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# ASSOCIATION OF H. PYLORI WITH CHRONIC ACTIVE GASTRITIS: A LITERATURE REVIEW

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## ABSTRACT
Helicobacter pylori infection and chronic active gastritis are in extricable linked and this organism is almost certainly responsible for inducing the resulting inflammatory changes H. Pylori primarily colonize the antral region of the stomach, although it can also be found in the corpus and in the duodenum in regions of gastric metaplasia.

## INCIDENCE
H. Pylori infection has worldwide distribution; about 50% of the world's population is infected. H. Pylori infection is highly prevalent in Asia and in developing countries.[1] H.pylori is present in 90% of patients with chronic gastritis affecting the antrum. Colonization rate varies with age, reaching 50% in asymptomatic American adults over 50 years age.[2] Children aged 2-8 years in developing nation acquire the infection at a rate about 10% per year; whereas in the United States, children become infected at the rate of less than 1% per year. H. pylori associated chronic gastritis appears to be more common among Asian and Hispanic people than in people of other races.[3]

## GASTRITIS
It is inflammation of mucosa. It is a group of disorders that have inflammatory changes in the gastric mucosa in common but that have different clinical factors, histological characteristics and pathogenesis.[4] Based on the severity of mucosal injury Gastritis is classified as erosive or non-erosive. It is also classified according to the site of involvement (cardia, body, and antrum). Histologically Gastritis can be further classified as acute or chronic based on the inflammatory cell type. Among different forms of gastritis some involve acid-peptic and H. pylori disease.

## ACUTE GASTRITIS
### Erosive Gastritis
The most common causes of acute gastritis is caused by acute infection with H. pylori. However, H. pylori induced acute gastritis has not been extensively studied. Hypochlorhydria lasting for up to 1 year may follow acute H. pylori infection.[5] *H. pylori* gastritis typically starts as an acute gastritis in the antrum, causing intense inflammation, and over time, it may extend to involve the entire gastric mucosa resulting in chronic gastritis.[6] Gastric mucosal erosion caused by damage to mucosal defenses Leads to erosive gastritis. Erosions may be flat which are superficial, limited to the muscularis mucosa. They may be multiple and vary in size. Diagnosis is by endoscopy Raised erosions have an elevated, inflamed border. They are usually multiple and may develop in the antrum but also found in corpus and fundus. Diagnosis is by endoscopy and they present as series of nodules or bulges on the crests of the folds, characteristically in the antrum endoscopically. Causes of erosive gastritis include NSAIDs, alcohol, stress and H. pylori infection. Beside the infective causes all others can cause acute hemorrhagic gastritis.[7]

**Table 1: Classification of Gastritis.**

| **Sydney- classification of gastritis** | |
|---|---|
| **Endoscopic criteria of gastritis** | **Classification according to etiology** |
| 1. Erythematous/exudative gastritis.<br>2. Superficially erosive gastritis<br>3. Polypoid gastritis with erosions<br>4. Atrophic gastritis<br>5. Hemorrhagic gastritis | Autoimmune gastritis (type A)<br>Bacteria related gastritis (type B)<br>Gastritis induced by Chemotoxic agents<br>Distinct forms of gastritis |

| | |
|---|---|
| 6. Bile gastritis<br>7. Giant folds gastritis | |
| Classification according to localization | Grading |
| 1. Pan gastritis<br>2. Gastritis of the body<br>3. Antral gastritis | Low<br>Middle<br>High |
| Histomorphologic criteria | |
| 1. Acute<br>2. Chronic<br>3. Chronically-active | |

Stolte & Edit concluded that chronic erosion of the antral mucosa represents a sequel of H. pylori gastritis. They demonstrated that the antral erosion showed the specificity of 92% and sensitivity of 22% with positive predictive value of 86% to H. pylori infection. They also conclude that the raised erosions were more precisely associated with H. pylori infection than flat erosions.[9] Svintsits'kyĭ AS et al had done a study where a total of 32 patients with chronic antral gastritis without erosion were examined together with 25 patients with chronic erosive antral gastritis. In chronic erosive antral gastritis vs erosion-free chronic antral gastritis H. pylori are found with higher frequency in the antral segment of the stomach, the mucous membrane exhibiting a higher degree of infectious lesion.[8] Kolarski V et al did a study with endoscopically proved chronic erosive gastritis (52 patients), erosive duodenitis (36 patients) and erosive gastroduodenitis (12 patients). The examinations revealed the presence of Helicobacter pylori in mean 77% of the patients with erosive gastritis, duodenitis and gastroduodenitis. Helicobacter pylori were found most often in patients with chronic erosive duodenitis--83.3%, whereas in the patients with erosive gastritis it was found in 73.07%. They concluded that one of the important pathogenetic factors of erosive gastritis, duodenitis and gastroduodenitis is the Helicobacter pylori infection of gastro duodenal mucosa.[9]

