



# *Helicobacter pylori* And Duodenal Ulcer: Systematic Review Of Controversies In Causation

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**Background:** There are controversies on the causal role of *H. pylori* in duodenal ulceration. *Helicobacter pylori* are curved gram-negative microaerophilic bacteria found at the layer of gastric mucous or adherent to the epithelial lining of the stomach. It's a public health significance bacteria starting from discovery, and the prevalence and severity of the infection varies considerably among populations. *H. pylori* are a risk for various diseases, while the extent of host response like gastric inflammation and the amount of acid secretion by parietal cells affects the outcome of infection.

**Method:** Relevant literature were searched from databases such as Google Scholar, PubMed, Hinari, Web of Science, Scopus, and Science Direct.

**Result:** The review evidence supports a strong causal relation between *H. pylori* infection and duodenal ulcer, as patients are more likely to be infected by virulent strains which later cause duodenal ulceration. Thus, eradication of *H. pylori* infection decreases the incidence of duodenal ulcers, and prevents its recurrence by reducing both basal gastrin release and acid secretion without affecting parietal cell sensitivity. On the other hand, some studies show that *H. pylori* infection is not associated with the development of duodenal ulcers and such a lack of association revealed that duodenal ulceration has different pathogenesis.

**Conclusion:** Despite controversies observed in the causal role of *H. pylori* to duodenal ulceration by various studies, Hill criteria of causation proved the presence of a causal relation between *H. pylori* infection and duodenal ulcers. Other factors are also responsible for the development of duodenal ulcers and such factors are responsible for the differences in the prevalence of the diseases.

**Keywords:** *H. Pylori*, duodenal ulcer, causation, controversies

## Introduction

*Helicobacter pylori* (*H. pylori*) are curved, gram-negative, microaerophilic bacteria<sup>1</sup> found in the gastric mucous layer or adherent to the epithelial lining of the stomach.<sup>2</sup> It has been a public health significance bacteria since 1983 as it infects the duodenum where hydrochloric acid and pepsin play a role in the digestion of food, which facilitates damage of the lining by gastric acid.<sup>3</sup> *H. pylori* can elevate acid secretion in people who develop duodenal ulcers<sup>4</sup> or hypersecretion of gastric acid can by itself evoke duodenal ulcers.<sup>5</sup>

The prevalence and the severity of the infection vary considerably among populations<sup>6</sup> due to geographical differences and ways of leading life.<sup>4</sup> In the US, 30–40% of people are infected with *H. pylori*<sup>7</sup> and the prevalence is still high in Eastern Mediterranean countries of the healthy asymptomatic population.<sup>8</sup> Most of the infection occurred during childhood with no difference in gender.<sup>9</sup>

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Before the discovery of *H. pylori*, spicy food, acid, stress, and lifestyle were considered to be the causes of ulcers.<sup>2</sup> Age, religion, and water sources are risk factors for *H. pylori* infection in Indonesia.<sup>10</sup> Poor socio-economic status, genetic predisposition, and being resident in a developing country are among known risk factors for *H. pylori* infection.<sup>11</sup> Sharing food or eating utensils, contact with contaminated water and with the stool, saliva, or vomit of an infected person are also potential risk factors.<sup>3,11</sup>

Dye endoscopy, forceps biopsies for culture, histology, and rapid urease test are used for diagnosis of *H. pylori* infection, and a patient is considered negative when the serum anti-*H. pylori* IgG and the three tests on biopsied specimens are all negative.<sup>12</sup> *H. pylori* are associated with an increased risk for the development of duodenal and gastric ulcers, gastric adenocarcinoma, and gastric B-cell lymphoma.<sup>6,9</sup> The bacterium attaches to epithelial cells of the stomach and duodenum, then it causes damage to the cells by secreting degradative enzymes (urease, lipases, and proteases) and bacterial virulence factors (cytotoxin-associated gene protein (CagA) and vacuolating cytotoxin (VacA)), and initiating a self-destructive immune response.<sup>13</sup> Eradication of infection reduces the risk of duodenal ulcer,<sup>14</sup> but the outcome depends on the extent of host response to the infection like gastric inflammation and the amount of acid secretion by parietal cells.<sup>4</sup> This review article aims to explore the controversies on the causal role of *H. pylori* in duodenal ulcers.

