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TOPIC HIGHLIGHT

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Role of dental plaque, saliva and periodontal disease in *Helicobacter pylori* infection

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Abstract

Helicobacter pylori (*H. pylori*) infection is one of the most common bacterial infections in humans. Although *H. pylori* may be detected in the stomach of approximately half of the world's population, the mechanisms of transmission of the microorganism from individual to individual are not yet clear. Transmission of *H. pylori* could occur through iatrogenic, fecal-oral, and oral-oral routes, and through food and water. The microorganism may be transmitted orally and has been detected in dental plaque and saliva. However, the role of the oral cavity in the transmission and recurrence of *H. pylori* infection has been the subject of debate. A large number of studies investigating the role of oral hygiene and periodontal disease in *H. pylori* infection have varied significantly in terms of their methodology and sample population, resulting in a wide variation in the reported results. Nevertheless, recent studies have not only shown that the microorganism can be detected fairly consistently from the oral cavity but also demonstrated that the chances of recurrence of *H. pylori* infection is more likely among patients who harbor the organism in the oral cavity. Furthermore, initial results from clinical trials have shown that *H. pylori*-positive dyspeptic patients may benefit from periodontal therapy. This paper attempts to review the current body of evidence regarding the role of dental plaque, saliva, and periodontal disease in *H. pylori* infection.

Key words: *Helicobacter pylori*; Dental plaque; Saliva; Oral cavity; Periodontitis; Periodontal therapy

Core tip: *Helicobacter pylori* (*H. pylori*) infection is one of the most common bacterial infections in humans. The mode of transmission of this bacterium has long puzzled researchers. Numerous studies have shown that this microorganism can be detected in dental plaque and saliva of human subjects, suggesting that the oral cavity may be an extra-gastric reservoir of *H. pylori* and play an important role in both transmission and recurrence. Recent data support this hypothesis and indicate that periodontal therapy may play a role in the management of *H. pylori*-associated gastric disease.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most common bacterial infections in humans[1]. It is a gram negative, microaerophilic, rod-shaped bacterium that colonizes the gastric mucosa. Although its presence in the human stomach has been reported from all parts of the world, the prevalence of *H. pylori* infection is higher in developing countries than developed countries[2,3]. First reported in 1983[4], *H. pylori* (initially termed *Campylobacter pyloridis*) is an important human pathogen associated with the etiology of chronic gastritis, peptic ulcer, gastric cancer, and mucosa-associated lymphoid tissue lymphoma[2,5,6] and has been designated as a Group 1 Carcinogen by the International Agency for Research on Cancer of the World Health Organization (WHO)[6,7]. In addition to gastrointestinal diseases, recent data seem to suggest a possible association of this microorganism with other conditions, such as recurrent aphthous stomatitis[8], anemia[9], altered serum levels of lipoproteins[10], and coronary atherosclerosis[11].

A limited number of anti-microbial agents are effective against *H. pylori* and therapeutic regimens to eradicate the microorganism usually consist of a combination of antibiotics, proton pump inhibitors, and gastroprotective drugs[12,13]. These therapeutic regimens, particularly the combination of two antibiotics and a proton pump inhibitor, can successfully eradicate the microorganism resulting in significant clinical improvement[14]. However, recurrence rates, particularly in developing countries, are high[15-17]. This high rate of recurrence led investigators to study the various possible routes of transmission of the microorganism. Although *H. pylori* may be detected in the stomach of approximately half of the world's population, the mechanisms of transmission of the microorganism from individual to individual are not yet clear. The possible routes of transmission of *H. pylori* include iatrogenic, fecal-oral, oral-oral, and through food and water[2,18-21]. *H. pylori* exists in two different morphological forms, spiral and coccoid. The coccoid form is considered a degenerative or dead form of *H. pylori*, and its role in transmission of disease is negligible[22,23]. There is ongoing debate about its virulence and transformation[24]. Although the coccoid form of *H. pylori* is metabolically active, it cannot be cultured *in vitro*[2]. The organism has been reported to be present in soil samples in public playgrounds[25]. However, no extra-gastric reservoirs of *H. pylori* have been clearly demonstrated, and although organisms resembling *H. pylori* may be detected in other animals, none except non-human primates[26]and cats[27] harbor *H. pylori*. Infections by *Helicobacter* species (*H. heilmannii* and *H. felis*) have been reported in dogs[28,29] and cats[29].

Regarding the various possible routes of transmission of *H. pylori,* the microorganism may be transmitted orally and has been detected in dental plaque and saliva[30-32]. However, the question still persists as to whether the oral cavity is a major extra-gastric reservoir for *H. pylori* or harbors the organism only transiently. If the oral cavity, particularly the dental plaque, serves as an extra-gastric reservoir of *H. pylori*, it may have potentially serious implications regarding the treatment of *H. pylori* infection. This is on account of the fact that treatment of *H. pylori* infection usually involves administration of systemic antibiotics in combination with other drugs, and dental plaque, being a microbial biofilm, provides protection for the resident microorganisms from systemically administered antimicrobial agents. Despite the current treatment regimens that lead to successful management of *H. pylori*-positive chronic gastritis, the re-infection rate is relatively high[14,33]. One of the suggested mechanisms of re-infection is the possible re-colonization from dental plaque[34]. A few studies have also suggested that periodontal disease may also favor colonization of dental plaque by *H. pylori*[35]. This paper attempts to review the role of dental plaque, saliva, and periodontal disease in *H. pylori* infection.

PRESENCE OF *H. PYLORI* IN DENTAL PLAQUE

The prevalence of *H. pylori* in dental plaque has been studied by several investigators. A summary of studies reporting the presence of *H. pylori* in dental plaque of participants is shown in Table 1. The prevalence of reported presence of *H. pylori* in dental plaque in these various studies ranged from 0%-100%. This wide variation in results may be explained by several factors, such as characteristics of the sample population, differing sampling procedures, and differing methodologies used to detect the microorganism in dental plaque.