## CHRONIC GASTRITIS

The unqualified term chronic gastritis is divided histologically into type A and B. With three stages which bare progressive over many years- chronic superficial gastritis, atrophic gastritis and gastric atrophy. The inflammatory cells infiltrate in chronic gastritis consist predominantly of lymphocytes and plasma cells. Polymorph nuclear leucocytes and eosinophils may be present in a small numbers but do not predominant. Chronic gastritis is often patchy and irregular in distribution.[10]

## CAUSES OF GASTRITIS

### H. Pylori infection

Some times after major surgery, traumatic injury, burns or severe infection.

Certain diseases - Pernicious anemia, autoimmune disorder, chronic bile reflux.

Dietary factors - Caffeine found in coffee, black tea, green tea, some soft drinks, Alcohol.

Drugs – Aspirin, NSAIDS.

## CLINICAL PRESENTATION

Patients with gastritis may be asymptomatic; however the following symptoms are frequently encountered: -

Abdominal pain or upset.

Belching

Abdominal bloating

Nausea, Vomiting or a feeling of fullness or of burning in the upper abdomen.

Blood in vomit or black stools

## HELICOBACTER PYLORI

### History of gastric Helicobacter Pylori

In 1875, German scientists found helical shaped bacteria in the lining of the human stomach. The bacteria could not be grown in culture and the results were eventually forgotten.[11] In 1893, the Italian researcher Giulio Bizzozero described helical shaped bacteria living in the acidic environment of the stomach of dogs. Professor Walery Jaworski of the Jagiellonian University in Kraków investigated sediments of gastric washings obtained from humans in 1899. Among some rod-like bacteria, he also found bacteria with a characteristic helical shape, which he called Vibrio rugula. He was the first to suggest a possible role of this organism in the pathogeny of gastric diseases. This work was included in the "Handbook of Gastric Diseases" but it did not have much impact as it was written in Polish.[12] The bacterium was rediscovered in 1979 by Australian pathologist Robin Warren, who did further research on it with Barry Marshall beginning in 1981; they isolated the organisms from mucosal specimens from human stomachs and were the first to successfully culture them. In their original paper, Warren and Marshall contended that most stomach ulcers and gastritis were caused by infection by this bacterium and not by stress or spicy food as had been assumed before.[13] The medical community was slow to recognize the role of this bacterium in stomach ulcers and gastritis, believing that no microorganism could survive for long in the acidic environment of the stomach. The community began to come around after further studies were done, including one in which Marshall drank a Petri dish of H. pylori,

developed gastritis, and the bacteria were recovered from his stomach lining, thereby satisfying three out of the four Koch's postulates. The fourth was satisfied after a second endoscopy ten days after inoculation revealed signs of gastritis and the presence of "H. pylori". Marshall was then able to treat himself using a fourteen-day dual therapy with bismuth salts and metronidazole. Marshall and Warren went on to show that antibiotics are effective in the treatment of many cases of gastritis. In 1994, the National Institutes of Health (USA) published an opinion stating that most recurrent gastric ulcers were caused by H. pylori, and recommended that antibiotics be included in the treatment regimen.[14] The bacterium was initially named Campylobacter pyloridis, then C. pylori (after a correction to the Latin grammar and in 1989, after DNA sequencing and other data showed that the bacterium did not belong in the Campylobacter genus, it was placed in its own genus, Helicobacter. The name pylori means "of the pylorus" or pyloric valve (the circular opening leading from the stomach into the duodenum, from the Greek word πυλωρός, which means gatekeeper. While H. pylori remains the most medically important bacterial inhabitant of the human stomach, other species of the Helicobacter genus have been identified in other mammals and some birds, and some of these can infect humans. Helicobacter species have also been found to infect the livers of certain mammals and to cause liver disease.[15]

