ORIGINAL INVESTIGATION

One-Day Quadruple Therapy Compared With 7-Day Triple Therapy for *Helicobacter pylori* Infection

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Background: Eradication of *Helicobacter pylori* infection has had an impact on the treatment and recurrence rates of peptic ulcer disease and malignancies such as mucosa-associated lymphoid tissue lymphoma. Treatment options are cumbersome, expensive, and associated with side effects.

Methods: Randomized, prospective, open-labeled equivalence trial with a parallel-group design to compare eradication rates of *H pylori* with a 1-day, 4-drug regimen with a 7-day, 3-drug regimen. A total of 160 patients with dyspepsia and a Glasgow Dyspepsia Severity Score of at least 3 had a urea breath test labeled with carbon 14. Patients who tested positive were randomized to 1 of the 2 study groups. The study was designed to test the therapeutic equivalence of 1-day and 7-day regimens based on the percentage of *H pylori* eradication in each group at 5 weeks.

Results: The 1-day treatment group (n=80) had a slightly higher eradication percentage (95%) than the 7-day group (90%). The possible inferiority of the 1-day treatment relative to the 7-day treatment, a 15% difference in the number of patients whose infection was not eradicated at 5 weeks, was rejected ($P<.001$; 90% confidence interval, 2.7%-11%). Both groups demonstrated a mean decrease of 7.5 points in the Glasgow Dyspepsia Severity Score. The 2 groups showed no significant differences in side effects. Patients whose treatment failed (4 in the 1-day treatment group and 7 in the 7-day treatment group) were retreated for 10 days. One patient from the 7-day treatment group still tested positive after the second treatment.

Conclusions: The 1-day treatment proved to be statistically similar to the 7-day treatment for the eradication of *H pylori* in patients with dyspepsia and a positive urea breath test. Further evaluation will be necessary to determine whether the 1-day regimen is adequate for patients with peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, or gastric adenocarcinoma.

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SINCE MARSHALL[1] and Warren[2] first described *Helicobacter pylori* in 1983, the observation that linked infection with this organism to gastritis and peptic ulcer disease has been extended. Despite recent reports of a decline in the prevalence of *H pylori* among patients with active ulcers, the association remains consistent.[1-8]

The eradication of *H pylori* infection in patients with peptic ulcer disease has been proven to be a cost-effective method to reduce ulcer recurrence rates and complications.[9-16] *Helicobacter pylori* is a well-described risk factor for the development of gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma, which have high rates of remission when treated in their early stages. It is also believed that treatment might prevent the progression of gastric metaplasia.[17-22] Treatment of *H pylori* infection is currently accepted for patients with dyspepsia, even though dyspepsia and gastroesophageal reflux symptoms may worsen after *H pylori* eradication.[23-27]

Multiple therapies to eradicate *H pylori* are available, and combinations have higher eradication rates than single-antibiotic regimens. Earlier therapies lasted up to 21 days and included up to 4 different medications. These therapies produced undesirable side effects such as nausea, vomiting, and diarrhea, which negatively affected compliance and, therefore, eradication rates.[26,28,29]

Shorter, triple-drug regimens have been developed, consisting of a proton-pump inhibitor (PPI), clarithromycin, and another antibiotic—typically, amoxicillin or metronidazole—given twice a day (bid). Fourteen-day, bid triple-drug regimens yield eradication rates of more than

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90%, but at a greater cost than shorter treatments and with adverse side effects.[30-34]

Seven-day, bid triple-drug regimens were shown to be as effective as 14-day regimens. They are recommended as first-time therapy by the European and Canadian *Helicobacter pylori* Consensus Conference because they produce high eradication rates, less severe side effects, and therefore good compliance.[28,32] To achieve successful eradication of *H pylori*, an ideal therapy should be as simple and cost-effective as possible, and have minimal side effects.[7,28]

There are several studies of shorter therapies—lasting less than 1 week—for the eradication of *H pylori*. Two nonrandomized, uncontrolled studies consisting of a single-day treatment for *H pylori* infection demonstrated eradication rates greater than 72%.[33-42] A randomized study comparing a 7-day triple therapy with a 1-day quadruple therapy was stopped when interim analysis showed very poor (20%) eradication rates for the 1-day group.[39] One-day therapeutic protocols, to our knowledge, have not been published in the United States. This equivalence trial compares eradication rates of a 1-day, 4-drug treatment with a 7-day, 3-drug treatment.

