

Prevalence and Associated Risk Factors of *Helicobacter pylori* Negative Gastritis

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Abstract

Background: *Helicobacter pylori* (Hp) infection has previously been thought to account for nearly all chronic gastritis. However, recent studies have suggested that Hp-negative gastritis is common and increasing in prevalence in the United States. The etiology and associated risk factors for Hp-negative gastritis remain uncertain.

Objective: Our primary aims were to: 1) Assess the prevalence of Hp-negative gastritis and 2) Characterize differences and similarities in associated demographics, clinical features, risk factors and medical co-morbidities between Hp-negative and Hp-positive gastritis.

Methods: We performed a retrospective study of 131 consecutive patients who were referred for EGD for upper gastrointestinal symptoms at a single tertiary care center from 7/2012-7/2013. Referral symptoms comprised dysphagia, abdominal pain, nausea, vomiting, iron deficiency anemia, bloating, belching, or Barrett's esophagus surveillance. All 131 cases had biopsies at this institution, and clinical, demographic, and laboratory data were compared between individuals with Hp-negative and Hp-positive gastritis.

Results: Among all patients surveyed, 50 (38.2%) had gastritis present on biopsy, of which 39 (78.0%) were Hp-negative and 11 (22.0%) were Hp-positive. Among Hp-negative gastritis patients, 61.5% had chronic chemical gastritis, while 33.2% had chronic inactive gastritis and 5.1% had chronic active gastritis. Among Hp-positive patients, 100% had chronic active gastritis. The distribution of Hp-negative vs. Hp-positive gastritis differed ($p = 0.016$): antrum only (76.9% vs. 36.0%), corpus (10.3% vs. 36.0%), antrum and corpus (12.8% vs. 27.0%). Racial distribution differed significantly between Hp-negative (61.5% Caucasian, 20.5% African American, 18.0% other races) and Hp-positive (0% Caucasian, 72.7% African-American, and 27.3% other races) patients ($p < 0.001$). The presence of medical co-morbidities was significantly associated with Hp-negative gastritis vs. Hp-positive gastritis: 82.1% vs. 18.2% ($p < 0.001$). GERD was the most common medical co-morbidity noted, being present in 66.7% of Hp-negative patients in contrast to only 9.1% of Hp-positive gastritis ($p = 0.001$). There were no significant differences between Hp-negative and Hp-positive patients in predominant symptoms, primary referral indication, age, gender, prior Hp infection, tobacco, alcohol, PPI, NSAID, or antibiotic usage.

Conclusions: Hp-negative gastritis is a common entity that comprised the majority of consecutive gastritis cases in our study. It was significantly associated with the presence of medical co-morbidities, particularly GERD, and Caucasian race. Hp-negative gastritis also appears to have an anatomic predilection for the antrum. No association with referral symptoms, PPI use, NSAID use, or other risk factors was identified. Large-scale prospective studies are needed to further delineate the natural history, etiology, risk factors, pathogenesis, and clinical relevance of this increasingly common disease entity.

Keywords: *Helicobacter pylori*; *Helicobacter pylori* negative gastritis; Hp negative; Hp negative gastritis risk factors; Hp positive gastritis; GERD; Gastroesophageal reflux disease; Gastritis; Chronic gastritis

Introduction

Gastritis typically presents as inflammation of the mucosal lining of the stomach, which can subsequently lead to the development of ulcers. The dominant etiology of gastritis worldwide has been thought

to be *Helicobacter pylori* (Hp) infection, which is also known to increase the risk of non-cardia gastric cancer by six to eightfold [1-3]. In cases of gastritis without evidence of Hp, the absence of bacteria expected has frequently been assumed to represent false negatives [4]. Explanations include sampling error, recent use of antibiotics that suppressed the infection but not the inflammation, and use of protein pump inhibitor (PPI) that decreased the numbers of bacteria and shifted their populations from the antrum to the corpus [5].

Emerging data, however, point to the distinct entity of Hp-negative gastritis. A cross-sectional study in 2013 involving 491 patients provided one of the robust, systemic evidence. The authors used the updated Sydney System to detect 200 patients with gastritis. 41 of them were found to be negative for Hp by serology, culture, and histology including histochemical and immunohistochemical staining [6]. Further circumstantial and direct evidence are now available, which demonstrated the lack of correlation between the Hp-negative and Hp-positive groups by epidemiology, clinical sequel of chronic Hp infection, and follow-up biopsies [5,7].

