Helicobacter pylori Infection and Perforated Peptic Ulcer Prevalence of the Infection and Role of Antimicrobial Treatment

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ABSTRACT

Although the role of Helicobacter pylori infection on noncomplicated peptic ulcer disease has been definitively established, the precise relationship between the organism and complicated ulcer has hardly been studied. The mean prevalence of H. pylori infection in patients with perforated peptic ulcer is of only about 65–70%, which contrasts with the almost 90–100% figure reported in noncomplicated ulcer disease. However, H. pylori infection rates in various studies range markedly from 0% to 100%, suggesting that differences in variables as number and type of diagnostic methods used to diagnose H. pylori infection, or frequency of nonsteroidal anti-inflammatory drug intake, may be responsible for the low prevalence reported in some studies. Recurrent ulcer disease after peptic ulcer perforation mainly occurs in patients with H. pylori infection, which suggests that the microorganism plays an important role in this complication. All patients with perforated peptic ulcer should be treated by simple closure of the perforation and with therapy aimed at healing of the ulcer and eradicating the H. pylori infection, as disappearance of the organism prevents, or at least decreases, ulcer recurrence and ulcer perforation in patients with H. pylori-associated perforated ulcers after simple closure. Therefore, H. pylori eradicating treatment should be started during the immediate postoperative period. The patients with intractable recurrent symptoms of peptic ulcer despite adequate medical treatment, but without H. pylori infection (e.g. a patient using nonsteroidal anti-inflammatory drugs), is probably the only remaining indication for elective definitive surgical treatment of peptic ulcer disease.

Keywords. Helicobacter pylori, peptic ulcer, peptic ulcer perforation, perforated peptic ulcer.

Perforation accounts for more than 70% of deaths associated with peptic ulcer disease, mortality rates for perforated duodenal and gastric ulcers being 0–10% and 10–40%, respectively [1]. Overall, the operative mortality for perforated peptic ulcer is ∼5% [2]. Simple closure of a perforated peptic ulcer has been compared with definitive surgery in several randomized trials [2–4]. Ulcer recurrence has been reported to occur in 61% and 6% of cases following simple closure and definitive surgical treatment, respectively, indicating that simple closure by no means is sufficient to prevent ulcer recurrence [5]. This high recurrence rate after simple closure of the ulcer has been the basis for arguments in favour of the addition of some surgical procedures. The conventional surgical approach includes acid-reducing procedures, such as partial gastrectomy or truncal vagotomy with gastric outflow drainage. On the other hand, with the advent of potent acid-suppressing agents like proton pump inhibitors (PPI), more patients are treated with simple patch repair and maintained on long-term acid suppressing drugs, although the effectiveness of this strategy in the long term has been insufficiently studied [6,7].

Although the role of Helicobacter pylori infection on noncomplicated peptic ulcer disease has been definitively established, the precise relationship between the organism and complicated ulcer has hardly been studied [8]. H. pylori has been identified in noncomplicated duodenal ulcer in a high proportion of the cases, the figures being almost 100% in many studies, with a mean prevalence value of ∼90%, especially if previous NSAID intake or antibiotic use is
excluded [9,10] (although, more recently, some studies mainly performed in the USA have found lower infection rates). However, the frequency of *H. pylori* infection in perforated peptic ulcer remains a matter of debate, as several authors have reported lower prevalence of the infection in patients with this complication. On the other hand, the relationship between the presence of *H. pylori* and the recurrence of the ulcer after surgery and the possible advantage of eradication of the organism on this complication has not been fully established. Our aim was therefore to systematically review the studies assessing the prevalence of *H. pylori* infection in patients with perforated peptic ulcer, and to evaluate with detail the role of the organism in the recurrence of the ulcer or the ulcer perforation and, especially, the effect of eradication of the infection on the recurrence of this important complication.

Bibliographical searches were performed in the PubMed (Internet) database including studies available until March 2002, looking for the following words (all fields): (*Helicobacter pylori* OR *H. pylori*) and (‘perforated’ OR ‘perforation’). We also conducted a manual search of abstracts from 1995 to 2001 from the International Workshop on Gastroduodenal Pathology and *Helicobacter pylori*, and American Digestive Disease Week. References of reviews on perforation in peptic ulcer disease, and from the articles selected for the study, were also examined in search of articles meeting inclusion criteria. Articles published in any language were included. The prevalence of *H. pylori* infection in patients with perforated peptic ulcer of each study was recorded, as was the ulcer type (duodenal or gastric) and the methods used to detect the organism were also identified. Weighted mean (taking into account the number of patients in each study) of *H. pylori* prevalence and 95% confidence interval was calculated. The effect of eradication of the infection on the recurrence of the ulcer or the ulcer perforation was assessed.