METHODS

STUDY DESIGN

This study is a randomized, prospective, open-label equivalence trial with a parallel-group design. Patients with dyspepsia and *H pylori* infection were included if they had a positive urea breath test labeled with carbon 14 (^{14}C-UBT) and a Glasgow Dyspepsia Severity Score (GDSS) above 2. They were identified during scheduled visits to the ambulatory internal medicine clinics of the Northeastern Ohio Universities College of Medicine Affiliated Hospitals at Canton (the Aultman Hospital and the Mercy Medical Center).

PATIENT SELECTION

Patients with dyspepsia symptoms were assessed with the GDSS, a validated tool for evaluating the severity and frequency of symptoms. This simple and rapidly administered test includes 8 items, with a maximum score of 20. Resolution of dyspepsia is considered to be successful if the GDSS decreases to less than 3.[43]

Patients were selected for a ^{14}C-UBT only if their GDSS scores were 3 or higher. This test is an inexpensive and reliable alternative to endoscopy plus biopsy and histological examination or to the CLO test.[40] We used the microCOUNT Model 9605 Liquid Scintillation Counter (Tri-Med Specialties Inc, Draper, Utah) for urea breath testing. Patients received an oral capsule of urea in which ^{12}C was replaced with radioactive ^{14}C (the exposure is less than for a chest radiography). The urea split by *H pylori* urease produces carbon dioxide and ammonia; the isotopes diffuse into the bloodstream and are expelled by the lungs as carbon dioxide C 14, which is qualitatively measurable. Measurements were taken 20 minutes after ingestion of the urea capsule to prevent a false-positive result due to oral flora. The patients were not taking antibiotics, bismuth, or acid-suppressive medications to avoid a false-negative result.[44-49]

Inclusion criteria were dyspepsia, a GDSS of 3 or higher, and a positive ^{14}C-UBT. Exclusion criteria included previous treatment of *H pylori* infection, pregnancy, age less than 18 years, personal or family history of gastrointestinal malignancy, antibiotic therapy in the previous 6 weeks, previous gastric surgery, hepatic insufficiency (Child-Pugh class B or C), creatinine clearance of less than 20 mL/min, use of a PPI in the previous 2 weeks, allergy to any of the medications included in the protocol, and danger signs or symptoms such as dysphagia, weight loss, or bleeding that would indicate a need for endoscopy.

TREATMENT GROUPS

Eligible patients signed an informed consent form approved by the institutional review board of both hospitals and were randomized to 1 of 2 study groups. The treatment group received a 1-day regimen consisting of two 262-mg tablets of bismuth subsalicylate 4 times daily (qid); of one 500-mg tablet of metronidazole qid; of 2 g of amoxicillin suspension qid; and of two 30-mg tablets of lansoprazole once daily. The control group received a 7-day regimen that included one 500-mg tablet of clarithromycin bid; two 500-mg tablets of amoxicillin bid; and one 30-mg tablet of lansoprazole bid.

All patients were asked to avoid antibiotics and acid suppression medications until a second ^{14}C-UBT was performed 5 weeks after termination of therapy. Eradication of infection with *H pylori* was defined as a negative ^{14}C-UBT 5 weeks after treatment. Patients in either group who had a positive second ^{14}C-UBT were treated for 10 days with 500 mg of clarithromycin bid, 1 g of amoxicillin bid, 30 mg of lansoprazole bid, and 524 mg of bismuth subsalicylate qid. The ^{14}C-UBT was repeated 5 weeks later. Side effects were identified using a questionnaire administered to patients after they finished the prescribed therapy, and patient compliance was assessed by direct pill counts. The GDSS was administered after therapy as well.

STATISTICAL METHODS

The trial was designed to test the therapeutic equivalence of 1-day and 7-day treatments based on the proportion of patients in each group whose *H pylori* infection was eradicated at 5 weeks.[50] An equivalence trial was appropriate because eradication with the 7-day treatment is reported to be approximately 90%, which might be difficult to improve on.[50,51] The sample size of 80 patients per group provided 90% power to reject the inferiority of the 1-day treatment at $\alpha = .05$. It was assumed in the sample size calculation that the 7-day treatment would eradicate *H pylori* in 90% of patients. A difference of 15% in the number of patients with eradication in the 1-day group at the 5-week follow-up visit was considered the threshold of inferiority. A 1-sided confidence interval (CI) for the difference between the groups is the standard for equivalence trials such as this one because it protects the nominal α level.[52] Other analyses compared GDSS scores at 5 weeks, adjusted for baseline differences between groups, and compared reported side effects with CIs.

RESULTS

Subjects with a GDSS score of at least 3 and a positive ^{14}C-UBT were recruited from August 1998 to December 2000. Of the 160 patients enrolled, 10 patients (3 from the 1-day and 7 from the 7-day group) did not return for the 5-week ^{14}C-UBT. **Table 1** provides a comparison of the 1-day and 7-day groups at baseline for GDSS, sex, and age. The 95% CIs indicate no significant baseline differences between the groups regarding GDSS, sex, and alcohol use (the 95% CIs include zero). Patients were slightly older in the 7-day group than in the 1-day group.