## BACTERIOLOGY AND EPIDEMIOLOGY OF H. PYLORI

H. pylori are a helical shaped Gram-negative bacterium, about 3 micrometers long with a diameter of about 0.5 micrometer. It has 4–6 flagella. It is microaerophilic, i.e. it requires oxygen but at lower levels than tho.se contained in the atmosphere. It contains a hydrogenase, which can be used to obtain energy by oxidizing molecular hydrogen ($H_2$) that is produced by other intestinal bacteria. It tests positive for oxidase, catalase, and urease. It is capable of forming biofilms and conversion from helical to coccoid form. Both likely to favor its survival and be factors in the epidemiology of the bacterium. The coccoid form of the organism has not been cultured, but has been found in the water supply in the US. This form has also been found to be able to adhere to gastric epithelial cells in vitro.[16]

## COLONIZATION

With its flagella, the bacterium moves through the stomach lumen and drills into the mucus gel layer of the stomach. It then finds ways to live in various areas of the stomach. The known areas include: inside the mucus gel layer (with a preference for the superficial area), above epithelial cells, and inside vacuoles formed by H. pylori in epithelial cells. It produces adhesins, which bind to membrane-associated lipids and carbohydrates and help its adhesion to epithelial cells. It produces large amounts of urease enzymes, which are localized inside and outside of the bacterium. Urease metabolizes urea (which is normally secreted into the stomach) to carbon dioxide and ammonia, which neutralizes gastric acid. The survival of H. pylori in the acidic stomach is dependent on urease, and it would eventually die without it. The ammonia that is produced is toxic to the epithelial cells, and with other products of H. pylori, including protease, catalase, and phospholipases causes damage to those cells. Some strains of the bacteria have a particular mechanism for "injecting" the inflammatory inducing agent peptidoglycan from their inflammation of own cell wall into epithelial stomach cells. This factor may play a role in allowing certain strains to invade host tissue.

## EFFECTS ON GASTRIC PHYSIOLOGY

In addition to producing local injury of gastric mucosa, H. pylorus alters normal gastric secretion. Interestingly, the location and severity of the infection seem closely associated with the ultimate clinical outcome, most likely because of effects on gastric physiology. Many studies have shown that patients with a duodenal ulcer who are infected with H. pylori have an increased serum level of gastrin, which—in turn—leads to increased acid output.[17] These patients tend to have a milder phenotypic expression of their gastritis, with inflammation mostly in the antrum or distal part of the stomach.[18] In contrast, patients with gastric adenocarcinoma, a known complication of H. pylori infection, tend to have pan gastritis, with involvement of the acid-secreting body of the stomach as well as the antrum. This condition leads to atrophy of parietal cells (which are responsible for producing acid) and gastrin-producing cells of the antrum (which stimulate acid secretion) and eventually produces achlorhydria. Patients with gastric adenocarcinoma also have impaired acid secretion in response to stimulation with gastrin.[19]

## EPIDMIOLOGY OF H. PYLORI

Helicobacter pylori have been isolated from persons in all parts of the world. Human are the major sole of reservoir for H. pylori; which spread from person to person by oral-oral, fecal-oral or gastro-oral routes. On occasion, transmission occurs from person to person through improperly cleaned endoscopes. H. pylori have now been isolated from faces especially in children.[20] The prevalence of H. pylori is related to age and geographical location. Males and females are equally affected. Infection is many times more common in developing countries than in developed ones. Within a given population, infection is more common in lower socio-economic groups.[21] In all population; infection is most commonly acquired in childhood possibly from parents or other children and usually lasts for the lifetime of the individual. There is a steady increase with age. In a preliminary study, 80% of the general population were infected with H. pylori.[22] In another study, it was found that there was a significant regional difference in an isolated rural village.[23] Numerous studies have tried to assess the incidence and prevalence of H. pylori infection, its mode of transmission, and any risk factors contributing to development of the infection. The annual incidence reported in 3 adult studies in developed

