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Special article

Has the Impact of *Helicobacter pylori* Therapy on Ulcer Recurrence in the United States Been Overstated?
A Meta-Analysis of Rigorously Designed Trials

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Objective: **The aim of this study was to assess the effect of *H. pylori* eradication on ulcer recurrence in North American duodenal ulcer patients by examining only treatment studies that met rigorous methodologic criteria.** ***Methods:*** **Data sources were computerized bibliographic searches from 1983, review of reference lists, communication with companies that manufacture medications used for *H. pylori* therapy in the U.S., and *H. pylori* investigators, review of open presentations to the Food and Drug Administration, and review of abstracts from annual scientific meetings. Criteria for study inclusion were double blind, randomized North American trials of *H. pylori* therapy for duodenal ulcer, scheduled endoscopic follow-up exams for ≥6 months, and *H. pylori* cure documented ≥4 wk after completion of therapy by at least two endoscopic biopsy tests. Seven relevant trials were identified. Data were abstracted independently and disagreement was resolved by consensus. We obtained missing data and identified erroneous assessments through contact with an author or sponsor of all studies.** ***Results:*** **The common odds ratio for ulcer recurrence was 0.20 (95% CI, 0.13–0.31) and 2.8 patients would need to be successfully treated to prevent one ulcer recurrence at 6 months. The pooled ulcer recurrence rate at 6 months in patients with *H. pylori* eradication was 20%.** ***Conclusion:*** **Results of North American studies of highest methodological quality confirm that *H. pylori* eradication markedly decreases ulcer recurrence. Nevertheless, 20% of patients in these studies had ulcer recurrence within 6 months, despite successful cure of infection and no reported use of NSAIDs. Non-*H. pylori*, non-NSAID ulcers may be more common in the U.S. than previously believed. (Am J Gastroenterol 1998;93: 1409–1415. © 1998 by Am. Coll. of Gastroenterology)**

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is now recognized to be the most important cause of peptic ulcer disease as well as a risk factor for the development of gastric malignancies (1–3). The advent of antisecretory therapy allowed successful healing of ulcers in most patients. However, ulcer disease has long been recognized to be a chronic disease, and most patients develop a recurrence after healing in the ensuing years (1, 4–6). Multiple studies have shown a large and significant decrease in ulcer recurrence if patients with *H. pylori*-associated ulcers are successfully treated for this infection. Duodenal ulcer recurrence is reported to be ≤6% in the 12 months after therapy (5, 6).

Most studies, however, have been open label trials that have not met rigorous study design criteria. In addition, most studies determining the effect of *H. pylori* eradication on ulcer recurrence are from overseas. Even in trials of excellent design, rates of ulcer healing and *H. pylori* eradication frequently differ in studies from overseas when compared with rates in similar studies in the United States (7–11). We therefore sought to determine the effect of *H. pylori* eradication on ulcer recurrence specifically in a North American population by synthesizing the data solely from studies that met rigorous methodologic criteria.

MATERIALS AND METHODS

Data identification

Two authors (L.L., L.S.G.) separately performed a computerized bibliographic search of published research (Medline, National Library of Medicine, Bethesda, MD) from 1983 onward using the following keyword search strategies: "pylori, ulcer, treatment", "pylori, ulcer, eradication"; "pylori, ulcer, recurrence"; "pylori, double-blind". An additional search was conducted of the above keyword combinations substituting "pyloridis" for "pylori". We also

scanned reference lists of articles obtained and other recent overviews of *H. pylori* therapy to identify additional research not found in the computerized bibliographic database searching.

Strategies to obtain unpublished material included communication with the pharmaceutical companies that manufacture medications used for *H. pylori* therapy in the U.S. (including Abbott Laboratories, Abbott Park, IL; Astra Merck, Wayne, PA; Glaxo Wellcome, Research Triangle Park, NC; Procter & Gamble, Cincinnati, OH; TAP, Deerfield, IL) and investigators in the field of *H. pylori* as well as review of open presentations made to the U.S. Food and Drug Administration. In addition, we reviewed abstracts over the period 1988–1996 from annual meetings of the American Gastroenterological Association, the American College of Gastroenterology, and the European *Helicobacter pylori* Study Group.

