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TOPIC HIGHLIGHT

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Helicobacter pylori and oral pathology: Relationship with the gastric infection

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Abstract

Helicobacter pylori (*H. pylori*) has been found in the oral cavity and stomach, and its infection is one of the most frequent worldwide. We reviewed the literature and conducted a Topic Highlight, which identified studies reporting an association between *H. pylori*-infection in the oral cavity and *H. pylori*-positive stomach bacterium. This work was designed to determine whether *H. pylori* is the etiologic agent in periodontal disease, recurrent aphthous stomatitis (RAS), squamous cell carcinoma, burning and halitosis. Record selection focused on the highest quality studies and meta-analyses. We selected 48 articles reporting on the association between saliva and plaque and *H. pylori*-infection. In order to assess periodontal disease data, we included 12 clinical trials and 1 meta-analysis. We evaluated 13 published articles that addressed the potential association with RAS, and 6 with squamous cell carcinoma. Fourteen publications focused on our questions on burning and halitosis. There is a close relation between *H. pylori* infection in the oral cavity and the stomach. The mouth is the first extra-gastric reservoir. Regarding the role of *H. pylori* in the etiology of squamous cell carcinoma, no evidence is still available.

Key words: *Helicobacter pylori*; Oral pathology; Gastric infection; Burning and halitosis; Recurrent aphthous stomatitis

Core tip: Infection by *Helicobacter pylori* (*H. pylori*) is one of the most frequent worldwide, with major implications for stomach pathology over the last twenty-five years. Early diagnosis is essential for control of the infection. There has been a growing interest in *H. pylori*-infection in the oral cavity, since the oral-oral is one of the major transmission routes. This review describes the association between *H. pylori* and different oral pathologies, such as periodontal disease, canker sores, squamous cell carcinoma, burning tongue and halitosis, and their correlation with the gastric pathology.

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INTRODUCTION

In 1984, Marshall and Warren[1] in the Royal Perth Hospital in Australia definitively identified the *Helicobacter pylori*

(*H. pylori*). It was cultured from gastric biopsy specimens from patients with gastric inflammation and peptic ulcer. Based on these results, they proposed that *H. pylori* could be the etiologic agent of these conditions[1,2]. In 1994, this microorganism was recognized as a type I carcinogen, and is now considered the most common etiologic agent of infection-related cancers. As a result, in 2005 Marshall and Warren were awarded the Nobel Prize of Medicine for their seminal discovery of this bacterium and its role in peptic ulcer disease. About 10% of *H. pylori* individuals develop peptic ulcer disease, 1% to 3% develop gastric adenocarcinoma, and less than 0.1% mucosa associated lymphoid tissue lymphoma[3]. The global prevalence of *H. pylori* infection is more than 50%. This prevalence may vary significantly within and among countries, according to geography, ethnicity, age, and socioeconomic factors. Prevalence is higher in developing countries and lower in the developed world. The risk of infection increases in lower economic and socio-cultural backgrounds[4]. The main reasons for these variations involve socioeconomic differences between populations. Transmission of *H. pylori* is largely by the oral-oral or fecal-oral routes. Lack of proper sanitation, safe drinking water and basic hygiene, as well as poor diets and overcrowding, all play a role in the overall prevalence of infection. *H. pylori* infection at younger ages is markedly more prevalent in developing countries than in developed countries, and *H. pylori*-seropositivity rates increase progressively with age[5]. Gastric *H. pylori* infection is treated with systemic antibiotic therapy. In some patients, however, persistent bacterial infection is observed after treatment[6,7]. Two questions arise as to how this persistent bacterial infection is transmitted, and how the reinfection process occurs. Some researchers have suggested that oral spread would be the main route of *H. pylori* transmission, and both the dental plaque and the saliva could act as a reservoir and have implications in reinfection once the bacterium is eradicated from the gastric tract[8]. Zou *et al*[9] consider that the mouth can be a reinfection source and that eradication from the oral cavity is more difficult than gastrointestinal eradication. As mentioned above, the search for *H. pylori* in dental plaque, saliva, periodontal disease, canker sores, cancer, burning mouth and halitosis was rather controversial due to the different diagnostic methods and research designs used, the inclusion/exclusion criteria, and the selected controls.

DENTAL PLAQUE AND SALIVA

Frequency of *H. pylori* isolation in dental plaque has been variable (Table 1)[10-56]. Dental plaque was first studied in 1989 in Canada by Krajden *et al*[10], who performed *H. pylori* isolation by culture in patients with *H. pylori*-positive gastric pathology. *H. pylori* was isolated from the stomach of 29 of 71 patients examined, with only one (3%) of the 29 patients having the organism present in dental plaque. That year the same group, also in Canada, studied *H. pylori* strains from the stomach and plaque of this patient to determine if they were epidemiologically linked. Eight colonies cultured from the stomach and plaque specimens were isolated and resubcultured until three to five plates of each colony type (clone) were available for restriction endonuclease analysis. DNA from each isolate was digested in HindⅢ, HaeⅢ, and BgⅢ (Boehringer Mannheim). It was therefore evident that at least one isolate from the plaque was genetically closely related or identical to the strain from the stomach. Krajden's team first described dental plaque as a common or rare ecological niche source of *H. pylori* infection[11]. Also in India, in 1991, Desai *et al*[13] reported that when administering the triple therapy to 24 patients with *H. pylori*-positive gastritis and dental plaque, stomach bacterium remitted in 100% of the patients, but *H. pylori* persisted in the 24 dental plaques. Therefore, they considered that the triple therapy was not sufficient for *H. pylori* eradication, and it should be simultaneously approached with local treatment. From 1989 to date, many researchers worldwide have identified *H. pylori* in plaque and saliva with varying results (Table 1). We emphasize that works such as Pustorino *et al*[23], in Italy, reported a low relative frequency that by dental plaque culture of 83 dyspeptic patients, and found in each patient the identical protein profile of the bacteria, both in the plate and in the stomach[23]. The persistence of bacteria in dental plaque was reported in 1996 by Pytko-Polonczyk *et al*[24], who after administering triple therapy, found that bacteria persisted in dental plaque in all patients. In the Kangnam Hospital of Korea, *H. pylori* was detected in dental plaque and saliva from 7% and 14% respectively, of patients with *H. pylori*-positive gastric pathology, suggesting that the oral cavity may be an important reservoir of *H. pylori*[31]. After triple therapy administration, Suk *et al*[35] in Taiwan reported an 84% resolution in stomach, but only 7% in dental plaque. Wang and colleagues conducted a comparison study of *H. pylori* cytotoxin genotypes in stomach and saliva. CagA, vacAm1, vacAm2, and vacAs1 genotypes were analyzed in 31 patients, and DNA sequencing in 3 subjects showed 78%, 64%, and 67% *H. pylori* homology from both sources, respectively. They suggested that more than one *H. pylori* strain could coexist in the saliva and stomach in the same patient[36]. In Venezuela, Berroteran *et al*[37] investigated *H. pylori* infection in dental plaque from 32 dyspeptic patients, and its relationship with gastric pathology. They found that 24/32 (75%) patients presented *H. pylori*-positive gastric pathology, and 12/32 (38%) also presented *H. pylori* in the dental plaque, assuming that this organism in the dental plaque could be a risk factor for gastrointestinal re-infection. On the basis of the results obtained with the rapid urease test (RUT) in the mouth, De Sousa *et al*[44] suggested that this methodology for *H. pylori* detection was not sufficiently sensitive for the determination of the microorganism in the oral cavity. The most frequent genotype in dental plaque and gastric mucosa was vacA *s1bm1*[51]. It was found that 47/196 (24%) patients were co-infected in both samples, 28% of whom had 2 different genotypes in saliva, and one or