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Table 1. Patient Characteristics at Baseline

Variable	Treatment Group: 7-Day (n = 80)	Treatment Group: 1-Day (n = 80)	95% CI for Difference Between the Groups
GDSS, mean (SD)	10 (3.3)	11 (3.4)	–0.1 to 2
Sex, % women	59	55	–11 to 2
Age, mean (SD), y	53 (16)	46 (12)	–11 to –3
History of smoking, %	12	34	8 to 35
Current alcohol consumption, %	52	52	–16 to 16
African American, %	14	16	–10 to 13

Abbreviations: CI, confidence interval; GDSS, Glasgow Dyspepsia Severity Score.

Table 2. Eradication Percentages and GDSS Scores by Group at 5-Week Follow-up

Variable	Treatment Group: 7-Day (n = 73)	Treatment Group: 1-Day (n = 77)	1-Sided CI for Difference Between the Groups
Eradication, % (No.)	90 (66)	95 (73)	–2.7%
GDSS change from baseline, mean (SD)*	–7.5 (3.2)	–7.5 (3.5)	1.3

*The 5-week Glasgow Dyspepsia Severity Score (GDSS) means were 2.8 for the 7-day and 3.8 for the 1-day treatment group. Note in Table 1 that the mean for the 1-day group is 1.0 higher than for the 7-day group at baseline.

Table 3. Percentage of Patients Reporting Side Effects by Group

Side Effect	Treatment Group: 7-Day (n = 73)	Treatment Group: 1-Day (n = 77)	95% CI for Difference Between the Groups
Diarrhea	7	12	–5 to 14
Stool discoloration	1	5	–2 to 10
Nausea	26	14	–25 to 1
Dizziness	1	1	–4 to 4
Metallic taste	4	6	–5 to 10
Loss of appetite	0	4	–0.6 to 8
Abdominal pain	4	1	–8 to 2
Headache	3	3	–5 to 5
Yeast infection	3	1	–6 to 3
Constipation	1	0	–4 to 1

Abbreviation: CI, confidence interval.

Statistical adjustments were made for all differences between groups in patient characteristics.

ERADICATION PERCENTAGE

The 1-day treatment had a higher eradication percentage (95%) than the 7-day treatment (90%). According to our primary hypothesis test, the inferiority (a difference in rates ≥15%) of the 1-day treatment relative to the 7-day treatment was rejected at $P<.001$. **Table 2** includes percentages of patients in each group whose ^{14}C-UBT was negative at the 5-week evaluation. Table 2 also provides the lower limit of the 90% CI on the difference between the 1-day and the 7-day groups. The –2.7% value is at the border of remaining consistent with these data, which allows the conclusion that, for a population similar to the one included in this study, the deficit in percentage of eradication in a 1-day treatment group, compared with a 7-day treatment group, would not be more than 2.7%. It is even possible that the 1-day treatment is superior to the 7-day treatment. (The upper limit of the CI on the difference indicates that the 1-day treatment is not more than 11% superior to the 7-day treatment; however, this study was not designed to test the superiority of the 1-day treatment, and it should be noted that it was not significantly superior.) Table 1 shows that the 7-day group was older, but that fewer patients in that group had a history of smoking. After adjusting for age and differences between the groups in sex, alcohol use, race, and history of smoking using a logistic regression model, it was found that the baseline differences had minimal impact on the results. The adjusted difference was 4% and the unadjusted difference was 4.5% in favor of the 1-day treatment. Table 2 also provides the change from baseline in GDSS scores. Both groups demonstrated a mean decrease of 7.5 percentage points.

SECONDARY ANALYSIS

None of the patients in either group expressed intolerance to their assigned treatment. None were grossly noncompliant with their treatment (ie, no 1-day patient crossed to the 7-day group or vice versa). Although intention-to-treat analyses are commonly used in superiority trials, they are inappropriate in equivalence trials because they bias toward equivalence.[50] This issue did not arise in our study because all participants remained on their assigned treatment. Side effects (**Table 3**) were surveyed at the 5-week ^{14}C-UBT. They included diarrhea, stool discoloration, nausea, dizziness, metallic taste in the mouth, loss of appetite, abdominal pain, headache, yeast infections, and constipation. Slightly more patients from the 7-day group (37%) than from the 1-day group (30%) said they experienced at least 1 of these side effects, but the difference was not significant. The 95% CIs on the difference did not reveal any significant differences between the 2 groups. Because side effects could have been associated with greater noncompliance in the 7-day treatment group, a search was done for a negative association between fewer side effects and eradication, and none was found (odds ratio, 0.9; $P=.9$). Adjusting for side effects had no impact on the positive difference observed between 1-day and 7-day eradication percentages.