Selecting research

We independently reviewed the titles and abstracts of all studies and retrieved all articles that concerned North American randomized, controlled trials. These articles were reviewed and were included in the meta-analysis if they met the following criteria: 1) design: double-blind, randomized trial of therapy for *H. pylori* with regularly scheduled follow-up endoscopy for ≥6 months after completion of therapy; 2) target population: patients with duodenal ulcers documented by endoscopy and *H. pylori* infection documented by endoscopic biopsy who do not use nonsteroidal antiinflammatory drugs (NSAIDs) and who had ulcer healing at posttreatment endoscopy; and 3) outcome measures: *H. pylori* eradication (documented by ≥2 endoscopic biopsy tests performed ≥4 wk after the completion of all medications active against *H. pylori*) and ulcer recurrence (documented by endoscopy). These same criteria were applied independently to information obtained from abstracts and unpublished studies that met the first eligibility screening to make a final selection of the studies to be included in the overview. Because we only included studies that achieved the highest methodologic quality, no methodological quality assessment was performed in this overview.

Data collection

We independently performed data abstraction and disagreement was resolved by consensus. We recorded data in terms of number of patients, and solicited missing or ambiguous data from the authors or sponsors of the studies. We communicated with an author or sponsor of all studies in order to obtain missing information and to identify erroneous assessments. We asked authors or sponsors to provide full information regarding methods and updated results.

Patients with duodenal ulcer and *H. pylori* infection, whose ulcer was documented to be healed and whose *H. pylori* infection was demonstrated to be cured ≥4 wk after therapy, were included in the analysis if they had endoscopic follow-up for 6 months after therapy or they had endoscopic evidence of recurrent ulcer at any time during the 6-month follow-up period.

Data analysis

The odds ratio (OR) was the measure of association used in this meta-analysis. The Breslow-Day method was used to test for homogeneity under the null hypothesis that the ORs were consistent across studies, and the corrected Mantel-Haenszel χ^2 test (1 df, two tailed) was used to test whether the ORs differed systematically from a value of 1. The software used was "OR2x2xka" (McMaster University, Department of Clinical Epidemiology and Biostatistics). A p value <0.05 was considered significant.

A priori, we developed three hypotheses to identify potential differences in treatment across studies. First, we proposed that the rate of ulcer recurrence may be related to type of therapy used. Therefore, we examined clarithromycin *versus* nonclarithromycin-containing regimens (regimens without and with amoxicillin), and ranitidine bismuth citrate (RBC) *versus* non-RBC containing regimens (regimens without and with omeprazole).

Second, we considered that studies which included treatment groups given no active medication (only placebo) might lead to different results from those in which all patients received at least one active agent (for example, investigators might have been more likely to "identify" an ulcer when they knew their patients may have received no active treatment). Therefore, we planned a separate analysis for studies in which some patients received no active medication and studies in which all patients received at least one active agent.

Third, we questioned whether fully published manuscripts might have results that differed systematically from those of studies that were presented only in abstract form or remained unpublished. Hence, we also performed a subgroup analysis for those studies published as a full manuscript and those published only as an abstract or not published.

RESULTS

Study selection

Computerized bibliographic search identified 782 articles for "pylori or pyloridis, ulcer, treatment" search strategy, 579 articles for "pylori or pyloridis, ulcer, eradication", 385 for "pylori or pyloridis, ulcer, recurrence", and 66 for "pylori or pyloridis, double-blind". Overall, seven trials involving patients met the inclusion criteria (12–17). Only one was published fully in a peer-review journal (14), four were published in abstract form (13, 15, 16) (two studies were published together in reference 16), and two were unpublished and obtained from pharmaceutical company sponsors (12, 17). However, corroborative, corrective, or missing information was provided by an author or sponsor for each of the seven trials included in the analysis. Agreement be-

TABLE 1
Design of Randomized, Double Blind North American Trials of H. pylori *Treatment With 6-Months Endoscopic Follow-up*