Table 1 *Helicobacter pylori* detection in dental plaque and saliva *n* (%)

Ref.	Sample	Diagnostic method	Patient profile	*Helicobacter pylori* detection rate
Krajden *et al*[10]	Pq	MCT	Dys	1/71 (1)
Shames *et al*[11] (Canada)	Pq/Sal	MCT, REA	Dys	Pq: 1/29 (3) Sal: 0/29 (0)
Majmudar *et al*[12]	Pq	MCT	Dys	40/40 (100)
Desai *et al*[13]	Pq	RUT	Dys Tripe-*H. pylori*ET	Gc: 0/24 (0) Pq: 24/24 (100)
D'Alessandro *et al*[14]	Pq	MCT, Giemsa, RUT	Dys	16/20 (80)
Nguyen *et al*[15]	Pq	RT-PCR (16S rRNA)	Dys	18/25 (72)
Bernander *et al*[16]	Pq	MCT	Dys	0/94 (0)
Mapstone *et al*[17]	Pq/Sal	PCR	Dys	Pq: 3/13 (23) Sal: 2/13 (15)
Von Recklinghausen *et al*[18]	Pq	MCT, RUT	Dys	0/55 (0)
Li *et al*[19]	Sal	PCR (860-bp DNA)	Dys	30/40 (75)
Hardo *et al*[20]	Pq	MCT, N-PCR (16S rRNA)	Dys	1/62 (2)
Cammarota *et al*[21]	Pq	Giemsa: PCR (*ure*A), RUT	Dys	0/31 (0)
Luman *et al*[22]	EGB Pq/Sal	MCT	Dys	EGB: 52/109 (47) Pq/Sal: 0/120 (0)
Pustorino *et al*[23]	Pq	MCT	Dys	5/83 (6)
Pytko-Polonczyk *et al*[24]	Pq/Sal	RUT, ^{13}-UBT	100 Dys 50 DU	Post-triple *H. pylori*ET DU Gc: 1/30 (3) DU Pq: 30/30 (100)
Cheng *et al*[25]	Pq	MCT, RUT	Dys	MCT: 1/122 (1) RUT: 71/122 (58)
Oshowo *et al*[26]	Pq/Sal OS	MTC, Giemsa, RUT, REA	Dys	EGB: 116/116 (100) Pq: 15/116 (13)
Améndola *et al*[27]	Pq	MCT	Dys	1/20 (5)
Mattana *et al*[28]	Pq	MCT	Dys	1/62 (2)
Song *et al*[29]	Pq	N-PCR[1]	Dys	41/42 (97)
Doré-Davin *et al*[30]	Pq/Sal	N-PCR (16S rRNA-*ure*C), UBT	DU	9/22 (40)
Kim *et al*[31]	Pq/Sal	MCT, Giemsa, PCR[1], RUT	Dys	Gc: 29/46 (63) Pq: 2/29 (7) Sal: 4/29 (14)
Miyabayashi *et al*[32]	Pq/Sal	N-PCR (*ure*A) MCT	Gtis, DU, *H. pylori*-pos	Diagnosis: 23/47 (49) Pos-*H. pylori*ET: 11/23 (48)
Ozdemir *et al*[33]	Pq Tg	RUT	Dys	Pq: 63/81 (78) Tg: 48/81 (59)
Allaker *et al*[34]	EGB Pq	PCR (*ure*A-cagA)	Dys, Children	EGB: 22/100 (22) Pq: 15/22 (68) and 21/88 (24)
Suk *et al*[35]	Pq	PCR (cag-A) RUT	Dys	Gc: 38/65 (58) Pq: 28/65 (43)
Wang *et al*[36]	Sal	PCR-Sequence (cagA-vacA)	Gtis, DU	More than one *H. pylori* strain in Gc and Sal, in same patient
Berroteran *et al*[37]	EGB Pq	PCR (urease gene cluster)	32 Dys 20 Asym	Gc: 24/32 (75) Pq: 12/32 (38), 3/20 (15)
Gürbüz *et al*[38]	Pq	RUT	Dys	Gc: 65/75 (86) Pq: 68/75 (90)
Nasrolahei *et al*[39]	Pq	MCT, PCR[1], RUT	Dys	$P > 0.05$
Siddiq *et al*[40]	EGB Pq	Giemsa, ^{13}-UBT	Dys	Gc: 32/52 (62) Pq: 48/52 (92)
Czesnikiewicz-Guzik *et al*[41]	Pq/Sal	MCT, ^{13}-UBT	Dys	Gc: 51/100 (51) Pq-Sal: 54/100 (54), $P > 0.05$
Kignel *et al*[42]	Pq/Sal	PCR	Dys	Gc: 20/49 (41) Pq-Sal: 1/20 (5)
Chitsazi *et al*[43]	Pq	RUT	Dys 44 Gc *H. pylori* 44 no-Gc *H. pylori*	Gc *H. pylori*: 16/44 (36) No-Gc *H. pylori*: 14/44 (32) $P = 0.7$
De Sousa *et al*[44]	EGB Pq/Sal	MCT, Giemsa, RUT	97 Dys 50 Asym	Gc: 111/147 (76) Pq/Sal (RUT): 0/147 (0)
Sudhakar *et al*[45]	Pq	MCT, RUT	50 Dys 25 control	Pq MCT: 5/50 (1) Pq RUT: 37/50 (74)
Bürgers *et al*[46]	SP-P Sal	MCT, Ser (ELISA), PCR	Dys	Gc: 29/94 (31) SP-P: 3/94 (3) Sal: 7/94 (7)
Liu *et al*[47]	EGB, Pq	Giemsa, PCR, RUT	Dys	EGB: 273/443 (62) Pq: 263/443 (59)