TREATMENT FAILURES

Treatment was unsuccessful for 4 patients in the 1-day treatment group and 7 patients in the 7-day treatment group. Of the 4 patients in the 1-day treatment group who were subsequently treated with the 10-day course, 1 did not return for the second 5-week ^{14}C-UBT and the other 3 tested negative. Of the 7 patients in the 7-day treatment group, 1 had a positive result at the second follow-up ^{14}C-UBT but refused endoscopic evaluation or further therapy.

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COMMENT

To successfully eradicate *H pylori* infection, the use of combination regimens known to have an acceptably high cure rate is vital. Therapies to treat *H pylori* infection should produce eradication rates of at least 90%.[26,30,33,53] Furthermore, when developing a treatment plan, compliance, adverse reactions, and cost are additional factors that need to be considered.

Current regimens use a combination of 2 antibiotics with 1 or 2 nonantibiotic adjunctive agents. Fourteen-day, bid triple therapy regimens almost uniformly produce eradication rates higher than 90%, but these regimens are expensive and adverse effects such as nausea and diarrhea are common.[33,53-65] Lind et al[55] demonstrated in the MACH (Metronidazole Amoxicillin Clarithromycin *Helicobacter pylori*) I study that a 7-day bid triple-therapy regimen achieves similar and acceptable results. This led to the Maastricht Consensus Report and the Canadian *Helicobacter pylori* Consensus Conference recommending a triple therapy consisting of a PPI, amoxicillin, plus 1 of 2 other antibiotics (clarithromycin or metronidazole) as first-line therapy to treat *H pylori* infection.[28,32] This regimen achieves an eradication rate higher than 80% with intention-to-treat analysis and higher than 90% per protocol, at a lower cost.[30,53,55-65]

Quadruple therapies lasting 7 to 14 days that include a bismuth compound produce excellent eradication rates, but these regimens are relegated to second-line therapy because their complex dosing schedule and less tolerable side-effect profiles decrease compliance.[26,66-68]

Shorter therapies achieving eradication rates similar to those of 7- or 14-day treatments would be desirable to ensure patient compliance. Short therapies could only be recommended if they produced an acceptable eradication rate, and if patients subsequently tested negative for *H pylori*.[33] The short therapies that have produced acceptable cure rates (up to 96%) have combined a bismuth salt, a PPI, and 2 antibiotics. Some of the regimens included a PPI for a longer time (up to 14 days) than the antibiotics.[33,35-38,54,56,69-77] Eradication is confirmed on long-term follow-up when short therapies are used.[54]

Three European studies have addressed eradication using a single-day quadruple drug regimen. Tucci et al[41] first achieved an eradication rate of 72%, and Takats et al[42] then reported eradication in 76.5% of patients with duodenal ulcer and 83% of patients with dyspepsia. The randomized study by Wermeille et al,[39] published after the initiation of our study, showed very poor eradication rates for their 1-day therapy group.

Amoxicillin is an antibiotic to which *H pylori* is sensitive in vitro, but has little impact when used in vivo as monotherapy at usual doses. However, when this antibiotic is used in high doses, only a short gastric contact time is needed to kill *H pylori*. Metronidazole is actively secreted into gastric juice and saliva, and its activity is independent of pH. Resistance to metronidazole can be avoided when it is given in combination with bismuth salicylate, a topical antimicrobial agent that directly disrupts the bacterial cell wall. Finally, PPIs increase intragastric pH, may enhance the effectiveness of the local immune response, reduce the mucosal washout of antibiotics, and may have bactericidal activity.[3,12,21,30,31,55,63,65,72,76]

The ^{14}C-UBT is accepted as the noninvasive gold standard to diagnose *H pylori* infection, with reported sensitivity of more than 90% and specificity of more than 95%.[26,30,47-49] Shorter therapies have been criticized because of the possibility of suppression without eradication of *H pylori*, leading to false-negative ^{14}C-UBT or histological findings, and there are concerns that sensitivity could drop to 90% in the follow-up ^{14}C-UBT. Even though it has been demonstrated that 14 days off PPI will eliminate the false-negative rate, we elected to wait 5 weeks to repeat the ^{14}C-UBT.[4,66,77,78] Noninvasive tests for *H pylori*, including serum antibody tests and carbon 14–labeled breath tests, are reportedly as accurate in diagnosing the presence of *H pylori* as invasive tests.[28,40,79,80] The ^{14}C-UBT is an ideal test as it is accurate, cost-effective, and 3 to 4 times less expensive than invasive testing.[40,44,79,81]