Study (Ref.)	Medication Arms (wk 1–2)	Medication Arms (wk 3–4)	Criteria for *H. pylori* Cure	Type of Publication
1 (12)	Omeprazole 40 mg *q.d.* Clarithromycin 500 mg *t.i.d.* Omeprazole + Clarithromycin	Omeprazole 20 mg *q.d.* Placebo Omeprazole 20 mg *q.d.*	Histology and culture negative 4–6 wk after end of therapy	Unpublished
2 (13)	Omeprazole 40 mg *q.d.* Clarithromycin 500 mg *t.i.d.* Omeprazole + Clarithromycin	Omeprazole 20 mg *q.d.* Placebo Omeprazole 20 mg *q.d.*	Histology and culture negative 4–6 wk after end of therapy	Abstract
3 (14)	RBC 400 mg *b.i.d.* Clarithomycin 500 mg *t.i.d.* RBC + Clarithromycin Placebo	RBC 400 mg *b.i.d.* Placebo RBC 400 mg *b.i.d.* Placebo	≥ 2 tests (histology, CLOtest, culture) negative, none positive 4 wk after end of therapy	Peer-review journal
4 (15)	RBC 400 mg *b.i.d.* Clarithromycin 500 mg *t.i.d.* RBC + Clarithromycin Placebo	RBC 400 mg *b.i.d.* Placebo RBC 400 mg *b.i.d.* Placebo	≥ 2 tests (histology, CLOtest, culture) negative, none positive 4 wk after end of therapy	Abstract
5 (16)	RBC 400 mg *b.i.d.* Amoxicillin 500 mg *q.i.d.* RBC + Amoxicillin Placebo	RBC 400 mg *b.i.d.* Placebo RBC 400 mg *b.i.d.* Placebo	≥ 2 tests (histology, CLOtest, culture) negative, none positive 4 wk after end of therapy	Abstract
6 (16)	RBC 400 mg *b.i.d.* Amoxicillin 500 mg *q.i.d.* RBC + Amoxicillin Placebo	RBC 400 mg *b.i.d.* Placebo RBC 400 mg *b.i.d.* Placebo	≥ 2 tests (histology, CLOtest, culture) negative, none positive 4 wk after end of therapy	Abstract
7 (17)	Omeprazole 40 mg *b.i.d.* Amoxicillin 500 mg *t.i.d.* Omeprazole + Amoxicillin	Omeprazole 20 mg *q.d.* if symptomatic Placebo if symptomatic Omeprazole 20 mg *q.d.* if symptomatic	≥ 2 tests (histology, CLOtest, culture) negative, none positive 14 wk after end of therapy	Unpublished

RBC, ranitidine bismuth citrate.
All studies had appropriate dummy medications in the monotherapy and no-active-therapy groups to maintain blinding.

tween reviewers for the selection of relevant studies was 100%.

Study characteristics

Selected design details for individual trials are outlined in Table 1. All seven studies employed 2-wk dual therapy for the treatment of *H. pylori* (two used omeprazole plus clarithromycin (12, 13), two used RBC plus clarithromycin (14, 15), two used RBC plus amoxicillin (16), and one used omeprazole plus amoxicillin (17) with comparison to monotherapy treatment groups receiving the components of the dual therapy. In addition, four of the studies also included a group receiving no active medication—*i.e.*, only placebo (14–16). All studies had appropriate dummy medications in the monotherapy and no-active-therapy groups to maintain blinding. In six studies (12–16), patients receiving dual therapy or the nonantibiotic monotherapy (omeprazole or RBC) received an additional 2 wk of anti-ulcer therapy (omeprazole or RBC); placebo was given in the monotherapy antibiotic arms. In one study (17), patients in the dual therapy arm or the omeprazole monotherapy arm received an additional 2 wk of omeprazole therapy only if they were symptomatic; placebo was given to symptomatic patients in the amoxicillin monotherapy arm.