Silva *et al*[48]	Pq/Sal	PCR (vacA)	Dys	Gc: 30/62 (48) Pq: 11/30 (37) Sal: 16/30 (53)
Rasmussen *et al*[49]	EGB Pq/Sal	SBlot	Dys	Gc: 66/78 (85), $P < 0.0001$
Medina *et al*[50]	EGB Pq	PCR (*ure*A)	43 Dys 55 control	18/98 (18) EGB: 38/43 (88) Pq/Sal: 15/43 (35)
Assumpção *et al*[51]	EGB Pq	PCR (cagA-vacA), Giemsa, RUT	Dys	Gc PCR: 95/99 (96) Gc Giemsa: 39/99 (48) Gc RUT: 47/99 (49) Pq PCR: 71/99 (72) Pq RUT: 48/99 (52)
Navabi *et al*[52]	MAS	MCT, PCR, RUT	Dys	925/1861 (49.7) (95%CI: 16-83.4)
Zou *et al*[9]	MAS	MCT, PCR, RUT	Dys	490/1088 (45) OR 3.61 (95%CI: 191-6.82)
Chaudhry *et al*[53]	Pq TBF	PCR (*ure*A-16S rRNA-860 bp DNA)	Dys	46/89 (52)
Momtaz *et al*[54]	EGB, Pq/Sal, Stool sample	PCR (cagA-vacA-*ure*C), RUT	Dys	PCR: EGB: 233/300 (78), Pq: 0/300 (0), Sal: 32/300 (11), Stool: 215/300 (72) RUT: 271/300 (90)
Román-Román *et al*[55]	EGB, Sal	PCR (vacA) N-PCR (cagA)	162 Gtis 32 GU	EGB/Sal: 47/196 (24) EGB: 103/196 (53) Sal: 13/196 (7)
Cai *et al*[56]	Pq	PCR (16S rDNA-CagA), RUT	Dys, Children	46/235 (20) Pq: 26/46 (57)

[1]Data not shown. Asym: Asymptomatic subject; Bs: Biopsy; DU: Duodenal ulcer; Dys: Dyspepsia; EGB: Endoscopic gastric biopsy; Gc: Gastric; Gtis: Gastritis; GU: Gastric ulcer; *H. pylori*ET: *Helicobacter pylori* eradication therapy; MAS: Meta-analysis study; MCT: Microbial culture techniques; N: Nested; OR: Odds ratio; OS: Oral swab; PCR: Polymerase chain reaction; Pq: Plaque; PS-P: Periodontal status; Ptis: Periodontitis; REA: Restriction endonuclease analysis; RT: Reverse transcription; RUT: Rapid urease test; Sal: Saliva; SBlot: Southern-blotting; SB-P: Subgingival plaque; Ser: Serology; SP-P: Supragingival plaque; TBF: Tooth brushing frequency; Tg: Tongue; ^{13}-UBT: ^{13}C-urea breath test.

both in the stomach. The *s1m1/s1m2* genotypes, alone or together, were found simultaneously in saliva and gastric biopsy from the same patient. Then they suggested that saliva could be the transmitting and re-infecting vector[55]. Dental plaque has been identified as the second reservoir of *H. pylori*, and the first extra-gastric reservoir. However, some studies revealed 100% negativity in plaque and saliva[16,18,20-22]. Microbial Culture Techniques are a useful tool for the identification of bacteria in gastric specimens. However, researchers have run into several difficulties with culture in the oral cavity. The sensitivity and specificity of *H. pylori* IgG antibodies in saliva (ELISA) have been estimated in 80% and 70%, respectively. On the other hand, disparate results were found regarding the effectiveness of brushing dental frequency with *H. pylori* presence in the dental plaque. Some investigators could not find any association[50,53].

In summary, we selected 48 works that reported on the presence of *H. pylori* in saliva and plaque, and further considered the gastric pathology. Three of them studied only the existence of the bacteria in the saliva of patients with dyspepsia, gastritis and gastric ulcer, with positive results[19,36,55]. Bacterial detection in plaque and saliva was reported in 15 investigations, 2 of which showed negative results, both in plaque and in saliva when attempting to culture the bacteria[22,44]. In plaque, exclusively 28 clinical trials were found. The diagnostic technique most commonly used was polymerase chain reaction (PCR), together with serology; RUT and Southern-blotting were the most sensitive methods. Microbial culture was the methodology used in 18 researches to isolate the bacteria, with negative results in 5 of them, positive results between 1% and 10% in 9, and results higher than 10% in 4. Electron microscopic studies have shown that *H. pylori* has three stages: spiral forms, coccoid forms and degenerative forms. Spiral forms are viable, culturable, and virulent. Coccoid forms may also be viable but are nonculturable, and less virulent. Degenerative forms are pyknotic, nonculturable, coccoid forms of dead *H. pylori*. These forms cannot be cultured and the cell membrane has disintegrated; however, gene material can be detected by PCR. *H. pylori* does not seem to participate in biofilm formation in the oral cavity, despite the presence of the bacterium. In Denmark, Andersen and Rasmussen[57] conducted a mini-review and observed that in dental plaque both spiral and coccoid forms exist. Fifteen papers used 2 or more diagnostic techniques. Two meta-analyses were included, which showed a prevalence > 40%, with an OR of 3.61[9,52]. The available evidence reveals that despite some adverse results in the search for the association, dental plaque is the first extra-gastric reservoir of *H. pylori*. It will play a key role in the relapse of the *H. pylori*-positive gastric pathology. We have displayed through various research designs, the effectiveness of the eradication therapy when accompanied by adequate hygiene by , and the strong association between bacterial infection and periodontal disease with deep pockets.

Table 2 *Helicobacter pylori* detection in periodontal disease *n* (%)

Ref.	Sample	Diagnostic method	Patient profile	*Helicobacter pylori* detection rate
Asikainen *et al*[58]	SB-Pq (United States)	PCR (urease A)	Ptis	0/336 (0)
Riggio *et al*[59]	SB-Pq	PCR (16S rRNA)	Chronic Ptis	11/29 (38)
Avcu *et al*[60]	SB-Pq, SP-Pq	Camphylobacter-like organism test gels	Gastric *H. pylori* and B12 deficiency: (1) good oral hygiene; (2) fair oral hygiene; (3) poor oral hygiene	(1) 6/21 (28); (2) 46/51 (90); (3) 36/36 (100)
				post-*H. pylori*ET: (1) 58%; (2) 41%; (3) 5%
Dye *et al*[61]	BL	Ser (ELISA)	NHANES Ⅲ; 1988-1991	Periodontal pocket ⩾ 5 mm: 493 (41)
Gebara *et al*[62]	SB-Pq, SP-Pq, Tg, Sal	PCR (16S rRNA)	GDis, RUT pos (15 gingivitis, 15 chronic Ptis)	13/30 (43)
Gebara *et al*[63]	EGB, SB-Pq, SP-Pq, Tg, Sal	PCR (16S rRNA)	Post-*H. pylori*ET: GDis RUT pos (15 gingivitis, 15 Chronic Ptis)	Gastric eradication 90% *H. pylori*: 3/30 (10). Oral eradication: 40% *H. pylori*: 18/30 (60)
Anand *et al*[64]	PS	Oral Hygiene	65 pos Ser/RUT/Giemsa; 69 control	Ptss: 30/65 (46);
Al Asqah *et al*[8]	SB-Pq	RUT	*H. pylori*-IgG	PDss: 37/50 (60)
Eskandari *et al*[65]	SB-Pq, SP-Pq	PCR (16S rRNA)	Chronic Ptis (23/67 Gtis)	4/67 (6)
Agarwal *et al*[66]	SB-Pq	MCT, PCR (16S rRNA)	Chronic Ptis (30 GDss-pos; 20 GDss-neg)	18/30 (60); 3/20 (15)
Bouziane *et al*[67]	MAS		Gtis (post-*H. pylori*ET)	RR 63%; [0.37 (95%CI: 0.21-0.64), P = 0.0004]