The diagnostic tests employed by different investigators to detect the presence of the microorganism in dental plaque include urease tests, polymerase chain reaction (PCR) techniques, immunoassays, cytology, and culture. Generally, the prevalence rates reported in studies employing urease tests were higher than studies employing other techniques. Lowest rates of detection have been reported when microbial culture was used to detect the presence of *H. pylori* in dental plaque. The use of urease tests for the detection of *H. pylori* in dental plaque has been subject to controversy. Although urease tests are reasonably specific for detection of the microorganism in gastric biopsy specimens, investigators have doubted its reliability for detecting *H. pylori* in oral specimens[36,37]. This controversy results from the fact that although *H. pylori* is the only urease-positive microorganism known to reside in the stomach, many urease-positive bacterial species, such as *Streptococcus* species, *Haemophilus* species, and *Actinomyces* species, may be detected as part of the normal oral flora. However, it has been reported that only *H. pylori* produces large amounts of urease, such that a positive urease test can occur within 20 min, while other urease-producing microorganisms are not positive within one hour[38]. Moreover, Gürbüz *et al*[39] reported that the rapid urease test for detection of *H. pylori* in dental plaque has a sensitivity of 89.7% and diagnostic accuracy of 86.7%.

Almost all of the studies utilizing urease tests for detection of *H. pylori* in dental plaque were conducted

Table 1 Studies evaluating the presence of *Helicobacter pylori* in dental plaque

Ref.	Method of *H. pylori* detection in dental plaque	Sample population and sample size	Prevalence of *H. pylori* in dental plaque
Agarwal and Jithendra[84], 2012	PCR	India; 30 *H. pylori*-positive and 20 *H. pylori*-negative patients	Overall-42% (n = 21); in *H. pylori*-positive group-60% (18/30); in *H. pylori*-negative group-15% (3/20)
Momtaz *et al*[85], 2012	PCR	Iran; 300 patients with gastro-duodenal diseases	0
Wichelhaus *et al*[86], 2011	PCR	Germany; 11 orthodontic patients	36% (n = 4)
Gao *et al*[46], 2011	PCR	China; 96 patients with *H. pylori* infection	82.30%
Chaudhry *et al*[45], 2011	PCR	Pakistan; 89 dyspeptic patients reporting for endoscopy	51.6% (n = 46) for both genes; 62.9% (n = 56) for 16srRNA; 61.7% (n = 55) for 860-bp DNA region; 73% (n = 65) if either of the 2 regions were considered
Bago *et al*[81], 2011	PCR	Croatia; 56 patients with chronic periodontitis and gastric *H. pylori*-positive	37.5% (n = 21)
Silva *et al*[71], 2010	PCR	Brazil; 115 patients-36 with dyspepsia and periodontal disease, 31 with dyspepsia but no periodontal disease, 22 with neither dyspepsia nor periodontal disease, 26 with periodontal disease and without dyspepsia	11.3% (n = 13)
Silva *et al*[87], 2010	PCR	Brazil; 30 dyspeptic patients	20% (n = 6) by 16S rDNA and 6.7% (n = 2) by vacA
Eskandari *et al*[88], 2010	PCR	Iran; 67 patients with chronic periodontitis-23 with *H. pylori*-positive gastritis	5.97% (n = 4/67)
Assumpção *et al*[89], 2010	PCR	Brazil; 99 adult patients who underwent upper gastro-intestinal endoscopy	72% (71) samples were positive for *H. pylori*. Overall, 63 (89%) of 71 positive dental plaque samples were positive for vacA and cagA. 58/71 (82%) were positive for cagA, while vacA genotypes had a prevalence ranging from 13%-59%
Medina *et al*[90], 2010	PCR	Argentina; 98 patients-43 dyspeptic patients and 55 asymptomatic controls	10.2% (n = 10)
Liu *et al*[70], 2009	PCR	China; 443 dyspeptic patients	59.4% (n = 263)
Gonçalves *et al*[69], 2009	PCR	Brazil; 23 HIV seropositive individuals (13 who had chronic periodontitis and 10 who were periodontally healthy) and 31 HIV seronegative individuals (17 who had chronic periodontitis and 14 who were periodontally healthy)	Not specified; frequency of detection was significantly higher in chronic periodontitis groups compared with periodontally healthy groups
Silva *et al*[91], 2009	PCR	Brazil; 30 individuals who were *H. pylori*-positive with gastric disease (cases) and 32 individuals who were *H. pylori*-positive with no gastric disease (controls)	Overall-17.7% (n = 11). Among cases, *H. pylori* DNA detected in 36.6% (11/30); control group-0%
Morales-Espinosa *et al*[62], 2009	PCR	Mexico; 66 hospitalized patients and 65 dental patients	Overall-19.9% (n = 26); 24% (n = 16) among hospitalized patients and 15% (n = 10) among dental patients
Souto and Colombo[68], 2008	PCR	Brazil; 225 patients-56 periodontally healthy and 169 chronic periodontitis patients	50% in patients with chronic periodontitis and 11.4% in periodontally healthy individuals
Liu *et al*[92], 2008	PCR	China; 214 children	58.9% (n = 126)
Bürgers *et al*[93], 2008	PCR	Germany; 94 patients who underwent upper gastro-intestinal endoscopy	5.4% (n = 5/92 dentate patients)
Teoman *et al*[94], 2007	PCR	Turkey; 67 dyspeptic patients	28.3% (n = 19)
Olivier *et al*[95], 2006	PCR	South Africa; 74 healthy members of a rural community	0
Kignel *et al*[96], 2005	PCR	Brazil; 49 dyspeptic patients	2% (n = 1)
Gebara *et al*[53], 2004	PCR	Brazil; 15 gingivitis and 15 periodontitis patients-all were *H. pylori*-positive in antral mucosa	20% (n = 6) in supra-gingival plaque and 26.6% (n = 8) in sub-gingival plaque
Fritscher *et al*[97], 2004	PCR	Brazil; 53 patients with recurrent aphthous stomatitis (cases) and 52 patients without recurrent aphthous stomatitis (controls)	Overall-3.8%; 5.7% (n = 3) in cases and 1.9% (n = 1) among controls
Umeda *et al*[35], 2003	PCR	Japan; 56 dental patients	25% (n = 14)
Suk *et al*[98], 2002	PCR	Taiwan; 65 patients with dyspeptic symptoms	43.1% (n = 28)
Berroteran *et al*[99], 2002	PCR	Venezuela; 32 dyspeptic patients and 20 asymptomatic controls	Overall-28.9%; 37.5% (n = 12) among dyspeptic patients and 15% (n = 3) among controls
Goosen *et al*[100], 2002	PCR	South Africa; 58 clinically healthy volunteers	1.7% (n = 1)