countries was between 0.3% and 0.5% per year.[24] Prevalence estimates vary greatly, depending on the location of the study group and the characteristics of the population studied. In general, prevalence increases with age and correlates positively with a low socioeconomic status during childhood.[25] Worldwide, but especially in developed nations, infection with H. pylori is declining. The acquisition of H. pylori occurs during childhood, most often by a fecal-oral or oral-oral route. Some studies have also indicated a role for a gastro oral route of transmission.[26] The role played by other factors, including ABO blood type, alcohol and tobacco use, dietary and nutritional influences, and genetic predisposition to infection, has also been studied, but results have been inconsistent.[27] Interestingly, a recent study of 655 subjects from a teaching hospital in Rome found an overall prevalence of infection of 40%, with a higher prevalence among nurses and auxiliary employees than among physicians.[28] Low socioeconomic factors namely lack of education, poverty, overcrowding, poor sanitation and unsafe water supplies are high risk factors. Interfamilial spread of the infection has been well documented. Major factors that may contribute for the possible association with H. Pylori positivity are smoking, alcohol consumption, diet, occupational exposures, waterborne exposures, hygiene practices, density/crowding, social factors, family history of gastric disease diet, occupational exposures and waterborne exposures.

**Smoking**

Smoking has a destructive effect on the immunity of gastric mucosa and lining layers and hence increases its susceptibility to infection by H. pylori. Cigarette smoking was found to have the highest statistically significant correlation with H. pylori infection.[29] Studies have assessed the possible association between H. pylori infection and smoking. Whereas some found that H. pylori-seropositive subjects were overall more likely than-seronegative subjects to be current smokers, results were often not consistent by race or gender. Hamajima et al.[30] Found an odds ratio of 7.8 for H. pylori infection for current male smokers but an odds ratio of only 1.2 for current female smokers. Conversely, Lin et al. found a significant association with current smoking for females (OR = 2.8) but not for male.[31] The positive finding (OR = 1.7) reported by Fontham et al. held for Blacks (OR = 3.1) but not for Whites (OR = 0.6), and Lin et al. found no association with intensity or age at which smoking began. Most of the recent studies found no significant association with current smoking or any other measure of tobacco use and one recent study from Japan reported a significant negative association with current smoking. Some authors have suggested that these contradictory results may be due to uncontrolled confounding by social class or to differential antibiotic use, since smoking appears to affect treatment success.[32] Heavy cigarette smokers were found to have the highest risk, followed by moderate to mild cigarette smokers.[33] The prevalence and relative risk of H. pylori infection was significantly higher in blood group O positive patients (90.3%) than in blood group A (41%), blood group B (27.4%), or blood group AB (62%) patients. This study suggested a significant correlation between active H. pylori infection and blood group O-positive patients.

## CLINICAL MANIFESTATIONS

**Gastritis and Gastric Cancer**

Once infected with H. pylori, most persons remain asymptomatic but the typical course of disease in infected patients begins with chronic superficial gastritis leading to atrophic gastritis. This appears to be a key event in the cellular cascade that results in the development of gastric carcinoma. H. pylorus stimulates lymphocytic infiltration of the mucosal stroma; this infiltration may act as a focus for cellular alteration and proliferation, ultimately resulting in neoplastic transformation to lymphoma. It appears that H. pylori also produce proteins that stimulate growth of lymphocytes in the early stages of neoplasia. Most tellingly, it has been reported that regression of low-grade gastric MALT lymphoma can be achieved in 70% to 90% of patients with eradication of H. pylori infection.[34]

**Peptic Ulcer Disease**

There is strong relationship between H. pylori infection and peptic ulcer disease and it is now accepted that the organism is the major cause. Following the eradicating of the infection the natural course of peptic ulcer disease by has been dramatically reduced its recurrence rate in treated patients, compared with untreated patients.

**Non ulcer Dyspepsia**

Non ulcer dyspepsia comprises of various symptoms, including dysmotility-like, reflux-like and ulcer-like symptoms. There can be many possible causes for non-ulcer dyspepsia, including lifestyle factors, stress, altered visceral sensation, and increased serotonin sensitivity, alterations in gastric acid secretion and gastric emptying, and H. pylori infection. A recent review also highlighted the role played by psychosocial impairment (eg, depression, somatization, anxiety) in patients with non-ulcer dyspepsia.[35]

**Gastro esophageal Reflux Disease**

Possibility of relationship between infection with H. pylori and gastro esophageal reflux disease (GERD) in its various manifestations have been focused (eg, esophagitis, Barrett's esophagus). Some investigators have suggested a link between the presence of H. pylori and a decreased risk for developing esophagitis and Barrett's esophagus; although this inverse association is supported by many prevalence studies, others fail to show it.[36]