**Prevalence of *H. pylori* infection in perforated peptic ulcer**

Only a few studies have evaluated the prevalence of *H. pylori* infection in patients suffering from perforated peptic ulcer. From the 19 studies detailed in Table 1, including 1169 patients, a mean prevalence (weighted mean) of only 68.1% could be calculated (95% confidence interval, 65–71%) [11–28]. This figure is similar to that reported in other ulcer complications, such as gastric outlet obstruction [29]. Nevertheless, more important is the information from comparative studies, where the prevalence of

<table>
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<tr>
<th>Author (reference)</th>
<th>Patients (number)</th>
<th>Ulcer type</th>
<th>Diagnosis of <em>H. pylori</em></th>
<th><em>H. pylori</em> prevalence (%)</th>
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<tr>
<td>Reinbach et al. (11)</td>
<td>80 DU</td>
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<td>29 DU or GU</td>
<td>83</td>
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<td>Debongnie et al. (13)</td>
<td>36 DU or GU</td>
<td>H, Cu, Ci</td>
<td>56</td>
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<td>Ng et al. (14)</td>
<td>73 DU</td>
<td>H</td>
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<td>29 DU</td>
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<td>Lasgla et al. (15)</td>
<td>27 GU</td>
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<td>Matskura et al. (16)</td>
<td>21 DU</td>
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<td>Matskura et al. (16)</td>
<td>5 GU</td>
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<td>Chowdhary et al. (17)</td>
<td>15 DU</td>
<td>RUT, Gram, Giemsa</td>
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<td>18 DU</td>
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<td>Chu et al. (20)</td>
<td>163 DU</td>
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<td>Sharma et al. (21)</td>
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<td>RUT, H</td>
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<td>RUT</td>
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<td>Oncel et al. (24)</td>
<td>52 DU</td>
<td>13UBT</td>
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<td>Kate et al. (25)</td>
<td>202 DU</td>
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<td>73</td>
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<td>RUT, H, S</td>
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<td>RUT, Cu, Ca, 14UBT, S</td>
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<td>RUT, H</td>
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<td>Tran et al. (28)</td>
<td>111 DU or GU</td>
<td>RUT, H, S</td>
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DU: duodenal ulcer; GU: gastric ulcer; RUT: rapid urease test; H: histology; S: serology; UBT: urea breath test; I: immunohistochical stain; Cu: culture; Ci: citology; Ca: carbol-fuchsin smear.

Overall *H. pylori* infection rate (weighted mean) including all studies (1169 patients) = 68.1% (95% confidence interval = 65–71%).

Mean *H. pylori* infection rate in studies including only duodenal ulcers: 61.4%; and only gastric ulcers: 72.2%.
**H. pylori and Perforated Ulcer**

*H. pylori* infection in cases with perforated peptic ulcer is compared with that of the controls. The first of these studies was performed by Reinbach et al. [11], where the prevalence of *H. pylori* in 80 patients presenting with acute perforated duodenal ulcer was examined (by serology) and compared with age and sex matched hospital control patients. Only 47% of the perforated duodenal ulcer patients were positive for *H. pylori* and this was similar to the value of 50% in the controls. Therefore, this was the first study to conclude that the lack of association of acute perforated duodenal ulcer and *H. pylori* infection suggested that perforated duodenal ulcer had a different pathogenesis from chronic duodenal ulcer disease, and that the first should not be regarded simply as a complication of the second [11]. Consequently, these findings suggested that other pathogenic factors different from *H. pylori* should participate in perforated duodenal ulcer disease. Other authors have reported that their prevalence of 56% in patients with perforated gastroduodenal ulcers lay between that seen in age and sex matched healthy blood donors (36%) and their patients with uncomplicated peptic ulcers matched for age, sex and ulcer location (86%) [13]. Lanas et al. [15] studied 76 patients with gastrointestinal perforation and 152 matched controls. Independent risk factors for ulcer perforation were smoking, alcohol, a history of peptic ulcer and, especially, nonsteroidal anti-inflammatory drug (NSAID) use; however, a positive *H. pylori* serology was not demonstrated to be a risk factor. Finally, some authors have reported a higher density of *H. pylori* in patients with perforated peptic ulcer than in others with bleeding and stenotic ulcers [18].

