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Eradication of *Helicobacter pylori* for prevention of ulcer recurrence after simple closure of perforated peptic ulcer: a meta-analysis of randomized controlled trials

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ABSTRACT

Background: Eradication of *Helicobacter pylori* has become part of the standard therapy for peptic ulcer. However, the role of *H pylori* eradication in perforation of peptic ulcers remains controversial. It is unclear whether eradication of the bacterium confers prolonged ulcer remission after simple repair of perforated peptic ulcer.

Methods: A systematic review and meta-analysis of randomized controlled trials was performed to evaluate the effects of *H pylori* eradication on prevention of ulcer recurrence after simple closure of perforated peptic ulcers. The primary outcome to evaluate these effects was the incidence of postoperative ulcers; the secondary outcome was the rate of *H pylori* elimination.

Results: The meta-analysis included five randomized controlled trials and 401 patients. A high prevalence of *H pylori* infection occurred in patients with perforated peptic ulcers. Eradication of *H pylori* significantly reduced the incidence of ulcer recurrence at 8 wk (risk ratio 2.97; 95% confidence interval: 1.06–8.29) and 1 y (risk ratio 1.49; 95% confidence interval: 1.10–2.03) postoperation. The rate of *H pylori* eradication was significantly higher in the treatment group than in the nontreatment group.

Conclusions: Eradication therapy should be provided to patients with *H pylori* infection after simple closure of perforated gastroduodenal ulcers.

1. Introduction

Perforation is a serious and potentially fatal complication of peptic ulcer disease. Depending on the patient's clinical condition, traditional treatment of perforated peptic ulcers usually involves a definite ulcer procedure or simple closure of the perforation hole.

Immediate acid-reduction procedures in addition to repair effectively reduced recurrence. However, these can be difficult to apply in an emergency setting, especially in critically ill

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patients, and are associated with long-term side effects [1]. Advances in research on the pathophysiology of peptic ulcer disease have led to changes in surgical treatment of perforated peptic ulcer disease. With the evolution of the proton pump inhibitor, a simple closure procedure for peptic ulcer disease has gained wide acceptance and can be performed laparoscopically [2,3]. However, it is associated with a high ulcer recurrence rate and complications such as reperforation, bleeding, or stenosis [4].

Previous research has identified *Helicobacter pylori* (*H pylori*) as an opportunistic pathogen attracted by changes in the gastric mucosa caused by inflammation and ulcer. It plays a critical role in the pathogenesis of peptic ulcer disease [5]. Appropriate antibiotic treatment combined with proton pump inhibitors or histamine (H_2) blockers eradicates *H pylori* infection in more than 90% of cases [6]. In the uncomplicated patient, eradication of *H pylori* is effective in prevention of ulcer recurrence. In cases of bleeding peptic ulcers, eradication of *H pylori* is as efficacious as maintenance acid-reduction medication at preventing recurrent ulcer hemorrhage [7].

Previous studies have extensively investigated the association between *H pylori* and perforated peptic ulcer, providing conflicting results. In patient with perforated peptic ulcer, the prevalence of *H pylori* infection varied from 47%, as determined using serologic testing [8], to more than 80% in biopsy-based studies [9]. The effectiveness of *H pylori* eradication for prevention of ulcer recurrence after simple closure of perforated peptic ulcer remains unclear. The present study, therefore, consists of a systematic literature review and meta-analysis of randomized controlled trials (RCTs), which are conducted to evaluate the role of *H pylori* eradication in the prevention of ulcer recurrence following simple repair of peptic ulcer perforation.

2. Methods

2.1. Data sources

Literature searches were performed using four electronic databases (MEDLINE, EMBASE, SCOPUS, and Cochrane databases). The searches were unlimited by time up to October 2012 without language restriction. The following medical search headings (MeSH) terms, words, and combinations of words were used in constructing the systematic search: *gastric* or *duodenal* or *peptic*, *ulcer*, *perforated* or *perforation*, *Helicobacter pylori*, *eradication*. All included studies were also entered into the PubMed "related articles" function and the science citation index. In addition, we attempted to identify other studies by hand-searching the reference sections of these papers and by contacting known experts in the field. Finally, unpublished trials were retrieved from the ClinicalTrials.gov registry (http://clinicaltrials.gov/).

