

Meta-analysis: Sequential Therapy Appears Superior to Standard Therapy for *Helicobacter pylori* Infection in Patients Naive to Treatment

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Background: Standard proton-pump inhibitor–based therapy for *Helicobacter pylori* infection fails in up to one quarter of patients. Sequential therapy may be more efficacious.

Purpose: To compare sequential therapy with standard triple therapy for *H. pylori* infection.

Data Sources: MEDLINE, EMBASE (1981 to October 2007), the Cochrane Central Register of Controlled Trials, and Google Scholar. PubMed and Ovid were the search engines used.

Study Selection: Randomized, controlled trials (RCTs) comparing sequential and standard triple therapies in treatment-naive patients with documented *H. pylori* infection.

Data Extraction: 3 reviewers independently assessed trial eligibility and quality and extracted data on eradication.

Data Synthesis: The crude rates of *H. pylori* eradication in 10 RCTs involving 2747 patients were 93.4% (95% CI, 91.3% to 95.5%) for sequential therapy ($n = 1363$) and 76.9% (CI, 71.0% to 82.8%) for standard triple therapy ($n = 1384$) (relative risk reduc-

tion, 71% [CI, 64% to 77%]; absolute risk reduction, 16 percentage points [CI, 14 to 19 percentage points]). The median rates of adherence were 97.4% (range, 90.0% to 98.9%) for sequential therapy and 96.8% (range, 93.0% to 100%) for standard therapy. Sequential therapy appeared superior in prespecified sensitivity (subgroup) analyses stratified by trial quality; smoking status; diagnosis (ulcer disease or nonulcer dyspepsia); resistance to clarithromycin, imidazoles, or both; duration of triple therapy; and method of diagnosis. Both treatments had similar side effect profiles.

Limitations: Only 1 study was double-blinded. Most patients were from Italy. There was clear evidence of publication bias.

Conclusion: Sequential therapy appears superior to standard triple therapy for eradication of *H. pylori* infection. If RCTs in other countries confirm these findings, 10-day sequential therapy could become a standard treatment for *H. pylori* infection in treatment-naive patients.

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H*elicobacter pylori* plays a crucial role in the pathogenesis of chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma. *Helicobacter pylori* is a major cause of illness and death worldwide (1).

The standard therapy for *H. pylori* infection in the United States and Europe consists of a triple-drug regimen containing a proton-pump inhibitor and clarithromycin, with either amoxicillin or an imidazole. Both U.S. and European authorities endorse these regimens. Outside the United States, ranitidine bismuth citrate may be recommended in place of a proton-pump inhibitor. In Europe, recommended treatment duration is usually 7 days, whereas in the United States, the Food and Drug Administration has approved regimens of 7, 10, or 14 days (2, 3). Although early results with this approach were promising, eradication rates have subsequently declined and these regimens now fail in nearly one quarter of all patients (4, 5). This is largely because of the increasing prevalence of *H. pylori* strains resistant to clarithromycin or imidazoles (4, 6). An ideal therapy should be short and should result in an eradication rate greater than 90%, as was seen more than a decade ago with the currently used triple-therapy regimens (7).

Recent interest has focused on 10-day sequential therapy (8, 9), which consists of 5 days of treatment with a proton-pump inhibitor and 1 antibiotic (usually amoxicillin) followed by 5-day treatment with the proton-pump

inhibitor and 2 other antibiotics (usually clarithromycin and a 5-nitroimidazole). The rationale for this more complicated approach is that amoxicillin may weaken bacterial cell walls in the initial phase of treatment, preventing the development of drug efflux channels that inhibit such drugs as clarithromycin from binding to ribosomes. This may help to improve the efficacy of clarithromycin in the second phase of treatment (10).

To understand the relative efficacy of sequential therapy compared with standard triple therapy, we performed a systematic literature review and meta-analysis of randomized, controlled trials (RCTs) comparing these 2 treatments.

See also:

Print

Editors' Notes 924
Editorial comment 962

Web-Only

CME quiz
Conversion of graphics into slides
Audio Summary

Context

Efficacy of treatment for *Helicobacter pylori* infection is declining, possibly because of antibiotic resistance. Sequential provision of antibiotics may help overcome that resistance.

Contribution

In this review and meta-analysis of 10 trials, the investigators found evidence consistently favoring sequential over standard triple therapy for *H. pylori* infection.

Caution

Most trials were performed in Italy, 1 was performed in children only, and the investigators found strong evidence of publication bias.

Implication

Sequential therapy seems superior to standard therapy for treatment of *H. pylori* infection.

—The Editors

METHODS**Study Sources and Searches**

We searched MEDLINE, EMBASE (1981 to October 2007), the Cochrane Central Register of Controlled Trials, and Google Scholar for RCTs comparing sequential with standard therapy for *H. pylori* infection; we used PubMed and Ovid as search engines. The search was limited to human studies but was otherwise unrestricted. We used *Helicobacter pylori*, *sequential therapy*, *triple therapy*, *standard therapy*, *standard triple therapy*, *proton pump inhibitor AND clarithromycin AND amoxicillin*, and *proton pump inhibitor AND clarithromycin AND imidazole* as Medical Subject Heading and text terms. Boolean operators (*NOT*, *AND*, *OR*) were also used in succession to narrow and widen the search. To increase the number of hits obtained with use of the Ovid search engine, we used the “explode” and “related article” functions. On the basis of the title and abstract, we downloaded or requested full articles. Reference lists in these trials were checked to identify any other published or unpublished data. We hand searched the references of review articles and evaluated symposia proceedings, poster presentations, and abstracts from major gastroenterologic meetings (including Digestive Diseases Week, United European Gastroenterology Week, the European Helicobacter Study Group, and Asia Pacific Digestive Diseases Week).