However, other studies have not found significant differences between the perforated and nonperforated peptic ulcer patients with respect to *H. pylori* infection. Kate et al. [25] compared the prevalence of *H. pylori* infection in patients with perforated duodenal ulcer (after simple closure) with that in controls, and could not demonstrate statistically significant differences. Matsukura et al. [16] conducted an age and gender matched case-control study between perforated and nonsurgical peptic ulcers in *H. pylori* infection and examined differences in the cytotoxin genes *cagA* and *vacA*. Serum *H. pylori* IgG antibody was positive in 95% of perforated vs. 93% of nonsurgical duodenal ulcers, and in 100% of perforated vs. 86% of nonsurgical gastric ulcer patients. There were no significant differences between the perforated and nonsurgical peptic ulcer groups for *H. pylori* *cagA* and *vacA* markers, in agreement with a recent study [30]. Although the authors conclude from these results that *H. pylori* infection is not etiologically related to perforation of peptic ulcer, this study seems to demonstrate, in fact, that *H. pylori* is probably the cause of almost all perforated and nonperforated ulcers, although the organism is not responsible for the perforation itself. In other words, uncomplicated and complicated ulcers would be similar in terms of *H. pylori* infection (both in prevalence and in strain virulence), although the explanation for the perforation of the ulcer only in some cases remains unknown; these results suggest therefore that host factors are perhaps more relevant pathogenic factors in perforation than *H. pylori* infection itself.

**Hypotheses to explain *H. pylori*-negative peptic ulcer perforations**

As previously shown, prevalence of *H. pylori* infection in perforated peptic ulcer varies markedly among studies, even when case-control studies are considered. These controversial results may be due, at least partly, to several factors, as differences in frequency of NSAID use, the type of the perforated ulcer considered (duodenal or gastric ulcer), the sensibility and specificity of diagnostic methods of *H. pylori*, or the possibility that the infection would have been eradicated by procedures aimed to treat the ulcer perforation.

**NSAID Use**

A possible explanation for the lower than expected prevalence of *H. pylori* in some studies of ulcer perforation may be the coexisting use of NSAIDs, which constitutes a well-known independent cause of ulcer complications. However, most studies have not determined NSAID intake prospectively using a structured questionnaire, and have not reported prevalence of *H. pylori* separately for patients with and without NSAID intake. As an exception, in the study by Ng et al. [14] the *H. pylori* infection rate demonstrated by intraoperative and antral biopsies in patients with perforated peptic ulcer was 70%, but this figure rose to 80% if NSAID users were excluded (while in patients taking these drugs the
infection was detected in only 23% of the cases. Other studies have reported a high proportion of NSAID use in patients with peptic ulcer perforation, especially in those uninfected [13], suggesting that these drugs represent a relevant factor associated with \textit{H. pylori}-negative ulcer perforations. Furthermore, some authors have demonstrated that NSAID use is strongly associated with an increased risk of upper gastrointestinal perforation, while \textit{H. pylori} is not different between patients with perforation and controls [15]. Finally, it should be remembered that even in patients refusing NSAID use we cannot absolutely exclude the surreptitious use of these drugs [15,31].

Ulc er Site (Duodenal or Gastric Ulcer)

\textit{H. pylori} infection is the most important etiologic factor for noncomplicated duodenal ulcer, where NSAIDs seem to play a less important role [9,10,32]. However, the prevalence of \textit{H. pylori} infection in gastric ulcer disease is considerably lower, suggesting that other factors different from the organism – mainly NSAIDs – are responsible for a relatively high proportion of ulcers located in the stomach [33]. As shown in Table 1, most of the protocols have included patients with duodenal or gastric ulcer disease in the same study, and only a few studies have separately studied the prevalence of the organism in each peptic disease. Unexpectedly, mean \textit{H. pylori} infection rate in studies including only duodenal ulcers was even lower (61%) than in those including only gastric ulcers (72%), but in both cases the prevalence was relatively low (Table 1).

