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Review Article

Relationship between *Helicobacter pylori* Infection and Recurrent Aphthous Stomatitis

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Abstract

Background: Recurrent aphthous stomatitis (RAS) is a very common ulcerative disease that affects about 20% of the population. *Helicobacter pylori* infection could be involved in the RAS pathogenesis by inducing an oral cytotoxic immunological response to these bacterial antigens. **Objective:** The objective of this study is to assess the possible relationship of *H. pylori* infection with RAS. **Methods:** A search for articles on *H. pylori* and RAS was performed in the following electronic databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WoS), and Spanish Medical Index (IME). Ninety-eight articles (29 in PubMed, 69 in WoS, and none in IME) were found between 1997 and 2018, 28 of them duplicates. From 26 articles with full-text availability, three studies with a score below 6 points on the Newcastle–Ottawa scale were excluded. After applying these criteria, 23 studies were included in this review. **Statistical Analysis:** For dichotomous outcomes, the estimates of effects of an intervention were expressed as odds ratios using Mantel-Haenszel method with 95% confidence intervals. The Pearson's Chi-square test was also used when necessary. **Results:** RAS patients were 2.16 times more likely to be infected by *H. pylori* than controls with a very significant statistical relationship ($P < 0.01$). 42.0% of RAS patients and 33.8% of controls were infected with *H. pylori* with a statistically significant association ($P = 0.001$). Nearly 45.9% of patients infected with *H. pylori* were located in Asia, 34.7% in the Americas, and 33.0% in Europe, with statistically significant differences ($P < 0.01$). **Conclusions:** There is a greater detection of *H. pylori* in RAS patients than in controls without the disease.

Keywords: *Bacteria, Helicobacter pylori, mouth diseases, stomatitis aphthous*

Introduction

Recurrent aphthous stomatitis (RAS) is a very common ulcerative disease that affects around 20% of the general population, with the prevalence intervals ranging from 5% to 60% according to different studies. Three clinical forms of RAS have been described considering the size of the lesions: Minor aphthous ulcers (90% of cases), major aphthous ulcers (8%), and herpetiform ulcers (2%). Despite its frequency, its etiology remains unknown, with triggers and immunological factors being involved. Sometimes, RAS is associated with systemic diseases that affect the rest of the digestive tract that also manifest with ulcerative lesions.[1] Its potential triggers are food allergy, stress, oral mucosal trauma, genetic factors, nutritional deficiencies, and certain infectious agents.[2] *Helicobacter pylori* is a bacterium identified in 1984 that is closely related to peptic ulcer and to a lesser extent, with gastric adenocarcinoma and other malignancies.[3] In the oral cavity, saliva and dental plaque could act as reservoirs of this bacterium facilitating reinfection, and making it difficult to eradicate. *H. pylori* infection could be involved in the etiopathogenesis of RAS, inducing an oral cytotoxic response against these bacterial antigens with the appearance of oral ulcers.[4] This study aimed to assess the possible relationship of the *H. pylori* bacteria with RAS.

Methods

A search for the studies on RAS and *H. pylori* was performed in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WoS), and the Database of Information and Documentation of Science in Spain (InDICEs-CSIC) which includes the Spanish Medical Index (IME). Search strategies were developed for each database with a combination of terms from Medical Subjects Headings (MeSH) and free text. The search terms were as follows:

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"stomatitis, aphthous" (MeSH Terms), "recurrent aphthous stomatitis" (All fields), "estomatitis aftosa recurrente" (All fields), and "*H. pylori*" (MeSH Terms). After this initial search, 98 articles were found (29 in PubMed, 69 in WoS, and none in IME) between 1997 and 2018, 28 of them duplicates. The inclusion criterion was articles with full-text availability (n = 26), and the exclusion criterion was a score below 6 points from a maximum of 9 on the Newcastle–Ottawa scale[5] to assess the methodological quality of case–control studies (n = 3). After applying the inclusion and exclusion criteria, 23 studies were included in this review [Figure 1].