Study Selection

Abstracts, full articles, and the grey literature that passed the primary screening were retrieved and scrutinized. For inclusion, an article had to be an RCT. All patients were *H. pylori* treatment-naïve and had not used a proton-pump inhibitor, ranitidine bismuth citrate, other histamine-2-receptor antagonists, or antibiotics in the pre-

ceding month. The 2 treatments compared were 10-day sequential therapy and 7- or 10-day standard triple therapy, as defined previously. Other criteria were diagnosis of *H. pylori* infection by histologic evaluation, biopsy urease test, fecal antigen test, or urea breath test; *H. pylori* eradication evaluated by any of these tests a minimum of 4 weeks after treatment; a defined length of treatment; and objective measurement of morbidity. If multiple publications of the same trial were retrieved or if there was a case mix between publications, only the most recent publication was included. Nonrandomized studies were excluded, as were case reports, letters, editorials, commentaries, reviews, and abstracts with insufficient details to meet the inclusion criteria.

Data Extraction and Quality Assessment

Three independent reviewers abstracted data by using a standardized data collection form to increase uniformity and reduce reporting bias. In cases of discrepancy, a consensus decision was made. From each report, reviewers abstracted the year of publication; institution; whether the study was a single-center or multicenter study; numbers of patients in the sequential and standard triple-therapy groups; name, dose, and timing of antibiotic administration; length of treatment; time after treatment when eradication was assessed; methods of diagnosing infection and confirming eradication; incidence of side effects; method of data analysis (intention-to-treat or per-protocol analysis); and method of diagnosing complications. The corresponding authors were contacted for any missing data points.

Once we selected a study, we rated its quality by using the method of Jadad and colleagues (11); scores range from 1 to 5, with a higher score indicating higher quality based on method of randomization, level of blinding, concealment of allocation, and accounting for dropouts. We considered RCTs with a score of 3 or greater to be high quality.

Data Synthesis and Analysis

Meta-analysis was performed according to the Quality of Reporting of Meta-Analyses (QUOROM) guidelines (12) and the recommendations of the Cochrane Collaboration (13). The effect measure was the relative risk for failure of *H. pylori* eradication among patients assigned to sequential therapy versus standard triple therapy. The relative risk was reexpressed as the relative risk reduction (1 – relative risk) and its 95% CI to gauge the clinical importance of the relative benefit of sequential therapy compared with standard triple therapy in terms of percentage reduction in failure to eradicate *H. pylori*. The absolute risk reduction was also computed to provide further information on the potential clinical value of sequential over standard triple therapy. The I^2 statistic was used to assess statistical heterogeneity among the reported treatment effects. An I^2 value of 50% or greater indicates substantial heterogeneity (14). A random-effects model was used to pool relative risks when statistical heterogeneity was present; otherwise, a Mantel–Haenszel fixed-effects model was used

to compute an overall estimate of the relative treatment effect (15). Analyses were conducted by using Comprehensive Meta-Analysis software, version 1.0.25 (Biostat, Englewood, New Jersey), and Review Manager software, version 4.2.8 (Cochrane Collaboration, Oxford, United Kingdom).

When heterogeneity was identified, we made every attempt to investigate the source. We assessed the presence of publication bias by visually inspecting funnel plot asymmetry (16, 17) and applying Egger and colleagues' (18) and Begg and Mazumdar's (19) tests for asymmetry. A *P* value of 0.10 or less was considered to represent a statistically significant difference.

We performed prespecified sensitivity analyses to evaluate differences in effect by trial quality; patient age; diagnosis (peptic ulcer disease vs. nonulcer dyspepsia); smoking status; resistance to clarithromycin, imidazoles, or both; duration of triple therapy; and adherence.

Role of the Funding Source

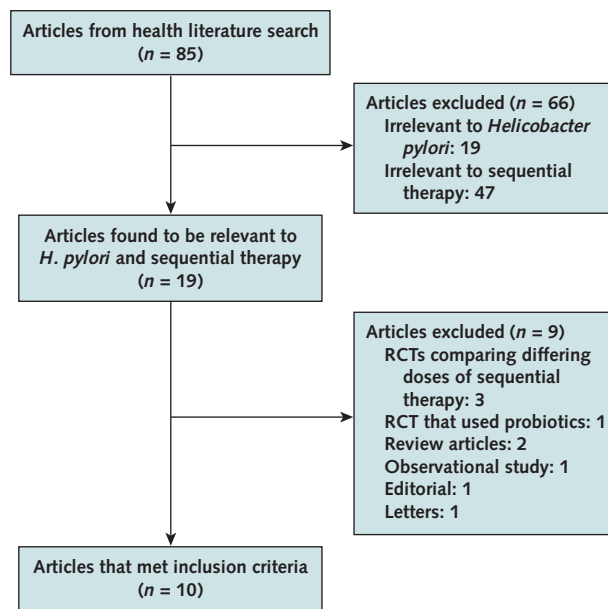
There was no external funding source for this work.

RESULTS

Our initial search yielded 85 citations (Figure 1). Of these, 66 were excluded after review of the full-text article because they were irrelevant to *H. pylori* or to sequential therapy. An additional 3 RCTs were excluded because they compared different sequential therapies. One RCT was excluded because it studied the use of probiotics. Two review articles, 1 observational study, 1 editorial, and 1 letter were also excluded. Ten RCTs were eligible for meta-analysis (20–29).