## Methods

Studies were obtained from electronic databases, including Google Scholar, PubMed, Hinari, Web of Science, Scopus, and Science Direct, with hand searches and iterative reviews of reference lists of papers using the keywords “*H. Pylori*”, “duodenal ulcer”, “causation” and in combination from February 7–13, 2019. A total of 107 papers were obtained from all sources. After the exclusion of redundant and irrelevant literature, a total of 26 separate published empirical articles (Table 1) in peer-reviewed journals were reviewed. The searching process is displayed in Figure 1.

The inclusion criteria were: type of study; randomized clinical trial, case-control, cohort, ecological, and cross-sectional, and systematic review, publication; academic journal (peer-reviewed) and non-reviewed reports, population; Global, time-period: 1989 to present, and language; English.

## Result And Discussion

### Evidence On Causal Relation Between *H. pylori* Infection And Duodenal Ulcer

*H. pylori* has a role in the etiology of duodenal ulcer.<sup>15–17</sup> Once ingested, the attachment of *H. pylori* to epithelial cells of the stomach and duodenum occurs through phosphorylation of a 145 kilo Dalton protein and activation of signal transduction pathways.<sup>18,19</sup> *H. pylori* infection blocks normal physiological mechanisms resulting in increased gastrin release and impaired inhibition of gastric acid secretion.<sup>18,20</sup> Such endogenous hypersecretion of acid causes gastric metaplasia<sup>4</sup> and synergizes ulceration.<sup>21</sup> Thus, the prevalence of *H. pylori* infection in duodenal ulcer patients is higher than the normal population,<sup>22</sup> as patients are more likely to be infected with virulent strains which later cause duodenal ulceration.<sup>23</sup> The disease manifestations start when alteration of epithelial cell growth and enhanced apoptosis occur.<sup>24</sup> *H. pylori* containing functional Cag pathogenicity island produce a vigorous inflammatory response,<sup>25</sup> and 12% of patients develop late complications with a further 6% mortality rate.<sup>26</sup>

*H. pylori* plays a role in the pathogenesis of duodenal ulcer disease in 84.9% of subjects and the single causative factor in 44.1% of patients.<sup>27</sup> Duodenal infection with *H. pylori* is a strong risk factor (RR=51),<sup>21</sup> (OR=4)<sup>28</sup> for the development of duodenal ulceration. Antral reinfection with *H. pylori* is also associated with relapse<sup>29</sup> (RR=7.6).<sup>21</sup> This evidence supports a strong causal relation between *H. pylori* infection and duodenal ulceration.<sup>30</sup>

Preexisting history of *H. pylori* is a risk for the development of duodenal ulcer,<sup>28</sup> and it is observed that in young Israelis with an odds ratio of 3.8, the association increased as diagnosis time exceeded 2 years with 56.6% attributable risk.<sup>31</sup>

Although cigarette smoking, age, sex, and ingestion of non-steroidal anti-inflammatory drugs (NSAID) were not found to be significant risk factors for duodenal ulceration,<sup>21,32</sup> *H. pylori* infection plays a role in the causation of non-NSAID-induced duodenal ulcer perforation.<sup>33</sup> Excluding patients taking NSAIDs and/or antibiotics, *H. pylori* prevalence increased up to 99.1% (98.1±99.6%) among duodenal ulcer patients.<sup>34</sup>

The current therapy for *H. pylori* induced ulcer (a proton pump inhibitor and at least two antimicrobials with or without bismuth) is highly effective in eradicating the infection.<sup>9</sup> Eradication of *H. pylori* infection decreases the incidence of duodenal ulcer and prevents its recurrence,<sup>22,35–37</sup> and the occurrence of NSAID induced peptic ulcers<sup>16</sup> without