Statistical analysis

For the meta-analysis, the data were processed with the RevMan 5.3 program (The Cochrane Collaboration, Oxford, UK). For dichotomous outcomes, the odds ratio (OR) with the Mantel-Haenszel Chi-square formula and a 95% confidence interval (95% CI) were used. Heterogeneity was determined according to the Higgins statistic (I^2). In cases of high heterogeneity, the random-effects model was applied. Pearson's Chi-square test was also applied when necessary. A value of $P < 0.05$ was considered as the minimum level of significance.

Results

According to the Newcastle-Ottawa Quality Scale,[5] only articles with low-to-moderate risk of bias (≥6 points from a maximum of 9 points) were considered in this study.

Table 1 shows the 23 studies[6-28] carried out in 13 different countries that reported *H. pylori* detection in patients with RAS and controls, taking into account the different detection methods used. Of a total of 955 RAS patients, 401 of them (42.0%) had *H. pylori*. In the 586 controls, 198 (33.8%) were *H. pylori*-positive. Considering detection methods, 11 studies[9-11,13-15,17-19,23,28] used the polymerase chain reaction (PCR) with detection percentages between 9.1% and 71.9% for RAS patients, and between 3.8% and 20.0% for controls; five,[7,12,16,23,24] the enzyme-linked immunosorbent assay (ELISA), detection range (RAS patients: 30.7%–70.8%, controls: 25.0%–59.1%); five,[8,21,25-27] the rapid urease test (RUT), range (RAS patients: 37.2%–89.5%, controls: 10.0%–55.8%); two studies[20,22] analyzed tissue samples from RAS patients with a range between 65.2% and 87.0%. Finally, a single study[6] used *in situ* hybridization (ISH).

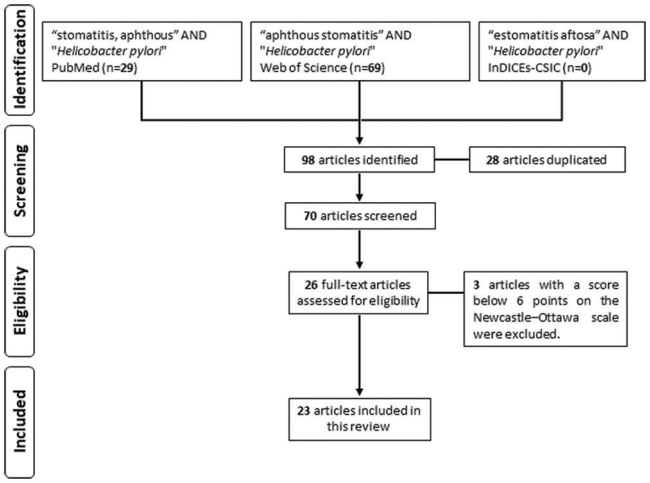

Figure 1: Study flow diagram

Eleven studies[7,13-15,19,21,23-28] with 12 interventions analyzed the *H. pylori* detection in RAS patients and controls [Figure 2]. RAS patients were 2.16 times more likely to be infected with *H. pylori*, with statistically highly significant differences (OR = 2.16; 95% CI: 1.32–3.54; $P < 0.01$).

Table 2 presents the comparison of *H. pylori* infection in RAS patients and controls.[6-28] There was a higher percentage of RAS patients than controls (42.0% vs. 33.8%) infected with *H. pylori*, observing a statistically significant relationship ($P = 0.001$).

When *H. pylori* infection was compared with gender [Table 3], a percentage of men (31.1%) slightly higher than that of women (26.4%) infected with *H. pylori* was found. However, after statistical analysis, no significant association was observed ($P = 0.47$).

The distribution of RAS patients according to *H. pylori* infection and the different geographical areas of the world is shown in Table 4. *H. pylori* infection was much more prevalent in Asia (45.9%), followed by lower percentages in the Americas (34.7%) and for Europe (33.0%) with statistically significant differences ($P < 0.01$).