Eradication of *H. pylori* infection was documented by at least two of the following endoscopic biopsy tests: histological examination [Giemsa and Genta stains used in the four RBC studies (14–16), Genta stain in the two omeprazole/clarithromycin studies (12, 13), Giemsa and Warthin-Starry Silver stains used in the omeprazole/amoxicillin study (17)], culture, and rapid ureast test (CLOtest, Delta West Ltd., Perth, Australia). Eradication was assessed 4 wk after completion of therapy (*i.e.*, wk 8) in four studies (14–16), 4–6 wk after the end of therapy (*i.e.*, wk 8–10) in two studies (12, 13), and 14 wk after the end of therapy (*i.e.*, wk 18) in one study (17). Ulcer healing was determined at the end of therapy (4 wk) in six studies (12–16) and at 8 wk in one study (17). Repeat endoscopic examinations with assessment for recurrent ulcers were performed 4–6, 12, and 24 wk after completion of therapy in six studies (12–16) and at 14 and 28 wk after therapy in one study (17).

Ulcers were not healed on the posttreatment endoscopy in 312 (32%) of the 989 *H. pylori*-positive duodenal ulcer patients in the seven studies; these patients were not eligible for evaluation of ulcer recurrence. Of the 619 patients with healed ulcers and posttreatment documentation of *H. pylori* status, 414 were *H. pylori*-positive (21 had received pla-

TABLE 2
Patients Who Dropped Out After Documentation of Ulcer Healing and H. pylori *Status ≥4 wk After End of Therapy*

Study (Ref.)	*H. pylori*-Negative	*H. pylori*-Positive
1 (12)	12/52 (23%)	12/97 (12%)
2 (13)	5/56 (9%)	21/108 (19%)
3 (14)	3/22 (14%)	3/46 (7%)
4 (15)	5/23 (22%)	4/39 (10%)
5 (16)	2/10 (20%)	4/44 (9%)
6 (16)	7/17 (41%)	7/52 (13%)
7 (17)	3/25 (19%)	0/28
Pooled results:	37/205 (18%)	51/414 (12%)

cebo, 316 monotherapy, and 77 dual therapy). Of those cured, 9–41% (pooled value 18%) were lost to follow-up as compared with 0–19% (pooled value 12%; $p = 0.07$) of patients with persistent infection (Table 2).

Ulcer recurrence

Ulcer recurrence was defined in all studies as endoscopic evidence of a break of the mucosa of any size with perceptible depth, without regard to symptoms. Individual study recurrence rates ranged from 8% to 40% for *H. pylori*-negative patients and from 43% to 65% for the *H. pylori*-positive group (Table 3). Despite this apparent variability, the 95% CIs overlapped for all studies within each group. All studies showed that patients whose *H. pylori* infection was cured had a lower rate of ulcer recurrence compared with those in whom infection persisted after therapy. This difference was statistically significant in five of the studies. Only one patient with a recurrent ulcer (16) had evidence of recrudescent or recurrent *H. pylori* infection.

The common odds ratio in this overview for ulcer recurrence in patients with cure of *H. pylori* as compared with those with persistent infection was 0.20 (95% CI, 0.13–0.31). Evidence of significant statistical heterogeneity among studies was not noted. Assuming an ulcer recurrence rate of 56% at 6 months (from our pooled data for ulcer recurrence in patients with persistent *H. pylori* infection) and an odds ratio of 0.20, 2.8 patients would need to be successfully treated to prevent one ulcer recurrence at 6 months.

If we assume that no patient with *H. pylori* eradication who was lost to follow-up had a recurrent ulcer, the pooled recurrence rate would be 16% (33 of 205), rather than 20%. We also performed a "sensitivity analysis" in which we calculated the common odds ratio assuming the worst and best case scenario for drop-outs in each of the seven studies. When we assessed the best case scenario, no patient with *H. pylori* eradication lost to follow-up had a recurrent ulcer, whereas all patients with *H. pylori* persistence lost to follow-up had a recurrent ulcer; the odds ratio was 0.12 (95% CI, 0.08–0.19). In the worst case scenario, all patients with *H. pylori* eradication lost to follow-up had a recurrent ulcer, whereas no patient with *H. pylori* persistence had recurrent ulcer; the common odds ratio was 0.57 (95% CI, 0.40–0.80), although statistical heterogeneity was present ($p = 0.006$). In the most positive scenario in this sensitivity analysis, 2.2 patients would need to be successfully treated to avert one ulcer recurrence at 6 months, and in the most negative scenario 7.3 patients would need to be successfully treated.

