Dental Implications of *Helicobacter pylori*

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Abstract

Helicobacter pylori *infections of the stomach are common worldwide and may cause serious medical problems, ranging from gastritis and its sequelae to gastric carcinoma or lymphoma. Current studies indicate that* H. pylori *is present in dental plaque, although the number of organisms in individual samples is very low, and these numbers appear to vary from one site to another within the mouth. The presence of this organism in plaque may be intermittent, perhaps occurring as the result of gastroesophageal reflux. It is still unclear if the low numbers of* H. pylori *present in the mouths of most patients would be sufficient to serve as a source of infection or reinfection for gastric conditions. Whether dental plaque is a significant source for reinfection of the gastric mucosa among patients with fair to poor oral hygiene remains to be confirmed. It has been suggested that attempting to improve oral hygiene through standard periodontal procedures would be prudent as an ancillary measure to conventional ulcer therapy, especially in patients whose gastric infections have proven recalcitrant.* H. pylori *may also be a cofactor in the recurrence of aphthous ulceration, especially in patients sensitized through gastric colonization and mucosal attachment.*

MeSH Key Words: *dental plaque/microbiology; helicobacter pylori; oral hygiene*

© J Can Dent Assoc 2002; 68(8):489-93
This article has been peer reviewed.

Helicobacter pylori is a gram-negative, microaerophilic, rod-shaped bacterium that colonizes the human stomach. It resides beneath the gastric mucous layer, adjacent to the gastric epithelial cells, and, although it is not invasive, it causes inflammation of the gastric mucosa. Infection with this organism is now recognized as a serious, transmissible infectious disease, linked to duodenal and gastric ulcers and gastric carcinoma.[1,2] Approximately 50% of the world's population is believed to be infected.[3] Developed countries typically have a lower prevalence of *H. pylori* infection at all ages, but this difference is especially noticeable among younger people.[4] In the United States, the prevalence of infection rises from less than 10% among Caucasians under age 30 to over 50% in those over age 60. Prevalence is higher among non-Caucasians and immigrants from developing countries and is inversely correlated with socioeconomic status.[5]

Most infections are probably acquired in childhood, although the exact route of transmission is unknown. These bacteria are also found in plaque and feces, so the route of infection could be oral–oral or fecal–oral. Acute infection may result in a transient clinical illness characterized by nausea and abdominal pain. In most cases the infection progresses to a chronic, asymptomatic illness.[5] Before the importance of *H. pylori* in the pathogenesis of ulcers was recognized, the recurrence rate of peptic ulcers was over 80% per year. Because eradication of *H. pylori* reduces recurrence rates to less than 20%, all patients with a history of peptic disease (active or inactive) and *H. pylori* infection should be given a course of eradication therapy.[5] However, it has often proven difficult to cure *H. pylori* infections.[6,7] Even triple-drug therapy has sometimes failed to eradicate *H. pylori* from the gastric mucosa. Nonetheless, it is now suggested that all currently recommended regimens should achieve eradication in more than 85% or 90% of patients after 1 to 2 weeks of treatment.[5]

Helicobacter pylori in Dental Plaque

It has long been speculated that dental plaque might harbour *H. pylori* and therefore might be a source of reinfection of the gastric mucosa.

Some authors[8] have suggested that *H. pylori* may belong to the normal oral flora of the human oral cavity, maintaining a commensal relation with the host, but present in very low numbers such that reliable identification is difficult. Others[9,10] have suggested that *H. pylori* is not consistently present in dental plaque and, when present, may be the result of occasional gastroesophageal reflux. Young and

others[11] found no morphological differences in *H. pylori* cells obtained from gastric biopsy and dental plaque and examined by scanning electron microscopy; both rod and coccoid forms were seen.