2.2. Study selection

To be included in the analysis, studies were required to meet the following criteria: they were randomized controlled trials that evaluated the efficacy of *H pylori* eradication on prevention of ulcer recurrence in patients with perforated peptic ulcer following simple closure; they clearly documented the inclusion and exclusion criteria used for patient selection; they adequately documented the administration of postoperative antibiotics and proton pump inhibitors; and they precisely documented the definition and evaluation of *H pylori* infection. Studies were excluded from the analysis if one or both of the following conditions applied: patients enrolled in the trials were undergoing other concomitant surgical procedures and receiving *H pylori* eradication therapy preoperatively; an overlap occurred between patient cohorts evaluated in two or more studies.

2.3. Data extraction and quality assessment

Two independent reviewers (C.S.W. and K.W.T.) extracted trial details pertaining to the participants, inclusion and exclusion criteria, administration of experimental drugs, prevalence and assessment of *H pylori* infection, complications, and postoperative recovery. Discrepancies were resolved through discussion; any disagreements were resolved by a third reviewer (C.F.C.). The authors of the studies were contacted for additional information when necessary.

The risk of bias in the included trials was assessed in individual domains, reporting the following aspects: adequacy of the randomization, allocation concealment, masking, duration of follow-up, numbers of drop-outs, and performance of intention-to-treat (ITT) analysis.

2.4. Outcome assessment

The ulcer healing rate and the *H pylori* eradication rate were the outcomes used to evaluate the efficacy of eradication of *H pylori* for perforated peptic ulcers following simple closure. The occurrence of residual and recurrent ulcers was identified using endoscopy. The occurrence of *H pylori* infection was determined using assessments of histology, culture, rapid urease tests, breath tests, or serum levels of anti–*H pylori* immunoglobulin G using enzyme-linked immunosorbent assay, at presentation with a perforated ulcer and at 6 wk, 8 wk, 16 wk, or 1 y after perforation closure. Patients with complete ulcer healing on the scheduled endoscopy were then invited for a follow-up endoscopy at 1 y for ulcer surveillance and determination of *H pylori* status.

2.5. Data analysis

Analysis was performed using the statistical package Review Manager, version 5.1 (Cochrane Collaboration, Oxford, England). Meta-analysis was performed according to recommendations in the PRISMA guidelines [10,11].

The dichotomous outcomes were statistically analyzed using risk ratios (RR) as the summary statistic. The results were reported with 95% confidence intervals (CIs). A pooled estimate of the RR was calculated using the DerSimonian and Laird random effect model [12]. This provides a more appropriate estimate of the average treatment effect when trials are statistically heterogeneous, and usually yields wider CIs,

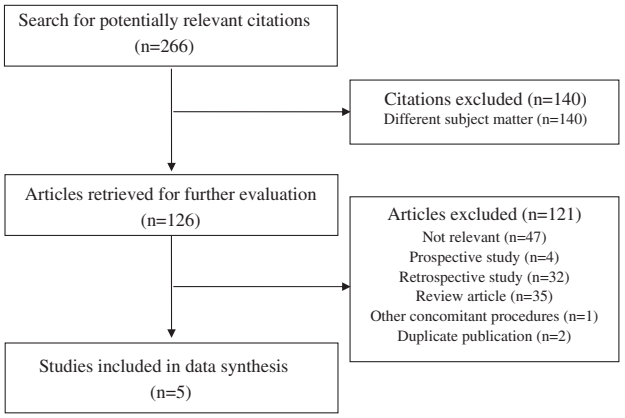

Fig. 1 – Flowchart for selection of studies.

thereby resulting in a more conservative statistical claim. χ^2 statistics tests (Q statistics) and I^2 test were used to test for heterogeneity between controlled trials.

3. Results

3.1. *Characteristics of the trials*

The review process is outlined in Figure 1. The initial search strategy yielded 266 citations, 140 of which were ineligible based on the screening of titles and abstracts. This left the full texts of 126 studies. Of these, 47 were excluded because of lack of relevance, two did not meet the eligibility criteria because of duplicate publication, four were prospective studies, 32 were retrospective studies, 35 were review articles, and one enrolled patients with simple closure of perforated peptic ulcer and concomitant partial gastrectomy. Five eligible trials thus remained [13–17]. Of these, all trials were peer-reviewed articles; one was a letter [16]. The study of Kate *et al.* included the retrospective review of a group 5 y or more after perforation closure; the data from this group were not included in the analysis [14].