Subgroup analyses

Separate subgroup analyses for ulcer recurrence were performed related to types of therapy (omeprazole-based or RBC-based, clarithromycin-based or amoxicillin-based), inclusion of a placebo-only treatment group in the study, and publication status of the study (fully published manuscript *versus* abstract or unpublished). The results of these subgroup analyses are shown in Table 4. Estimates of efficacy were similar in the subgroups tested with widely overlapping confidence intervals, precluding statements about differences associated with the type of therapy, the use of a placebo-only group, or publication status.

DISCUSSION

The purpose of this meta-analysis was to assess the effect of *H. pylori* eradication in North American patients with duodenal ulcer disease on the endoscopic recurrence of ulcers over a 6-month follow-up period, using only studies of the highest methodological quality. Although a meta-analysis does not replace a large scale, well designed, randomized controlled trial, individual studies may be limited by small sample sizes—especially for endpoints with relatively low incidences. By synthesizing all available data, the meta-analysis allows a more precise estimate than can be obtained from the results of any individual study.

A concern about meta-analyses is the fact that studies with varying designs, patient populations, methodological quality, and types of intervention are included together in a single analysis. Ideally, this concern could be overcome by a meta-analysis that included trials of high methodological quality with identical study designs, patient populations, and interventions—analogous to combining data from a multicenter trial in which each center follows the same protocol. Although no meta-analysis can achieve this ideal, our overview included studies that were very similar in design and of the highest methodological quality. The trials we selected had the same patient populations (patients with duodenal ulcers, *H. pylori* infection, and no NSAID use), and nearly identical design (double-blind, randomized studies of dual and monotherapy using multiple endoscopic biopsy tests for diagnosis of *H. pylori* and scheduled endoscopies over 6 months after therapy for assessment of ulcer recurrence). Furthermore, publication bias is unlikely in our meta-analysis because only one study has been published in full manuscript form; most of the data included in our review have not been published but were provided by the authors or sponsors of the studies. The lack of peer review and full publication of the studies also may be considered to weaken

TABLE 3
Ulcer Recurrence Related to H. pylori *Status After Therapy*

Study (Ref.)	*H. pylori*-Negative (%; 95% CI)	*H. pylori*-Positive (%; 95% CI)	Odds Ratio (95% CI)	Risk Difference (95% CI)
1 (12)	13/40 (33%; 19–49%)	51/85 (60%; 49–70%)	0.32 (0.13–0.76)	28% (7–45%)
2 (13)	4/51 (8%; 2–19%)	51/87 (58%; 48–69%)	0.06 (0.13–0.20)	51% (35–59%)
3 (14)	6/19 (32%: 13–57%)	28/43 (65%; 49–79%)	0.25 (0.07–0.89)	34% (3–58%)
4 (15)	3/18 (17%; 4–41%)	15/35 (43%; 26–61%)	0.27 (0.05–1.26)	26% (5–44%)
5 (16)	1/8 (13%; 0.3–53%)	25/40 (63%; 46–77%)	0.09 (0.004–0.83)	50% (5–64%)
6 (16)	4/10 (40%; 12–74%)	20/45 (44%; 30–60%)	0.83 (0.17–4.02)	4% (−33–36%)
7 (17)	2/22 (9%; 1–29%)	12/28 (43%; 24–63%)	0.13 (0.02–0.18)	34% (5–47%)
Pooled Results:	33/168 (20%; 14–26%)	202/363 (56%; 50–61%)		

TABLE 4
Results of Subgroup Analyses: Common Odds Ratios for Patients With H. pylori *Eradication Compared With Patients With Persistent* H. pylori *Infection*