An important consideration is the significantly lower cost of the 1-day regimen ($32), vs the 7-day regimen of the control group ($182). Eradication was achieved in 9 (82%) of 11 patients for whom initial therapy was not successful (subsequent therapy was not successful in 1 patient, and 1 patient did not have the follow-up ^{14}C-UBT). Quadruple therapy, typically including bismuth, is very efficacious to treat patients for whom triple therapy has failed. Acceptable eradication rates have been achieved in as few as 7 days of quadruple therapy.[80-84]

The GDSS was used to evaluate the severity of symptoms before and after therapy. There was a substantial decline in severity in both groups relative to baseline, but the mean scores were still above normal. This is consistent with other studies demonstrating the modest benefit of *H pylori* eradication in dyspepsia.[26,27]

The results observed in the present study demonstrate that eradication of *H pylori* infection can be achieved with a short-treatment regimen at a mean ± SD success rate of 95% ± 2.5%, a rate similar to those of longer combination therapies. The approach to *H pylori* eradication reported in this study is cost-effective, promotes patient compliance, and could simplify the role of primary care physicians in the treatment of *H pylori* infection. We advocate posttreatment testing in patients in whom eradication confirmation is desirable, eg, patients with persistent symptoms or a history of peptic ulcer disease.

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REFERENCES

1. Marshall BJ, Warren JR. Unidentified curved bacilli on gastric epithelium in active chronic gastritis [letter]. *Lancet.* 1983;1:1273-1275.
2. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet.* 1984;1:1311-1315.
3. Megraud F. Duodenal ulcer disease: a new infectious disease. *Eur J Gastroenterol Hepatol.* 1993;5(suppl):S17-S22.
4. Peterson WL, Fendrick AM, Cave DR, Peura DA, Garabedian-Ruffalo SM, Laine L. *Helicobacter pylori*-related disease: guidelines for testing and treatment. *Arch Intern Med.* 2000;160:1285-1291.
5. Laine L, Hopkins RJ, Girardi LS. Has the impact of *Helicobacter pylori* therapy on ulcer recurrence in the United States been overstated? a meta-analysis of rigorously designed trials. *Am J Gastroenterol.* 1998;93:1409-1415.
6. Graham DY. Therapy of *Helicobacter pylori*: current status and issues. *Gastroenterology.* 2000;118(suppl):S2-S8.
7. Graham DY, Lew GM, Malaty HM, et al. Factors influencing the eradication of *Helicobacter pylori* with triple therapy. *Gastroenterology.* 1992;102:493-496.
8. Graham DY. The only good *Helicobacter pylori* is a dead *Helicobacter* pylori. *Lancet.* 1997;349:1020-1022.
9. Graham DY, Lew GM, Klein PD, et al. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer: a randomized, controlled study. *Ann Intern Med.* 1992;116:705-708.
10. Hopkins RJ, Girardi LS, Turney EA. Relationship between *Helicobacter pylori* eradication and reduced duodenal and gastric ulcer recurrence: a review. *Gastroenterology.* 1996;110:1244-1252.
11. Imperiale TF, Speroff T, Cebul RD, McCullough AJ. A cost analysis of alternative treatments for duodenal ulcer. *Ann Intern Med.* 1995;123:665-672.
12. Hunt RH. Eradication of *Helicobacter pylori* infection. *Am J Med.* 1996;100 (suppl):42S-50S.
13. Hunt RH, Sumanac K, Huang JQ. Review article: should we kill or should we save *Helicobacter pylori*? *Aliment Pharmacol Ther.* 2001;15(suppl 1):51-59.
14. Graham DY. Can therapy even be denied for *Helicobacter pylori* infection? *Gastroenterology.* 1997;113(suppl):S113-S117.
