

***Helicobacter pylori* and its reservoirs: A correlation with the gastric infection**

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Abstract

Helicobacter pylori (*H. pylori*) has long been found to cause gastric diseases such as gastritis, gastric ulcers and gastric cancer. The transmission medium of this bacterium has yet to be determined, though several studies have speculated that the oral cavity is a reservoir for *H. pylori*. Others have also reported that the oral cavity may be a source of both transmission and gastric reinfection; however, such results are controversial. We reviewed the literature and selected studies that report an association among *H. pylori* detections in the oral cavity (dental plaque, saliva, tongue, tonsil tissue, root canals, oral mucosa) in humans and in animals, as well as in the human stomach. The oral cavity may be considered the main reservoir for *H. pylori*. There are correlations between *H. pylori* infection in the oral cavity and periodontal disease, oral tissue inflammation, *H. pylori* transmission, and gastric reinfection. We believe that the mouth is a reservoir and that it plays a crucial role in both *H. pylori* transmission and gastric infection.

Key words: *Helicobacter pylori*; Reservoirs; Oral cavity; Infection; Gastric disease

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Core tip: This review focuses on some aspects of infection and reinfection by *Helicobacter pylori* (*H. pylori*), particularly in the possible reservoirs of this bacterium. It also explores the association between gastric infection and these reservoirs. In addition, this review highlights possible reservoirs in animals and some routes of infection, and it considers the techniques used to diagnose this bacterium in different environments. The difficulty in accessing bacteria in reservoirs is a problem for *H. pylori* eradication

in particular, and new discoveries in this field will contribute to the understanding of *H. pylori* infection mechanisms.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative and microaerophilic bacterium that has been associated with some certain diseases, including chronic gastritis, peptic ulcers, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma. In 1994, the International Agency for Research on Cancer of the World Health Organization defined *H. pylori* as a Group 1 carcinogen^[1,2].

It is estimated that the *H. pylori* is present in the stomachs of 50% of the world's population, but despite this high prevalence, we do not yet clearly understand its transmission. Possible routes are oral-oral and fecal-oral, but no consensus has been reached^[3].

Currently, the main area of research into natural reservoirs for *H. pylori* has included oral *H. pylori* with gastric infection and the presence of *H. pylori* in the stomach^[1,4]. Many studies have suggested that the primary reservoir for *H. pylori* is the oral cavity, but overall, the results have been very inconsistent^[1-7].

Several previous studies reported success in diagnosing *H. pylori* from oral samples from dental plaque, saliva, tongue, tonsil tissue and root canals. These other researchers have raised the question of whether the mouth is a common source of stomach reinfection, even after treatment is received^[4-8].

Miyabayashi *et al.*^[9] were the first to investigate the influence of oral *H. pylori* on the stomach. In short, their patients with oral *H. pylori* were found to be at a significantly higher risk for gastric reinfection after having received successful treatment. The authors also determined that drugs recommended for the eradication of the *H. pylori* from the stomach seem to have no effect on oral *H. pylori*^[10].

At this stage of research, the crucial questions are whether the oral cavity is a reservoir and whether it plays a role in *H. pylori* transmission. Therefore, this review includes all relevant studies that report the detection of *H. pylori* in a reservoir and the possible relationship between gastric and extra-gastric infection.

EXTRA-GASTRIC RESERVOIR FOR *H. PYLORI*

Saliva and dental plaque

Krajden *et al.*^[11] were the first authors to perform

H. pylori isolation in *H. pylori*-positive patients with gastric symptoms of infection^[1]. Twenty-six years later, researchers have yet to reach a conclusion about the role of the oral cavity in gastric infection by *H. pylori*.