All RCTs were conducted in Italy, although 2 (23, 29) also recruited patients from a U.S. site. Table 1 shows information on the RCTs. Nine RCTs compared sequential therapy with a triple-therapy regimen containing a proton-pump inhibitor; 1 (20) compared sequential therapy with a triple-therapy regimen containing ranitidine bismuth citrate. One RCT studied an exclusively pediatric population (27). Patients were recruited directly from a clinic or were referred for dyspeptic symptoms. They were naive to *H. pylori* therapy and had not received a proton-pump inhibitor, ranitidine bismuth citrate, a histamine-2-receptor antagonist, or an antibiotic in the preceding month. There were 2747 patients (1402 men); 1363 were randomly assigned to sequential therapy and 1384 to standard triple therapy (Table 2). Pooled crude eradication rates were 93.4% (95% CI, 91.3% to 95.5%) for sequential therapy and 76.9% (CI, 71.0% to 82.8%) for standard triple therapy. The relative risk reduction was 71% (CI, 64% to 77%), and the absolute risk reduction was 16 percentage points (CI, 14 to 19 percentage points). No significant heterogeneity was noted ($I^2 = 0\%$). Adherent patients were reported as those who "completed treatment" or were "compliant." Overall adherence was reported in all but 2 RCTs (21, 22). Median adherence rates were 97.4%

Figure 1. Identification of eligible randomized, controlled trials (RCTs).



(range, 90.0% to 98.9%) for sequential therapy and 96.8% (range, 93.0% to 100%) for standard triple therapy.

Sequential therapy was superior to standard triple therapy in all sensitivity (subgroup) analyses (Table 3). In the 2 RCTs that evaluated treatment in smokers, neither defined whether the term *smoker* meant current smokers or ever-smokers, and neither reported pack-year history (24, 25). Analysis of clarithromycin-resistant strains was based on De Francesco and colleagues' (30) post hoc analysis of the study published by Zullo and colleagues (23), which reported clarithromycin resistance in 81 patients treated with sequential therapy and 75 treated with standard triple therapy, and on Vaira and colleagues' (29) report of clarithromycin resistance in 9 patients treated with sequential therapy and 21 patients treated with standard triple therapy. Two RCTs evaluated imidazole-resistant strains (23, 29). Twenty-six patients from 2 RCTs (26, 29) had strains resistant to clarithromycin and imidazoles. Eradication was successful in 8 of 13 patients receiving sequential therapy and 4 of 13 receiving standard triple therapy, but these numbers were too small to allow us to draw firm conclusions about treatment of dual-resistant strains.

The analysis of treatment that lasted longer than 5 days excluded the RCT of De Francesco and colleagues (20), which had randomly assigned patients to 5 days of standard triple therapy or 10 days of sequential therapy and was also the only trial to have used ranitidine bismuth citrate. In the sensitivity analysis comparing 10-day sequential therapy with 7- or 10-day triple therapy, we included 2 trials that randomly assigned patients to 3 treat-

Table 1. Characteristics of Included Randomized, Controlled Trials*

Study, Year (Reference)	Center/Recruitment Site	Study Design	Diagnosis of <i>Helicobacter pylori</i> Infection	Confirmation of Eradication	Sequential Therapy/ Standard Triple Therapy	Men/ Women, n/n	Mean Age, y	Study Quality
Vaira et al., 2007 (29)	Multicenter/Italy and United States	Double-blind	Positive UBT results plus positive results on 2 of 3 tests: rapid urease test, histologic analysis, or culture	UBT at 4 and 8 wk after treatment	Sequential: 5 d of pantoprazole, 40 mg; amoxicillin, 1000 mg; and placebo, then 5 d of pantoprazole, 40 mg; clarithromycin, 500 mg; and tinidazole, 500 mg, all twice daily	58/92	48.6	5
					Standard: 10 d of pantoprazole, 40 mg; clarithromycin, 500 mg; and amoxicillin, 1000 mg, all twice daily	51/99	49.2	
Scaccianoce et al., 2006 (28)	Multicenter/Italy	Open-label	Positive results on rapid urease test and histologic analysis	UBT at 4–6 wk after treatment	Sequential: 5 d of esomeprazole, 20 mg, and amoxicillin, 1000 mg, then 5 d of esomeprazole, 20 mg; clarithromycin, 500 mg; and tinidazole, 500 mg, all twice daily	32/40	55	3
					Standard: 10 d of esomeprazole, 20 mg; clarithromycin, 500 mg; and amoxicillin, 1 g, all twice daily	33/38	53	
Francavilla et al., 2005 (27)	Single/Italy	Single-blind	Positive results on 2 of 3 tests: histologic analysis, rapid urease, and UBT	UBT at 8 wk and 6 mo after treatment	Sequential: 5 d of omeprazole, 1 mg/kg daily, and amoxicillin, 50 mg/kg daily, then 5 d of omeprazole, 1 mg/kg daily; clarithromycin, 15 mg/kg daily; and tinidazole, 20 mg/kg daily	15/23	11.0 (median)	3
					Standard: 7 d of omeprazole, 1 mg/kg daily; amoxicillin, 50 mg/kg daily; and metronidazole, 15 mg/kg daily	15/22	9.9 (median)	
Zullo et al., 2005 (26)	Multicenter/Italy	Open-label	Rapid urease test and histologic analysis	Rapid urease test and histologic analysis at 4–6 wk after treatment	Sequential: 5 d of rabeprazole, 20 mg, and amoxicillin, 1000 mg, then 5 d of rabeprazole, 20 mg; clarithromycin, 500 mg; and tinidazole, 500 mg, all twice daily	50/39	69	2
					Standard: 7 d of rabeprazole, 20 mg; clarithromycin, 500 mg; and amoxicillin, 1000 mg, all twice daily	56/34	70	
De Francesco et al., 2004 (25)	Multicenter/Italy	Open-label	Positive results on 2 of 3 tests: histologic analysis, rapid urease test, and UBT	Rapid urease test, histologic analysis, and UBT 6–8 wk after treatment conclusion	Sequential: 5 d of rabeprazole, 20 mg, and amoxicillin, 1000 mg, then 5 d of rabeprazole, 20 mg; clarithromycin, 500 mg; and tinidazole, 500 mg, all twice daily	54/62	46	3
					Standard: 10 d of rabeprazole, 20 mg; clarithromycin, 500 mg; and amoxicillin, 1000 mg, all twice daily	57/59	49	