BL: Blood; EGB: Endoscopic gastric biopsy; Gtis: Gastritis; GDss: Gastric disease; *H. pylori*ET: *Helicobacter pylori* eradication therapy; *H. pylori*-IgG: Presence of anti-*H. pylori*-IgG; MAS: Meta-analysis study; MCT: Microbial culture techniques; Neg: Negative; PDss: Negative periodontal disease; PS: Periodontal status; Ptis: Periodontitis; PCR: Polimerase chain reaction; Pos: Positive; RUT: Rapid urease test; Sal: Saliva; SB-Pq: Subgingival plaque; Ser: Serology; SP-Pq: Supragingival plaque; Tg: Tongue.

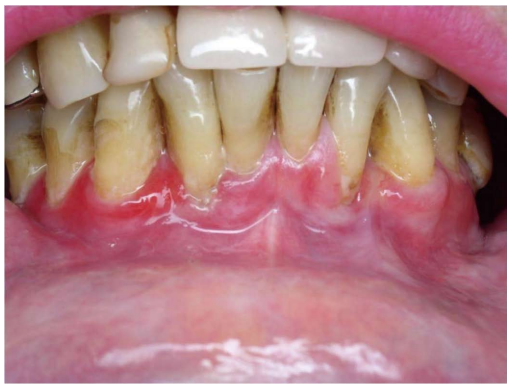

Figure 1 Periodontal disease. *Helicobacter pylori*-positive finding in subgingival plaque and stomach.

PERIODONTAL DISEASE

The bacterial plaque or oral biofilm is a translucent film, mixing a biotic array (bacteria and fungi), and inter- or extracellular matrix (organic compounds and minerals), which adheres to the dental surfaces, gingival and oral epithelium, prostheses and restorations, but is not deletable with simple rinsing. It has a variable composition depending on the location and ripening time (Figure 1). When located in dental and periodontal surfaces, the biofilm is immediately responsible for both dental caries and periodontal disease. The dental plaque hosts different microbiota, and in the absence of good oral hygiene, it develops quickly and adheres to the teeth surface at the supra- and subgingival level. In periodontal lesions, the number of bacteria increases with periodontitis development, and could comprise *Porphyromonas gingivalis*, *Fusobacterum nucleatum*, and *Fusobacterum periodonticum*, co-aggregated with *H. pylori* strains.

Table 2 shows a meta-analysis selection list of *H. pylori* detection in dental plaque between the years 1994 and 2012[58-67]. In 1994 Asikainen *et al*[58] carried out the first *H. pylori* search in the subgingival plaque of patients with periodontitis in Finland. They concluded that periodontal pockets are not a natural reservoir for *H. pylori*. In 1999, in Great Britain, Riggio *et al*[59] demonstrated the presence of *H. pylori* in 11/29 (38%) subgingival plaques of patients with chronic periodontitis. They suggested that, in this patient group at least, subgingival plaque may be a reservoir for *H. pylori* infection. But none of these researchers evaluated the gastric condition. It was determined that proper oral hygiene is required to remove *H. pylori* from dental plaque. They further suggested that the presence of *H. pylori* in dental plaque must be controlled in order to avoid its recurrence[60]. Periodontal pockets ⩾ 5 mm in depth were associated with increased odds of *H. pylori* seropositivity (OR = 1.47, 95%CI: 1.12-1.94)[61]. The bacterium was detected in saliva, supra- and subgingival plaque, suggesting that these sites may be considered reservoirs for *H. pylori* in urease-positive patients. The bacterium was not found on the dorsum of the tongue of any patient[62]. Eradication of *H. pylori* after therapy was more effective from the stomach than from the mouth[63]. The periodontal relative frequency of *H. pylori* infection increased with gastric infection[65]. Bouziane *et al*[67] carried out a systematic review and meta-analysis which evaluated the effect of dental plaque control, periodontal therapy and bacterial eradication treatment *vs* eradication treatment alone in patients with gastric disease. *H. pylori* eradication therapy (*H. pylori*ET) alone would not be effective for gastric reinfection control.

To summarize, twelve clinical trials and a meta-anal-

Table 3 *Helicobacter pylori* detection in aphthous stomatitis *n* (%)

Ref.	Sample (study design)	Diagnostic method	Patient profile	*H. pylori* detection rate
Leimola-Virtanen *et al*[69]	Bs (TS)	Giemsa, ISH	RAS	Giemsa: 14/29 (50); ISH: 6/29 (20)
Porter *et al*[70]	BL (CCS)	Ser (ELISA)	75 RAS, 83 (15 other oral ulcerative disorders, 41 other oral mucosal lesions, 27 oral dysaesthesia), 25 control	23/75 (31) 27/83 (33) 6/25 (24)
Birek *et al*[71]	OS (CCS)	PCR (ureC)	RAS	23/32 (72)
Riggio *et al*[72]	Bs (CCS)	PCR (16S rRNA)	28 RAS, 20 OLP, 13 control	3/28 (11), 0/20 (0); 0/13 (0)
Shimoyama *et al*[73]	BL, OS (CCS)	MCT, Ser (ELISA)	RAS	0/12 (0)
Victória *et al*[74]	OS (CCS)	N-PCR[1]	36 RAS, 48 control	14/36 (38); 16/48 (33)
Iamaroon *et al*[75]	OS (CCS)	N-PCR (*H. pylori*aA)	22 RAU, 15 control (Tg)	1/22 (5); 3/15 (20)
Elsheikh *et al*[76]	Bs (CCS)	PCR (16S rRNA)	58 RAS and Lymp 88 RAS, 20 control	39/58 (67); 9/88 (10); 0/20 (0)
Mansour-Ghanaei *et al*[77]	BL, OS (CCS)	Ser (ELISA), PCR[1]	RAS	*H. pylori*-IgG: 26/50 (52); PCR: 1/50 (2)
Albanidou-Farmaki *et al*[78]	Sal, BL, RUT (CSS)	Ser (ELISA), ^{13}-UBT	RAS	34/48 (71)
Karaca *et al*[79]	Gastric Bs (CSS)	Giemsa (PTE)	RAS	20/23 (89); $P < 0.05$
Maleki *et al*[80]	RUT (CCS)	^{13}-UBT	43 RAS, 44 control	16/43 (37); 14/44 (32); $P = 0.597$
Taş *et al*[81]	Gastric Bs, BL (CSS)	^{13}-UBT (PTE)	MAL (vitamin B12)	Pre: 30/46 (65); post: 12/30 (40)

[1]Data not shown. *Helicobacter pylori*: *H. pylori*; BL: Blood; Bs: Biopsy; CCS: Case-control study; CSS: Cross-sectional study; *H. pylori*-IgG: Presence of anti-*H. pylori*-IgG; ISH: *In situ* hybridization; Lymp: Lymphoma; MAL: Minor aphthous lesions; MCT: Microbial culture techniques; N: Nested; OLP: Oral lichen planus; OS: Oral swab; PCR: Polymerase chain reaction; PTE: Post-treatment evaluation; RAS: Recurrent aphthous stomatitis; RAU: Recurrent aphthous ulceration; RUT: Rapid urease test; Ser: Serology; Sal: Saliva; Tg: Tongue; TS: Transversal study; ^{13}-UBT: ^{13}C-urea breath test.