The prevalence, etiology and associated risk factors for Hp-negative gastritis are yet to be clearly defined. Associations with alcohol, smoking, and PPI use have been implicated in prior studies. Histamine 2 receptor antagonists and NSAIDs have also been considered [6]. Others have suggested a significantly increased frequency of Hp-negative gastritis, of unclear etiology, in patients with functional dyspepsia, non-erosive gastroesophageal reflux, and erosive esophagitis [8]. Also, one recent community-based study reported that Hp antibody status was inversely associated with a GERD diagnosis and GERD symptoms [9]. A theory has thus emerged that the absence of Hp infection may be associated with both GERD symptoms and complications.

In light of the gap in current evidence, we sought to assess the prevalence of Hp-negative gastritis at a single tertiary care institution, and characterize the differences in demographics, clinical features, risk factors and medical co-morbidities including GERD between Hp-negative and Hp-positive gastritis.

Materials and Methods

Study group

We performed a retrospective study of 131 consecutive patients referred for esophagogastroduodenoscopy (EGD) for the evaluation of upper GI symptoms at a single tertiary care center during a one-year period (from 7/2012 to 7/2013). Referral symptoms included dysphagia, abdominal pain, nausea, vomiting, weight loss, iron deficiency anemia, bloating, belching, or Barrett's esophagus surveillance. Gastric biopsies were taken from all subjects. Biopsy sites included two from the gastric antrum and two from the corpus (body).

The presence or absence of gastritis (Hp-positive or negative) and the localization of Hp in the stomach (antrum or body) were assessed in all patients. Correlations with demographic factors and Hp-negative vs. Hp-positive gastritis were performed for age, gender, race or ethnicity, proton pump inhibitor (PPI) usage, tobacco use, alcohol intake, NSAIDs, antibiotics, and additional medical co-morbidities.

Survey of co-morbidities

Demographic assessments were made systematically in all subjects by chart review. Co-morbidities were determined by evaluating past medical history or were self-reported by the subjects.

We included the medical co-morbidities of esophagitis, GERD, functional dyspepsia, gastric or other cancers, dysmotility (e.g. gastroparesis or esophageal motility disorders), small bowel obstruction, diverticulitis, functional bowel disease including IBS,

autoimmune disease with GI involvement, and small intestinal bacterial overgrowth (SIBO).

Esophagogastroduodenoscopy (EGD)

All patients underwent EGD at a single endoscopy unit (JHMI) and had two gastric biopsies performed in the antrum and corpus and placed in two separate biopsy containers. The presence of gastritis, ulceration, erosions and other lesions was also derived from the endoscopy report.

Histopathology, serology, cultures

Diff-Quik staining method was used as the standardized method for all the cases of *H. pylori*. Biopsies were taken from the mid antrum and the greater curvature of mid corpus.

Statistical analysis

Statistical analyses were carried out using STATISTICA (version 4.2, Stat Soft, Tulsa, OK). Two-tailed Student's t-test was used for the comparison for two groups for continuous datasets. Two-tailed Fisher's exact test and Chi-squared test were used for the comparison of two groups for categorical datasets with two and three or more categories, respectively, unless otherwise stated. Cases lacking data were excluded from statistical analyses, unless otherwise stated. Statistical significance was noted at a p-value of less than 0.05, while non-significant trends were noted at a p-value of less than 0.1.

Results

To determine the prevalence, demographics, and clinicopathological characteristics of Hp-positive and Hp-negative gastritis, records of 131 consecutive patients were reviewed. Among all patients, 50 (38.2%) had histologic evidence of gastritis on biopsies. Among these 50 patients, 39 (78.0%) had Hp-negative gastritis, while 11 (22.0%) had Hp-positive gastritis.

Demographic characteristics in gastritis patients are presented in Table 1. Among the 39 patients with Hp-negative gastritis, 24 (61.5%) were Caucasian, 8 (20.5%) were African-American, 3 (7.7%) were other races, and racial identity was unavailable in 4 (10.2%). Among the 11 patients with Hp-positive gastritis, 8 (72.7%) were African-American and 3 (27.3%) were other races.

No Hp-positive gastritis cases were Caucasian. There was no significant difference in gender distribution or age was observed. Thus, the Caucasian race was the sole demographic factor significantly associated with Hp-negative gastritis (24 of 39 Hp-negative cases, 61.5% vs. 0 of 11 Hp-positive cases, 0%; $p < 0.001$).