Song *et al*[63], 2000	PCR	Germany; 15 dyspeptic patients and 6 orthodontic patients	100% (*n* = 21)
Song *et al*[101], 2000	PCR	Germany; 20 dyspeptic patients	In dental plaque-not specified; 100% in oral samples (plaque and saliva)
Song *et al*[58], 2000	PCR	Germany; 42 patients who underwent upper gastro-intestinal endoscopy	97% (*n* = 41)-82% in molar region, 64% in premolar region and 59% in incisor region
Miyabayashi *et al*[79], 2000	PCR	Japan; 47 patients with chronic gastritis or peptic ulcer	38.3% (*n* = 18)
Agarwal and Jithendra[84], 2012	Culture	India; 30 *H. pylori*-positive and 20 *H. pylori*-negative patients	Overall-18% (*n* = 9); in *H. pylori*-positive group-30% (9/30); in *H. pylori*-negative group-0
Loster *et al*[49], 2009	Culture	Poland; 46 dentists without known co-morbidities	48%
Sudhakar *et al*[102], 2008	Culture	India; 50 patients with duodenal and gastric ulcer (study group) and 25 students (control group)	Overall 6.7% (*n* = 5); in study group-10% (*n* = 5), in control group-0%
Teoman *et al*[94], 2007	Culture	Turkey; 67 dyspeptic patients	0
Czesnikiewicz-Guzik *et al*[47], 2005	Culture	Poland; 100 female patients	48.3%
Czesnikiewicz-Guzik *et al*[48], 2004	Culture	Poland; 100 female patients	48.3%
Umeda *et al*[35], 2003	Culture	Japan; 18 dental patients	5.6% (*n* = 1)
Goosen *et al*[100], 2002	Culture	South Africa; 58 clinically healthy volunteers	13.8% (*n* = 8)
Checchi *et al*[103], 2000	Culture	Italy; 35 patients from a Periodontology clinic	8.6% (*n* = 3)
Sambashivaiah *et al*[73], 2011	RUT/CLO test	India; 36 patients in 3 groups-group Ⅰ, healthy subjects, group Ⅱ, chronic periodontitis patients, group Ⅲ, chronic periodontitis patients with type Ⅱ diabetes mellitus	Overall-66.7% (*n* = 24); among group Ⅰ-41.7% (*n* = 5), group Ⅱ-75% (*n* = 9), group Ⅲ-83.3% (*n* = 10)
Bali *et al*[65], 2010	RUT/CLO test	India; 124 dyspeptic patients of which 60 were *H. pylori*-positive (cases) and 64 were *H. pylori*-negative (controls)	Overall-51.6% (*n* = 64); among cases-86.7% (*n* = 52)
Assumpção *et al*[89], 2010	RUT/CLO test	Brazil; 99 adult patients who underwent upper gastro-intestinal endoscopy	52% (*n* = 48/93)
Al Asqah *et al*[64], 2009	RUT/CLO test	Saudi Arabia; 62 dyspeptic patients with periodontitis and 39 dyspeptic patients without periodontitis	Overall-65%; 79% in periodontitis group and 43% in non-periodontitis group
Sudhakar *et al*[102], 2008	RUT/CLO test	India; 50 patients with duodenal and gastric ulcer (study group) and 25 students (control group)	Overall 49.3% (*n* = 37); in study group-70% (*n* = 35), in control group-8% (*n* = 2)
Chitsazi *et al*[40], 2006	RUT/CLO test	Iran; 88 dyspeptic patients-44 with *H. pylori* infection and 44 without *H. pylori* infection	Overall 18.2% (16/88); 36.4% (16/44) in *H. pylori*-positive group
Anand *et al*[104], 2006	RUT/CLO test	India; 65 dyspeptic patients with *H. pylori* infection (cases) and 69 dyspeptic patients without *H. pylori* infection (controls)	Overall-79.9% (*n* = 107/134); 89.2% (*n* = 58) among cases and 71% (*n* = 49) among controls
Gürbüz *et al*[39], 2003	RUT/CLO test	Turkey; 75 dyspeptic patients	91.7% (*n* = 68)
Choudhury *et al*[67], 2003	RUT/CLO test	India; 124 patients with dyspepsia	43% (*n* = 54)
Al-Refai *et al*[105], 2002	RUT/CLO test	Saudi Arabia; 75 dyspeptic patients and 60 healthy controls	Overall-88.1% (*n* = 119); among dyspeptic patients-89.3% (*n* = 67); among controls-86.7% (*n* = 52)
Butt *et al*[74], 2002	RUT/CLO test	Pakistan; 78 dyspeptic patients	100%
Suk *et al*[98], 2002	RUT/CLO test	Taiwan; 65 patients with dyspeptic symptoms	100%
Ozdemir *et al*[106], 2001	RUT/CLO test	Turkey; 81 dyspeptic patients	79% (*n* = 64)
Avcu *et al*[75], 2001	RUT/CLO test	Turkey; 241 *H. pylori*-positive patients with gastric histologic changes	44.8% (*n* = 108)
Namiot *et al*[107], 2010	EIA	Poland; 155 patients	65.6% (*n* = 101)
Leszczyńska *et al*[108], 2009	EIA	Poland; 164 dyspeptic patients referred for endoscopy-95 *H. pylori* infected and 69 non-infected	82.1% in *H. pylori*-positive subjects and 17.7% in *H. pylori*-negative subjects
Checchi *et al*[103], 2000	EIA	Italy; 35 patients from a Periodontology clinic	11% (*n* = 4)
Butt *et al*[74], 2002	Cytology	Pakistan; 78 dyspeptic patients	88%
Butt *et al*[82], 2001	Cytology	Pakistan; 135 dyspeptic patients	81.5% (*n* = 110)
Rasmussen *et al*[109], 2010	Southern blot	Brazil; 78 dyspeptic patients	47.4% (*n* = 37)

HIV: Human immunodeficiency virus; PCR: Polymerase chain reaction; RUT: Rapid urease test; CLO: Campylobacter-like organism; EIA: Enzyme immunoassay; *H. pylori*: *Helicobacter pylori*.

among Asian populations. In studies utilizing urease tests, the reported prevalence of the microorganism in dental plaque generally ranged from 80%-100%, with only one study reporting a prevalence below 40%[40].