Table 1—Continued

Study, Year (Reference)	Center/Recruitment Site	Study Design	Diagnosis of <i>Helicobacter pylori</i> Infection	Confirmation of Eradication	Sequential Therapy/ Standard Triple Therapy	Men/ Women, n/n	Mean Age, y	Study Quality
De Francesco et al., 2004 (24)	Multicenter/Italy	Open-label	Positive results on 2 of 3 tests: histologic analysis, rapid urease test, and UBT	UBT at 6–8 wk after treatment conclusion	Sequential: 5 d of rabeprazole, 20 mg, and amoxicillin, 1000 mg, then 5 d of rabeprazole, 20 mg; clarithromycin, 500 mg; and tinidazole, 500 mg, all twice daily	20/25	44.2	3
					Standard: 10 d of rabeprazole, 20 mg; clarithromycin, 500 mg; and amoxicillin, 1000 mg, all twice daily	21/31	46.0	
Zullo et al., 2003 (23)	Multicenter/Italy and United States	Open-label	Positive results on 2 of 3 tests: histologic analysis, rapid urease test, and UBT	Histologic analysis, rapid urease test, and UBT at 6 wk after treatment conclusion	Sequential: 5 d of rabeprazole, 20 mg, and amoxicillin, 1000 mg, then 5 d of rabeprazole, 20 mg; clarithromycin, 500 mg; and tinidazole, 500 mg, all twice daily	258/264	52	2
					Standard: 7 d of rabeprazole, 20 mg; clarithromycin, 500 mg, and amoxicillin, 1000 mg, all twice daily	287/240	53	
Focareta et al., 2003 (22)	Single/Italy	NR	Rapid urease test	Stool antigen test and UBT at 6 wk after treatment conclusion	Sequential: 5 d of esomeprazole, 20 mg, and amoxicillin, 1000 mg, all twice daily, then 5 d of esomeprazole, 20 mg; clarithromycin, 500 mg; and tinidazole, 500 mg, all twice daily	NR	NR	1
					Standard: 7 d of esomeprazole, 20 mg; clarithromycin, 500 mg; and amoxicillin, 1000 mg, all twice daily	NR	NR	
Focareta et al., 2002 (21)	Single/Italy	NR	Rapid urease test	Stool antigen test and UBT at 6 wk after treatment conclusion	Sequential: 5 d of esomeprazole, 20 mg, and amoxicillin, 1000 mg, all twice daily, then 5 d of esomeprazole, 20 mg; clarithromycin, 500 mg; and tinidazole, 500 mg, all twice daily	NR	NR	1
					Standard: 7 d of omeprazole, 20 mg; clarithromycin, 500 mg; and amoxicillin, 1000 mg, all twice daily	NR	NR	
De Francesco et al., 2001 (20)	Multicenter/Italy	Open-label	Rapid urease test and histologic analysis	Rapid urease test and histologic analysis at 4–6 wk after treatment conclusion	Sequential: 5 d of omeprazole, 20 mg, and amoxicillin, 1000 mg, then 5 d of omeprazole, 20 mg; clarithromycin, 500 mg; and tinidazole, 500 mg, all twice daily	31/32	52	2
					Standard: 5 d of ranitidine bismuth citrate, 400 mg; clarithromycin, 500 mg; and tinidazole, 500 mg, all twice daily	33/31	54	

* NR = not reported; UBT = urea breath test.