Table 1 displays the characteristics and patient demographic data from each of the five trials included in the review. The publication dates of the studies were between 2000 and 2011, and sample sizes ranged from 40–124. All trials evaluated patients admitted with perforated duodenal ulcers. Baseline characteristics were balanced and similar between the two treatment groups in the five included RCTs. Evaluation of *H pylori* differed across the trials: four trials used histologic assessment of hematoxylin-eosin or Giemsa staining at ulcer presentation, four studies used rapid urease tests, one study used breath tests, and two trials used culturing. Trials mainly performed postoperative assessment of *H pylori* using urease tests and serology. Only *H pylori*–positive patients who had undergone simple repair were eligible for randomization. After resuming an oral diet, patients were randomly assigned to one of the two treatment options. The dosages of *H pylori* eradication therapy were adjusted according to various protocols. The most commonly applied modality for *H pylori* eradication was amoxillicin and metronidazole for 1 wk, and omeprazole for 4 wk. Two trials compared the effects of triple therapy on eradication of *H pylori* with those for proton pump inhibitors [13,15], one trial used ranitidine [14], one trial used sequential treatment [17], and one trial applied different durations of therapy [16].

Table 2 displays the methodological quality of the five included RCTs. Of these, four studies clearly documented the use of random allocation [13–15,17]. Four studies described the concealing of patient allocation to different treatment groups from the participants [13–15,17]. None reported the masking of the patients, personnel, and investigators who assessed the outcomes. Three included studies that based their analyses on the intention-to-treat principle [13,15,16]. Loss to follow-up was acceptable (<20%) in all studies except that of *Kate et al.*, which reported the loss of 35.7% patients at 1 y follow-up [14].

3.2. H pylori *infection rate at perforation*

The analysis included five studies and 582 patients with perforated duodenal ulcers. The prevalence of *H pylori* infection at perforation was 73.9%, ranging from 60.3%–84.8% (Table 1).

3.3. H pylori *eradication rate*

3.3.1. *Eradication* versus *control*

Three studies with a total of 288 patients evaluated the eradication of *H pylori* at 8 wk [13–15]. These studies reported an *H pylori* eradication rate of 83.9% in the eradication group compared with 35.2% in the control group. The two groups thus differed significantly, with fewer patients in the eradication group experiencing *H pylori* infection after surgical repair of ulcer perforation (RR = 2.97; 95% CI: 1.06–8.29) (Fig. 2). Results showed significant heterogeneity across the studies (I^2 = 92%, $P < 0.00001$). Two studies with a total of 137 patients evaluated eradication of *H pylori* at 1 y [13,14]. The *H pylori* eradication rate was 67.1% in the eradication group and 45.3% in the control group (RR = 1.49; 95% CI: 1.10–2.03) (Fig. 2).

3.3.2. *High dose* versus *low dose*

The study of Oncel *et al.* compared two different durations of *H pylori* eradication regimens in patients with perforated duodenal ulcers [16]. The 7-d group received 500 mg clarithromycin and 1 g amoxicillin twice daily for 7 d and omeprazole for 28 d; the 14-d group received the same antibiotics for 14 d and omeprazole for 28 d. After 6 wk, the authors evaluated *H pylori* eradication and identified an *H pylori* eradication rate of 65% in the 14-d group and 30% in the 7-d group (RR = 2.17; 95% CI: 1.03–4.55).

3.3.3. *Standard therapy* versus *sequential therapy*

The study of Valooran *et al.* compared the eradication rate of *H pylori* using a standard triple-drug therapy and a sequential therapy [17]. The standard triple-drug therapy consisted of omeprazole, clarithromycin, and amoxicillin for 10 d. The sequential therapy consisted of omeprazole and amoxicillin for the first 5 d, followed by omeprazole, clarithromycin, and