The PCR technique for detection of *H. pylori* provides the advantage of detecting the target DNA regardless of the viability of the bacteria and detecting even small numbers of the target species. PCR also provides the advantage of identifying specific genotypes of the micro-organism. The results of studies utilizing PCR techniques

have been very variable, with the reported prevalence ranging from 0%-100%. Generally, the initial studies[41-44] utilizing PCR reported very low prevalence rates, while the later studies reported higher prevalence rates[45,46].

Microbial culture of *H. pylori* permits anti-microbial susceptibility testing as well as detailed study of the isolates[2]. However, the reported rates of prevalence in studies in which microbial culture was employed to detect *H. pylori* in dental plaque was generally low, with only three studies reporting prevalence rates above 20%[47-49]. Moreover, in two of these three studies that reported higher prevalence rates[47,48], each of which had a reported sample size of 100, the prevalence was reported to be 48.3%, which could not be interpreted accurately because the percentage data in a sample size of 100 should have a whole number value rather than a fraction. Low rates of prevalence of *H. pylori* in dental plaque reported in studies which have used culture methods have been attributed to the existence of *H. pylori* in the metabolically active but unculturable coccoid form in the dental plaque. *H. pylori* in the dental plaque, being outside its normal habitat in the stomach, may respond to the altered environment by altering its morphology, metabolism, and growth behavior resulting in the formation of a viable but non-culturable coccoid form[50,51]. Other factors which account for the low rates of prevalence reported with culture methods include the fastidious nature of the microorganism, complex nature of the oral microflora, and inhibition of *H. pylori* by other oral microorganisms[37,52].

Although different rates of detection of *H. pylori* in the dental plaque have been reported by various investigators, data generated from these studies show that the microorganism can be reliably detected in plaque samples, especially when PCR techniques are employed. While some investigators have suggested that the occurrence of *H. pylori* in dental plaque is significant in terms of management of *H. pylori*-associated gastric disease[53], others have suggested that the microorganism is present only transiently in the oral cavity[54].

Dental plaque is a microbial biofilm that adheres tenaciously to teeth and other hard surfaces in the oral cavity, such as restorations. In this biofilm, microbial communities are embedded in an extracellular matrix composed of organic and inorganic materials of both host and microbial origin[55]. The microbial flora of dental plaque is very complex; more than 500 different species of bacteria have been detected in plaque samples[56]. These bacterial species inhabit the biofilm not at random as passive neighbors but interact with other bacterial species through specific interactions. These interactions, along with the biofilm structure, confer a large number of advantages to the resident bacterial species. One major advantage that biofilm bacteria enjoy is an increased resistance to host defense mechanisms and anti-microbial agents[55,57]. Thus, *H. pylori* present in the dental plaque, being biofilm-associated, are protected from systemic antibiotics administered for the management of gastric *H. pylori* infection. As a result, the microorganism may persist in the oral cavity even after successful eradication from the stomach and hence, the possibility exists that dental plaque-associated *H. pylori* may serve as a possible source of re-infection and re-colonization of the stomach.

PREVALENCE OF *H. PYLORI* IN SALIVA

Compared with studies on dental plaque, there are fewer reports on the prevalence of *H. pylori* detection in saliva. Table 2 shows a summary of studies reporting on detecting *H. pylori* in saliva. The majority of these studies utilized either PCR or culture methods. The detection rates in saliva were generally less than in dental plaque, with only few studies reporting detection rates of 50%[46,58-60]. The prevalence rates were even lower in studies in which culture was used for detecting *H. pylori* compared with studies using PCR techniques[30,44,61].

As mentioned previously, detection rates of *H. pylori* from saliva were less than that from dental plaque. This may be due to the fact that, while dental plaque, being a biofilm, allows the bacteria to adhere to solid surfaces, the constant flow of saliva may contribute to a reduction in bacterial load, making detection difficult[62]. As with dental plaque, investigators have differed in their opinions regarding the significance of detection of *H. pylori* in the saliva. The detection of *H. pylori* in saliva and dental plaque may precede or be independent of gastric infection[59,63]. It is not yet clear whether the presence of the microorganism in the oral cavity represents long-term colonization or whether its presence is transient due to either gastric reflux or because it is in route to the stomach. While some authors maintain that *H. pylori* may be a normal commensal organism in the oral cavity with no relation to gastric infection[58,61], others, based on detection of *H. pylori* from dental plaque and saliva of patients with and without *H. pylori* infection, have suggested that the oral cavity may be a permanent reservoir of the organism, acting both as source of re-infection and a route of transmission[59,62].

ASSOCIATION OF ORAL HYGIENE/ PERIODONTAL STATUS WITH *H. PYLORI* INFECTION

Studies that evaluated the association between oral hygiene status and periodontal status with *H. pylori* infection are shown in Table 3. Considerable variability was observed in the methods used in these studies to evaluate oral hygiene status and periodontal status. While some of these studies evaluated the association of oral hygiene and periodontal status with gastric *H. pylori* infection, others evaluated the association of these oral health variables with the oral carriage of *H. pylori*. Few studies considered the presence of *H. pylori* in both the stomach and oral cavity. While the majority of the studies did not show an association between periodontal status and gastric *H. pylori* infection, a few studies showed an association between