Miyabayashi and others[12] reported on a recent Japanese study of 47 patients with *H. pylori* gastritis. They analyzed the correlation between the success of gastric eradication and the prevalence of *H. pylori* in the oral cavity, as determined by nested polymerase chain reaction (PCR) before and after eradication therapy (nested PCR improves the specificity of the PCR amplification process). Of the 24 patients who tested negative for oral *H. pylori* before eradication therapy, *H. pylori* was completely eradicated from the stomach in 22 (92%). None of these 22 patients experienced recurrence during the mean follow-up period of 19.7 months (range 1–48 months). In contrast, 4 weeks after initial therapy, complete eradication of gastric *H. pylori* was achieved for only 12 (52%) of the 23 patients who tested positive for oral *H. pylori*. Of these 12 cases, 7 remained oral positive and 5 became oral negative and 2 of the oral positive cases relapsed within 2 years of initial therapy. Among the 23 patients, oral *H. pylori* was eradicated by the therapy in only 8 cases (35%) and one of these relapsed within 2 years of initial therapy. The authors concluded that the presence of oral *H. pylori* was an important marker of potentially refractory or recurrent gastric *H. pylori* infection. Oshowo and others[13] conducted PCR analysis on dental plaque and saliva obtained from 208 unselected dyspeptic patients who had been referred for upper gastrointestinal endoscopy in England. A total of 116 of these patients tested positive for gastric *H. pylori*, and 15 of these also tested positive for oral *H. pylori*. However, only 2 of the 15 with both oral and gastric infections also tested positive for *H. pylori* in dental plaque. In contrast, none of the 92 patients with no evidence of the organism in the stomach had oral *H. pylori*. This finding links colonization of the mouth with colonization of the stomach, a conclusion further supported by restriction endonuclease digestion studies. The authors suggested that *H. pylori* sometimes colonizes dental plaque but that such colonization would appear to be transient. In their view these data gave little support for the hypothesis that the mouth is a sanctuary from antibiotic therapy and hence a source of later reinfection.

Song and others[8] found *H. pylori* in almost 100% of plaque samples obtained in a German study, albeit in very small numbers. These small numbers may explain the wide variation in results of other studies.[14] Song and others[8] speculated that *H. pylori* may be a commensal organism but its presence does not appear to mean that the infection will occur in the stomach. The presence of *H. pylori* in most dental plaque samples was independent of the presence of the organism in the stomach. In another German study, Song and others[15] have also shown variation in the prevalence of *H. pylori* depending on the location of origin of the supragingival plaque samples. *H. pylori* was detected in samples from molars, premolars and incisors but with great differences in prevalence: 82% (32/39), 64% (25/39) and 59% (23/39) respectively. This distribution may be explained by the microaerophilic characteristics of *H. pylori*. Theoretically, exposure to oxygen might decrease gradually from the incisors to the molars, which would favour the growth of *H. pylori* in the molar area. This was the first report documenting such a high prevalence in developed countries and might have been related to the particularly sensitive testing techniques used by these authors. They suggested that the high detection rate might support the assumption that *H. pylori* is part of the normal flora of the oral cavity in humans, although the absolute number of viable organisms may be very low. It was not known why only a small proportion of patients with *H. pylori* in plaque had active infection in the stomach.

Further studies are necessary to investigate whether the presence of H. pylori *in the mouth is transient and whether there are risk factors that favour its growth in the oral cavity.*

The number of *H. pylori* organisms necessary to cause infection or disease in the stomach is unknown, and further studies are necessary to investigate whether the presence of *H. pylori* in the mouth is transient and whether there are risk factors that favour its growth in the oral cavity. Whether the small numbers of organisms in dental plaque could serve as a reservoir for reinfection of the gastric mucosa in susceptible patients, after eradication of gastric infection by antibiotics, is also unknown.

There are differing views as to whether antibiotic therapy affects *H. pylori* in plaque; Shankaran and Desai[16] claimed that it does not, but Song and others[8] found plaque samples negative for *H. pylori* only in patients who had recently been treated with triple-antibiotic therapy. Butt and others[17] recently reported that effective elimination of *H. pylori* from dental plaque can be achieved by local dental measures. Addition of triple therapy did not confer any advantage over local dental hygiene in the attempted eradication of *H. pylori* from dental plaque. These authors also concluded that it would be prudent to assess periodontal status, give treatment to remove dental plaque and improve periodontal health, in addition to administering triple-therapy regimens, for patients with *H. pylori* gastritis. Combination (triple-therapy) regimens that employ

2 antibiotics in combination with either bismuth or proton pump inhibitors decreased the rate of failure due to antibiotic resistance.[5]

Studies that have used different identification techniques have produced different results with respect to the prevalence of *H. pylori* in plaque, with figures ranging from 0% to 100%.[14] The difficulties associated with identifying *H. pylori* in dental plaque may explain these differences. One problem is that the results depend on the test used. For example, the reported variation in the detection range of PCR analysis may reflect variations in the prevalence of *H. pylori* but is more likely due to differences in the specificity and sensitivity of the primers used.[18] A second problem is that *H. pylori* can assume a basally respiring but nonculturable coccoid state if subjected to physical or chemical stress; in this state the organism may escape detection by culture methods.[14] *H. pylori* is not uniformly distributed in the mouth, so repeat sampling is recommended to obtain a valid assessment of its presence.[8,14] It has also been suggested that intermittent gastroesophageal reflux may lead to intermittent occurrence of *H. pylori* in dental plaque.[9] Differences between developed and developing countries, where *H. pylori* infection appears more prevalent, may make it difficult to compare results from different parts of the world.[19] The very small numbers of organisms, the presence of coccoid forms (probably caused by the increased oxygen supply in the supragingival plaque) and the presence of numerous other microorganisms may have contributed to the failure to cultivate the bacterium from the oral cavity in some studies.[8]

Aphthous Ulcers

Because of similarities in the histologic characteristics of gastric ulcers and oral aphthous ulcers and because the latter often respond to treatment with broad-spectrum antibiotics such as tetracycline, it seems reasonable to assume that *H. pylori* could play a role in the development of recurrent aphthous ulcers.