Subgroup	Odds Ratio (95% CI)
Regimens with clarithromycin (N = 4)	0.19 (0.11–0.31)
Regimens with amoxicillin (N = 3)	0.26 (0.11–0.63)
Regimens with RBC (N = 4)	0.30 (0.15–0.59)
Regimens with omeprazole (N = 3)	0.16 (0.09–0.28)
Studies with "placebo only" arm (N = 4)	0.30 (0.15–0.59)
Studies without "placebo only" arm (N = 3)	0.16 (0.09–0.28)
Studies published in full manuscript form (N = 1)	0.25 (0.08–0.79)
Studies in abstract form or unpublished (N = 6)	0.20 (0.12–0.31)

the database. We would like to note that all of these studies were designed for and submitted to the FDA for potential approval of new therapies. Thus, they all met the rigorous standards required for FDA submissions and were fully reviewed by the FDA.

The results of our study clearly confirm that eradication of *H. pylori* infection in patients with duodenal ulcer disease dramatically decreases the chance of recurrent ulcer in the 6 months after completion of therapy; just under three patients with *H. pylori*-associated ulcer need to be successfully treated to prevent one ulcer recurrence.

The most surprising finding in our overview was the unexpectedly high rate of ulcer recurrence in patients who were successfully cured of their infection and who denied taking NSAIDs. A total of 20% of patients had recurrent ulcers within 6 months despite eradication of *H. pylori* infection. This contrasts with the standard teaching that recurrent ulcers should occur in only a small percentage of patients within 6 to 12 months after *H. pylori* eradication. However, most published studies indicating a lower rate of ulcer relapse have been less rigorously designed: *e.g.*, unblinded, less regularly scheduled endoscopies, and fewer diagnostic tests with less stringent criteria for documentation of cure. Furthermore, virtually all studies providing data on ulcer recurrence after *H. pylori* therapy were performed outside the United States. Unexplained differences have been noted repeatedly in comparable studies from inside and outside the U.S. This is best demonstrated by the fact that a number of rigorously designed European trials with study design similar to those in our overview report much lower 6-month ulcer recurrence rates of only 1–6% after *H. pylori* eradication (18–22).

What are potential explanations for higher recurrence rates in these rigorously designed, North American trials? Evidence of recrudescent *H. pylori* infection (*i.e.*, persistent infection that was not diagnosed on the initial posttherapy diagnostic tests) or recurrent infection was present in only one patient with a recurrent ulcer, indicating that this was not an important cause of recurrent ulcers. The use of multiple gastric biopsies from the antrum and body evaluated by histological exam with special stains, rapid urease tests, and culture on repeated endoscopic examinations over a 6-month period make the likelihood of missed *H. pylori* infection very low in these trials.

Unreported NSAID use always must be considered in patients with recurrent ulcers despite cure of *H. pylori* infection. Although patients in these studies denied NSAID use, surreptitious NSAID use is common—at least in patients with refractory ulcers (23). Smoking is also a risk factor for ulcer disease. We did not assess the effect of smoking in our review, but a recent study that included two trials summarized in our review and two additional overseas trials of nearly identical design failed to identify a significant effect of smoking on ulcer recurrence (24). Differences in acid secretion also may play a role in recurrent ulcer disease. Basal and peak acid output are higher in *H. pylori*-positive duodenal ulcer patients than in infected healthy volunteers or uninfected subjects, but 6–12 months after eradication most measures of acid secretion return to the range seen in uninfected controls (25, 26). However, El-Omar *et al*. reported no decrease in maximal acid response to exogenous gastrin 1 yr after cure of the infection (26), indicating a factor other than *H. pylori* influenced acid secretion and the development of duodenal ulcer disease. Furthermore, McColl *et al*. (27) have suggested that a group of patients with idiopathic ulcers have elevated gastrin and acid secretion. Thus, differences between U.S. and overseas populations in genetic factors or environmental factors (*e.g.*, NSAIDs, smoking, other undiscovered infections) predisposing to ulcers possibly may lead to differences in ulcer recurrences rates.