15. Macri G, Milani S, Surrenti E, Passaleva MT, Salvadori G, Surrenti C. Eradication of *Helicobacter pylori* reduces the rate of duodenal ulcer rebleeding: a long term follow-up study. *Am J Gastroenterol.* 1998;93:925-927.
16. Vergara M, Casellas F, Saperas E, et al. *Helicobacter pylori* eradication prevents recurrence from peptic ulcer haemorrhage. *Eur J Gastroenterol Hepatol.* 2000; 12:733-737.
17. Sung JJ, Lin SR, Ching JY, et al. Atrophy and intestinal metaplasia one year after cure of *H pylori* infection: a prospective, randomized study. *Gastroenterology.* 2000;119:7-14.
18. Wotherspoon AC. Gastric lymphoma of mucosa-associated lymphoid tissue and *Helicobacter pylori. Annu Rev Med.* 1998;49:289-299.
19. Kaore SB, Kurhade GA, Phatak MS. Role of *Helicobacter pylori* in gastric pathophysiology: a review. *Indian J Med Sci.* 1997;51:432-435.
20. Vakil N. The cost of diagnosing *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 2001;15:10-15.
21. Rubin G, Meineche-Schmidt V, Roberts A, Childs S, deWit N. The management of *Helicobacter pylori* infection in primary care: guidelines from the ESPCG. *Eur J Clin Pract.* 1999;5:98-104.
22. Genta RM, Rugge M. Pre-neoplastic states of the gastric mucosa: a practical approach for the perplexed clinician. *Aliment Pharmacol Ther.* 2001;15:43-50.
23. American Gastroenterological Association Medical Position Statement: evaluation of dyspepsia. *Gastroenterology.* 1998;114:579-581.
24. Howden CW, Hunt RH. Guidelines for the management of *Helicobacter pylori* infection. *Am J Gastroenterol.* 1998;93:2330-2337.
25. National Institutes of Health. *Helicobacter pylori in Peptic Ulcer Disease.* Vol 12. Bethesda, Md: US Dept of Health and Human Services. 1994:1-23 NIH Consensus Statement.
26. Blum AL, Talley NJ, O'Morain C, et al. Lack of effect of treating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med.* 1998;339:1875-1881.
27. McColl K, Murray L, El-Omar E, et al. Symptomatic benefit from eradicating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med.* 1998; 339:1869-1874.
28. Malfertheiner P, Graud F, O'Morain C, et al. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht 2-2002 consensus report. *Aliment Pharmacol Ther.* 2002;16:167-180.
29. Goodwin CS. Antimicrobial treatment of *Helicobacter pylori* infection. *Clin Infect Dis.* 1997;25:1023-1026.
30. Yamamoto I, Fukuda Y, Okui M, Tamura K, Shimoyama T. Proton pump inhibitors for *Helicobacter pylori* eradication in patients with peptic ulcer disease. *J Clin Gastroenterol.* 1995;20(suppl):S38-S42.
31. Vogt K, Hahn H. Bactericidal activity of lansoprazole versus omeprazole in vitro. *Gut.* 1996;39(suppl):S9-S10.
32. Hunt R, Thomson AB. Canadian *Helicobacter pylori* consensus conference. *Can J Gastroenterol.* 1998;12:31-41.
33. Lai JY, De Boer WA, Driessen WM, Geuskens LM. Long-term follow-up after cure of *Helicobacter pylori* infection with 4 days of quadruple therapy. *Aliment Pharmacol Ther.* 1996;10:645-650.
34. di Mario F, Battaglia F, Dal Bo N, et al. Cure of *Helicobacter pylori*-positive active duodenal ulcer patients: a double-blind, multicentre, 12-month study comparing a two-week dual vs a one-week triple therapy. *Dig Liver Dis.* 2000;32:116-118.
35. Treiber G, Wittig J, Ammon S, Walker S, van Doorn LJ, Klotz U. Clinical outcome and influencing factors of a new short-term quadruple therapy for *Helicobacter pylori* eradication: a randomized controlled trial (MACLOR study). *Arch Intern Med.* 2002;162:153-160.
36. Nagahara A, Miwa H, Yamada T, Kurosawa A, Ohkura R, Sato N. Five-day proton pump inhibitor-based quadruple therapy regimen is more effective than 7-day triple therapy regimen for *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 2001;15:417-421.