Birek and others[20] determined the frequency of detection of *H. pylori* DNA in oral samples from recurrent aphthous ulcers (RAUs), tongue, saliva and plaque. A total of 71.9% of the RAU samples exhibited *H. pylori* DNA. The results for plaque and saliva (obtained with a PCR assay) indicated that these were not likely sources of *H. pylori* in healthy individuals. The authors postulated a causal relationship between *H. pylori* and RAUs, although they recognized that the causes of RAU are complex, encompassing genetic, environmental, hormonal, infectious and immunologic factors. Focal T-cell-mediated immunity (a delayed type of hypersensitivity reaction or a cytotoxic response) may be the mechanism responsible for tissue destruction in RAU. Birek and others[20] raised the possibility that adherence of *H. pylori* to the oral mucosa and subsequent production of autoantibodies to epitopes shared by oral epithelium cells and *H. pylori* might result in the tissue destruction associated with RAU. Because of similarities in the inflammatory process that produces gastritis associated with *H. pylori* and that causes RAU, they postulated that *H. pylori* may be a cofactor in the pathogenesis of RAU, especially in people sensitized through gastric colonization and mucosal attachment.

Riggio and others,[21] who also used PCR analysis, detected *H. pylori* DNA at a much lower frequency (11%) from RAU biopsy samples. They suggested that this finding could result from variation within different patient groups. They concluded that their results did not support a definitive causative role for *H. pylori* in RAU, although the possibility that this organism may be involved in a small proportion of RAU cases could not be excluded.

Vitamin B_{12} Deficiency Anemia and *H. pylori* Infection

In a recent Turkish study, Avcu and others[22] tried to establish whether the eradication of *H. pylori* was associated with an improvement of vitamin B_{12} levels and hence with treatment of anemia, whether *H. pylori* in dental plaque was associated with oral hygiene levels, and whether there was a relationship between *H. pylori* in dental plaque and gastric recurrence of *H. pylori* infection. One hundred and eight patients with vitamin B_{12} deficiency who also had *H. pylori* in their gastric mucosa underwent assessment of gingival health according to the Oral Hygiene Index (OHI) and were divided into 3 groups according to their score on this index (good, fair or poor). The OHI is composed of the combined debris index and the calculus index and is an indication of the extent of debris and calculus present and therefore the level of oral hygiene. In this study *H. pylori* was detected in plaque by means of gels specific for *Campylobacter*-like organisms. *H. pylori* was detected in all patients with poor OHI scores, in 90.2% of those with fair OHI scores and in 28.5% of those with good OHI scores. Gastric *H. pylori* infection recurred most frequently in patients with poor or fair OHI, and the differences in rates of recurrence between patients with poor or fair OHI and those with good OHI were statistically significant. All patients were then treated with triple therapy (clarithromycin, omeprazol and amoxicillin) to attempt eradication. After treatment, no *H. pylori* was found on gastric biopsy in 61 of the patients. Average serum vitamin B_{12} levels as well as erythrocyte count, hemoglobin levels, hematocrit and mean corpuscular volume recovered in these 61 successfully treated patients. The authors hypothesized that gastritis caused by *H. pylori* resulted in hypochlorhydria and malabsorption of vitamin B_{12} and that successful treatment of *H. pylori* infection resolved the vitamin deficiency. Because *H. pylori* recolonization of the gastric mucosa was most frequently seen in patients with

poor or fair OHI, the authors suggested that efforts to control *H. pylori* in plaque could help to prevent recolonization of the stomach.

Additional Dental Implications

H. pylori infections of the stomach are common worldwide, and they sometimes cause serious medical problems, ranging from gastritis and its sequelae to gastric carcinoma or lymphoma. Epidemiological studies[23-25] have confirmed that the prevalence of *H. pylori* infection is no higher among dentists in developed countries than within the general population, although gastroenterologists are more likely to be affected by this infection. However, Honda and others[19] recently concluded that Japanese dentists are at higher risk of contracting *H. pylori* infections. They suggested that transmission could be the result of exposure to aerosolized dental plaque within a population with a high prevalence of seropositivity for *H. pylori.*

For any patient with a history of gastritis or stomach ulcers, it is common practice to avoid prescribing acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs to avoid precipitating further gastric mucosal damage. Acetaminophen is commonly used as an alternative analgesic for these patients.