**Table I** Study Characteristics Of Reviewed Articles

No	Author	Study Design	Sample Size	Year	Country	Method	Result
1	Carrick J, Lee A, Hazell S, Ralston M, Daskalopoulos G	Cohort	137	1989	Australia	Congo Red staining	Strong risk factor (RR=51) <sup>21</sup>
2	Moss SF, Calam J	Randomized clinical trial	9	1993	England	Endoscopy and biopsies	Eradication reduce basal plasma gastrin concentration ( $P<0.05$ ), and basal acid secretion ( $P<0.01$ ) <sup>39</sup>
3	Reinbach DH, Cruickshank G, McColl KE	Matched hospital case control	80	1993	United Kingdom	Serum anti-H pylori IgG and <sup>14</sup> C-urea breath tests	Prevalence 47% <sup>32</sup>
4	Batista SA, et al	Experimental	112	2011	Brazil	Endoscopy	Number of EPIYA C segments did not associate with duodenal ulcer <sup>41</sup>
5	Cekin AH, et al	Matched case control	222	2012	Turkey	Esophago-gastroduodenoscopy	<i>H. pylori</i> located in the corpus [OR]=3.00; incisura OR=2.07; and antrum [OR]=2.71. <i>Hp</i> positivity was 84.9% <sup>27</sup>
6	Gisbert JP, et al	Cross-sectional	774	1999	Spain	Endoscopy	Prevalence 95.3% <sup>34</sup>
7	Tsuji H, et al	Cross-sectional	120	1999	Japan	Endoscopic, rapid urease test and forceps biopsies	1.7% <i>H. pylori</i> -negative rates <sup>12</sup>
8	Gdalevich M, et al	Nested case control	29	2000	Israel	ELISA IgG-Ab	OR=3.8 <sup>31</sup>
9	Khan MM, Shahzed MN, Jibran M, Rabbani MJ	Cross-sectional	116	2009	Pakistan	ACON®	116 patients (92 males and 24 females) have perforated DU and more common in 30–50 age groups <sup>48</sup>
10	Lario S, et al	Cohort	88	2013	Spain	Microarrays	Higher levels of IL8 and IL12p40 mRNAs and lower levels of GATA6 and SOCS2 mRNAs <sup>49</sup>
11	Labenz JO, et al	Cross-sectional	16	1996	Germany	pH metry, glass electrode, urea breath test, culture, histology, and rapid urease	<i>H. pylori</i> eradication decrease the pH-increasing effect of omeprazole; $P<0.002$ <sup>36</sup>
12	Olbe L, Hamlet A, Dalenback J, Fandriks L	Cross-sectional	16	1996	Sweden	Urea breath test, culture, histology, and rapid urease	Inhibitory mechanism was reconstituted in 8 of 10 patients within 9 months after eradication of <i>H. pylori</i> infection <sup>5</sup>
13	Chu KM, Kwok KF, Law S, Wong KH	Cross-sectional	1343	2005	China	Endoscopic, rapid urease test and biopsies	Male preponderance (M:F=2.5:1) <sup>13</sup>
14	Syam AF, et al	Cross-sectional	267	2014	Indonesia	Culture, histology and rapid urease test	Prevalence 22.1% <sup>10</sup>

(Continued)

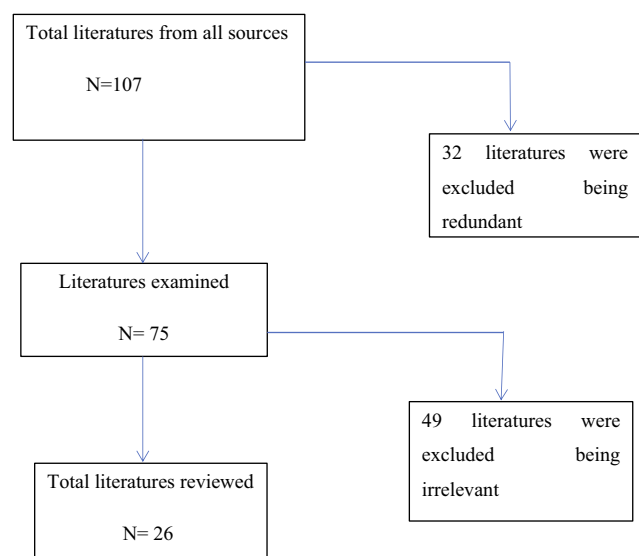
Table 1 (Continued).