Table 2 Studies evaluating the presence of *Helicobacter pylori* in saliva

Ref.	Method of detection of *H. pylori* in saliva	Sample population and sample size	Prevalence of *H. pylori* in saliva
Momtaz *et al*[85], 2012	PCR	Iran; 300 patients with gastro-duodenal diseases	8.3% (*n* = 25)
Gao *et al*[46], 2011	PCR	China; 96 patients with *H. pylori* infection	51.10%
Momtaz *et al*[110], 2010	PCR	Iran; 250 dyspeptic patients	14.4% (*n* = 36)
Silva *et al*[87], 2010	PCR	Brazil; 30 dyspeptic patients	30% (*n* = 9) by 16S rDNA and 6.7% (*n* = 2) by vacA
Medina *et al*[90], 2010	PCR	Argentina; 98 patients-43 dyspeptic patients and 55 asymptomatic controls	9.2% (*n* = 9)
Silva *et al*[91], 2009	PCR	Brazil; 30 individuals who were *H. pylori* positive with gastric disease (cases) and 32 individuals who were *H. pylori* positive with no gastric disease (controls)	Overall-25.8% (*n* = 16). Among cases, *H. pylori* DNA detected in 53.3% (16/30); in control group-0%
Morales-Espinosa *et al*[62], 2009	PCR	Mexico; 66 hospitalized patients and 65 dental patients	Overall-35.9% (*n* = 47); 52% (*n* = 34) among hospitalized patients and 20% (*n* = 13) among dental patients
Suzuki *et al*[111], 2008	PCR	Japan; 326 non-dyspeptic subjects	6.4% (*n* = 26)
Bürgers *et al*[93], 2008	PCR	Germany; 94 patients who underwent upper gastro-intestinal endoscopy	7.4% (*n* = 7)
Kignel *et al*[96], 2005	PCR	Brazil; 49 dyspeptic patients	0
Gebara *et al*[53], 2004	PCR	Brazil; 15 gingivitis and 15 periodontitis patients-all were *H. pylori*-positive in antral mucosa	10% (*n* = 3)
Goosen *et al*[100], 2002	PCR	South Africa; 58 clinically healthy volunteers	3.4% (*n* = 2)
Song *et al*[101], 2000	PCR	Germany; 20 dyspeptic patients	In saliva-not specified; 100% in oral samples (plaque and saliva)
Song *et al*[58], 2000	PCR	Germany; 42 patients who underwent upper gastro-intestinal endoscopy	55% (*n* = 23)
Miyabayashi *et al*[79], 2000	PCR	Japan; 47 dyspeptic patients and 10 healthy controls	34% (*n* = 16) among dyspeptic patients
Umeda *et al*[35], 2003	PCR and culture	Japan; 15 dyspeptic patients	26.7% (*n* = 4)
Czesnikiewicz-Guzik *et al*[47], 2005	Culture	Poland; 100 female patients	54.10%
Cześnikiewicz-Guzik *et al*[48], 2004	Culture	Poland; 100 female patients	54%
Rasmussen *et al*[109], 2010	Southern blot	Brazil; 78 dyspeptic patients	42.3% (*n* = 33)

PCR: Polymerase chain reaction; *H. pylori*: *Helicobacter pylori*.

periodontal disease and gastric *H. pylori* infection[39,64-66]. An epidemiological study conducted in the USA based on the National Health and Nutritional Examination Survey Ⅲ data showed that periodontal disease may be associated with *H. pylori* infection, as determined by serological tests[66]. A positive association between periodontal disease and oral carriage of *H. pylori* has been reported by a few investigators[35,39,64,67-73]. Regarding oral hygiene status, while the majority of the studies did not show an association between oral hygiene status and gastric or oral carriage of *H. pylori*, Gürbüz *et al*[39] reported a positive association between plaque scores and both gastric and oral *H. pylori*. Similar to these findings, Butt *et al*[74] reported a positive association between the amount of plaque and detection of *H. pylori* in the oral cavity, while Bali *et al*[65] have reported that poor oral hygiene was significantly associated with gastric *H. pylori* infection.

As discussed in the previous sections, it is clear that *H. pylori* may be detected in dental plaque. Although the organism is microaerophilic, it has been reported that in the oral cavity, it prefers the supragingival plaque[35,41,75]. However, a few investigators have reported an equal presence of *H. pylori* in supra-gingival and sub-gingival plaque samples[53,76]. Supra- and sub-gingival plaque represent two different microenvironments that differ in their pH, nutrient supply, oxygen availability, and host defense mechanisms[77]. Subgingival plaque is generally present in periodontal disease where tissue destruction results in progressive deepening of the periodontal pockets. The transformation from supra-gingival to sub-gingival environment and from health to disease is associated with a change in the resident microbial flora[57]. Because dental plaque is a biofilm in which several different bacterial species co-exist through specific interactions between different species, survival of *H. pylori* in dental plaque depends on its ability to interact with other bacterial species. Studies have shown that *H. pylori* can selectively adhere to certain bacteria, such as *Fusobacterium* species (*Fusobacterium nucleatum*)[52,78], *Porphyromonas gingivalis*[52], and *Bacteroides forsythus*[35]. Because the numbers of these bacterial species are increased in periodontitis patients, it is more likely that dental plaque in periodontitis patients may harbor *H. pylori* by interacting with these bacterial species.

EFFECTS OF ANTI-*H. PYLORI* THERAPY ON *H. PYLORI* IN DENTAL PLAQUE

Table 4 shows the studies that evaluated the effects of

Table 3 Studies evaluating the association of oral hygiene status and gingival/periodontal status with *Helicobacter pylori* infection

Ref.	Oral health status evaluated	Definition of oral hygiene/periodontal status	Sample population and sample size	Association with oral *H. pylori*	Association with gastric *H. pylori*
Sambashivaiah *et al*[73], 2011	Periodontal status	Mean probing depth > 5 mm	India; 36 patients in 3 groups-group Ⅰ, healthy subjects, group Ⅱ, chronic periodontitis patients, group Ⅲ, chronic periodontitis patients with type Ⅱ diabetes mellitus	Significant	Not evaluated
Silva *et al*[71], 2010	Periodontal status	At least 4 teeth with PD ≥ 5 mm and CAL > 3 mm	Brazil; 115 dyspeptic patients	Significant	Not evaluated
Namiot *et al*[107], 2010	Oral hygiene/ periodontal status	Oral Hygiene index/ Russell's periodontal index	Poland; 155 dyspeptic patients	Non-significant	Not evaluated
Bali *et al*[65], 2010	Oral hygiene status/ periodontal status	Oral hygiene index-simplified/probing pocket depth	India; 124 dyspeptic patients of which 60 were *H. pylori* positive (cases) and 64 were *H. pylori* negative (controls)	Not evaluated	Significant
Gonçalves *et al*[69], 2009	Periodontal status	At least 3 sites with PD ≥ 5 mm and/or CAL ≥ 4 mm and BOP	Brazil; 23 HIV seropositive patients of whom 13 had periodontitis and 10 were periodontally healthy; 31 HIV seronegative patients of whom 17 had periodontitis and 14 were periodontally healthy	Significant	Not evaluated
Al Asqah *et al*[64], 2009	Periodontal status	BOP + PD ≥ 3 mm on at least 4 teeth	Saudi Arabia; Dyspeptic patients-62 patients with periodontitis and 39 without periodontitis	Significant	Significant
Liu *et al*[70], 2009	Gingival status	Gingival index	China; 443 dyspeptic patients	Significant	Not evaluated
Zaric *et al*[72], 2009	Gingival and periodontal status	Mean PD, CAL and gingival index scores	Serbia; 66 dyspeptic patients with *H. pylori* infection of gastric mucosa	Significant for mean PD but not for CAL and gingival index scores	Not evaluated
Bürgers *et al*[93], 2008	Periodontal status	Periodontal Screening Index	Germany; 94 dyspeptic patients	Non-significant	Non-significant
Souto and Colombo[68], 2008	Periodontal status	≥ 10% of teeth with probing depth and/ or clinical attachment loss ≥ 5 mm, or ≥ 15% of teeth with probing depth and/ or clinical attachment loss ≥ 4 mm, and > 10% of sites with bleeding on probing	Brazil, 225 patients-56 periodontally healthy and 169 chronic periodontitis patients	Significant	Not evaluated
Namiot *et al*[112], 2007	Periodontal status	Russell's periodontal index	Poland; 137 *H. pylori*-positive patients with peptic ulcer	Not evaluated	Non-significant
Anand *et al*[104], 2006	Oral hygiene status/ periodontal status	Oral hygiene index-simplified/patients with one or more sites with a PD ≥ 3 mm and CAL ≥ 3 mm at the same site	India; 65 dyspeptic patients with *H. pylori* infection (cases) and 69 dyspeptic patients without *H. pylori* infection (controls)	Not evaluated	Non-significant