Of course, it is also possible that *H. pylori* infection is an opportunistic colonization or even an incidental finding superimposed on a weakened mucosa. Bosch and others[26] recently published a study that aimed to determine whether stress-mediated biochemical alterations in mucosal secretions (salivary levels of sulfo-Le^a) could be directly linked to changes in the host–microbe interface (i.e., saliva-mediated adherence of *H. pylori*). They found that ex vivo saliva-mediated adherence of *H. pylori* was enhanced during acute stress, although they cautioned that the findings could not be extrapolated to the in vivo situation. They concluded that their study demonstrated a direct link between stress-mediated biochemical changes and altered host–microbe interactions in humans. Increased bacterial adherence may be a contributing factor in the observed relationship between stress and susceptibility to infectious disease.

Conclusions

In conclusion, *H. pylori* is a micro-organism that causes or is associated with a curable chronic infection. This infection responds to triple-therapy antibiotic treatment, although in some patients the infection can be difficult to eradicate and there is a significant rate of recurrence. Whether the rate of recurrence can be reduced by concomitant emphasis on improving oral hygiene and treating periodontal disease remains to be clarified. However, there is some evidence that *H. pylori* infection is yet another systemic condition that could be ameliorated by recognizing and managing concomitant oral infection. It also remains to be clarified whether these systemic and oral conditions result from some common etiological factor or factors, such as stress. ➧

Acknowledgment: I would like to thank Dr. E. Fillery for his helpful comments during the preparation of this paper.

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The author has no declared financial interests.

Editor's note: The online version of this article contains an appendix on tests commonly used to identify *Helicobacter pylori*. See the *eJCDA* Web site at: http://www.cda-adc.ca/jcda/vol-68/issue-8/489.html.

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Web Appendix
Tests Commonly Used to Identify *H. pylori*

The following information is provided as background to the tests commonly used to identify *H. pylori*, primarily from the oral cavity.

H. pylori can be identified by several methods.

Culture in combination with histological examination:[1] The culture medium currently in use may be unsatisfactory when specimens harbouring abundant flora are tested, as for specimens from the mouth. Lack of growth of *H. pylori* in these cases may be due to low numbers of viable *H. pylori* organisms, to inhibition of growth by other oral commensal organisms or the presence of viable but nonculturable coccoid forms.

Serologic testing: Serologic methods (the testing of blood for antibodies to *H. pylori*) are recommended for initial screening of patients with symptoms of gastritis. False-negative results may be obtained.[2] Porter and others[3] found no significant differences in the frequency of serum anti-*H. pylori* IgG antibodies in patients with recurrent apthous ulcers (a condition linked to *H. pylori*, discussed in the main text), patients with other oral mucosal lesions and control subjects.

Campylobacter-Like Organism Test and Urea Breath Tests: *H. pylori* produces large amounts of urease, a property that has been used as the basis for 2 fast, simple diagnostic tests: the *Campylobacter*-like organism test and the urea breath tests. Although these tests are effective in identifying *H. pylori* infections in the stomach, where it is the only micro-organism producing urease,[1] the same is not true of the oral cavity, where there are several micro-organisms exhibiting urease activity.

Smear cytology: Samples of dental plaque are air-dried and stained with Giemsa stain. *H. pylori* appears as dark bluish violet, curved, spiral-shaped rods approximately 2–3 µm long.[4] However, other micro-organisms may have the same appearance, so the results may not be reliable. Indirect immunoperoxidase tests have also been used; these seem more reliable.[5]

Polymerase chain reaction assays: Polymerase chain reaction (PCR) and nested PCR are DNA amplification procedures resulting in the rapid production of multiple copies of a target DNA sequence. Most of these assays have been based on the sequence of urease genes or 16S ribosomal RNA (rRNA) genes.[1] Song and others[6] recently showed that primers directed to an 860-base pair fragment of *H. pylori* genomic DNA were more sensitive and specific than primers directed to the urease A gene or the 16S rRNA gene. A criticism of the tests using urease gene primers is that urease-positive organisms are commonly present in samples from the mouth, so conclusions based on primer pairs derived from urease genes alone may be unreliable (because of the potential for cross-reactivity).[7,8] However, the fact that PCR sometimes finds evidence of *H. pylori* in gastric samples and even the duodenal juice, even though the organism is particularly sensitive to extremes of pH, suggests that this molecular technique might be demonstrating fragments of dead organisms that still contain intact targets of the primer.[9] PCR is still classified primarily as a research technique in the *H. pylori* field.[10]

Currently, none of these diagnostic tests can be used alone to obtain a definitive diagnosis because none, including PCR, is ideal.[10]

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