Table 1 – Characteristics of the included trials.*

Author [year]	Disease / surgery	*H pylori* assessment	*H pylori* infection rate, %	No. of patients (male)	Age (y), mean ± SD	Intervention
El-Nakeeb [2009]	PDU/open	Rapid urease test; histology by H&E stain; culture and Gram stain and biochemical tests	84.8 (65/77)	E: 34 (32) C: 31 (27)	E: 46.0 ± 12.9 C: 46.6 ± 10.5	E: Amoxicillin 750 mg 3 times daily × 1 wk, metronidazole 500 mg twice daily × 10 d, and omeprazole 40 mg daily × 4 wk C: Omeprazole 40 mg daily × 4 wk
Kate [2001]	PDU/not mentioned	Serology; urease test; histology by Giemsa stain	73.3 (148/202)	E: 64 C: 60	Unknown	E: Bismuth subcitrate 120 mg and tetracycline 500 mg 4 times, metronidazole 400 mg 3 times, and ranitidine 150 mg twice daily C: Ranitidine 150 mg twice daily × 4 wk
Ng [2000]	PDU/open or laparoscopic	Rapid urease test; culture and Gram stain; histology	80.6 (104/129)	E: 51 (43) C: 48 (41)	E: 44.0 ± 14.0 C: 45.0 ± 15.0	E: Bismuth subcitrate 120 mg, tetracycline 500 mg, metronidazole 400 mg 4 times daily × 1 wk; omeprazole 20 mg twice daily × 4 wk C: Omeprazole 20 mg twice daily × 4 wk
Oncel [2001]	PDU/not mentioned	Breath test	75.5 (40/53)	E(h): 20 E(l): 20	Unknown	E(h): Clarithromycin 500 mg, amoxicillin 1 g twice daily × 1 wk, and omeprazole x 4 wk E(l): Clarithromycin 500 mg, amoxicillin 1 g twice daily × 2 wk, and omeprazole x 4 wk
Valooran [2011]	PDU/not mentioned	Urease test; histology by Giemsa stain	60.3 (73/121)	E: 36 (34) S: 37 (35)	E: 42.0 ± 13.5 S: 45.0 ± 12.7	E: Omeprazole, clarithromycin, and amoxicillin × 10 d S: Omeprazole, amoxicillin × 5 d followed by omeprazole, clarithromycin, and amoxicillin for subsequent 5 d

C = control; E = eradication; E(h) = eradication with high dose; E(l) = eradication with low dose; H&E = hematoxylin-eosin; PDU = perforated duodenal ulcer; S = sequential therapy; SD = standard deviation.
* All peer-reviewed except Oncel [2001] as letter.

amoxicillin for a subsequent 5 d. After 8 wk, the authors evaluated *H pylori* eradication, identifying an eradication rate of 81.3% for standard triple therapy and an eradication rate of 87.1% for the sequential regimen (RR = 0.93; 95% CI: 0.75–1.16).

3.4. *Ulcer recurrence*

Two studies with a total of 144 patients with documented complete ulcer healing on the scheduled endoscopy were then evaluated for ulcer recurrence at 1 y follow-up using endoscopy [13,15]. Ulcer recurrence was significantly lower in the eradication group than in the control group (5.3% *versus* 34.8%, RR = 0.16; 95% CI: 0.06–0.44) (Fig. 3).

3.5. *Symptomatic ulcer recurrence*

Two studies with a total of 144 patients with documented complete ulcer healing on the scheduled endoscopy were then evaluated for symptomatic ulcer recurrence, including ulcer pain, bleeding, obstruction, and reperforation, at 1 y follow-up using endoscopy [13,15]. Symptomatic ulcer recurrence was significantly lower in the *H pylori* eradication group than in the control group (2.7% *versus* 20.3%, RR = 0.13; 95% CI: 0.03–0.57) (Fig. 4).

4. Discussion

H pylori infection plays a critical role in the pathogenesis of peptic ulcer disease. Although the relationship between *H pylori* infection and peptic ulcers has been well defined, the relationship between *H pylori* infection and perforated ulcers remains controversial [18]. In the present study, the prevalence of *H pylori* infection rate at perforation was 73.9%. This reveals a close relationship between *H pylori* infection and ulcer perforation.

The National Institutes of Health consensus development panel on *H pylori* concluded that ulcer patients with *H pylori* infection require treatment with antimicrobial agents in addition to antisecretory drugs [19]. Investigators have studied several antimicrobial agents and their efficacies at eradicating *H pylori* infection as a single agent or as a combination therapy. Single-drug regimens are usually not advocated

Table 2 – Methodological quality assessment of included trials.