Another potential explanation of the relatively high ulcer

recurrence rate in North America may relate to the fact that the prevalence of *H. pylori* is lower in North America than in many other parts of the world. Kurata and Nogawa demonstrated that the proportion of peptic ulcers that can be attributed to *H. pylori* (attributable risk) decreases as the prevalence of *H. pylori* infection decreases in a population (28). As the prevalence of *H. pylori* infection decreases with each birth generation (29), the absolute number of ulcers also will decrease, inasmuch as *H. pylori* is the most common cause of ulcer disease. As the number of cases of ulcer disease (and *H. pylori* infection) decreases, the proportion of this smaller number of ulcer patients who have non-*H. pylori*-associated ulcer disease will increase. If *H. pylori* infection disappeared, some ulcers would still occur, and, although ulcers would be far fewer in absolute number, the proportion due to *H. pylori* would be zero.

The age-matched prevalence of *H. pylori* infection in the general population is similar in the U.S. and western Europe, raising the question of whether a lower prevalence of *H. pylori* can explain differences between U.S. and western European studies. However, recent U.S. studies have reported *H. pylori* prevalences in duodenal ulcer patients, which are lower than the previously suggested values of ≥90%. Peterson *et al*. (14) found *H. pylori* infection in 136 (74%) of 185 patients with duodenal ulcer, whereas Lanza *et al*. (15) reported *H. pylori* in only 129 (70%) of 183 duodenal ulcer patients.

A potential concern with the studies reviewed, despite their excellent methodological criteria, is the relatively high rate of patient drop-out between posttreatment assessment of *H. pylori* status and the final endoscopic evaluation. Although not surprising in a long-term endoscopic study, these drop-outs potentially could confound the applicability of the results. However, even if we assume that not one of the patients with *H. pylori* eradication who was lost to follow-up developed a recurrent ulcer, the rate of recurrence at 6 months is still 16%—a value higher than suggested by other original articles and reviews.

Could the high number of patients lost to follow-up have confounded the results by indicating a significant or larger benefit from *H. pylori* eradication than is really true? If we assume that all patients with *H. pylori* eradication who were lost to follow-up had a recurrent ulcer and no drop-outs with persistent infection developed a recurrent ulcer, *H. pylori* eradication still is clearly beneficial (odds ratio 0.57, 95% CI, 0.40–0.80), although the number needed to treat to avert one ulcer recurrence at 6 months is higher, at 7.3 patients.

Rates of eradication in the studies assessed were lower than those that can be achieved in clinical practice because of the use of inactive treatment arms, relatively ineffective monotherapies, and modestly effective dual therapies. However, the type of therapy should not explain a higher rate of recurrence in our overview because our endpoint was *H. pylori* eradication based on multiple biopsies and multiple diagnostic tests.

Most of the patients who had persistent *H. pylori* infection had received monotherapies or dual therapies that suppress *H. pylori* infection. Monotherapy with all of the agents used produces apparent clearance of *H. pylori* on diagnostic testing immediately after therapy, despite evidence of persistent infection 4 wk later. Furthermore, clarithromycin, the most potent single agent available against *H. pylori* leads to ulcer healing in a majority of patients (12, 13) despite failure to cure the infection in most patients and a lack of other known ulcer-healing properties. Thus, the rate of ulcer recurrence at 6 months in the patients with persistent *H. pylori* infection conceivably could have been an underestimate of recurrent ulcer disease due to the suppressive effects of therapy even in patients with unsuccessful treatment. However, subgroup analysis of patients in trials including clarithromycin-containing regimens *versus* those in trials without clarithromycin revealed comparable results.

In conclusion, eradication of *H. pylori* in North American patients with duodenal ulcer disease significantly decreases ulcer recurrence: the odds of developing a recurrent ulcer if *H. pylori* infection persists is five times greater than the odds of recurrence if *H. pylori* infection has been cured. However, pooled results from studies of the highest methodological quality reveal that about 20% of patients will develop a recurrent ulcer within 6 months after therapy. Although knowledge of *H. pylori* has led to a revolution in our managment of ulcer disease and, overall, patients with *H. pylori*-associated ulcer disease will benefit greatly from antibacterial therapy, a significant minority of patients fail to be cured of their ulcer disease despite eradication of *H. pylori*.

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