In 2015, two relevant studies were published on this topic. In the first, Ismail *et al.*^[12] developed a new nested-PCR assay that can be used to identify *H. pylori* DNA in dental plaque samples. These authors report that this new nested PCR is as sensitive as tests that rely on histology, and also that it may be useful when patients must be tested for *H. pylori* but are unable to undergo endoscopic examinations. In the second study, Amiri *et al.*^[13] analyzed 45 samples of dental plaque and detected *H. pylori* in 44% (20/45), 66.67% (30/45) and 77.78% (35/45) using PCR, LAMP reaction, and positivity for both the PCR test and the LAMP test, respectively. In addition to their reports of a high frequency of *H. pylori* in the dental plaque samples, they also determined that dental plaque may be one of the main causes of reinfection, as well as the cause of oral-oral transmission.

Ahmed *et al.*^[5] used PCR for 16S rRNA to establish the presence of *H. pylori*. They analyzed saliva and gastric biopsy samples from 400 symptomatic subjects and detected *H. pylori* in 246 (61.5%) and 240 (60%) samples from gastric biopsies and saliva, respectively. They also found that *H. pylori* prevalence in both samples was higher in older populations, and their report highlighted the oral-oral transmission.

Liu *et al.*^[4] analyzed 443 symptomatic patients and verified the presence of *H. pylori* in 59.4% (263/443) of their dental plaque samples and in 61.6% (273/443) of their stomach samples. These results corroborate the findings reported by Liu *et al.*^[14], who found 126 (58.9%) of 214 children's dental plaque samples to be *H. pylori* positive and who also reported a statistically significant correlation between the *H. pylori* infection and dental caries.

In addition, Souto and Colombo^[15] studied 225 adult subjects who sought dental treatment and detected *H. pylori* in 24% of the samples. More subgingival biofilm samples (33.3%) than saliva samples (20%) tested positive for *H. pylori*. The same authors also offered the theory that "periodontal pocketing and inflammation may favor the colonization by (*H. pylori*)".

Rasmussen *et al.*^[16] used southern blots on DNA extracts from saliva and dental plaque samples in order to detect *H. pylori* in 78 patients with gastric disease. A total of 33 saliva samples (42%) were found to be positive for *H. pylori*, and 37 dental plaque samples (47.4%) were found to be positive. In another study by our group, Rasmussen *et al.*^[17] reported significant genotypic diversity among *H. pylori* cytotoxins that had been found in stomach, saliva, and dental plaque samples. The study revealed the strains from the stomach to be more virulent than those from the oral cavity.

Results described by Silva *et al.*^[7] are more

convincing. They detected *H. pylori* in 30/30 (100%) of their patients' gastric biopsies, in 16/30 (53.3%) of their saliva samples, and in 11/30 (36.6%) of their dental plaque samples. These researchers also detected the *cagA* gene in 13/30 (43.3%) of their patients' gastric biopsies, in 7/16 (43.8%) of their saliva samples, and in 3/11 (27.3%) of their dental plaque samples. Similar results found by Assumpção *et al.*^[18] who found that 96% of their patients' gastric mucosa samples and 72% of their dental plaque samples were positive for *H. pylori*. Furthermore, they determined 63/71 (89%) of their patients' dental plaque samples to be both positive for *H. pylori* and to possess identical *vacA* and *cagA* genotypes in gastric mucosa.

All authors mentioned above suggest that dental plaque and saliva may be an important reservoir for *H. pylori* and that the presence of *H. pylori* in the oral cavity may contribute to oral diseases, oral transmission, gastric reinfection, and also virulence strains.

Meanwhile, Silva Rossi-Aguiar *et al.*^[19] analyzed saliva, tongue dorsum, and supra gingival dental plaque samples from 43 patients with gastric disease and did not detect *H. pylori* in these oral samples. Their results that consistent with those of Olivier *et al.*^[20], who also failed to detect *H. pylori* in dental samples. Both studies question the theory of the oral cavity serving as a reservoir for *H. pylori* in patients with symptoms of gastric disease.