37. Wong BC, Wang WH, Wong WM, et al. Three-day lansoprazole quadruple therapy for *Helicobacter pylori*-positive duodenal ulcers: a randomized controlled study. *Aliment Pharmacol Ther.* 2001;15:843-849.
38. Calvet X, Comet R, Campo R, Brullet E. Four-day, twice daily, quadruple therapy for amoxicillin, clarithromycin, tinidazole and omeprazole to cure *Helicobacter pylori* infection: a pilot study. *Helicobacter.* 2000;5:52-59.
39. Wermeille J, Cunningham M, Armenian B, et al. Failure of a 1-day high-dose quadruple therapy for cure of *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 1999;13:173-1737.
40. Romagnuolo J, Schiller D, Bailey RJ. Using breath tests wisely in a gastroenterology practice: an evidence-based review of indications and pitfalls in interpretation. *Am J Gastroenterol.* 2002;97:1113-1126.
41. Tucci A, Corinaldesi R, Stanghellini V, et al. One-day therapy for treatment of *Helicobacter pylori* infection. *Dig Dis Sci.* 1993;38:1132-1136.
42. Takats A, Racz I, Boga B, Gero G. Efficacy of a "one-day triple therapy" with potentialization of omeprazole for eradication of *Helicobacter pylori. Am J Gastroenterol.* 1994;89:1399.
43. El-Omar EM, Banerjee S, Wirz A, McColl KEL. The Glasgow Dyspepsia Severity Score: a tool for the global measurement of dyspepsia. *Eur J Gastroenterol Hepatol.* 1996;8:967-971.
44. de Boer WA. Diagnosis of *Helicobacter pylori* infection. *Scand J Gastroenterol Suppl.* 1997;223:35-42.
45. Atherton JC. Non-endoscopic methods for the diagnosis of *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 1997;11:11-20.
46. Lewis JD, Kroser J, Bevan J, Furth EE, Metz DC. Quantitative noninvasive testing for *Helicobacter pylori* does not predict gastroduodenal ulcer disease. *Gastrointest Endosc.* 1996;44:679-682.
47. Katelaris PH, Jones DB. Testing for *Helicobacter pylori* infection after antibiotic treatment. *Am J Gastroenterol.* 1997;92:1245-1247.
48. Stubbs JB, Marshall BJ. Radiation dose estimates for the carbon-14-labeled urea breath test. *J Nucl Med.* 1993;34:821-825.
49. Chey WD. Accurate diagnosis of *Helicobacter pylori*: 14C-urea breath test. *Gastroenterol Clin North Am.* 2000;29:895-902.
50. Blackwelder W. Equivalence trials. In: Armitage P, Colton T, eds. *Encyclopedia of Biostatistics.* New York, NY: Wiley; 1998.
51. Farrington CP, Manning C. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk differences or non-unity relative risk. *Stat Med.* 1990;9:1447-1454.
52. Barker L, Rolka H, Rolka D, Brown C. Equivalence testing for binomial random variables: which test to use? *J Am Stat.* 2001;44:279-287.
53. Moayyedi P, Langworthy H, Shanahan K, et al. Comparison of one or two weeks of lansoprazole, amoxicillin and clarithromycin in the treatment of *Helicobacter pylori. Helicobacter.* 1996;1:71-74.
54. de Boer WA, van Etten RJ, Schade RW, et al. One-day intensified lansoprazole-quadruple therapy for cure of *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 1997;11:109-112.
55. Lind T, Veldhuyzen van Zanten S, Unge P, et al. Eradication of *Helicobacter pylori* using one-week triple therapies combining omeprazole with two antimicrobials: the MACH I study. *Helicobacter.* 1996;1:138-144.
56. Lind T, Megraud F, Unge P, et al. The MACH2 study: role of omeprazole in eradication of *Helicobacter pylori* with 1-week triple therapies. *Gastroenterology.* 1999; 116:248-253.
57. Bazzoli F, Zagari RM, Fossi S, et al. Short-term low-dose triple therapy for the eradication of *Helicobacter pylori. Eur J Gastroenterol Hepatol.* 1994;6:773-777.
58. Labenz J, Stolte M, Ruhl GH, Becker T, et al. One-week low-dose triple therapy for the eradication of *Helicobacter pylori* infection. *Eur J Gastroenterol Hepatol.* 1995;7:9-11.

