric acid. The bacteria also induce an inflammatory response, which weakens the stomach lining and allows for damage by gastric acids, ulcer formation, and gastric cancer. If left untreated, *H. pylori* infections have a 10% to 15% lifetime risk of developing into peptic ulcers and a 1% to 2% lifetime risk of developing into gastric cancers.¹⁴

■ Recommendations

Based on current recommendations, anyone with dyspepsia, anemia, daily dependence on a H2RA such as ranitidine, or a PPI such as esomeprazole or omeprazole should be tested for *H. pylori*.^{11,15} Patients who are asymptomatic, have family members, or close friends with the condition and wish to be screened may also be tested. These results compare favorably with other studies using UBT to aid in the diagnosis of *H. pylori* gastritis and therapy for patients presenting with chronic urticaria.¹⁶ For patients negative for *H. pylori*, a majority achieved reasonable control of symptoms with a combination of H1RA/H2RA.

Demographics of *H. pylori*-positive patients (n=20)

Gender	Age	Symptoms*	History of reflux#	Reflux medication use	TOC**	Urticaria	Medication use post treatment
F	61	B, CI, C, LOV	No	No	Negative	Resolved	No
F	33	N, B, CI, H	No	No	ND	No change	Ranitidine
F	65	None	No	No	ND	Resolved	Ranitidine
F	42	None	Yes	No	Negative	Resolved	No
F	43	N, LOV, B	Yes	Yes	Negative	Resolved	No
F	60	C, LOV	No	No	ND	Resolved	No
F	27	H, CI, N, C	No	No	ND	Resolved	No
F	46	CI, H, N, B	No	No	Negative	Resolved	No
F	35	B	Yes	No	ND	Resolved	No
M	49	B	Yes	No	ND	Resolved	Ranitidine
M	68	None	No	No	Negative	Resolved	No
F	29	N	No	No	1st Positive, 2nd ND	No change	No
F	32	CI	Yes	No	1st Positive, 2nd ND	Resolved	Ranitidine
F	42	H, CI	No	No	Negative	Resolved	Levocetirizine
F	36	B, CI	Yes	No	Negative	Resolved	Levocetirizine, Ranitidine
F	72	B, CI, N	No	No	ND	Resolved	No
F	39	None	No	No	ND	Resolved	No
F	28	None	No	No	ND	Resolved	No
F	68	B	No	No	1st Positive, 2nd Negative	Resolved	No
M	76	None	Yes	No	Negative	Resolved	Ranitidine

*B = belching; C = cough; CI = clearing of throat; H = hoarseness; LOV = loss of voice; N = nausea

Documented history of reflux prior to evaluation

**TOC: Test of cure; ND: not done, patient lost to follow-up



In most cases, eradication of *H. pylori* gastritis, as demonstrated by TOC, resulted in the elimination of chronic urticaria. UBT testing is a simple, convenient office procedure that provides results within 20 minutes. Patients unable to receive UBT testing at the initial evaluation included patients currently taking antibiotics or PPIs; a 2-week antibiotic or PPI elimination period was required prior to administering UBT. Patients needing interim gastritis treatment could use ranitidine at bedtime. Warnings about prolonged PPI use (greater than 1 year) and reports of bone fractures and other complications was a concern for PPI-dependent patients with or without *H. pylori*. The use of ranitidine as an interim or chronic treatment is well tolerated and appreciated, as documented in subsequent patient evaluations and patient satisfaction surveys. The office handouts on *H. pylori* and PPIs have been extremely popular and enabled other family members and friends to consider testing when appropriate.

■ The NP's role

In conclusion, this retrospective study supports the conclusions that a subset of patients presenting with chronic urticaria may also have *H. pylori* gastritis and that office-based UBT testing enables early detection and eradication of acute *H. pylori* infection. NPs are involved in providing care to patients presenting with chronic gastritis and/or urticaria; therefore, it is important for NPs to be aware that *H. pylori* infection can directly contribute to chronic urticaria and that treating and testing for treatment can reduce patient morbidity from the infection. **NP**

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Marjohn M. Rasooly is a family nurse practitioner at Allergy and Asthma Health Care, Glen Burnie, Md.

Nancy A. Moye is a family nurse practitioner at WellOne Primary Medical & Dental Care, North Kingstown, RI.

Arnold S. Kirshenbaum is the owner of Allergy and Asthma Health Care, Glenn Dale, Md.

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