Table 2. Data Abstracted from Included Studies*

Study, Year (Reference)	Treatment	Patients with Peptic Ulcer Disease, n	Eradication Rate, n/n	Eradication Rate in Smokers, n/n	Eradication Rate in Patients with Clarithromycin Resistance, n/n	Eradication Rate in Patients with Peptic Ulcer Disease, n/n	Eradication Rate in Patients with Nonulcer Dyspepsia, n/n	Ulcer Healing Rate, n/n	Adherence, %	Most Commonly Reported Adverse Events
Vaira et al., 2007 (29)	Sequential therapy	11	134/150	NR	8/9	NR	NR	NR	94	Epigastric pain (n = 8), diarrhea (n = 7)
	Standard therapy	10	116/150	NR	6/21	NR	NR	NR	93	Epigastric pain (n = 7), diarrhea (n = 4), heartburn (n = 4)
Scaccianoce et al., 2006 (28)	Sequential therapy	NR	68/72	NR	NR	NR	NR	NR	95.8	Diarrhea (n = 3), abdominal pain (n = 3)
	Standard therapy	NR	58/71	NR	NR	NR	NR	NR	95.8	Diarrhea (n = 3), abdominal pain (n = 2), glossitis (n = 2)
Francavilla et al., 2005 (27)	Sequential therapy	1	36/38	NR	NR	NR	NR	NR	97.4	Abdominal pain (n = 2), nausea (n = 2), diarrhea (n = 1)
	Standard therapy	0	28/37	NR	NR	NR	NR	NR	100	Abdominal pain (n = 2), nausea (n = 1), diarrhea (n = 1)
Zullo et al., 2005 (26)	Sequential therapy	89	84/89	NR	NR	NR	NR	85/89	98.9	Diarrhea (n = 3), abdominal pain (n = 3), glossitis (n = 2)
	Standard therapy	90	72/90	NR	NR	NR	NR	83/90	97.8	Diarrhea (n = 5), abdominal pain (n = 2), vomiting (n = 2)
De Francesco et al., 2004 (25)	Sequential therapy	37	110/116	62/66	NR	36/36	74/79	NR	97.4	Diarrhea (n = 3), abdominal pain (n = 2), nausea (n = 3)
	Standard therapy	24	93/116	57/71	NR	32/34	61/79	NR	99.1	Diarrhea (n = 3), abdominal pain (n = 2), glossitis (n = 3)
De Francesco et al., 2004 (24)	Sequential therapy	9	43/45	14/15	NR	8/8	35/36	NR	97.8	NR
	Standard therapy	11	42/52	9/17	NR	17/17	25/34	NR	98.0	NR
Zullo et al., 2003 (23)	Sequential therapy	128	481/522	NR	66/81	124/128	357/394	124/127	90	Diarrhea (n = 14), abdominal pain (n = 8), glossitis (n = 2)
	Standard therapy	135	389/527	NR	33/75	101/135	288/392	101/133	93	Diarrhea (n = 16), abdominal pain (n = 13), glossitis (n = 5)
Focareta et al., 2003 (22)	Sequential therapy	NR	166/174	NR	NR	NR	NR	NR	NR	None
	Standard therapy	NR	149/184	NR	NR	NR	NR	NR	NR	None
Focareta et al., 2002 (21)	Sequential therapy	NR	90/94	NR	NR	NR	NR	NR	NR	None
	Standard therapy	NR	75/93	NR	NR	NR	NR	NR	NR	None
De Francesco et al., 2001 (20)	Sequential therapy	31	61/63	NR	NR	30/31	31/32	31/31	98.4	Diarrhea (n = 4), glossitis (n = 2), urticaria (n = 1)
	Standard therapy	27	43/64	NR	NR	20/27	23/37	27/27	>95	Diarrhea (n = 3), glossitis (n = 2), dizziness (n = 1)

* NR = not reported.

ment groups (7- and 10-day standard triple therapy and 10-day sequential therapy) (25, 28), but we included only patients from trials that randomly assigned them to 10-day standard triple therapy and 10-day sequential therapy. In the sensitivity analysis examining trials that used more than 1 test for diagnosing *H. pylori* infection, we excluded a single trial that used only a rapid urease test.

The funnel plot for the log relative risks from the 10 RCTs showed clear asymmetry favoring sequential therapy, as evidenced by the absence of trials in the lower right-hand portion of the triangle (Figure 2). Neither Egger and colleagues' test ($P = 0.197$) nor Begg and Mazumdar's test ($P = 0.211$) provided statistical evidence for publication bias. However, the former test

Table 3. Pooled and Sensitivity Analyses

Analysis (References)	Participants, n	Studies, n	Eradication Rate with Sequential Therapy, %	Eradication Rate with Triple Therapy, %	Relative Risk Reduction (95% CI), %	Absolute Risk Reduction (95% CI), percentage points	P, %
All studies	2747	10	93.4	76.9	71 (64–77)	16 (14–19)	0
High-quality studies (Jadad score ≥ 3) (23, 24, 26–28)	841	5	92.8	79.1	34 (23–51)	14 (9–18)	0
Outcome: ulcer healing (19, 22, 25)	497	3	97.2	84.4	19 (8–41)	13 (8–17)	0
Diagnosis: peptic ulcer disease (19, 22–24)	416	4	97.5	79.8	18 (12–24)	13 (5–30)	0
Diagnosis: nonulcer dyspepsia (19, 22–24)	1083	4	91.9	73.2	30 (22–42)	19 (14–43)	0
Adults only (19–25, 27, 28)	2417	9	93.2	76.7	29 (23–37)	17 (14–20)	0
Smokers only (23, 24)	169	2	93.8	75.0	25 (10–63)	19 (9–29)	0
Clarithromycin-resistant strains (28, 29)	186	2	82.2	40.6	70 (54–82)	41 (28–53)	0
Imidazole-resistant strains (22, 28)	130	2	95.8	78.0	21 (5–39)	17 (6–28)	0
Standard treatment duration >5 d (20–28)	2620	9	93.2	77.4	30 (24–37)	16 (13–18)	0
10-d sequential therapy vs. 7-d standard triple therapy (20–22, 24–27)	2207	7	93.7	75.5	26 (20–33)	18 (15–21)	0
10-d sequential therapy vs. 10-d standard triple therapy (23, 24, 27, 28)	772	4	92.7	79.4	35 (24–53)	13 (9–18)	0
>1 test used to diagnose <i>Helicobacter pylori</i> infection (19, 22–28)	2202	8	92.8	76.0	30 (23–38)	17 (14–20)	0

has 50% power or less to detect severe publication bias with only 10 studies.