Attributes	Categories	Hp-negative	Hp-positive	Total	p-value
		39 (78.0%)	11 (22.0%)	50	
Gender	Men	17 (43.6%)	5 (45.5%)	22	1
	Women	22 (56.4%)	6 (54.5%)	28	
Age (mean)		56.3 ± 16.1	49.5 ± 11.6	N/A	0.196
Race	White	24 (61.5%)	0 (0.0%)	24	<0.001
	Black	8 (20.5%)	8 (72.7%)	16	
	Other*	3 (7.7%)	3(27.3%)	6	
	Unknown	4 (10.1%)	0 (0.0%)	4	
Nationality	American	33 (84.6%)	8 (72.7%)	41	0.392
	Non-American	6 (15.4%)	3 (27.3%)	9	

*Other consists of 2 Asian and 1 Middle Eastern for both Hp-negative and Hp-positive gastritis.

Table 1: Patient demographics of Hp-positive and Hp-negative gastritis.

We also compared clinical and histopathological features (Table 2). Among all 39 Hp-negative gastritis patients, 2 (5.1%) had active chronic gastritis, while 37 (94.9%) had other forms of chronic gastritis consisting of 24 (61.5%) chronic chemical gastritis and 13 (33.2%)

chronic non-active gastritis. In contrast, all 11 (100.0%) Hp-positive patients had active gastritis (vs. 2 of 11 Hp-negative gastritis cases, 5.1%; $p < 0.001$).

Attributes	Categories	Hp-negative	Hp-positive	Total	p-value
		39	11		
Gastritis activity	Chronic active	2 (5.1%)	11(100.0%)	13	<0.001
	Chronic chemical	24 (61.5%)	0 (0.0%)	24	
	Chronic inactive	13 (33.2%)	0 (0.0%)	13	
Gastritis location	Antrum	30 (76.9%)	3 (27.3%)	33	0.016
	Corpus	4 (10.3%)	3 (27.3%)	7	
	Antrum and Corpus	3 (7.7%)	3 (27.3%)	6	
	Unknown	2 (5.1%)	2 (10.5%)	4	

Table 2: Histopathological features of Hp-positive and Hp-negative gastritis.

Hp-negative and Hp-positive gastritis differed with respect to the anatomical distribution of the affected regions ($p = 0.016$, Table 2): Hp-negative gastritis had 30 cases (76.9%) limited to antrum, compared to Hp-positive gastritis with 3 cases (27.3%); 4 (10.3%) Hp-negative and 3 (27.3%) Hp-positive patients had corpus-only disease, while 3 (7.7%) Hp-negative and 3 (27.3%) Hp-positive patients had corpus and antrum disease. 2 (5.1%) Hp-negative and 2 (18.2%) Hp-positive patients were missing biopsy site information. Thus, patients with Hp-negative gastritis exhibited a significant predilection for antrum.

The study assessed the indications for EGD in Hp-positive vs. Hp-negative gastritis patients (Table 3), and compared previous history of Hp eradication, usage of PPIs, antibiotics, NSAIDs, alcohol, tobacco, and medical co-morbidities in the two patient groups (Table 4).

No indication for EGD was more prevalent with statistical significance in Hp-negative than in Hp-positive cases. Medical co-morbidities were the only factor significantly associated with Hp-negativity (28 cases, 71.8% vs. 2 cases, 18.2%; $p = 0.004$).

Among the co-morbidities, GERD was the most common and the only co-morbidity that demonstrated significant association with Hp-negative gastritis (26 cases, 66.7% vs. 1 case, 9.1%; $p = 0.001$, Table 5).

Indication		Hp-negative	Hp-positive	p-value
Suspected Hp	+	2 (5.1%)	2 (18.2%)	0.206
	-	37 (94.9%)	9 (81.8%)	
BE	+	4 (10.3%)	0 (0.0%)	0.564
	-	35 (89.7%)	11 (100.0%)	
IM	+	2 (5.1%)	0 (0.0%)	1
	-	37 (94.9%)	11 (100.0%)	
GERD symptoms	+	14 (35.9%)	3 (27.3%)	0.728
	-	25 (64.1%)	8 (72.7%)	
Abdominal pain	+	8 (20.5%)	3 (27.3%)	0.688
	-	31 (79.5%)	8 (72.7%)	
Nausea/vomiting	+	3 (7.7%)	2 (18.2%)	0.301
	-	36 (92.3%)	9 (81.8%)	
Bloating/belching	+	2 (5.1%)	0 (0.0%)	1
	-	37 (94.9%)	11 (100.0%)	
Dysphagia	+	5 (12.8%)	1 (9.1%)	1
	-	34 (87.2%)	10 (90.9%)	
Hx/FHx of GI malignancy	+	3 (7.7%)	0 (0.0%)	1
	-	36 (92.3%)	11 (100.0%)	
Anemia	+	1 (2.7%)	1 (9.1%)	0.403
	-	36 (97.3%)	10 (90.9%)	
Combined upper GI symptoms	+	16 (41.0%)	5 (45.5%)	0.455
	-	23 (59.0%)	6 (54.5%)	
Other	+	2 (5.1%)	0 (0.0%)	1
	-	37 (94.9%)	11 (100.0%)	
Multiple indications	+	7 (17.9%)	1 (9.1%)	0.666
	-	32 (82.1%)	10 (90.9%)	

Table 3: Indications for EGD in Hp-positive and Hp-negative gastritis.