Discussion

Data from 23 studies have been included in the present review of the possible influence of *H. pylori* infection on RAS.

In the present study, 42.0% of RAS patients and 33.8% of controls were *H. pylori* carriers. These percentages varied according to the detection method used. With PCR, the detection percentages ranged from 3.8% to 71.9%, with the ELISA (25%–70.8%), with RUT (10.0%–89.5%), and with tissue samples (65.2%–87.0%). The PCR was the most used detection method due to its high sensitivity and specificity,[9-11,13-15,17-19,23,28] indicating a positive association between infection by the *H. pylori* bacteria and the RAS. Higher percentages of *H. pylori*-infected RAS patients were observed compared to the controls. This possible association is reinforced by the detection of *H. pylori* in ulcerative oral lesions (aphthae) in RAS patients and not in dental plaque or saliva of these patients.[10] However, one of the main limitations of many of these studies is that the detection of *H. pylori* is not performed in oral ulcers or the oral cavity, but the gastric mucosa. This is the case of the RUT, a test that is performed on a sample collected during gastroscopy that is placed in a medium with urea

Table 1: Studies on *Helicobacter pylori* detection in patients with recurrent aphthous stomatitis and controls

First author	Year	Country	Detection method	History of gastric ulcer	RAS patients			Controls		
					n	*N*	Percentage of positive cases	*n*	*N*	Percentage of positive cases
Leimola-Virtanen[6]	1995	Finland	ISH	No	6	29	20.7			
Porter[7]	1997	UK	ELISA	No	23	75	30.7	6	24	25.0
Chapman[8]	1998	Lebanon	RUT	No	0	4	0.0			
Mravak-Stipetić[9]	1998	Croatia	PCR	Yes	4	32	12.5			
Birek[10]	1999	Canada	PCR	No	23	32	71.9			
Riggio[11]	2000	UK	PCR	No	3	28	10.7			
Shimoyama[12]	2000	Japan	ELISA	No	5	12	41.7			
Iamaroon[13]	2003	Thailand	PCR	No	2	22	9.1	3	15	20.0
Victória[14]	2003	Brazil	PCR	No	14	36	38.9	16	48	33.3
Fritscher[15]	2004	Brazil	PCR	No	5	53	9.4	2	52	3.8
Albanidou-Farmaki[16]	2005	Greece	ELISA	Yes	34	48	70.8			
Elsheikh[17]	2005	Egypt	PCR	No	9	88	10.2			
Mansour-Ghanaei[18]	2005	Iran	PCR	Yes	26	50	52.0			
Long[19]	2007	China	PCR	No	36	82	43.9	12	74	16.2
Karaca[20]	2008	Turkey	TS	Yes	20	23	87.0			
Maleki[21]	2009	Iran	RUT	Yes	16	43	37.2	14	44	31.8
Taş[22]	2013	Turkey	TS	Yes	30	46	65.2			
Uyar[23]	2014	Turkey	ELISA	No	22	36	61.1	13	22	59.1
Uyar[23]	2014	Turkey	PCR	No	9	36	25.0	0	22	0.0
Erfan[24]	2014	Turkey	ELISA	No	45	87	51.7	30	72	41.7
Ding[25]	2015	China	RUT	Yes	5	10	50.0	73	135	54.1
Gülseren[26]	2016	Turkey	RUT	Yes	34	38	89.5	24	43	55.8
Sharma[27]	2016	India	RUT	Yes	21	30	70.0	2	20	10.0
Rajendra[28]	2017	India	PCR	Yes	9	15	60.0	3	15	20.0
			Total		401	955	42.0	198	586	33.8

ISH: *In situ* hybridization, ELISA: Enzyme-linked immunosorbent assay, RUT: Rapid urease test, PCR: Polymerase chain reaction, TS: Tissue samples, n/N: Number of *Helicobacter pylori* positive cases/total number of cases, RAS: Recurrent aphthous stomatitis