Previous Use of Antibiotics

The course of intravenous antibiotics that are routinely prescribed for patients with perforated ulcer might eradicate \textit{H. pylori} in some of these patients. Thus, a single shot antibiotic treatment with two antibiotics including metronidazole in patients undergoing proximal gastric vagotomy was reported to be associated with eradication of \textit{H. pylori} [34]. In this respect, some studies that used serology – a method uninfluenced by the recent use of antibiotics – have found prevalence rates of infection of almost 100% in perforated ulcers [16]. Nevertheless, other studies could not confirm these results, and reported relatively low infection rates even with serology [11,25].

Effect of Surgery on \textit{H. pylori} Infection

Some authors have performed a systematic review to answer the question whether surgery for peptic ulceration eradicates \textit{H. pylori} [35]. Among \textit{H. pylori}-positive patients who had undergone vagotomy alone the prevalence of persistent \textit{H. pylori} infection was of 83%, whereas for partial gastrectomy it was only about 50%. On one hand, these results indicate that, when the true prevalence of \textit{H. pylori} in ulcer perforation is to be assessed, infection status should be evaluated before surgery, when the prevalence is higher. On the other hand, the main clinical implication of the persistently high prevalence of \textit{H. pylori} infection postoperatively is that patients who have undergone surgery, particularly vagotomy, should be reviewed and considered for antibiotic treatment that will cure their chronic infection [35].

Diagnostic Methods

Finally, the number and type of diagnostic methods to detect \textit{H. pylori} may also be partly responsible for the controversial results. Mendes et al. [26] studied with detail a group of patients with perforated peptic ulcer disease. After surgery, the patients were submitted to endoscopy, and \textit{H. pylori} was searched by five different methods including culture, rapid urease test, carbolfuchsin smear, $^{14}$C-urea breath test, and serology. The infection was demonstrated by at least one test in 100% of the patients. Therefore, the authors conclude that the use of several diagnostic methods allowed us to demonstrate that \textit{H. pylori} prevalence in perforated peptic ulcer disease is similar to noncomplicated ulcer disease. Similarly, Tran et al. [28] evaluated \textit{H. pylori} status in 111 patients by means of three diagnostic methods (rapid urease test, histology and serology), and reported an infection rate as high as 96%.

In summary, the mean prevalence of \textit{H. pylori} infection in patients with perforated peptic ulcer is only about 65–70%, which contrasts with the almost 90–100% figure reported in noncomplicated ulcer disease and also with the higher frequency of the infection in other ulcer complications, such as upper gastrointestinal bleeding [36]. However, \textit{H. pylori} infection rates in various studies range markedly from 0% to 100%, suggesting that differences in variables as number and type of diagnostic methods used to
diagnose *H. pylori* infection, or frequency of NSAID intake, may be responsible for the low prevalence reported in some studies.

Based on the high prevalence of *H. pylori* infection in patients not taking NSAIDs who present with uncomplicated duodenal ulcer, it could be argued that the probability of *H. pylori* infection would be so high that, from a practical point of view, it would not be necessary to confirm the presence of the infection before administering eradication therapy. In patients with ulcer perforation, therapy could be started intravenously immediately after the perforation is diagnosed and the surgical procedure performed. However, the multiple studies reporting low prevalence of the infection in perforated ulcer (Table 1) suggest, obviously, that ‘empirical’ antibiotic therapy without confirming *H. pylori* infection cannot be generally recommended in acute perforated ulcers [37]. We must not forget the potential disadvantages of the ‘empirical’ strategy: cost and adverse effects of antibiotic treatment in patients without the infection, possible development of drug resistance also in these patients, complications as a consequence of the delayed diagnosis of diseases not caused by the organism, and the false sensation of safeness against future episodes of perforation when only eradication therapy – without antisecretory maintenance therapy – is prescribed. In conclusion, *H. pylori* status should be determined when the patients recover from the acute episode, by either endoscopic biopsy or, if this exploration is thought to be unnecessary, by serology or $^{13}$C-urea breath test.