Study [year]	Allocation generation	Allocation concealment	Double masking	Data analysis	Loss to follow-up, %
El-Nakeeb [2009]	Sealed envelope	Adequate	Unclear	ITT	7.7 at 16 wk
Kate [2001]	Random number table	Adequate	Unclear	PP	16.9 at 6 mo 34.7 at 1 y
Ng [2000]	Computer-generated	Adequate	Unclear	ITT	9.0 at 8 wk
Oncel [2001]	Unclear	Unclear	Unclear	ITT	No loss to follow-up
Valooran [2011]	Computer-generated	Adequate	Unclear	PP	13.7 at 1 y

PP = per protocol; ITT = intention-to-treat.

because of the potential for development of antibiotics resistance, especially to macrolides and metronidazole, which are the key agents in the multi-drug regimens for *H pylori*. Currently, the most effective first-line regimen for eradication of *H pylori* is a triple-therapy regimen including the combination of a proton pump inhibitor with amoxicillin and clarithromycin or metronidazole [20]. Proton pump inhibitors have a synergistic effect with several antibiotics by increasing the pH to optimal levels for antibiotic activity [21]. Recent studies have confirmed and provided evidence that *H pylori* eradication can prevent recurrent ulceration and bleeding in nonperforated patients [22]. The results of this meta-analysis indicate lower recurrence of ulcers in the eradication group than in the control group at 1-y follow-up after simple closure of the perforated ulcer, and a very low rate of symptomatic ulcer recurrence, including ulcer pain, bleeding, obstruction, and reperforation, in the eradication group (2.7%). This confirms the importance of *H pylori* eradication for prevention of ulcer recurrence in perforated ulcer patients.

The use of H_2 receptor antagonists and proton pump inhibitors to reduce ulcer recurrence after simple patch closure has produced conflicting results. Chen *et al.* reported that the overall efficacies of H_2 receptor antagonists and proton pump inhibitors as adjuvants for *H pylori* were similar (78% *versus* 81%) [23]. Schrauwen *et al.*, however, reported that the overall efficacies of proton pump inhibitors were superior to those of H_2 receptor antagonists (74% *versus* 69%, odds ratio: 1.31, 95% CI: 1.09–1.58) [24]. The present meta-analysis also compared different *H pylori* eradication regimens in patients with perforated duodenal ulcers. The study of Kate *et al.* was the only one to administer ranitidine rather than a proton pump inhibitor as an adjuvant for *H pylori* infection. However, ulcer recurrence was also significantly lower in the eradication group than in the control group.

The study of Valooran *et al.* compared the *H pylori* infection eradication rates using standard triple-drug therapy and sequential therapy [17]. Jafri *et al.* reported that a sequential therapy displayed superior efficacy to a standard triple therapy for eradication of *H pylori* (93.4% *versus* 76.9%) [25]. Choi *et al.*, however, revealed similar eradication rates between sequential and standard therapies (77.9% *versus* 71.6%), with a nonsignificant trend favoring the sequential therapy [26]. In the present meta-analysis, the eradication rate for standard triple therapy was 81.3%; that for the sequential regimen was 87.1% ($P = 0.732$). These findings were similar to those found in the study conducted by Choi *et al.* The