There is a large variability in the oral cavity *H. pylori* frequency rates described in the literature. These differences could be explained by variations in sample demographics, the use of different sampling procedures or detection methods, the patients' oral health statuses, differences in *H. pylori* infection statuses, the type and number of clinical samples used, and varying complexities among the oral microbiota samples used across the studies^[7,15-17,21].

Tongue

Gastric heterotopia (GH) can occur throughout the digestive tract; however, the involvement of the tongue is rare, and fewer than 40 cases have been reported to date. When GH is found in the head and neck region, it is frequently in cases of children or young adults, and it is more prominent among males^[22,23].

A histologic evaluation was given to a 21-year-old man who reported the growth of a mass on his tongue 4 years prior to the exam and who presented ulcerations in the last 3 mo. The evaluation revealed the presence of gastric tissue that extended into the striated muscle layer of the tongue. There were scattered intestinal metaplasia foci containing Goblet cells. Toluidine-blue-stained sections suggested the presence of *H. pylori* in the lumina of the glandular epithelium. Colonization by *H. pylori* was determined

by the immunohistochemical method using polyclonal *H. pylori* antibody, and the finding was confirmed using the PCR method^[23].

There is also a great diversity in the different biological surfaces of the oral cavity that are subject to colonization by different bacterial species^[24]. Different studies have isolated *H. pylori* from samples taken from oral cavities, dental plaque (supragingival and subgingival plaque), dorsa of tongue, and salivary secretions. *H. pylori* findings in oral cavities and dental plaque are conflicting. The differing results of tests to determine the prevalence of *H. pylori* in oral cavities are partly due to the use of different detection methods^[25,26].

Clinical presentation varies depending on the site considered and on the extent of the lesion. An GH issue of note is the colonization by *H. pylori* and its association with complications. In their study, Berber *et al.*^[23] reports the first case of a peptic ulcer and intestinal metaplasia associated with the colonization of *H. pylori* in a case of GH of the tongue^[23].

Tonsillar tissues

Although the oral cavity has been suggested as a reservoir for *H. pylori* infection, the findings have not been definitive. Some authors have proposed the theory that in cases of gastroesophageal reflux disease (GERD), gastric fluid that is contaminated with *H. pylori* enters the nasopharyngeal cavity, thus allowing the bacterium to colonize in dental plaque and adenotonsillar tissue^[27]. Other researchers have also recently offered evidence of *H. pylori* in gastric mucosa that was bound to MALT. Because of these findings, more efforts have recently been placed on detecting *H. pylori* in adenotonsillar tissue^[6].

Some studies have used different detection methods to determine the presence of *H. pylori* in tonsil and adenoid tissue^[28-30].

Nártová *et al.*^[31] detected and genotyped *H. pylori* and found data supporting the possible role played by *H. pylori* in the etiologies of both chronic tonsillitis and sleep apnoea syndrome (SAS). *H. pylori* was detected through the use of real-time polymerase chain reaction. A total of 89 patients were tested, 60 of whom had received a diagnosis of chronic tonsillitis and 29 of whom had SAS. In the chronic tonsillitis group, *H. pylori* was detected in 48 (80%) of the samples, the *cagA* gene was detected in 12 samples (25%), and 12 samples were negative. In the SAS group, *H. pylori* was found in 24 samples (82.76%), *cagA* gene was detected in 5 samples (20.83%), and 5 samples (17.24%) were negative.

Nártová *et al.*^[31]'s study shows that the oropharynx represents a reservoir for *H. pylori* infection that could be an etiopathogenetic factor in chronic tonsillitis and tonsillar hyperplasia caused by SAS. No conclusion has been drawn regarding the mechanisms of the process.