Factor		Hp-negative Gastritis	Hp-positive Gastritis	p-value
Previous Hp Tx	+	5 (12.8%)	0 (0.0%)	0.573
	-	34 (87.2%)	11 (100.0%)	
Co-morbidity	+	28 (71.8%)	2 (18.2%)	0.004
	-	11 (28.2%)	9 (81.8%)	
PPI	+	16 (41.0%)	3 (27.3%)	0.498
	-	23 (59.0%)	8(72.7%)	

ABX	+	1 (2.6%)	1 (9.1%)	0.402
	-	37 (94.9%)	10 (90.9%)	
	Unknown	1 (2.6%)	0 (0.0%)	
NSAIDs	+	5 (12.8%)	3 (27.3%)	0.351
	-	34 (87.2%)	8 (72.7%)	
Tobacco	+	11 (28.2%)	5 (50.0%)	0.283
	-	25 (64.1%)	5 (45.5%)	
	Unknown	3 (7.7%)	1 (9.1%)	
Alcohol	+	17 (43.6%)	7 (63.6%)	0.314
	-	22 (56.4%)	4 (36.4%)	

Note. Hp: *Helicobacter pylori*; Tx: Treatment; PPI: Proton Pump Inhibitor; ABX: Antibiotics; NSAID: Nonsteroidal Anti-Inflammatory Drugs.

Table 4: Use of PPI, antibiotics, NSAID, Alcohol, tobacco and presence of medical co-morbidities in Hp-positive and Hp-negative gastritis.

Co morbidities		Hp-negative gastritis	Hp-positive gastritis	Total	p-value
		39	11	50	
All co-morbidities	+	32 (82.1%)	2 (18.2%)	34 (68.0%)	<0.0001
	-	7 (17.9%)	9 (81.8%)	16 (32.0%)	
GERD (includes esophagitis and BE)	+	26 (66.7%)	1 (9.1%)	27 (54.0%)	0.001
	-	13 (33.3%)	10 (90.9%)	23 (46.0%)	
Esophagitis	+	9 (23.1%)	0 (0.0%)	9 (18.0%)	0.177
	-	30 (76.9%)	11(100.0%)	41 (82.0%)	
IBS	+	4 (10.3%)	1 (9.1%)	5 (10.0%)	1
	-	35 (89.7%)	10 (90.9%)	45 (90.0%)	
All cancer	+	5 (12.8%)	0 (0.0%)	5 (10.0%)	0.573
	-	34 (87.2%)	11(100.0%)	45 (90.0%)	
Gastric cancer specifically (includes gastric carcinoid)	+	1 (2.6%)	0 (0.0%)	1 (2.0%)	1
	-	38 (97.4%)	11(100.0%)	49 (98.0%)	
Esophageal or gastric motility disorder (includes gastroparesis and esophageal motility disorders such as spasm)	+	3 (7.7%)	0 (0.0%)	3 (6.0%)	1
	-	36 (92.3%)	11(100.0%)	47 (94.0%)	
Connective tissue & Autoimmune disease (RA, CD, CRPS, fibromyalgia, lupus)	+	5 (12.8%)	2 (18.2%)	7 (14.0%)	0.641
	-	34 (87.2%)	9 (81.8%)	43 (86.0%)	
all "other" co-morbidities (includes diverticulitis, SBO, etc)	+	2 (5.1%)	0 (0.0%)	2 (4.0%)	1
	-	37 (94.9%)	11(100.0%)	48 (96.0%)	

Table 5: Correlations between co-morbidities and Hp-positive and Hp-negative gastritis.

Discussion

Hp-negative gastritis comprised the majority (78.0%) of 50 consecutive gastritis cases at our institution. We found that it was much more common in Caucasians (61.5%) than in other races, particularly African-Americans, where the prevalence was only 20.5%. Other studies corroborated the increased prevalence in Caucasians (70.7%) vs. African-Americans (26.8%) [6]. Overall, this suggests that this common entity may be increasing in prevalence, at least at this tertiary care institution [5,6].