**Helicobacter pylori infection and vascular diseases**

Helicobacter pylori has been found to be associated with vascular diseases like atherosclerosis; coronary artery disease (actual myocardial infarction; primary Raynaud

phenomenon and primary headache. Mendall et at, reported for the first time a higher seroprevalence of H. pylori infection in male patients with established coronary artery disease compared with age – and sex matched controls. The pathogenetic mechanisms involved in coronary heart diseases are:

1) Development of procoagulant status,
2) Action through inflammatory mediators' e.g C-reactive protein, TNF-alpha.
3) Decrease in the level of antioxidants.

**Helicobacter pylori infection and autoimmune diseases**

H. pylori infection had been found to be associated with some autoimmune diseases like Sjogren's syndrome, Schonlein-Henoch purpura, autoimmune thyroiditis, idiopathic arrhythmias, Parkinson's diseases and nonarterial anterior optic ischemic neuropathy. The pathogenetic mechanism relating H.pylori to any of these immunological diseases is unknown.

**Helicobacter pylori infection and skin diseases**

H. pylori infection has been linked to several skin diseases like chronic idiopathic urticaria, rosacea, alopecia etc. There is an association with chronic idiopathic urticaria with the pathogenetic mechanism related to an increase in gastric vascular permeability during H.pylori infection ultimately leading to greater exposure of the host to alimentary allergens.

## DIAGNOSTIC METHODS OF H. PYLORI INFECTION

No single method can be considered to be ideal for the detection of H. pylori infection (Anonymous, 1997). On the other hand, the cost-effectiveness of the different diagnostic strategies is based on the prevalence of the infection and on the price and accuracy of different tests.[37]

There are several both invasive and non-invasive methods for the diagnosis of h pylori infection,

**Table 2: Special characteristics of the diagnostic tests for the detection of h pylori infection introduced into clinical practice.**

| Diagnostic method | Special characteristics |
|---|---|
| Invasive tests | Gastroscopy needed |
| RUT | Quick, cheap, reduced sensitivity if low number of bacteria |
| Histology | Enables the assessment of gastric pathology, expensive |
| Culture from gastric biopsies | High specificity, enables the testing of antimicrobial susceptibility, needs sophisticated laboratory skills |
| PCR | Sophisticated method enables the testing of antimicrobial susceptibility, detection of virulence factors, and comparison of clinical isolates. |
| FISH | Sophisticated method helps in testing of antimicrobial susceptibility. |
| Non-invasive tests | Gastroscopy not needed |
| EIA-based quantitative antibody tests | Accurate after validation, low cost, easy to perform, slow decline in antibody titers after eradication, need for paired serum samples in post eradication setting |
| Rapid blood-based tests | Low accuracy |
| Immunoblot assay | Detects antibodies to specific antigens e.g. CagA |
| Urea blood test | Promising, not well studied |
| Urea breath Test | High accuracy, needs sophisticated laboratory equipment |
| Stool antigen tests | Monoclonal EIA-based Test accurate, in-office tests have low accuracy, easy to perform, moderately expensive. |

## INVASIVE METHODS

**Rapid urease Test (RUT)**

Rapid urease test was introduced as a simple and convenient method for diagnosing Helicobacter pylori infection. This test is based on the presence of large amounts of preformed urease enzymes in H. pylori. The breakdown of urea by urease produces a high local concentration of ammonia leading to raises in the gastric pH. A phenol indicator that changes the color from yellow at pH 6.8 to magenta at pH 8.4 can detect this pH alteration. The color change with the introduction of the gastric biopsy is an indication for the presence of H.pylori.[38] Despite many advances on the study of H. pylori, the use of the biopsy urease test still remains invaluable in the diagnosis and management of gastro duodenal disease.[39] It is based on the strong urease activity of H. pylori. Urea embedded in culture media generates ammonia when broken down by H. pylori urease leading to an increase in pH and is usually detected by a change in color with an indicator. RUTs are considered highly accurate with sensitivity and specificity over 90%. The rapid urease test is able to offer a sensitivity of 80-99% and a specificity of 92-100% in untreated patients when compared with histology as the gold standard in the diagnosis of H. pylori.[40] The ultra-rapid urease test (URUT), as described by Arvind is reported to overcome the latter shortcoming by enabling most positive tests to be apparent even before the end of the endoscopy.[41] The better sensitivity could be obtained if the test continued

to be read over a 24-h period although this was achieved at the expense of an increase in the number of false positive cases. In the CLO test, the use of two biopsy specimens has been shown to hasten the time for positive reaction.[42]