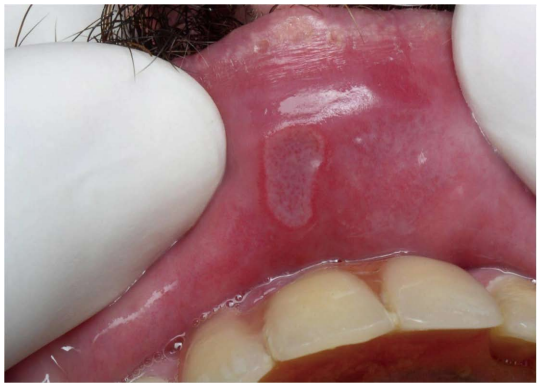

Figure 2 Recurrent aphthous stomatitis. Erosive necrotic lesion in lip mucosa. *Helicobacter pylori*-negative finding by molecular biology.

ysis have been included in the information assessment. In order to be able to demonstrate the association between periodontal diseases and bacterial infection, PCR was used in 7 of these trials as a diagnostic method. Only the trial by Asikainen *et al*[58] reported negative results. The *H. pylori* prevalence found with this technique was higher than 40%. The RUT was carried out in 4 clinical trials, with results similar to the PCR. Only 1 work was conducted in 4504 subjects using serology anti-*H. pylori*, with OR of 1.47 in patients with periodontal pocket $\geqslant$ 5 mm[61]. Emphasis is laid on the meta-analysis that evaluates the effective response to the *H. pylori*ET in *H. pylori*-positive patients presenting periodontal disease[67]. To our knowledge, there is a likelihood of super-infection of sub-gingival plaque in patients who have a poor oral hygiene and are exposed to *H. pylori* infection due to chronic gastric infections.

APHTHOUS STOMATITIS

Aphthous stomatitis (also termed canker sores, RAS, recurring oral aphthae and recurrent aphthous ulceration) is considered an inflammatory disease of the oral cavity characterized by the presence of erosions/ulcerations, ulcerations with necrosis, erythematous halo underlying the mucous membrane lining, which respects the keratinized mucosa (Figure 2). Its most frequent location is labial and buccal mucosa, floor of the mouth, ventral surface of the tongue, soft palate, gingiva, posterior pillars, and alveolar gum. Three variants of aphthous stomatitis exist, distinguished by the size, number and location of the lesions, the healing time of individual ulcers and whether a scar is left after healing: minor, major and herpetiform. Aphtae can recur between 1 and 6 mo later. Despite their high prevalence, etiopathogenesis remains unclear. However, canker sores are thought to have an immune pattern associated with hematological disorders, hormonal disturbances, gastric complications, food hypersensitivity, emotional states and local trauma as the most characteristic feature[68].

The presence of *H. pylori* in patients with canker sores (Table 3) has been analyzed, given the histological similarities between this condition and gastric ulcer[69-81]. Back in 1995, in Finland, Leimola-Virtanen *et al*[69] studied the biopsies of human immunodeficiency virus-positive patients with canker sores using Giemsa and *in situ* hybridization (ISH), and found positive results. Positive serology in RAS has been reported by Porter *et al*[70] in 1997, in London, who determined the relative frequency of anti-*H. pylori* IgG antibodies in minor aphthous ulceration, with no significant differences compared with control groups. The association between canker sores and *H. pylori* tried to be demonstrated through molecular biology, with disparate results (Table 3). In Turkey, the effect of *H. pylori* eradication on RAS patients was deeply studied. Thus, 23 subjects were regularly monitored for 1 year after anti-*H. pylori* therapy. A significant difference was observed compared with the reduction in canker

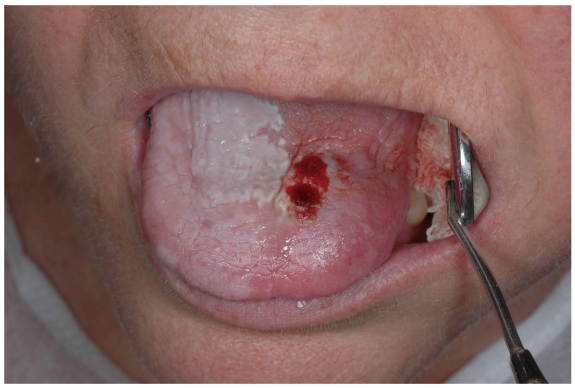

Figure 3 Oral squamous cell carcinoma grade 2 in lingual dorsum. *Helicobacter pylori*-negative finding by molecular biology. Biopsy area.

sores recurrence and improvement ($P < 0.05$)[79]. Later, in 2013, again in Turkey, Taş *et al*[81] conducted a clinical trial including 46 patients with minor aphthous ulceration. Vitamin B12 serum levels were measured, gastric biopsy was done, and presence of *H. pylori* analyzed. Of 46 study subjects, 30 (65%) were *H. pylori*-positive, and followed an *H. pylori*ET. Three months later, they were evaluated with 13-UBT, and 18/30 (60%) were negative. New measurements of vitamin B12 were carried out, and increased levels were observed in the group that received the antibiotic therapy. It was estimated that the effects of the *H. pylori*ET and the increase in vitamin B12 serum levels improved the clinical course of RAS.

In summary, we evaluated 13 articles reporting the potential association between recurrent canker sores and the action of *H. pylori* in their etiology. The designs were 9 case-control studies, 1 cross-sectional, 2 clinical trials of the effectiveness of eradication therapy and 1 meta-analysis. The latter evaluated nine of the works included in our analysis, whose data and conclusions are, in our opinion, correct. The samples used in the research were 3 tissue (lesion biopsy), 4 swabs, 3 sera, 2 expired air and 1 saliva. In 3 papers, 2 or more samples were used. The diagnostic methods were PCR in 6 of the publications, ELISA in 3, 13-UBT in 2. Other techniques were Giemsa, ISH and culture. Four reports used 2 diagnostic methods. Results showed no association in 6 researches, 4 of them using PCR as a diagnostic method. Clinical trials of therapeutic effectiveness showed reduction in episodes of relapse of canker sores after the eradication therapy in patients with gastric *H. pylori*-positive and recurrent canker sores. These patients were anemic, and the presence of the bacterium had not been evaluated in canker sores injury[79,81]. We have investigated the presence of the bacterium in canker sores from patients with dyspepsia. Samples were taken by biopsy, and the following diagnostic techniques were used: HE, Periodic acid-Schiff (PAS), Giemsa and PCR. Negative results were obtained with all the methods. All the patients underwent video-esofagogastricoduodenoscopy with biopsy of the greater and lesser curvature of the gastric antrum up to 5 cm from the pylorus. Erosive and chronic active *H. pylori*-positive gastritis was found in 63% of the patients, who had an iron deficiency anemia[82]. We believe that the action of the bacteria in the RAS is due to *H. pylori*-positive gastric disease and deficiency conditions. The presence of bacterial infection in the occurrence and recurrence of canker sores would be associated with anemia, produced by *H. pylori*-positive stomach diseases. Antibiotic therapy and the return to normal hematological values lead to a decrease in the number of canker sores, their size and relapse.