Table 2: *Helicobacter pylori* infection in recurrent aphthous stomatitis patients and controls

Helicobacter pylori	RAS patients, *n* (%)	Controls, *n* (%)	*P*[a]
Positive	401 (42.0)	196 (33.8)	0.001*
Negative	554 (58.0)	388 (66.2)	
Total	955 (100)	586 (100)	

[a]Pearson Chi-square test, *Statistically significant. *n*: Number of cases, RAS: Recurrent aphthous stomatitis

Table 3: Distribution of patients with recurrent aphthous stomatitis according to *Helicobacter pylori* infection and gender

Helicobacter pylori	Males, *n* (%)	Females, *n* (%)	*P*[a]
Positive	38 (31.1)	37 (26.4)	0.47
Negative	84 (68.9)	103 (73.6)	
Total	122 (100)	140 (100)	

[a]Pearson Chi-square test. *n*: Number of cases

and a color change takes place from yellow (negative) to red (positive) showing the presence of *H. pylori*.[8,21,25,26] The same occurs with studies[20,22] that use tissue samples from the gastric mucosa, not from oral lesions to detect *H. pylori*.

In this study, RAS patients were 2.16 times more likely to be infected by *H. pylori* bacteria than controls, with statistically highly significant differences ($P < 0.01$). Ten studies with ten interventions[7,14,15,19,21,23,24,26-28] agreed with this finding and two disagreed, observing higher percentages of *H. pylori* in the controls.[13,25]

The possible role of *H. pylori* in the pathogenesis of RAS would be justified by the histological similarity between aphthae and gastric ulcers, and in the fact that *H. pylori* eradication therapy with broad-spectrum antibiotics improves lesions both gastric and oral ones. It has also been proposed that oral colonization by *H. pylori* could arise from gastric colonization through the gastroesophageal reflux.[26] The oral cavity is an extragastric reservoir of *H. pylori*, and some strains are shared in the dental plaque and the gastric mucosa. Patients who are positive for oral *H. pylori* have a lower gastric eradication rate for *H. pylori* than for patients without oral *H. pylori*.[29]

Birek *et al*.[10] suggested that *H. pylori* detection in the oral mucosa would be related to a cross-reaction between antigens shared by oral epithelial cells and *H. pylori* that would induce the production of tissue autoantibodies and the subsequent destruction of the tissue associated with RAS.

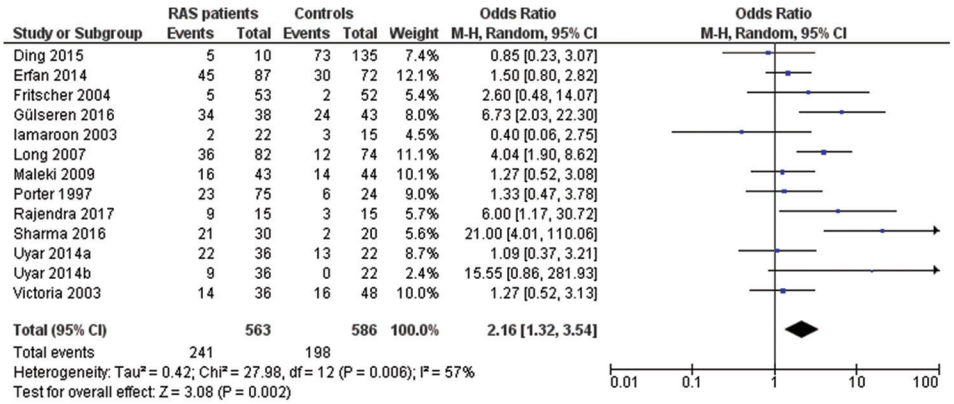

Figure 2: Study data and forest plot graph for *Helicobacter pylori* detection in patients with recurrent aphthous stomatitis and controls

Table 4: Distribution of patients with recurrent aphthous stomatitis taking into account *Helicobacter pylori* infection and geographical areas