Seven RCTs reported adverse effects (20, 23, 25–29) (Table 2). The 3 adverse events most commonly reported with sequential and standard triple therapy were diarrhea ($n = 35$ in each group), abdominal pain ($n = 26$ and 28, respectively), and glossitis ($n = 6$ and 12, respectively). None of the RCTs quantified the effect of adverse events on quality of life.

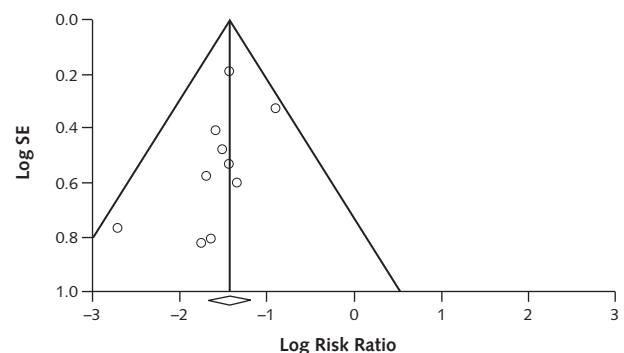
DISCUSSION

Sequential therapy appears superior to standard triple therapy for the eradication of *H. pylori* infection among patients naive to treatment for the infection. The benefit of sequential over standard triple therapy was maintained when the analysis was confined to RCTs of high methodological quality, as well as in the other sensitivity analyses (Table 3). Ten days of sequential therapy appeared superior to 7 or 10 days of standard triple therapy. We did not identify any RCT that found standard triple therapy to have a higher eradication rate than sequential therapy. Inspection of the funnel plot showed asymmetry favoring sequential treatment, although this pattern also suggests the possibility of publication bias among the included studies. The benefit of sequential over standard triple therapy was seen among subgroups of patients with risk factors for failure of eradication, including a diagnosis of nonulcer dyspepsia (30–34), smoking, and antimicrobial resistance (34, 35). Adherence was similar for the 2 treatments. However, because it is more complicated, sequential therapy might be associated with reduced adherence in clinical practice.

Our results are consistent with 2 previous reviews (8, 9). Moayyedi (8) pooled eradication rates for RCTs based

on duration of treatment. Zullo and colleagues (9) conducted a descriptive analysis of RCTs and observational studies and pooled eradication rates according to pathologic findings, duration of therapy, proton-pump inhibitor used, antibiotic resistance, and age. All the RCTs included in our meta-analysis were included in these previous reviews. However, we set predefined inclusion and exclusion criteria that limited inclusion to RCTs. We conducted a systematic review and meta-analysis according to current guidelines and performed further sensitivity analyses.

Our analysis had some limitations, including variation in elements of primary study design (for example, inclusion criteria, duration and dosing of antibiotic therapy, and methods used to diagnose infection and evaluate eradica-

Figure 2. Funnel plot of all included studies.


The vertical axis represents the line of no effect, and the horizontal axis represents the log risk ratio. The diagonal lines represent the 95% CI. The circles represent individual studies in the fixed-effects model. The diamond represents the pooled risk ratio and its 95% CI.

Table 4. Quality of Studies Included in the Meta-analysis*

Study, Year (Reference)	Randomization	Double Blinding	Withdrawals and Dropouts, n		Jadad Score
			Sequential Therapy	Standard Therapy	
Vaira et al., 2007 (29)	Block	Yes	3	3	5
Scaccianoce et al., 2006 (28)	Computer-generated	No	2	2	3
FrancaVilla et al., 2005 (27)	Computer-generated	No	1	0	3
Zullo et al., 2005 (26)	Computer-generated	No	NR	NR	2
De Francesco et al., 2004 (25)	Computer-generated	No	3	1	3
De Francesco et al., 2004 (24)	Computer-generated	No	1	1	3
Zullo et al., 2003 (23)	Computer-generated	No	NR	NR	2
Focareta et al., 2003 (22)	NR	No	NR	NR	1
Focareta et al., 2002 (21)	NR	No	NR	NR	1
De Francesco et al., 2001 (20)	NR	No	1	1	2

* NR = not reported.

tion). Furthermore, with the exception of 2 RCTs that recruited some U.S. patients (24, 30), all RCTs were conducted in Italy, which may limit generalizability. Other notable limitations include the possibility of publication bias, small numbers of patients in some RCTs, and inclusion of some relatively low-quality RCTs. Four RCTs did not adequately describe withdrawals, 3 did not describe the randomization process, 6 were open label, and only 1 was double-blinded (Table 4). However, the results of the open-label trials are consistent with those of the double-blinded trial.

Although proton-pump inhibitor–based triple therapy is still considered by some to be the standard of care (3, 4), recently reported eradication rates have been disappointingly low—around 75% in the United States (36, 37); around or below 50% in Portugal, Germany, Iceland, and Turkey (38); and around 60% in Russia and Malaysia (38). In our analysis, the pooled crude eradication rate was 76.9%. Indeed, the ethics of continued use of standard triple therapy has recently been questioned and the use of sequential therapy recommended in its place (39). However, we do not know whether sequential therapy will be superior to standard triple therapy in U.S. patients because no RCTs have been conducted here. Because patterns of antimicrobial resistance vary geographically, it will be important to study sequential therapy in RCTs in the United States and in other countries. One potential disadvantage to sequential therapy is that patients with failed eradication would have limited options for further treatment because they would already have received 3 different antibiotics (8).