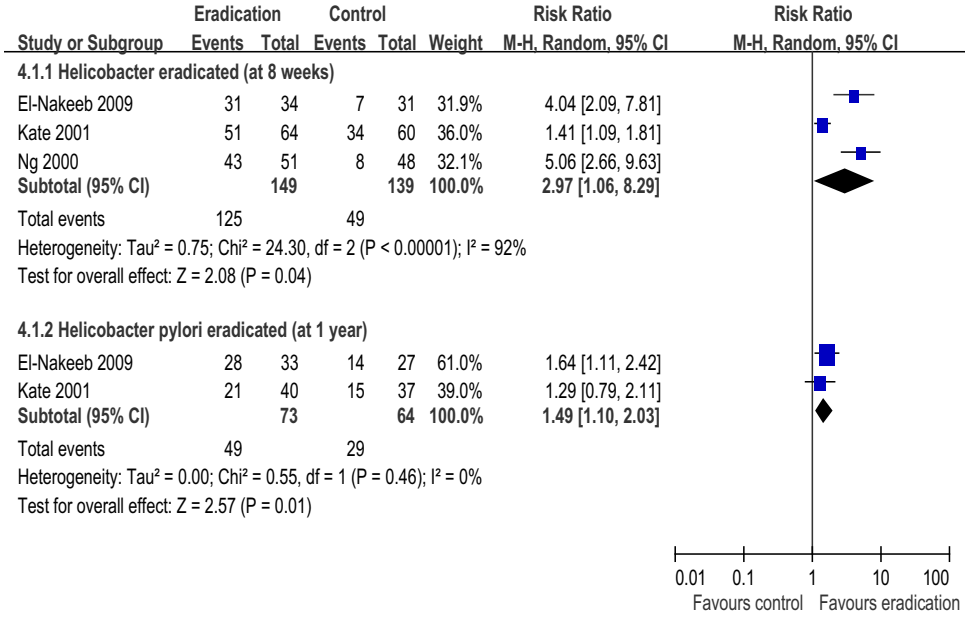

Fig. 2 – Forest plot for comparison of *H pylori* eradication *versus* control–Outcome: *H pylori* eradicated at 8 wk and 1 y postoperatively. Weights are from random-effects analysis. Risk ratios and 95% CIs were computed by the Mantel-Haenszel method.

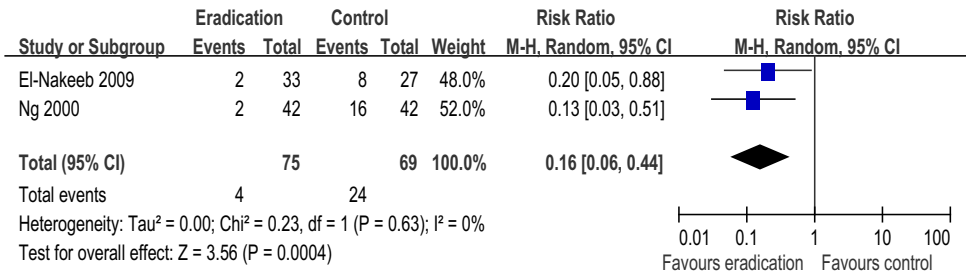

Fig. 3 – Forest plot for comparison of *H pylori* eradication *versus* control–Outcome: ulcer recurrence at 1 y postoperatively. Weights are from random-effects analysis. Risk ratios and 95% CIs were computed by the Mantel-Haenszel method.

incidences of side effects and compliance were similar in each group; however, the cost of sequential therapy was lower. Sequential therapy and standard triple-drug therapy are, therefore, equally efficient in the eradication of *H pylori* infection, with sequential therapy incurring lower costs. This makes sequential therapy an economical alternative option for *H pylori* eradication treatment.

In Oncel *et al.*, comparison of the eradication rates of *H pylori* infection using 7-d and 14-d therapies revealed an *H pylori* eradication rate of 65% in the 14-d group and 30% in the 7-d group [16]. This indicates that a 14-d therapy is more effective than a 7-d drug therapy. However, the lower eradication rates in the Oncel study might be because of the ineffectiveness of amoxicillin, due to its widespread and unnecessary use in the authors' country. Fuccio *et al.* summarized the benefits and harms of different durations of proton pump inhibitor–based triple therapy: meta-analysis of 11 studies yielded a relative risk for eradication of 1.07 (95% CI: 1.02–1.12) for 7-d compared with 14-d amoxicillin-containing triple therapy [27]. The authors concluded that extending triple therapy beyond 7 d is unlikely to be a clinically useful strategy.

Investigation of the etiology and pathophysiology of *H pylori* and peptic ulcer disease, and advances in laparoscopy in general surgery, have led to the changes in the surgical approach for perforated ulcer. Simple closure of perforation using an omental patch, either conventional or laparoscopic, is the procedure of choice for ulcer perforation [2]. Its combination with anti–*H pylori* treatment can prevent a high proportion of ulcer relapse. The present meta-analysis confirmed that eradication of *H pylori* significantly reduces ulcer recurrence following simple closure of perforation.

This study's results of high prevalence of *H pylori* infection in perforated ulcer patients and few recurrences after eradication indicate that diagnosis of *H pylori* infection is important in cases of ulcer perforation. *H pylori* status should therefore be determined as soon as possible, using tissue biopsy, cultures during operation, or serology. Anti–*H pylori* therapy must then be recommended for all *H pylori*–positive patients.