ORAL CANCER

In 2011, the American Cancer Society estimated 39400 new cases of oral and pharynx cancer, and 7900 deaths from this cause. The incidence varies according to gender, racial or ethnic group, and geographic location. The latter is directly related to particular habits and the differential exposure to environmental carcinogens[83]. The most frequent cancer in the oral cavity is squamous cell carcinoma of the mucosa, which represents 90% of all malignant neoplasms in this location (Figure 3). The remaining 10% includes salivary gland tumors, sarcomas of the soft tissues and jaw bones, non-Hodgkin's lymphoma, metastasis of extra oral primary tumors and melanomas. Oral squamous cell carcinoma is the sixth most common cancer in the world, with approximately 350000 deaths and 650000 new diagnoses per year[84-86]. It was estimated that biological carcinogens cause 18% of all cases of cancer[87]. In 1994, *H. pylori* was considered a carcinogenic agent type 1 by the Organización Mundial de la Salud/International Agency for Research on Cancer, OMS/IARC (http://www.iarc.fr).

Few studies have addressed the relationship between oral cancer and *H. pylori* action (Table 4)[88-93]. The first study was carried out by Grandis *et al*[88] who studied the serology of 21 patients with oral cancer and 21 controls, and observed a similar seroprevalence in both patients and controls, and they could not establish a significant association. Serologic studies showed a similar relative frequency in patients with cancer and controls[92]. A group of Indian researchers evaluated the presence of *H. pylori* in serum and tissue samples from 20 patients with oral cancer and 20 controls, using culture and PCR. While this study showed no significant differences, the OR of *H. pylori*-positive patients was 3.0 (95%CI: 0.34-26.4), while it was lower for only PCR-positive subjects (OR = 1.5, 95%CI: 0.28-8.0)[93].

In summary, only a few researchers have looked for the bacteria in oral cancer. All of them have included patients with squamous cell carcinoma. We have analyzed 6 works, 4 of which are case- control studies, and 2 prospective studies. The samples used to search the bacteria were biopsy, swabs and serum, and the diagnostic methods were culture, serology, histopathology, 13-UBT, ISH, RUT and PCR. No relationship was found with the bacteria. These results are in line with those found by our group in the study of 8 oral squamous cell carcinomas in

Table 4 ***Helicobacter pylori*** **detection in oral cancer** ***n*** **(%)**

Ref.	Sample (study design)	Diagnostic method	Patient profile	*H. pylori* detection rate
Grandis *et al*[88]	BL (CCS)	Ser (ELISA)	21 HNSCC	12/21 (57)
			21 controls	13/21 (62), $P > 0.05$
Singh *et al*[89]	Bs (CCS)	MCT,	26 OC	MTC: 0/26 (0); 0/26 (0)
		Giemsa,	26 controls	Giemsa: 4/26 (15); 0/26 (0)
		RUT		RUT: 3/26 (11); 0/26 (0)
Okuda *et al*[90]	Bs, OS (PRS)	MTC, RT PCR[1]	GDss (58 OC)	Bs: 54/116 (46); OS: 14/116 (12); OC: 11/58 (19)
Kanda *et al*[91]	Bs, urine (PRS)	MTC, Ser (ELISA), PCR[1], IHC	HNSCC	Bs: 0/31 (0) MTC, IHC, PCR. Urine: 21/31 (68) Ser
Fernando *et al*[92]	BL (CCS)	Ser (ELISA)	53 cases	14/53 (23)
			60 controls	10/60 (17)
Dayama *et al*[93]	Bs (CCS)	MTC; PCR (16S rRNA)	20 OC	OC: 3/20 (15) MCT, PCR
			20 controls	Controls: 1/20 (5) MTC and 2/20 (10) PCR

[1]Data not shown. BL: Blood; Bs: Biopsy; CCS: Case-control study; GDss: Gastric disease; HNSCC: Head and neck squamous cell carcinomas; ISH: *In situ* hybridization; MCT: Microbial culture techniques; OC: Oral cancer; OS: Oral swab; PCR: Polymerase chain reaction; PRS: Prospective study; RUT: Rapid urease test; Ser: Serology.

patients with dyspepsia. We studied biopsy, and used HE, PAS, Giemsa and PCR as diagnostic techniques, with negative results for all these methods. The relationship between *H. pylori* and the pathogenesis of gastric cancer has been well described, due to the ability of *H. pylori* to modify the host's immune response. It might behave similarly in the progression of oral carcinoma; however, this association has not been demonstrated yet. In the future, a prospective cohort design will be required to be able to determine a potential association between *H. pylori* and oral cancer.

BURNING, HALITOSIS, AND LINGUAL DORSUM HYPERPLASIA

The oral burning sensation can be a symptom of an underlying disease or a syndrome of unknown etiology. If the local or systemic factors involved are identified, these are referred to as the cause of the burning[94,95].

Halitosis means abnormal odour of exhaled air regardless of its origin. Halitosis can be oral, nasal, gastric or systemic (diabetes, nephropathies, trimethylaminuria). Miyazaki *et al*[96] have classified.

Genuine halitosis

It was subdivided into: (1) Physiological-halitosis, in which there is no disease; and (2) Pathologic-halitosis, which may be oral or extra-oral. Oral pathologic-halitosis occurs as a result of a pathological process in the mouth, either dental or mucosal (caries, periodontal disease, canker sores, cancer, *etc.*). Non-oral pathological-halitosis can originate from the upper respiratory tract and from other sources that are carried by blood and exhaled in the lung[96-98].

Pseudo-halitosis

It is characterized by absence of halitosis. However, the patient believes that he has oral malodour.

Halitophobia

It occurs when the patient perceives his bad breath after treatment of a true halitosis or pseudohalitosis, with physical evidence or a negative effect in his social life, which indicates the persistence of the bad smell. However, the patients are convinced that their "Halitosis" is socially offensive[96,99,100].