No	Author	Study Design	Sample Size	Year	Country	Method	Result
15	Segal ED, Cha J, Lo J, Falkow S, Tompkins LS	Laboratory		1999	USA	ELISA IgG-Ab	145-kDa protein and activation of signal transduction pathways associated with the attachment of <i>H. pylori</i> <sup>19</sup>
16	Borody TJ, et al	Cohort	302	1991		Endoscopic, rapid urease test and biopsies	94% were found to have associated <i>H. pylori</i> <sup>44</sup>
17	Ng EK, et al	Cohort	73	1996		Intra-operative gastroscopy and antral biopsies	70% had evidence of <i>H. pylori</i> <sup>33</sup>
18	Rauws EA, Tytgat GN	Randomized clinical trial	50	1990			Eradication achieved 7 of the 45 patients and there was no ulcer relapse during the first 12 months of follow-up <sup>38</sup>
19	Patchett S, Beattie S, Leen E, Keane C, O'Morain C	Cohort	51	1992		Endoscopic, biopsies	Recurrence of <i>H. pylori</i> infection occurred in 35.3% <sup>29</sup>
20	Chan FK	Randomized clinical trial	100	1997	Hong Kong	Endoscopy	Eradication of <i>H. pylori</i> before NSAID therapy reduces the occurrence <sup>16</sup>
21	Blaser MJ, Chyou PH, Nomura A	Case control	313	1995	USA		<i>H. pylori</i> do not increases risk of developing duodenal ulcer <sup>40</sup>
22	Nomura A, Stemmermann GN, Chyou PH, Perez-Perez GI, Blaser MJ	Nested case control	5443	1994	USA	ELISA IgG-Ab	92% patients and 78% of the matched controls had a positive test result, OR=4.0 <sup>28</sup>
23	Kim JG, Graham DY	Cross-sectional	181	1994		ELISA IgG-Ab	36% developed a duodenal ulcer <sup>45</sup>
24	Borody TJ, Brandl S, Andrews P, Jankiewicz E, Ostapowicz N	Cross-sectional	115	1992	Australia	Endoscopy	47 (66%) no detectable causal factors, 21 (30%) regularly taking NSAIDs, and three (4%) had malignant GU <sup>17</sup>
25	Bytzer P, Teglbjærg PS, Group DU	Randomized clinical trial	276	2001		Culture, immunohistochemistry, and urea breath test	Eradication therapy over 2 years is significantly poorer in <i>H. pylori</i> -negative patients <sup>7</sup>
26	Escobar MA, et al	Cross-sectional	169	2004			12% of patients develop late complications <sup>26</sup>

altering acid output.<sup>38</sup> As a result, eradication resulted in falls in both basal gastrin release and acid secretion without affecting parietal cell sensitivity.<sup>39</sup> On the other hand, the clinical outcome of eradication therapy over 2 years is significantly poorer in *H. pylori*-negative patients.<sup>7</sup>

## Evidence Against Causal Relation Between *H. pylori* Infection And Duodenal Ulcer

A cohort study of 73 participants revealed that prior life acquisition of *H. pylori* was not associated with duodenal ulcer<sup>40</sup> and only a minority of infected persons develop



**Figure 1** Data searching process.

duodenal ulceration.<sup>22</sup> This indicates that different pathogenesis had existed for duodenal ulceration.<sup>32</sup> Moreover, *H. pylori* strain with high number of CagA EPIYA-C segments was not associated with duodenal ulcer.<sup>41</sup>

Duodenal ulcer can relapse after eradication of *H. pylori* infection, and the ulcer may remain healed after reduction of acid secretion in the presence of infection. Additionally, hypersecretion of gastric acid is strongly associated with the development of duodenal ulcers while it may result in a spontaneous eradication of *H. pylori* infection.<sup>23</sup> The virulent strains cause delayed healing of an ulcer produced by acid hypersecretion<sup>42</sup> by interfering with neoangiogenesis

of wounded duodenal epithelial cells<sup>23</sup> indicating the bacteria delay the healing of ulcer rather than causing it.