Gebara *et al*[53], 2004	Gingival and periodontal status	Gingivitis group-patients with PD ⩽ 3 mm and BOP on at least 4 sites; periodontitis group-BOP + PD ⩾ 5 mm on at least 4 teeth	Brazil; 15 gingivitis and 15 periodontitis patients-all were *H. pylori*-positive in antral mucosa	Non-significant	Not evaluated
Gürbüz *et al*[39], 2003	Oral hygiene/ periodontal status	Plaque index/ Russell's index	Turkey; 75 dyspeptic patients	Significant	Significant
Umeda *et al*[35], 2003	Periodontal status	Presence of periodontal pockets ⩾ 4 mm	Japan; 28 patients who harbored *H. pylori* in stomach/duodenum	Significant	Not evaluated
Choudhury *et al*[67], 2003	Periodontal status	CPI	India; 124 dyspeptic patients	Significant	Not evaluated
Butt *et al*[74], 2002	Oral hygiene status/ periodontal status	Community Periodontal Index of treatment needs	Pakistan; 78 dyspeptic patients	Significant with amount of dental plaque but not with gingival or periodontal inflammation	Not evaluated
Dye *et al*[66], 2002	Periodontal status	Presence of 1 dental site with PD ⩾ 5 mm	United States; data from 4504 participants of National Health and Nutrition Examination Ⅲ Survey	Not evaluated	Significant
Berroteran *et al*[99], 2002	Gingival status	Gingival index-scoring from 0-3	Venezuela; 32 dyspeptic patients and 20 asymptomatic controls	Non-significant	Non-significant
Al-Refai *et al*[105], 2002	Oral hygiene/ gingival/ periodontal status	Plaque index/ gingival index/ Community Periodontal Index of treatment needs	Saudi Arabia; 75 dyspeptic patients and 60 healthy controls	Non-significant	Non-significant

PD: Pocket depth; CAL: Clinical attachment level; BOP: Bleeding on probing; CPI: Community periodontal index; *H. pylori*: *Helicobacter pylori*.

systemic *H. pylori* eradication therapy on oral *H. pylori*. The majority of these studies reported that systemic *H. pylori* eradication therapy alone (*i.e.*, in the absence of any form of periodontal therapy), although successful in managing the gastric infection, had very little effect on oral *H. pylori*[46,79]. Although Gebara *et al*[80] reported an increase in the prevalence of *H. pylori* in dental plaque in their patients after one week of triple therapy, Bago *et al*[81] reported that one week of triple therapy resulted in complete eradication of oral *H. pylori* in all 56 periodontitis patients who had *H. pylori*-associated gastric disease.

The systemic *H. pylori* eradication therapy in these studies usually included two antibiotics and a proton pump inhibitor administered orally. Because microorganisms in the dental plaque are afforded greater protection from systemically administered anti-microbial agents, it may be assumed that systemic *H. pylori* eradication therapy has little impact on oral *H. pylori*, hence the observed failure of these therapeutic regimens to eradicate oral *H. pylori*.

IMPACT OF PERIODONTAL THERAPY ON *H. PYLORI* INFECTION

Studies that evaluated the effect of periodontal therapy on *H. pylori* infection are shown in Table 5. Among these, two studies[73,82] evaluated the effect of periodontal therapy on oral *H. pylori*. While Sambashivaiah *et al*[73] evaluated the effect of non-surgical therapy on oral *H. pylori* in patients with and without type Ⅱ diabetes mellitus, Butt *et al*[82] compared the effects of triple therapy and periodontal therapy alone and in combination in 82 patients who were positive for *H. pylori* in dental plaque. They reported that the greatest reduction in plaque *H. pylori* was in the group of patients who received only periodontal therapy, followed by those who received combination therapy, while *H. pylori* persisted in dental plaque of all of the patients who received only triple therapy. Jia *et al*[83] evaluated the effect of periodontal therapy on prevalence of *H. pylori* in the stomach of dyspeptic patients in whom *H. pylori* was eradicated from the stomach by systemic *H. pylori* eradication therapy prior to periodontal intervention. They reported that 6 mo after periodontal therapy, the prevalence of *H. pylori* in the gastric mucosa was significantly lower among patients who received periodontal therapy compared with controls who did not receive any form of periodontal therapy. However, in this particular study, the authors did not evaluate the presence of *H. pylori* in the dental plaque of the study participants at any time point.