In another study, Abdel-Monem *et al.*^[28] tested 30 adenotonsillectomy specimens (20 tonsils and 10 adenoids). RUT results were positive in 16 of their samples (12 tonsils and 4 adenoids; 53.3%). The authors report that, "according to the 'gold standard', 11/16 were considered a false positive, yielding a sensitivity of 100% and specificity of 56%". The authors also used PCR, and the ureC gene sequence was detected in 5 specimens (3 tonsils and 2 adenoids; 16.6%), all of which also tested positive when RUT was used. In these cases, the patients were considered to be infected by *H. pylori*. For this reason, the authors reported PCR sensitivity and specificity to be 100%. Serology testing results were positive for *H. pylori* IgG antibodies in 4/20 patients (20%), only two of whom were found to have *H. pylori*-infected adenotonsillar tissue.

On the other hand, Aliakbari *et al.*^[32] reported that neither gastrointestinal symptoms nor *H. pylori* seropositivity were correlated with the presence of *H. pylori* or *H. hepaticus* in adenotonsillar tissues. The findings did not support the idea that adenotonsils is a reservoir for *H. pylori* or *H. hepaticus*. The study included 90 patients (36% female and 64% male) who had been diagnosed with chronic tonsillitis and adenoid hypertrophy; the average age of the study group was 36 ± 22 years. In their study, Aliakbari *et al.*^[32] detected *H. pylori* and *H. hepaticus* using *glmM* gene and 16S rRNA-specific primers, respectively. Out of all of their patients, 58 (65%) were found to be seropositive for the *H. pylori* IgG, though only 7 (8%) patients presented any gastrointestinal symptoms and all 7 were cases of gastritis. According to the authors, neither *H. pylori* nor *H. hepaticus* was detected in any of the patients when PCR was used^[32].

In conclusion, there are inconsistent results regarding the detection of *H. pylori* in the tonsils and adenoids; however, we believe that there is enough evidence to support the theory that such tissues can be considered a reservoir of such bacteria.

Root canals and oral mucosa

Most of the studies considered in this review analyzed dental plaque, saliva, and/or oral mucosa samples. In these studies, several *H. pylori* markers were identified through the use of various tests, including the urea breath test, the rapid urease test, the *Campylobacter*-like organism test, and/or polymerase chain reaction (PCR). Some PCR studies found *H. pylori* DNA in samples from oral cavities, but overall, reports of live *H. pylori* are very rare and inconclusive^[33].

In light of this literature review, we agree with Zou and Li^[34] and their report that *H. pylori* can be identified unequivocally only through the use of direct cultures. This limitation exists because erroneous PCR results can result from the presence of transient *H. pylori* in

the mouth. This transient presence occurs in cases of interference from food or from acid that includes *H. pylori* or its DNA that reaches the mouth *via* reflux from the stomach^[33,35,36]. Hirsch *et al.*^[8] "erroneous results can also arise from the misclassification of other urease-producing microorganisms. Thus, it is still unclear whether *H. pylori* can indeed survive in the oral environment".

In another study by Hirsch *et al.*^[8], electron microscopy, selective growth techniques, urease assays, 16S rRNA PCR, and western blotting were used to determine whether live *H. pylori* were present in 10 root canal and corresponding plaque samples taken from endodontic-infected deciduous teeth from three children. In their study, they report that PCR was able to identify *H. pylori* DNA in several plaque and root canal samples. However, bacterial colonies were successfully grown from two root canals, but not from plaque. As the authors report, "these colonies were unequivocally identified as *H. pylori* by microscopic, genetic, and biochemical approaches"^[8]. The authors showed that root canals performed on endodontic-infected teeth may create a reservoir for live *H. pylori*, and that this reservoir may serve as a potential source of transmission.

Genomic DNA was isolated from samples taken during 25 root canals of teeth from patients with asymptomatic and chronic apical periodontitis and from 25 patients with aspirates from acute apical abscess. These DNA samples were first amplified using the multiple displacement amplification approach and were then used as a template in species-specific PCR in order to determine whether *H. pylori* and *C. pneumoniae* were present. Neither *H. pylori* nor *C. pneumoniae* were found in samples from primary endodontic infections. These findings suggest that these species are not possible endodontic pathogens and that the necrotic root canal does not serve as a reservoir for these human pathogens in healthy patients^[37].