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59. Bell GD, Powell KU, Burridge SM, et al. Rapid eradication of *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 1995;9:41-46.
60. de Boer WA, van Etten RJ, Coremans A, Schneeberger PM. Two-day 'weekend' lansoprazole-quadruple therapy for *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 1998;12:77-81.
61. Byrne MF, Murray FE. Current views on *Helicobacter pylori* eradication therapy. *Ir Med J.* 1998;91:8-10.
62. Laine L, Estrada R, Trujillo M, et al. Once-daily therapy for *H pylori* infection: a randomized comparison of four regimens. *Am J Gastroenterol.* 1999;94:962-966.
63. Laine L, Suchower L, Frantz J, Connors A, Neil G. Twice-daily, 10-day triple therapy with omeprazole, amoxicillin and clarithromycin for *Helicobacter pylori* eradication in duodenal ulcer disease: results of three multicenter, double-blind, United States trials. *Am J Gastroenterol.* 1998;93:2106-2112.
64. Bhasin DK, Sharma BC, Ray P, Pathak CM, Singh K. Comparison of seven and fourteen days of lansoprazole, clarithromycin, and amoxicillin therapy for eradication of *Helicobacter pylori*: a report from India. *Helicobacter.* 2000;5:84-87.
65. Calvet X, Garcia N, Lopez T, Gisbert JP, Gene E, Roque M. A meta-analysis of short versus long therapy with a proton pump inhibitor, clarithromycin and either metronidazole or amoxycillin for treating *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 2000;14:603-609.
66. de Boer WA. Quadruple therapy: first- or second-line anti-*Helicobacter pylori* therapy? *Res Clin Forums.* 1998;20:43-47.
67. Seppala K, Kosunen TU, Nuutinen H, et al. Cure of *Helicobacter pylori* infection after failed primary treatment: one-center results from 120 patients. *Scand J Gastroenterol.* 2000;35:929-934.
68. Baena-Diaz JM, Lopez-Mompo C, Rams-Rams F, Garcia-Lareo M, Hernandez-Ibanez RM, Teruel-Gila J. Efficacy of a multistep strategy for *Helicobacter pylori* eradication: quadruple therapy with omeprazole, metronidazole, tetracycline and bismuth after failure of a combination of omeprazole, clarithromycin and amoxicillin. *Med Clin (Barc).* 2000;115:617-619.
69. Tucci A, Poli L, Paparo GF, et al. Weekend therapy for *Helicobacter pylori* infection. *Am J Gastroenterol.* 1998;93:737-742.
70. Kimura, K, Ido K, Saifuku , et al. A 1 hour topical therapy for the treatment of *Helicobacter pylori* infection. *Am J Gastroenterol.* 1995;90:60-63.
71. Nagahara A, Miwa H, Yamada T, Kurosawa A, Ohkura R, Sato N. Five-day proton pump inhibitor-based quadruple therapy regimen is more effective than 7-day triple therapy regimen for *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 2001;15:417-421.
72. Catalano F, Catanzaro R, Branciforte G, et al. Five-day triple therapy in *Helicobacter pylori*-positive duodenal ulcer: an eighteen-month follow-up. *J Clin Gastroenterol.* 2000;31:130-136.
73. Isumoto H, Furusu H, Morikawa T, et al. 5-day vs 7-day triple therapy with rabeprazole, clarithromycin and amoxicillin for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther.* 2000;14:1619-623.
74. Calabrese C, DiFebo G, Areni A, Scialpi C, Biasco G, Miglioli M. Pantoprazole, azithromycin and tinidazole: short duration triple therapy for eradication of *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 2000;14:1613-1617.
75. Hurenkamp GJ, VanDerEnde A, Grundmeijer HG, Tytgat GN, VanDerHulst RW. Equally high efficacy of 4, 7 and 10-day triple therapies to eradicate *Helicobacter pylori* infection in patients with ulcer disease. *Aliment Pharmacol Ther.* 2000; 14:1065-1070.
76. Nagahara A, Miwa H, Ogawa K, et al. Addition of metronidazole to rabeprazole-amoxicillin-clarithromycin regimen for *Helicobacter pylori* infection provides an excellent cure rate with five-day therapy. *Helicobacter.* 2000;5:88-93.
77. van de Wouw BA, de Boer WA, Hermsen HW, Valkenburg JG, Geuskens LM, Tytgat GN. Usefulness of the 14C urea breath test as a semi-quantitative monitoring instrument after therapy for *Helicobacter pylori* infection. *Scand J Gastroenterol.* 1997;32:112-117.
78. Laine L, Estrada R, Trujillo M, Knigge K, Fennerty MB. Effect of a proton-pump inhibitor therapy on diagnostic testing for *Helicobacter pylori. Ann Intern Med.* 1998;129:547-550.
79. Cutler AF. Diagnostic tests for *Helicobacter pylori* infection. *Gastroenterologist.* 1997;5:202-212.
80. Gomoll F, Ferrero M, Cabezudo J, Guirao R, Montoro M. Quadruple therapy is effective for eradicating *Helicobacter pylori* after failure of triple proton-pump inhibitor-based therapy: a detailed, prospective analysis of 21 consecutive cases. *Helicobacter.* 1999;4:222-2225.
81. Cutler AF, Havstad S, Ma CK, Blaser MJ, Perez-Perez GI, Schubert TT. Accuracy of invasive and noninvasive tests to diagnose *Helicobacter pylori* infection. *Gastroenterology.* 1995;109:136-141.
82. Danese S, Armuzzi A, Romano A, et al. Efficacy and tolerability of antibiotics in patients undergoing *H pylori* eradication. *Hepatogastroenterology.* 2001;48:465-467.
83. Dore MP, Graham DY, Mele R, et al. Colloidal bismuth subcitrate-based twice-a-day quadruple therapy as primary or salvage therapy for *Helicobacter pylori* infection. *Am J Gastroenterol.* 2002;97:857-860.
84. Chiun-Ku L, Ping-I H, Kwok-Hung L, et al. One-week quadruple therapy is an effective salvage regimen for *Helicobacter pylori* infection in patients after failure of standard triple therapy. *J Clin Gastroenterol.* 2002;34:547-551.

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