Bad breath or oral malodour is the term used for halitosis of oral origin[101]. Oral halitosis is caused by volatile sulfur compounds (VSC), such as methyl mercaptan, hydrogen sulfide, methyl disulfide, which are generated by the action of bacterial metabolism that degrades the sulfur containing amino acids present in the oral cavity. Anaerobic and gram-negative bacteria are the agents most frequently involved[102-104]. These bacteria are found in gingival grooves, in periodontal pockets, and in posterior lingual dorsum[105]. De Boever *et al*[106] considered that the anaerobic flora of the tongue plays an essential role in halitosis origin. There are different research lines that postulate lingual anaerobic flora action as one of the causes of halitosis appearance. These researches argue that the tongue acts as a reservoir that allows the accumulation and stagnation of bacteria and food waste[107-110]. The three main methods of diagnosing halitosis are gas chromatography, organoleptic measurement, and sulphide monitoring[99]. Loesche *et al*[110] reported that 74% of the bacteria cultured from the lingual dorsum were *Veillonella parvula*, *Actinomyces odontolyticus*, *Streptococcus intermedius* and *Clostridium innocuum*.

Table 5 shows the different research groups that attempted to relate halitosis to *H. pylori*[111-123]. The first were Tiomny *et al*[111], who in 1992 in Israel studied 6 patients with halitosis, 5 of whom were *H. pylori*-positive. They found that halitosis had disappeared after *H. pylori*ET, and highlighted the possible connection between halitosis and *H. pylori* infection. At the University of Bari (Italy), Ierardi and partners associated halitosis with *H. pylori* infection and correlated *H. pylori*-eradication in dyspeptic patients. They established the levels of VSCs at diagnosis and in subsequent controls after *H. pylori*ET was established[112]. In 2001 we reported a patient with severe BHH of lingual dorsum, who underwent biopsy of the affected tongue area. *H. pylori* was observed by Giemsa and

Table 5 *Helicobacter pylori* detection in burning, halitosis, and lingual dorsum hyperplasia *n* (%)

Ref.	Diagnostic method	Patient profile	*H. pylori* detection rate	Hal detection rate
Tiomny *et al*[111]	SHal	6 Hal	5/6 (83)	Post-*H. pylori*ET: 0/11(0)
Ierardi *et al*[112]	OHal	Dys [Hal: 52 (90)]	Diagnosis: 30/52 (58) Double *H. pylori*ET: 11/30 (64) Triple *H. pylori*ET: 2/11 (18)	Diagnosis: 52/52 (100) Double *H. pylori*ET: 11/30 (64) Triple *H. pylori*ET: 2/11 (18)
Adler *et al*[113]	EGB, SHal, OHal, Giemsa, PCR (SSA)	Dys, BHH	Tg: 1/1; Gc: 1/1	Case report
Gall-Troselj *et al*[114]	N-PCR (*ure*A)	AG: 87 (32) BMG: 37 (14) BMS: 144 (54) (54 Tg, 90 no-Tg)	Tg: 43/268 (16)	17/87 (20), 1/37 (3), 12/54 (22), 13/90 (14)
Serin *et al*[115]	EGB, Giemsa	Dys, Hal, EGB: *H. pylori*-pos, no lesion and no atrophy	EGB pos-*H. pylori*ET: 39/148 (26)	Hal post-*H. pylori*ET: 40/148 (3)
Adler *et al*[113]	EGB, SHal, OHal, Giemsa, PCR (SSA) y (16SrRNA)	GDSS [BHH: 46 (37), no-BHH: 78 (63)]	40/46 (87); 2/78 (3)	RR 13.01 CI 6-28.20
Brailo *et al*[116]	Ser (ELISA)	150 BMS	29/150 (19)	19/150 (13)
Katsinelos *et al*[117]	EGB, Giemsa, RUT	Dys, Hal,	Diagnosis: 18/18 (100) Triple *H. pylori*ET: 4/18 (22) Quad *H. pylori*ET: 0/18 (0)	Diagnosis: 18/18 (100) Triple *H. pylori*ET: 2/18 (11) Quad *H. pylori*ET: 2/18 (11)
Moshkowitz *et al*[118]	EGB, RUT	GDSS [GERD: 72 (55)]	*H. pylori vs* Hal: $P > 0.05$	Hal *vs* GERD: $P < 0.05$
Suzuki *et al*[119]	OLT, GC, PCR (16S rRNA)	Non-Dys (251 Hal, 75 no-Hal)	Sal: 21/326 (6)	*H. pylori*-pos: Higher VSC and OLT Score
Yoo *et al*[120]	OHal, GC, 13-UBT	*H. pylori*-pos [EGL: 24 (33), NEGL: 48 (675)]	72/72 (100)	VSC: EGL *vs* NEGL: $P < 0.01$
Lee *et al*[121]	EGB, OHal	Dys, Hal	Gc: 68/88 (77)	Korea Red Ginseng Supplementation
Kinberg *et al*[122]	EGB	Hal [GDSS: 36 (38)]	14/94 (15)	OHal: 74/94: (78)
Tangerman *et al*[123]	EGB, OLT, GC, RUT	GDSS, Hal	11/49 (22)	VSC: 9/49 (18); *H. pylori*: 1/9 (11)

AG: Atrophic glossitis; BHH: Burning, halitosis, and lingual dorsum hyperplasia; BMS: Burning mouth syndrome; BMG: Benign migratory glossitis; Dys: Dyspepsia; EGB: Endoscopic gastric biopsy; EGL: Erosive gastric lesions; GC: Gas chromatography; Gc: Gastric; GERD: Gastroesophageal reflux disease; GDSS: Gastric disease; Hal: Halitosis; *H. pylori*ET: *Helicobacter pylori* eradication therapy; N: Nested; NEGL: Non-erosive gastric lesions; OHal: Objective halimeter levels > 100 ppb; OLT: Organoleptic test; PCR: Polymerase chain reaction; Pos: Positive; Quad: Quadruple; RR: Relative risk; RUT: Rapid urease test; Sal: Saliva; Ser: Serology; SHal: Subjective halitosis; SSA: 26-kDa species-specific antigen gene; Tg: Tongue; VSC: Volatil sulfur compounds; ^{13}-UBT: ^{13}C-urea breath test.

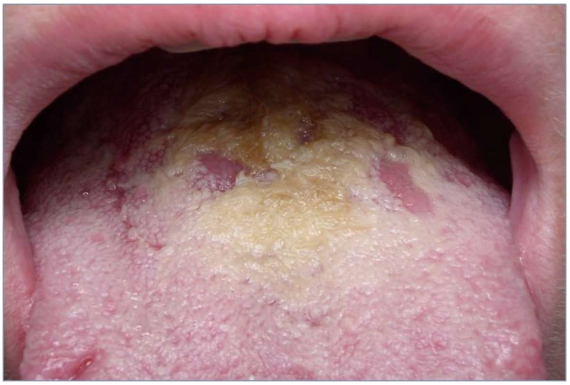

Figure 4 Burning, halitosis, and lingual dorsum hyperplasia. Negative for mycological microscopy and culture. *Helicobacter pylori*-positive finding in lingual dorsum and stomach.