**Role of *H. pylori* in the recurrence of the ulcer or the ulcer perforation**

Primary treatment of a perforated ulcer involves either patch closure or definitive surgery for the ulcer. As previously mentioned, simple closure is associated with an unacceptably high recurrence rate of the ulcer [38]. On the other hand, definitive surgery may have long-term side-effects in patients who may otherwise have been cured by simple closure alone [25]. Prescription of H$_2$ receptor antagonists or proton pump inhibitors with the intention to reduce ulcer recurrence after simple patch closure has produced conflicting results [6,7]. Therefore, the best therapy for peptic ulcer perforation is still a matter of debate. Peptic ulcer, and the perforation itself, may recur after operation for perforation. It is uncertain, however, why in some patients ulcers recur, whereas in others they do not. Gastric acid secretion and serum gastrin levels do not predict ulcer recurrence in patients after simple closure of perforation [39].

The role of *H. pylori* infection in the recurrence of the ulcer or the ulcer perforation in patients with a history of perforated peptic ulcer has been evaluated in some studies. Sebastian et al. [12] identified *H. pylori* in most of the patients who underwent simple closure of perforated peptic ulcer; 6 weeks later some patients had an endoscopy performed, and persistence of duodenal ulceration was demonstrated in seven out of the 12 infected patients; from another point of view, all patients with unhealed duodenal ulcer had *H. pylori* infection. Debongnie et al. [13] studied the prevalence of *H. pylori* in 36 patients with a perforated ulcer; seven out of the nine infected patients with a follow-up of at least 12 months and no preventive treatment had a symptomatic relapse; one patient without *H. pylori* had a second perforation, the only relapse in this group. Pescatore et al. [40] studied six patients with ulcer perforation treated with closure of the orifice by an omental plug and *H. pylori* eradication regimen; at endoscopy performed 1 month after surgery, all ulcers except one had disappeared; in this patient, persistent *H. pylori* gastritis was diagnosed and successfully treated by a second regimen with subsequent ulcer healing at endoscopic evaluation performed 2 months later. In the study by Chu et al. [20] 163 patients with history of perforated duodenal ulcer unrelated to NSAIDs underwent upper endoscopy a mean of 74 months after operation; recurrent duodenal ulcer was found in 18% of the patients and these recurrences were significantly related to *H. pylori* status. Koyama et al. [41] studied a group of patients with acute duodenal perforation; among the 42 patients who received nonoperative treatment, three developed reperforation; endoscopic biopsy or serum anti-*H. pylori* IgG measurement confirmed the infection in all three patients. Kate et al. [25] reviewed a group of 60 patients 5 years or more after perforation closure, and found that 90% of patients with a recurrent ulcer had *H. pylori* infection compared with only 19% in those with no ulcer. Finally, Kumar et al. [27] studied 30 patients presenting with perforated duodenal ulcer and who underwent emergency laparotomy and simple omental patch repair; upper gastrointestinal endoscopy
was done 11 weeks after surgery, when active duodenal ulcer was present in 13 out of 17 patients with evidence of *H. pylori* infection and in none of the noninfected patients.

In summary, recurrent ulcer disease after peptic ulcer perforation mainly occurs in patients with *H. pylori* infection, which suggests that the microorganism plays an important role in this complication.