Clarithromycin- and imidazole-resistant strains of *H. pylori* are prevalent around the world, with rates as high as 24% in Europe (40, 41). Antimicrobial resistance is largely responsible for the poor eradication rates with standard triple therapy (42). A meta-analysis reported an almost 60% decline in eradication rates with standard triple therapy if clarithromycin resistance was present (42). In our analyses, prevalence of clarithromycin resistance was 7% and the prevalence of clarithromycin or imidazole re-

sistance was 13%. Clarithromycin resistance was responsible for a 37% decline in eradication rates with standard triple therapy. However, eradication rates among clarithromycin-resistant strains were only 8% lower with sequential therapy. If the prevalence of resistance to both clarithromycin and nitroimidazoles continues to increase, the efficacy of the sequential regimen may decrease.

In conclusion, our analysis suggests that 10-day sequential therapy is superior to 7- or 10-day standard triple therapy for *H. pylori* treatment-naïve patients. However, sequential therapy has not been compared with proton-pump inhibitor–based quadruple therapy (a proton-pump inhibitor, bismuth salt, tetracycline, and a nitroimidazole) or with standard triple therapy given for 14 days. In the United States, 14-day regimens of standard triple therapy are approved by the Food and Drug Administration and widely used. Therefore, further RCTs comparing these treatment approaches are indicated. If such RCTs confirm superiority of sequential therapy over existing treatment regimens, it could become standard treatment for treatment-naïve patients.

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References

1. Graham DY, Lu H, Yamaoka Y. A report card to grade *Helicobacter pylori* therapy [Editorial]. *Helicobacter*. 2007;12:275-8. [PMID: 17669098]