**Histology**

Histological examination of gastric biopsy samples is considered to be the gold standard for diagnosing H. pylori infections. Special staining enhances the identification of organisms in the biopsy specimen and a variety of staining options exist.[43] Invasive endoscopy is needed to obtain biopsy specimens and can be used to evaluate gastritis, presence of a peptic ulcer and its complications, malignancy and gastric MALT lymphoma. Following treatment, a biopsy can also be used to confirm eradication· Because of an inadequate number of biopsy specimens obtained or failure to obtain specimens from different areas of the stomach, Limitations also arise at times. Histology is widely available in hospital practice but is relatively slow and take at least a day to be reported. Histology is an expensive test and if the cost of endoscopy is included all invasive tests become expensive. An advantage that histology holds over other tests is the ease with which retrospective examination of slides can be undertaken. This can be valuable if discrepant results need to be checked. The other tests require relatively expensive storage facilities to permit retrospective analysis.[44]

**Culture**

Because H. pylori are difficult to grow on culture media, the role of culture in diagnosis of the infection is limited mostly to research and epidemiologic considerations. Culture is costly, time-consuming, and labor-intensive however it have a role in antibiotic susceptibility studies and studies of growth factors and metabolism.

**Polymerase Chain Reaction**

With the advent of PCR, many exciting possibilities emerged for diagnosing and classifying H. pylori infection. PCR allows identification of the organism in small samples with few bacteria present and entails no special requirements in processing and transport. PCR also is being evaluated for its utility in identifying H. pylori in samples of saliva, dental plaque and other easily sampled tissues. The major limitation of PCR is that very few laboratories currently have the capability to run the assay. One of the demerits of PCR is it can detect segments of H. pylori DNA in the gastric mucosa of previously treated patients, false-positive results can occur, and errors in human interpretation of bands on electrophoretic gels can likewise lead to false-negative results.[45]

**Urea Breath Test**

This test relies on the urease activity of H. pylori to detect the presence of active infection. Here a patient with suspected infection ingests either14C- labeled or 13C- labeled urea; 13C- labeled urea has the advantage of being non-radioactive and thus safer (theoretically) for children and women of childbearing age. Urease, if present, splits the urea into ammonia and isotope-labeled carbon dioxide; the carbon dioxide is absorbed and eventually expired during breathing is detected. Besides the excellent use for documenting active infection, this test is also used for establishing the absence of infection after treatment which is an important consideration in patients with a history of complicated ulcer disease with perforation or bleeding. In addition, a urea breath test is relatively inexpensive, is easy to perform, and does not require endoscopy.

**Serologic Tests**

In response to H. pylori infection, the immune system typically mounts a response through production of immunoglobulin to organism-specific antigens. These antibodies can be easily detected in serum or whole blood samples obtained in a physician's office. There is presence of IgG antibodies to H. pylori which can be detected by use of a biochemical assay. Serologic tests offer an easy, relatively inexpensive and fast means of identifying patients who have been infected with the organism but this method is not a useful means of confirming eradication of H. pylori. In addition, few patients become truly seronegative, even after eradication of the organism. Serologic tests should be a second-line methodology in low-prevalence populations; because of low positive predictive value and a tendency toward false-positive results. Serologic tests may be useful in identifying certain strains of more virulent H. pylori by detecting antibodies to virulence factors associated with more severe disease and complicated ulcers, gastric cancer, and lymphoma.

**Stool Antigen Testing**

It is a relatively new methodology that uses an enzyme immunoassay to detect the presence of H. pylori antigen in stool specimens. The test has a sensitivity and specificity comparable to those of other noninvasive tests. Questions remain regarding possible cross reactivity with other Helicobacter species present in the intestines, but definitive studies are lacking.[46]

## CONCLUSION

Helicobacter Pylori is strongly associated with Chronic Active Gastritis.

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