**Role of *H. pylori* eradication treatment in perforated peptic ulcer**

In previous years a tendency existed to perform definitive surgery on perforated peptic ulcer. However, in recent years, the theory that eradication of *H. pylori* decreases the rate of ulcer relapse has resulted in a return to primary repair with an omental patch over the perforated ulcer [19]. Thus, as *H. pylori* infection seems to cause ulcer recurrence after this complication, eradication of the organism is imperative after patch closure [25]. The effect of *H. pylori* eradication on the natural history of perforated peptic ulcer has been addressed in a few studies. Ng et al. [42] randomized patients with perforated duodenal ulcers to receive either omeprazole alone or a quadruple anti-*H. pylori* therapy. At 1-year follow-up ulcer relapse was 38% in the omeprazole group compared with only 5% in the group receiving anti-*H. pylori* regimen. This study is the first study examining the effect of *H. pylori* eradication in patients with perforated duodenal ulcer, and noteworthy demonstrates that after *H. pylori* eradication, and without maintenance acid-suppression agents, 95% of patients remain ulcer-free at 1-year follow-up. Thus, the remission rate seems to be similar to that previously reported in uncomplicated ulcers after *H. pylori* eradication [43]. In the study by Alamowitch et al. [44], 35 patients with perforated duodenal ulcer were treated by simple closure, peritoneal lavage and omentoplasty; no recurrence was found after eradication of *H. pylori* with a follow-up of 38 months. Metzger et al. [23] prospectively studied 47 patients suffering from acute peptic ulcer perforation and treated them with simple closure and *H. pylori* eradication; follow-up (median 43.5 months) revealed no need for reoperation for peptic ulcer disease and no mortality. Kate et al. [25] prospectively followed 202 patients for 2 years after simple closure of a perforated duodenal ulcer; patients were randomized to receive either ranitidine alone or quadruple therapy (ranitidine, colloidal bismuth subcitrate, metronidazole and tetracycline) after operation; the authors showed that the *H. pylori* infection rate was significantly higher at all intervals of follow-up to 2 years in patients with recurrent or residual ulcer after closure of a duodenal ulcer compared with that in patients in whom ulcer remained healed (although the precise data of recurrence in the ranitidine and in the *H. pylori* eradication group were not given). Finally, Tran et al. [28] prescribed an eradication regimen with omeprazole, clarithromycin and amoxicillin to a group of patients with perforated gastro-duodenal ulcer treated with surgical suture; follow-up endoscopy was performed 4–6 weeks after treatment cessation, when ulcer healing was demonstrated in 93% of the patients.

It has been suggested that patients with peptic ulcer that perforate be divided into those with prior evaluation for *H. pylori* and appropriate therapy for the ulcer and those without adequate prior evaluation or treatment for the ulcer [45]. In the first group, *H. pylori*-negative patients (both because they were initially *H. pylori*-negative or because the organism has been eradicated), an ulcer-definitive surgery should be performed, as the cause of the perforation cannot be attributed to the infection. Due to the important role that *H. pylori* plays in peptic ulcer disease, it has even been suggested that the presence or the absence of the infection may be assessed at the time of perforation with a rapid serological test (office-based test) and, thus, *H. pylori*-negative cases could then be treated, as previously mentioned, with ulcer-definitive surgery [45]. However, whole blood tests have achieved discouraging results in many studies and they are, at present, of doubtful usefulness [46].

On the other hand, when inadequate prior evaluation or treatment of *H. pylori* infection has been undertaken, three premises have been considered, as suggested by Donovan et al. [45] [1]: Most duodenal ulcers will be associated with *H. pylori* [2]. Ulcer-definitive surgery should not be employed until an ulcer associated with *H. pylori* infection has had the benefit of *H. pylori* eradication therapy. And [3] treatment at the time of perforation should be an assured closure of the perforation, pending determination of *H. pylori* status. When the patient has recovered from the consequences of the perforation, the status of *H. pylori* should be investigated. If positive, *H. pylori* eradication regimen
will be prescribed. Ulcer-definitive surgery should be considered in an infected patient only if there is relapse after appropriate eradication therapy.

Based on previous findings, that *H. pylori* eradication prevents ulcer recurrence in patients with *H. pylori*-associated perforated ulcers, it could be argued that maintenance antisecretory therapy may not be necessary after confirming eradication success. In other ulcer complications, as upper gastrointestinal bleeding, it has been reported in a recent meta-analysis comparing the effect of *H. pylori* eradication with long-term maintenance antisecretory therapy that recurrent bleeding occurred in only 1% of patients with *H. pylori* eradication success [47]. Nevertheless, in perforated ulcers there is less information, and the role of maintenance antisecretory needs to be assessed in prospectively comparative studies.

In summary, all patients with perforated peptic ulcer should be treated by simple closure of the perforation and with therapy aimed at healing of the ulcer and eradicating the *H. pylori* infection [48,49], as disappearance of the organism prevents, or at least decreases, ulcer recurrence and ulcer perforation in patients with *H. pylori*-associated perforated ulcers after simple closure. Therefore, *H. pylori* eradicating treatment should be started during the immediate postoperative period [50]. The patients with intractable recurrent symptoms of peptic ulcer despite adequate medical treatment, but without *H. pylori* infection (e.g. a patient using NSAIDs), is probably the only remaining indication for elective definitive surgical treatment of peptic ulcer disease [5]. Nevertheless, as *H. pylori* infection or NSAIDs are not the cause for all peptic ulcer perforations, other therapeutic strategies might also be of major impact.

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