Two of the five studies listed in Table 5 evaluated the effects of periodontal therapy on oral and gastric *H. pylori*[46,72]. Gao *et al*[46] reported that among the 43 *H. pylori*-positive patients who received both anti-*H. pylori* therapy and periodontal therapy, the gastric eradication rates at 4 wk and 1 year after intervention were 81.4% (n = 35/43)

Table 4 Studies evaluating the effects of systemic *Helicobacter pylori* eradication therapy on oral *Helicobacter pylori*

Ref.	Sample population and sample size	Prevalence of *H. pylori* in dental plaque	Type of anti-*H. pylori* therapy	Prevalence of *H. pylori* in dental plaque after anti-*H. pylori* therapy	Effect on *H. pylori* infection
Gao *et al*[46], 2011	China; 80 patients with *H. pylori* infection-37 treated with anti-*H. pylori* therapy (gp A) and 43 treated with anti-*H. pylori* therapy and periodontal therapy (gp B)	82.3% in dental plaque and 51.1% in saliva	Gp A-2 wk proton pump inhibitor or triple therapy; gp B-2 wk triple therapy and initial periodontal therapy (oral hygiene education and scaling)	After 4 wk-29.7% (n = 11) in gp A and 4.7% (n = 2) in gp B; after 1 yr-43.2% (n = 16) in gp A and 18.6% (n = 8) in gp B	Eradication rate of gastric *H. pylori* After 4 wk-73% (27/37) in gp A and 81.4% (35/43) in gp B After 1 yr-32.4% (11/37) in gp A and 62.8% (27/43) in gp B
Bago *et al*[81], 2011	Croatia; 56 patients with chronic periodontitis and gastric *H. pylori*-positive	37.5% (n = 21)	One week therapy consisting of amoxicillin 1 g, clarithromycin 500 mg, and omeprazole 20 mg twice a day	0	Eradication rate in stomach was 76.2% (16/21)
Zaric *et al*[72], 2009	Serbia; 44 patients-21 patients positive for *H. pylori* in subgingival dental plaque and gastric mucosa (G+O+t) and 23 patients who were positive for *H. pylori* only in gastric mucosa (G+O-t)- all 44 received only anti-*H. pylori* (triple) therapy	47.7%	Triple therapy consisting of amoxicillin 2 g/d, clarithromycin 1 g/d, and pantoprazole 80 mg/d for 7 d	In G+O+t-66.7% (14/21)	In the G+O+t group, only 47.6% (10/21) showed eradication of gastric *H. pylori* compared with 87.4% (20/23) in G+O-t
Gebara *et al*[80], 2006	Brazil; 30 dentate patients with gingivitis/ periodontitis and *H. pylori* infection who received anti-*H. pylori* therapy	20% (n = 6) in supra-gingival plaque and 26.6% (n = 8) in sub-gingival plaque	Triple therapy consisting of amoxicillin 1 g, clarithromycin 500 mg, and lansoprazole 30 mg twice a day for 7 d	30% (n = 9) in supra-gingival plaque and 46.7% (n = 14) in sub-gingival plaque	Eradication rate of 90%
Gürbüz *et al*[39], 2003	Turkey; 75 dyspeptic patients of which 61 were *H. pylori*-positive and also had *H. pylori* in dental plaque	90.7% (n = 68); 81.3% (n = 61) had co-infection	Amoxicillin 1 g, clarithromycin 500 mg, and ranitidine bismuth citrate 400 mg twice a day for 7 d	100% in 61 patients	Eradication rate of 83%
Suk *et al*[98], 2002	Taiwan; 65 patients with dyspeptic symptoms	Overall-43.1% (n = 28), 73.7% (28/38) among *H. pylori*-positive patients	Colloidal bismuth subcitrate 1 g, amoxicillin 500 mg, and metronidazole 250 mg four times daily for 2 wk or cimetidine 200 mg, amoxicillin 500 mg, and metronidazole 250 mg 4 times a day for 2 wk	92.9% (26/28)	*H. pylori* eradicated from 84.2% (n = 32/38) *H. pylori* infected individuals
Butt *et al*[82], 2001	Pakistan; 82 patients positive for *H. pylori* in dental plaque-27 received only anti-*H. pylori* therapy (gp 1); 25 received anti-*H. pylori* therapy+periodontal therapy (gp 2); 30 received only periodontal therapy (gp 3)	100%	Gp 1-twice daily omeprazole 20 mg, clarithromycin 500 mg and metronidazole 400 mg; gp 2-triple therapy and dental scaling and chlorhexidine mouthwashes twice daily for 7 d; gp 3-only dental treatment	100% in gp 1; 16% in gp 2 (4/25); 10% in gp 3 (3/30)	Not evaluated

Miyabayashi *et al*[79], 2000	Japan; 47 patients with chronic gastritis or peptic ulcer-48.9% (n = 23) were positive for oral *H. pylori* and 38.3% (n = 18) had *H. pylori* in plaque	48.9% (n = 23) were positive for oral *H. pylori* and 38.3% (n = 18) had *H. pylori* in plaque	Lansoprazole 30 mg/d, metronidazole 750 mg/d, and clarithromycin 400 mg/d for 2 wk	Oral prevalence at 4 wk-34% (16/47)	At 4 wk-91.6% (22/24) of subjects negative for oral *H. pylori* were successfully eradicated of *H. pylori* infection compared to 52.2% (12/23) in oral *H. pylori*-positive patients. At 2 years, 95.8% (23/24) of subjects negative for oral *H. pylori* were successfully eradicated of *H. pylori* infection compared with 69.5% (16/23) in oral *H. pylori*-positive patients

H. pylori: *Helicobacter pylori*.

Table 5 Studies evaluating the effect of periodontal therapy on oral and gastric *Helicobacter pylori*