All patients in the five evaluated RCTs suffered from perforated duodenal ulcers. The meta-analysis excluded some prospective studies that included patients with perforated gastric ulcers. The results in patients with perforated gastric ulcers also indicated a high prevalence of *H pylori* infection and verified that the eradication of *H pylori* reduced relapse rates after simple closure of perforated peptic ulcer [28,29]. Besides the investigation of *H pylori* infection, the importance of biopsy in perforated gastric ulcer is to rule out cancer.

Surgical treatment for perforated ulcers has changed during the last 3 decades; duodenorrhaphy or gastrorrhaphy with omentoplasty have basically replaced gastric resection as emergency operations [30,31]. Panendoscopy can be arranged 8 wk after resuming oral feeding because the surgeon should avoid reperforation of the ulcer immediately after operation. According to the present study's findings, eradication of *H pylori* immediately after operation reduces the rate of ulcer recurrence following simple closure of perforated peptic ulcers. However, assessment of *H pylori* during or after surgery has yet to become routine clinical practice. Detection of *H pylori* using intraoperative biopsy, cultures, urease tests, or histology with Gram and Giemsa stain should, therefore, be recommended as routine practice.

The heterogeneity of the reviewed studies was considerable, as demonstrated by the I^2 value of 50%. However, the

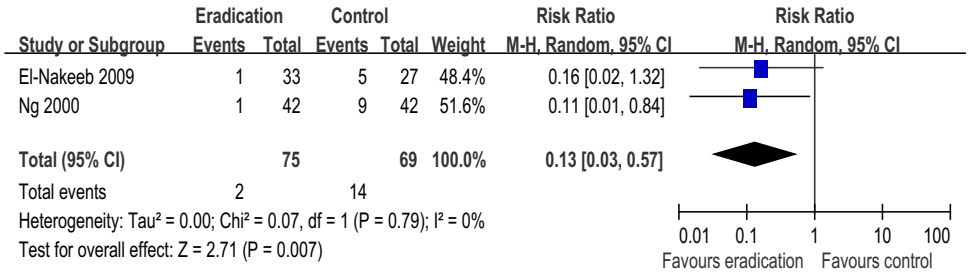

Fig. 4 – Forest plot for comparison of *H pylori* eradication *versus* control–Outcome: symptomatic ulcer recurrence at 1 y postoperatively. Weights are from random-effects analysis. Risk ratios and 95% CIs were computed by the Mantel-Haenszel method.

published RCTs were not in total agreement and their results were inconsistent. This could have resulted from heterogeneity among patients' demographics and characteristics, as well as among study methods, inclusion and exclusion criteria, and the dose and route of administration of *H pylori* treatment.

The strengths of this review include the comprehensive search for eligible studies, systematic and explicit application of eligibility criteria, careful consideration of study quality, and a rigorous analytical approach. The high quality of the evidence on key outcomes increases the strength of inferences. However, all meta-analyses are prone to certain limitations, some of which were evident in the present study. First, despite the comprehensive search strategy, the possibility of publication bias exists. Second, the included studies used small samples, ranging from 40–124 patients per group, and high-quality data from RCTs were insufficient. All the reviewed trials displayed inadequate methodological rigor, as indicated by their lack of and unclear descriptions regarding double-masking and the concealment of patient allocation to different treatment groups (Table 2). Finally, the present study is unable to provide conclusions on the long-term effects of *H pylori* eradication, because only two studies reported results after 1 y, with most patients lost to 1-y follow-up. Although eradication is a permanent measure and its effect should be expected to persist, it seems difficult to predict whether this occurs in the long term. This problem highlights the need for long-term outcome studies on the effects of *H pylori* eradication on ulcer recurrence rates after simple closure of perforated ulcers.

In conclusion, the evidence reviewed in the present meta-analysis indicated the presence of *H pylori* infection in a high proportion of patients with ulcer perforation, and implied that this infection played an important role in ulcer relapse following simple closure of perforated ulcers. Eradication of *H pylori* after simple closure of a perforated ulcer significantly reduces the relapse of ulcers. *H pylori* infection should, therefore, be assessed at operation, and an appropriate eradication therapy should be initiated as soon as possible after confirming its presence.

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