Helicobacter pylori	Geographical areas			*P**
	Asia[a], *n* (%)	Europe[b], *n* (%)	Americas[c], *n* (%)	
Positive	208 (45.9)	70 (33.0)	42 (34.7)	<0.01[†]
Negative	245 (54.1)	142 (67.0)	79 (63.3)	
Total	453 (100)	212 (100)	121 (100)	

[a]12 studies,[8,12,13,17-22,26-28] [b]5 studies,[6,7,9,11,16] [c]3 studies,[10,14,15] *Pearson Chi-square test, [†]Statistically significant. *n*: Number of cases

Long *et al*.[19] observed that only in RAS patients infected with *H. pylori* was there a higher incidence of chronic gastric disorders, suggesting the relationship between infection by the bacterium, RAS, and chronic gastric diseases. Furthermore, *H. pylori* eradication therapy was able to significantly alleviate the symptoms and promote the resolution of RAS. However, further studies are required to determine the true role of this eradication treatment in RAS.

Six studies[7,14,15,21,23,24] found a higher prevalence of *H. pylori* in RAS patients, although the results did not reach statistical significance. Probably, the particular characteristics of the populations considered in them could have conditioned these results. Conversely, two studies[13,25] found a higher prevalence of *H. pylori* in controls without RAS. All these discrepancies could be explained by the enormous variability in detection according to the technique used, with differences in the collection and the bacterial concentrations of the samples, the differences in the populations studied, or the different primers used in the PCR.[13] In other cases, the small sample of patients with RAS (n = 10) may induce the appearance of biases that do not allow the results to be properly interpreted.[25]

In the present study, although among RAS patients, there was a slightly higher percentage of men (31.1%) than women (26.4%) positive for *H. pylori*, gender did not affect significantly *H. pylori* infection (P = 0.47). Nevertheless, in the literature reviewed, a possible explanation for this predilection for the male gender was not found. It is probably related more to digestive diseases than to RAS itself. Men are twice as likely to develop stomach cancer as women.[22]

The prevalence of *H. pylori* infection in different areas of the world was also analyzed in this study, observing a statistically significant difference (P < 0.01) between that found in Asia (45.9%) compared to those found in the Americas (34.7%) and Europe (33.0%). This higher prevalence in the Asian continent would be closely related to the higher incidence of gastroduodenal ulcer and stomach cancers in certain countries such as China or Japan.[12,25] Furthermore, in Asian countries, more virulent *H. pylori* strains have been detected that could condition the biological behavior of gastric and/or oral lesions. Other factors such as the special forms of tobacco consumption (betel and areca) and the dietary habits of the populations of this region of the world might influence the *H. pylori* colonization of the tissues.[19]

The results of this metaanalysis should be interpreted with caution due to the relatively high heterogeneity found in the meta-analytical analysis and the differences in the individual results of the different studies. These discrepancies between studies may be conditioned by the type of design and/or analysis, the methods used to collect the information or the characteristics of the study populations.

The main limitations of this study lie in the large differences observed in the *H. pylori* detection rates, highly influenced by the detection method used and in the fact that very few studies perform direct *H. pylori* detection in the oral cavity. This does not allow establishing a direct causal relationship between *H. pylori* infection and RAS.

New studies are required to assess the degree of involvement of *H. pylori* detected directly in oral lesions or in the oral cavity in the pathogenesis of RAS.

Conclusions

In this study, RAS patients were 2.16 times more likely to be infected with *H. pylori* than controls with a highly significant statistical relationship ($P < 0.01$). Nearly 42.0% of RAS patients and 33.8% of controls were infected with *H. pylori* with a statistically significant association ($P = 0.001$). 45.9% of patients infected with *H. pylori* were located in Asia, 34.7% in the Americas, and 33.0% in Europe, with statistically significant differences ($P < 0.01$).

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Conflicts of interest

There are no conflicts of interest.

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