Ref.	Sample population and sample size	Prevalence of *H. pylori* in dental plaque	Details of periodontal therapy	Prevalence of *H. pylori* in dental plaque after periodontal therapy	Effect on *H. pylori* infection
Gao *et al*[46], 2011	China; 80 patients with *H. pylori* infection-37 treated with anti-*H. pylori* therapy (gp A) and 43 treated with anti-*H. pylori* therapy and periodontal therapy (gp B)	82.3% in dental plaque and 51.1% in saliva	Gp A-2 wk proton pump inhibitor or triple therapy; gp B-2 wk triple therapy and initial periodontal therapy (oral hygiene education and scaling)	After 4 wk, 29.7% (n = 11) in gp A and 4.7% (n = 2) in gp B; after 1 yr, 43.2% (n = 16) in gp A and 18.6% (n = 8) in gp B	Eradication rate of gastric *H. pylori* After 4 wk, 73% (27/37) in gp A and 81.4% (35/43) in gp B, after 1 year, 32.4% (11/37) in gp A and 62.8% (27/43) in gp B
Sambashivaiah *et al*[73], 2011	India; 36 patients in 3 groups-group Ⅰ, healthy subjects, group Ⅱ, chronic periodontitis patients, group Ⅲ, chronic periodontitis patients with type Ⅱ diabetes mellitus	Overall-66.7% (n = 24); among group Ⅰ-41.7% (n = 5), group Ⅱ-75% (n = 9), group Ⅲ-83.3% (n = 10)	Group Ⅱ and Ⅲ patients received full mouth scaling and root planning	Group Ⅱ, 0 and group Ⅲ, 8.3% (n = 1)	Not evaluated
Zaric *et al*[72], 2009	Serbia; 43 patients positive for *H. pylori* in sub gingival dental plaque and gastric mucosa-21 received only anti-*H. pylori* (triple) therapy (G+O+t); 22 received anti-*H. pylori* (triple) therapy)+periodontal therapy (G+O+tp)	100%	Triple therapy consisting of amoxicilin 2 g/d, clarithromycin 1 g/d, and pantoprazole 80 mg/d for 7 d. Periodontal therapy included oral hygiene orientation, plaque and calculus removal with an ultrasonic device, scaling, and root planing, as well as irrigation of periodontal pockets with 0.12% chlorhexidine-gluconate performed during triple therapy, in one sitting	In G+O+t-66.7% (14/21); in G+O+tp-27.3% (6/22)	In the G+O+tp group, 77.3% (17/ 22) showed eradication of gastric *H. pylori* compared with 47.6% (10/21) in G+O+t
Jia *et al*[83], 2009	China; 107 dyspeptic patients in whom *H. pylori* was eradicated from the gastric mucosa-56 received dental plaque control (test) and 51 did not (control)	Not evaluated	Full-mouth scaling, root planning and polishing, and dental plaque control instructions by dentist	Not evaluated	Prevalence of *H. pylori* in gastric mucosa was 19.64% (11/56) in test group and 84.31% (43/51) in control group
Butt *et al*[82], 2001	Pakistan; 82 patients positive for *H. pylori* in dental plaque-27 received only anti-*H. pylori* therapy (gp 1); 25 received anti-*H. pylori* therapy+periodontal therapy (gp 2); 30 received only periodontal therapy (gp 3)	100%	Gp 1-twice daily omeprazole 20 mg, clarithromycin 500 mg and metronidazole 400 mg; gp 2-triple therapy and dental scaling and chlorhexidine mouthwashes twice daily for 7 d; gp 3-only dental treatment	100% in gp 1; 16% in gp 2 (4/25); 10% in gp 3 (3/30)	Not evaluated

H. pylori: *Helicobacter pylori*.

and 62.8% (n = 27/43), respectively, while the eradication rates over the same time periods among the 37 *H. pylori*-positive patients who received only anti-*H. pylori* therapy were 73% (n = 27/37) and 32.4% (n = 11/37), respectively. They also reported that the detection rates of *H. pylori* in dental plaque of patients who received both forms of therapy at 4 wk and 1 year after intervention were 4.7% (n = 2/43) and 18.6% (n = 8/43), respectively, while the corresponding rates for the patients who received only anti-*H. pylori* therapy were 29.7% (n = 11/37) and 43.2% (n = 16/37), respectively. In another study by Zaric *et al*[72], 43 patients positive for *H. pylori* in both subgingival plaque and gastric mucosa were categorized into two groups in which 21 patients received only anti-*H. pylori* therapy and 22 received anti-*H. pylori* therapy along with periodontal therapy. Three months after treatment completion, 77.3% (n = 17/22) of the patients who received both anti-*H. pylori* therapy and periodontal therapy showed gastric eradication compared with only 47.6% (n = 10/21) of the patients who received only anti-*H. pylori* therapy. Among the 22 patients who received both anti-*H. pylori* therapy and periodontal therapy, *H. pylori* was detected in dental plaque of only six (27.3%) patients 3 mo after completion of treatment, whereas the microorganism was detected in 66.7% (n = 14) of the 21 patients who received only anti-*H. pylori* therapy. The authors also reported that eradication in the stomach coincided with eradication in the oral cavity (*i.e.*, all 16 of the individuals who received both forms of therapy and showed eradication of oral *H. pylori* also showed eradication of gastric *H. pylori*). Five of the participants in this group who were positive for oral samples were also positive for gastric *H. pylori*.

The periodontal therapy provided to the patients in these studies consisted of non-surgical periodontal therapy, in which the microbial deposits on the surfaces of the teeth are professionally removed by the dentists, along with other plaque control measures, such as use of mouthwashes and patient education in plaque control. This phase of treatment is referred to as the Etiotropic phase and is considered to be very important because the microbial etiological factors of periodontal disease are removed in this phase. As mentioned previously, because of its biofilm properties, dental plaque provides resistance to the resident microflora from systemically administered antimicrobial agents. Thus, the *H. pylori* present in the dental plaque are seldom affected by systemic *H. pylori* eradication therapy, as shown in previous studies conducted[39,80]. As a result, the removal of *H. pylori* in the dental plaque may necessitate periodontal therapy in which all microbial deposits, along with the resident bacteria, including *H. pylori*, will be eliminated. The initial studies in this regard have shown promising results in the management of both oral and gastric *H. pylori*.

CONCLUSION

Although *H. pylori* has long been known to be detected in the oral cavity, the significance of such findings was controversial. If the oral cavity is an important extra-gastric reservoir of *H. pylori*, then this finding may have major implications because the oral cavity can serve as both a source of re-infection and route of transmission. Because plaque-associated *H. pylori* would be resistant to systemic *H. pylori* eradication therapy, it can affect the success rates of the anti-*H. pylori* therapy. Thus, it is imperative to identify the role of dental plaque, saliva, and periodontal disease in *H. pylori* infection. Once these factors are clearly understood and whether the oral cavity is a major extra-gastric reservoir of *H. pylori* is confirmed, then newer treatment modalities, such as periodontal therapy, may be incorporated in the protocol for the management of *H. pylori* infection. The initial studies on the role of periodontal therapy in the management of *H. pylori* infection have shown promising results, suggesting that oral *H. pylori* may play an important role in re-infection of the gastric mucosa. These observations also create new avenues for both future research and more effective management of *H. pylori* infection.

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