Though the true prevalence is unknown, the decreasing rate of the Hp infection in developed countries may contribute to this finding, by accentuating previously minor proportion occupied by Hp-negative gastritis [10,11]. On the other hand, it may represent HSSdit mit an umbrella term encompassing purportedly associated factors, including PPI, s, alcohol, tobacco, IBD, celiac disease, autoimmune gastritis, a small portion of missing the bacteria by sampling error, and infection with other species including *H. heilmannii*, *Streptococcus* and *Prevotella*. Among these, prior studies have highlighted a significant association with PPI, NSAID, alcohol, and tobacco use [12-14].

In contrast, however, we found no association of Hp-negativity with PPI, NSAID, alcohol, tobacco, referral symptoms, or any specific risk factor. It was only significantly associated with the presence of medical co-morbidities, especially GERD which was found in 66.7% of Hp-negative pool. An explanation that ties these findings together with prior studies is that patients with GERD symptoms are likely to be on PPI treatment. Thus, it is possible that GERD has the direct correlation with Hp-negative gastritis, while PPI use is simply a confounding variable.

Prior studies suggested that the incidence of GERD has increased in parallel with decreasing incidence of Hp-positive gastritis [15]. Currently available literature support that Hp infection and GERD exhibit associations that are anatomically dependent. For example, with Hp eradication, Hp-positive gastritis patients tend to exhibit worsening of GERD symptoms, except antrum-dominant gastritis patients who show improvement [16]. Exact mechanism is unclear, and role of local inflammation and cytokines, such as tumor necrosis factor alpha and interleukin-1-beta have been implicated. Furthermore, Hp infection enhances the acid suppression by PPI therapy [17-19]. These interesting finding coupled with our result supports previous speculation that Hp infection may even be protective against development of GERD [20]. The standard of care still is to eradicate Hp because of the risk of development or recurrence of peptic ulcer disease as well as two to three times higher incidence of gastric adenocarcinoma [21-28]. In the end, the possibility of protection against GERD conferred by Hp infection remains and needs to be further explored.

In our study, Hp-negative gastritis was frequently mild, focal, and chronic, where Hp-positive gastritis tended to be chronic-active or active. This is in line with current literature demonstrating low prevalence of sequelae such as peptic ulcer disease and gastric cancer associated with Hp-negativity [17,18]. Anatomically, we found that the antrum was uniquely prone to Hp-negative gastritis as compared to other types of gastritis. We also observed that chronic chemical gastritis was a very common histopathologic entity in Hp-negative patients (61.5%), although other studies have reported a lower prevalence of chemical gastritis [6]. This finding suggests that chemical gastritis, not associated with Hp infection, may now be the predominant forms of this disease in the United States. Proposed

etiologies of chemical gastritis include GERD, chronic bile reflux, NSAID, and aspirin, of which GERD is highlighted as the most significant factor in the result of our study [24].

The clinical relevance and prognosis of Hp-negative gastritis remain unknown and need to be further examined given the relatively high prevalence of this entity. For example, it is unclear if the risk of ulcer or cancer is increased, or if it predisposes to upper gastrointestinal symptoms. However, at least it is clear that in clinical practice, empirical treatment for *H. pylori* is not warranted in patients with gastritis without clear evidence for the presence of this infection. Also, it is worth noting that in pediatric gastritis patients with Hp-negativity, it is now recognized that their chief complaints and gastritis demonstrated poor association. In fact, evidence-based clinical guidelines for Hp infection in children suggest that the presence or absence of gastritis is not a part of the diagnostic workup [25]. Thus, routine treatment with PPI or H2 blockers is not advised.

Limitations of our study include the characteristics inherent to retrospective studies including imperfect control of bias and confounding variables. Also, as it was retrospective the biopsy procedure was not in accordance with the updated Sydney System requiring at least five specimens, and there was only one pathologist for review. Consideration of past history of Hp treatment was attempted where possible, but it could not be done for every case.

In summary, Hp-negative gastritis was a distinct entity characterized by the tendency to affect antrum, and it represented 78.0% of all gastritis at this institution. Caucasian race and co-morbidity of GERD were significantly associated, while notably PPI, NSAID, alcohol, and tobacco use were not. This result raises the question whether Hp infection may provide protection against GERD through unclear mechanisms [26-28]. Clinically, this study provides implications for screening and management for appropriate population with Hp-negative gastritis. Future, prospective studies are needed to further delineate the natural etiology, risk factors, prognosis of this poorly understood and increasing clinical entity, as well as possible interactions associated with GERD and Hp infection.

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