In another study by Correia-Silva Jde *et al.*^[38], many *H. pylori*-positive results were found in the oral mucosa of 46 haematopoietic stem cell transplantation (HSCT) patients. The authors report that their findings may be due to the patients' poor oral hygiene during the transplantation and/or immunosuppression procedures involved in HSCT therapy^[38]. Other authors note that, because "the oral cavity is a frequent site of local infections and an important port of entry for systemic infections in HSCT recipients...", the presence of *H. pylori* in the oral cavity may be a risk factor for infection or reinfection of the stomach of these patients^[9,38]. Though this literature review shows that the exact role played by *H. pylori* in oral cavity infections has not been confirmed, these findings may be relevant to the gastrointestinal pathology of HSCT patients.

H. PYLORI IN ANIMALS: A POSSIBLE RESERVOIR

According to Momtaz *et al.*^[39], there is a possibility that zoonotic transmission of *H. pylori* occurred, but this transmission has not been proven in non-primate reservoirs.

In the first report of infection by *H. pylori* in animals in 1990, Jones and Elridge^[40] isolated a strain of *H. pylori* from a pig stomach and suggested that pigs may be a possible reservoir for this bacterium. Eaton *et al.*^[41] and Engstrand *et al.*^[42] supported this hypothesis; both authors have succeeded in infecting pigs, specimens which subsequently developed gastritis. However, De Groote *et al.*^[43] more recently sequenced the 16S of rDNA of *H. pylori* and then named the bacterium *Helicobacter suis*. Mégraud and Broutet^[44] analyzed all of these studies and concluded that pigs are not a reservoir for *H. pylori*. They suggest the bacterium isolated by Jones and Elridge^[40] was probably acquired from human beings.

Four years later, Jones and Elridge^[40] detected *H. pylori* in a pig stomach sample. Handt *et al.*^[45] diagnosed the *H. pylori* in six cats - their identification was confirmed through the use of 16S rDNA sequencing. However, no other studies confirm these results. These studies argue that cats serve as a reservoir for *H. pylori*, but additional studies are necessary to determine whether cats are actually an important route of transmission. Based on the overall data available, having a cat as a pet does not put owners at risk of acquiring *H. pylori* infection.

More recently, Momtaz *et al.*^[39] analyzed 800 samples, 200 of which were from human beings and 600 of which came from healthy animals (200 cows, 200 sheep and 200 goats). They detected *H. pylori* and main virulence markers (gene *cagA* and *vacA*) using PCR and selected 6 *H. pylori*-positive samples (3 samples from cows and 3 samples from sheep) for DNA sequencing analysis.

They reported that the *H. pylori* was detected in 0/200 goat samples, 6/200 (3%) cow samples and in 32/200 (16%) sheep samples. Out of 200 human samples, 164 (82%) were infected with the bacterium. They also considered the virulence markers: A high prevalence of the *cagA* gene and of *s1/m1* genotypes of the *vacA* gene were found in all of the samples. When the sequences of *H. pylori* isolates of sheep and humans were compared, 3.4%-8.4% variability and a 92.9%-98.5% homology were found. However, the greatest sequence similarity (98.5%) was found between the *H. pylori* isolates from Iranian sheep and those from German humans (FN598874), while the weakest relationship observed (91.6%) was between the Iranian cow and the South African population (NC017361).

According to Momtaz *et al.*^[39], cows and sheep were

found to have *H. pylori* in their gastric tissue. The authors also theorize that sheep may be the natural reservoir for the bacteria and may be the source of *H. pylori* in human populations.

CONCLUSION

This literature review provides information to help determine the relevance of the several *H. pylori* reservoirs wherein each one possesses specific characteristics that favor or hinder the presence of *H. pylori*. Failure to eradicate and detection of *H. pylori* in reservoirs, may suggests an important route of reinfection and transmission, in addition to increase a risk of gastrointestinal disease.

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