PCR[113]. In Croatia a group of researchers, using PCR, detected *H. pylori* in the lingual dorsum of 43/268 (16%) patients with burning mouth syndrome (BMS), migratory glossitis and atrophic glossitis, with controls being *H. pylori*-negative[114]. Serin *et al*[115] administered triple *H. pylori*ET for 2 wk (omeprazole 20mg, clarithromycin 500mg, amoxicillin 1000mg), to subjects with halitosis and *H. pylori*-positive gastric disease. They reported that in patients with confirmed *H. pylori*ET, halitosis was the most successfully resolved symptom (62% to 3%). Therefore, they considered that halitosis is a frequent and treatable symptom of *H. pylori*-positive non-ulcer dyspepsia, and may be a valid indication for *H. pylori*ET. In the year 2005 in Argentina, we designed a case-control study to determine whether *H. pylori* was a risk factor in subjects with burning, halitosis, and lingual dorsum hyperplasia or BHH (Figure 4). A total of 124 subjects with different gastric diseases were studied: 46 patients with BHH and 78 patients with other oral diseases. *H. pylori* detection in the oral cavity by histopathologic diagnosis and molecular biology was confirmed in 40/46 (87%) patients with BHH, and in 2/78 (2.6%) subjects with other diseases (RR 13.01, 95%CI: 6-28.20). Gastric relative risk was RR 8.02, 95%CI 4.28-15.01. This trial showed, for the first time, an association between *H. pylori* and BHH, and further considered this bacterium a risk factor for gastric infection[82]. In Greece, Katsinelos *et al*[117] carried out a cohort-study with 18 patients with dyspepsia. All patients underwent gastric biopsy, and *H. pylori* status was determined histopathologically by hematoxylin and eosin, and Giemsa staining. A biopsy specimen was also taken from the antrum for RUT (CLOtest, Kimberly-Clark/Ballard Medical Products). All *H. pylori*-positive patients were

prescribed a 10-d course of triple drug for *H. pylori*ET (20 mg omeprazole, 500 mg clarithromycin and 1000 mg amoxicillin, all twice daily). In case of eradication failure, a 10-d course of quadruple drug for *H. pylori*ET (20 mg omeprazole twice daily, 600 mg bismuth subcitrate twice daily, 500 mg metronidazole twice daily, and 500 mg tetracycline, 4 times daily) was administered. Four to six weeks after completion of *H. pylori*ET, the symptom of halitosis was re-evaluated, and repeated endoscopy or 13-UBT was performed to assess *H. pylori*-status in the gastric mucosa. Triple *H. pylori*ET was sufficient to eradicate *H. pylori* in 14/18 (78%) patients. In the 4/18 (22%) patients who remained *H. pylori*-positive after triple drug *H. pylori*ET, quadruple drug *H. pylori*ET successfully eradicated the bacterium. Halitosis did not recur in 16/18 (89%) patients. The results obtained revealed that *H. pylori*ET should be indicated to *H. pylori*-positive patients with halitosis[117]. Suzuki *et al*[119] studied the relationship between halitosis and *H. pylori*-presence in saliva. A total of 326 subjects were recruited, 251 with halitosis and 75 without halitosis. The clinical symptoms associated with oral malodour and periodontal symptoms were significantly greater in the *H. pylori*-positive subjects. In South Korea, Yoo *et al*[120] evaluated halitosis in 72 *H. pylori*-positive patients. Patients were divided into two groups, 24 with erosive gastric lesions and 48 with non-erosive gastric lesions. Researchers considered that halitosis could be an effective biomarker predicting that the gastric mucosa of affected patients might show erosive change beyond inflamed condition.

In summary, in this chapter we have analyzed 10/14 studies on the possible association between halitosis and *H. pylori* infection. Nine of them included patients with *H. pylori*-positive gastric disease, and 5/10 were based on *H. pylori*ET results. In these researches, halitosis had been resolved in 90% to 100% of the cases. Regarding burning sensation, 2/14 articles reported *H. pylori*-positivity in 10% to 20% of the cases. A burning tongue was reported in one of them. In 2/14 we have described a particular clinical syndrome (BHH)[82,113]. We estimated a high risk of *H. pylori*-infection in patients with this syndrome. Our data suggest that halitosis is not a consequence of gastric pathology; however the work shows that in lingual dorsum, the action of the bacterium is the etiologic agent of BHH syndrome. *H. pylori* is one of the risk factors of halitosis, with an oral or gastric origin. Therefore, the search for the bacterium must be oral and gastric. Oral and/or gastric infection by *H. pylori* may occur with intense burning. In those cases, it is necessary to determine whether the patient experiences gastric discomfort. If so, it would be necessary to look for the bacteria. We have described a clinical syndrome characterized by "burning, halitosis and lingual dorsum hyperplasia". Discrepancies in the diagnosis of those patients who consulted due to these symptoms and further referred chronic gastric discomfort made us hypothesize about the association between *H. pylori* both in tongue and stomach. In our opinion, and given the biological implications of the bacteria, it is necessary to focus on patients with BHH. Then, we must objectively diagnose halitosis, ask the patient if he/she has experienced discomfort in the gastric tract, evaluate burning and properly inspect his/her mouth. Lab tests must include anti-*H. pylori* antibodies. Cytobrush on tongue surface must also be performed to reach an *H. pylori* diagnosis by molecular biology. Before a positive result in mouth might be obtained and prior to any therapy, the patient must be referred to the gastroenterology unit for his/her examination, given the biological behavior of *H. pylori*.

CONCLUSION

Infection by *H. pylori* is one of the most frequent infections in the world, and has revolutionized the gastric pathology in the last twenty-five years. Early diagnosis is essential for infection control. The interest in *H. pylori*-infection in the oral cavity has progressively increased, since the presence of this bacterium in the mouth determines an oral-oral way of transmission. This review describes the relation between *H. pylori* and different oral pathologies, such as periodontal disease, canker sores, squamous cell carcinoma, burning tongue and halitosis, and its association with gastric pathology.

Designs for prospective cohorts are required to demonstrate the bacterial action in the mouth using sensitive and specific diagnostic methodologies. In terms of *H. pylori* identification methods, culture is considered the gold standard. However, though sensitive, the method is not specific, since additional testing must be performed on the isolates. *H. pylori* PCR amplification is the method of choice[124]. However, several *H. pylori* genes have extensive polymorphism and particular genes are absent in some strains, as cagA[125]. Among the genes that have been tested, *ure*A and *ure*C (also named *glm*M) appear sensitive, but lack specificity. Therefore, the concurrent *H. pylori* detection of multiple genes and the use of different sets of primers are required to reach a specific and sensitive diagnosis of the infection[82]. Another alternative has been the use of *H. pylori* ribosomal gene 16SrRNA, which is present in all bacteria and is specific to a given bacterial genus[126,127]. Reviewing the literature herein cited, we found that the additional post-culture methods or the chosen molecular targets are not always described. In this sense, a methodological consensus would be required to validate the real location of the bacteria in the mouth, since this methodological diversity hinders the proper interpretation of the results.

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