The annual proportion of patients with *H. pylori*-negative duodenal ulcers increased as the ulcers are more likely to occur in individuals with old age, pre-existing malignancy, recent surgery, underlying sepsis,<sup>43</sup> NSAID use,<sup>43–45</sup> a concomitant medical problem like Crohn's disease and hypergastrinaemia,<sup>46</sup> specific geographical distribution,<sup>47</sup> and recent intake of antibiotics.<sup>44</sup> Smoking and the presence of dietary lipids are also risk factors.<sup>4,23</sup> Among 71 *H. pylori*-positive duodenal ulcer patients, 66% had no other detectable causal factors, 30% were regularly taking NSAIDs, and 4% had malignancy.<sup>17</sup> Thus, *H. pylori* is not the primary cause of duodenal ulcer.<sup>47</sup>

## Evaluation Of Causal Relation Between *H. pylori* Infection And Duodenal Ulcer Through Hill's Criteria

The review assessed the causal relation between *H. pylori* infection and duodenal ulcer by using criteria for assessing causation proposed in 1965 by Sir Austin Bradford Hill. Despite controversies observed on the causal role of *H. pylori* to duodenal ulceration in various literature, Hill criteria of causation proved a causal relation between *H. pylori* infection and duodenal ulcer (Table 2).

## Conclusion

There are controversies among studies on the causal relation between *H. pylori* infection and duodenal ulcer. Several

**Table 2** Hill Criteria For Assessing The Causal Role Of *H. Pylori* On Duodenal Ulcer

Sr. No	Hill Criteria's	Description
1	Biological plausibility	Biologically plausible explanations for causation exist. <sup>18–20</sup>
2	Dose response relationship	Eradication of <i>H. pylori</i> infection decreases the incidence of duodenal ulcer and prevents its recurrence. <sup>22,35–37,39</sup>
3	Strength of association	Strong association. <sup>21,28,29</sup>
4	Consistency	The association between <i>H. pylori</i> and duodenal ulcer has been consistently demonstrated in a number of different types of epidemiological studies (ecological, case-control, cohort, randomized clinical trial and cross-sectional).
5	Temporality	Proved in epidemiological studies (case-control, cohort, randomized clinical trial)
6	Study design	All types of epidemiological study designs (ecological, case-control, cohort, randomized clinical trial, and cross-sectional).
7	Reversibility	The removal of a possible cause ( <i>H. pylori</i> ) led to reduction of disease risk. <sup>22,35–37,39</sup>
8	Specificity of association	No, exposure to <i>H. pylori</i> is also associated with other diseases like gastric ulcer, <sup>31,40</sup> gastric cancer, <sup>28,41</sup> gastro esophageal reflux disease. <sup>25</sup>

studies reported *H. pylori* is a strong risk factor for the development of duodenal ulcers, whereas other studies showed duodenal ulcers can recur after eradication of *H. pylori* infection, and the ulcer may remain healed after reduction of acid secretion in the presence of active infection, indicating the absence of a causal relation between *H. pylori* infection and duodenal ulcer. Despite controversies observed in the causal role of *H. pylori* to duodenal ulcer by various studies, critical examination of empirical evidence through Hill criteria of causation proved the presence of a causal relation between *H. pylori* infection and duodenal ulcer.

## Abbreviations

*H. pylori*, *Helicobacter pylori*, NSAID, Non-steroidal anti-inflammatory drug.

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## Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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