2. Chey WD, Wong BC. Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007;102:1808-25. [PMID: 17608775]
3. Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, et al. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. *Gut*. 2007;56:772-81. [PMID: 17170018]
4. Saad RJ, Chey WD. Treatment of *Helicobacter pylori* infection in 2006. *Gastroenterology and Hepatology Annual Review*. 2006;1:30-5.
5. Fuccio L, Minardi ME, Zagari RM, Grilli D, Magrini N, Bazzoli F. Meta-analysis: duration of first-line proton-pump inhibitor based triple therapy for *Helicobacter pylori* eradication. *Ann Intern Med*. 2007;147:553-62. [PMID: 17938394]
6. Meyer JM, Silliman NP, Wang W, Siepmann NY, Sugg JE, Morris D, et al. Risk factors for *Helicobacter pylori* resistance in the United States: the surveillance of *H. pylori* antimicrobial resistance partnership (SHARP) study, 1993-1999. *Ann Intern Med*. 2002;136:13-24. [PMID: 11777360]
7. Hopkins RJ. In search of the Holy Grail of *Helicobacter pylori* remedies [Editorial]. *Helicobacter*. 2001;6:81-3. [PMID: 11422461]
8. Moayeddi P. Sequential regimens for *Helicobacter pylori* eradication. *Lancet*. 2007;370:1010-2. [PMID: 17889226]
9. Zullo A, De Francesco V, Hassan C, Morini S, Vaira D. The sequential therapy regimen for *Helicobacter pylori* eradication: a pooled-data analysis. *Gut*. 2007;56:1353-7. [PMID: 17566020]
10. De Francesco V, Margiotta M, Zullo A, Hassan C, Troiani L, Burattini O, et al. Clarithromycin-resistant genotypes and eradication of *Helicobacter pylori*. *Ann Intern Med*. 2006;144:94-100. [PMID: 16418408]
11. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1-12. [PMID: 8721797]
12. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet*. 1999;354:1896-900. [PMID: 10584742]
13. Bero L, Rennie D. The Cochrane Collaboration. Preparing, maintaining, and disseminating systematic reviews of the effects of health care. *JAMA*. 1995;274:1935-8. [PMID: 8568988]
14. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-60. [PMID: 12958120]
15. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.5 [updated May 2005]. In: *The Cochrane Library*. Issue 3 Chichester, UK: J Wiley; 2005.
16. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. *Evidence based Medicine: How to Practice and Teach EBM*. 2nd ed. Edinburgh: Churchill Livingstone; 2000:133-8.
17. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. *JAMA*. 1992;268:240-8. [PMID: 1535110]
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-34. [PMID: 9310563]
19. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088-101. [PMID: 7786990]
20. De Francesco V, Zullo A, Hassan C, Faleo D, Ierardi E, Panella C, et al. Two new treatment regimens for *Helicobacter pylori* eradication: a randomised study. *Dig Liver Dis*. 2001;33:676-9. [PMID: 11785713]
21. Focareta R, Forte G, Ciarleglio A, et al. *Helicobacter pylori* eradication: one week triple therapy vs. 10-day sequential regimen [Abstract]. *Dig Liver Dis*. 2002;34(Suppl 1):A17.
22. Focareta R, Forte G, Forte F, et al. Could the 10-days sequential therapy be considered a first choice treatment for the eradication of *Helicobacter pylori* infection? [Abstract]. *Dig Liver Dis*. 2003;35(Suppl 4):S33.
23. Zullo A, Vaira D, Vakil N, Hassan C, Gatta L, Ricci C, et al. High eradication rates of *Helicobacter pylori* with a new sequential treatment. *Aliment Pharmacol Ther*. 2003;17:719-26. [PMID: 12641522]
24. De Francesco V, Zullo A, Margiotta M, Marangi S, Burattini O, Berloco P, et al. Sequential treatment for *Helicobacter pylori* does not share the risk factors of triple therapy failure. *Aliment Pharmacol Ther*. 2004;19:407-14. [PMID: 14871280]
25. De Francesco V, Zullo A, Hassan C, Della Valle N, Pietrini L, Minenna MF, et al. The prolongation of triple therapy for *Helicobacter pylori* does not allow reaching therapeutic outcome of sequential scheme: a prospective, randomised study. *Dig Liver Dis*. 2004;36:322-6. [PMID: 15191200]
26. Zullo A, Gatta L, De Francesco V, Hassan C, Ricci C, Bernabucci V, et al. High rate of *Helicobacter pylori* eradication with sequential therapy in elderly patients with peptic ulcer: a prospective controlled study. *Aliment Pharmacol Ther*. 2005;21:1419-24. [PMID: 15948808]
27. Francavilla R, Lionetti E, Castellaneta SP, Magistà AM, Boscarelli G, Piscitelli D, et al. Improved efficacy of 10-day sequential treatment for *Helicobacter pylori* eradication in children: a randomized trial. *Gastroenterology*. 2005;129:1414-9. [PMID: 16285942]
28. Scaccianoce G, Hassan C, Panarese A, Piglionica D, Morini S, Zullo A. *Helicobacter pylori* eradication with either 7-day or 10-day triple therapies, and with a 10-day sequential regimen. *Can J Gastroenterol*. 2006;20:113-7. [PMID: 16482238]
29. Vaira D, Zullo A, Vakil N, Gatta L, Ricci C, Perna F, et al. Sequential therapy versus standard triple-drug therapy for *Helicobacter pylori* eradication: a randomized trial. *Ann Intern Med*. 2007;146:556-63. [PMID: 17438314]
30. De Francesco V, Margiotta M, Zullo A, Hassan C, Troiani L, Burattini O, et al. Clarithromycin-resistant genotypes and eradication of *Helicobacter pylori*. *Ann Intern Med*. 2006;144:94-100. [PMID: 16418408]
31. Huang JQ, Hunt RH. Are one-week anti-*Helicobacter pylori* treatments more effective in patients with peptic ulcer disease than in those with non ulcer dyspepsia? A meta-analysis [Abstract]. *Am J Gastroenterol*. 1998;93:1639.
32. De Francesco V, Sgarro C, Cela E, et al. *Helicobacter pylori* eradication rates in non-ulcer dyspepsia (NUD) and duodenal ulcer (DU) patients [Abstract]. *Gut*. 2001;48(Suppl 11):A94.
33. Gisbert JP, Marcos S, Gisbert JL, Pajares JM. *Helicobacter pylori* eradication therapy is more effective in peptic ulcer than in non-ulcer dyspepsia. *Eur J Gastroenterol Hepatol*. 2001;13:1303-7. [PMID: 11692055]
34. Broutet N, Tchamgoué S, Pereira E, Lamouliatte H, Salomon R, Mégraud F. Risk factors for failure of *Helicobacter pylori* therapy—results of an individual data analysis of 2751 patients. *Aliment Pharmacol Ther*. 2003;17:99-109. [PMID: 12492738]
35. Gessner BD, Bruce MG, Parkinson AJ, Gold BD, Muth PT, Dunaway E, et al. A randomized trial of triple therapy for pediatric *Helicobacter pylori* infection and risk factors for treatment failure in a population with a high prevalence of infection. *Clin Infect Dis*. 2005;41:1261-8. [PMID: 16206100]
36. Laine L, Fennerty MB, Osato M, Sugg J, Suchower L, Probst P, et al. Esomeprazole-based *Helicobacter pylori* eradication therapy and the effect of antibiotic resistance: results of three US multicenter, double-blind trials. *Am J Gastroenterol*. 2000;95:3393-8. [PMID: 11151867]
37. Vakil N, Lanza F, Schwartz H, Barth J. Seven-day therapy for *Helicobacter pylori* in the United States. *Aliment Pharmacol Ther*. 2004;20:99-107. [PMID: 15225176]
38. Laheij RJ, Rossum LG, Jansen JB, Straatman H, Verbeek AL. Evaluation of treatment regimens to cure *Helicobacter pylori* infection—a meta-analysis. *Aliment Pharmacol Ther*. 1999;13:857-64. [PMID: 10383518]
39. Graham DY, Yamaoka Y. Ethical considerations of comparing sequential and traditional anti-*Helicobacter pylori* therapy [Letter]. *Ann Intern Med*. 2007;147:434-5. [PMID: 17876031]
40. Koletzko S, Richey F, Bontems P, Crone J, Kalach N, Monteiro ML, et al. Prospective multicentre study on antibiotic resistance of *Helicobacter pylori* strains obtained from children living in Europe. *Gut*. 2006;55:1711-6. [PMID: 16603633]
41. De Francesco V, Margiotta M, Zullo A, Hassan C, Valle ND, Burattini O, et al. Clarithromycin resistance and *Helicobacter pylori* genotypes in Italy. *J Microbiol*. 2006;44:660-4. [PMID: 17205045]
42. Houben MH, van de Beek D, Hensen EF, Craen AJ, Rauws EA, Tytgat GN. A systematic review of *Helicobacter pylori* eradication therapy—the impact of antimicrobial resistance on eradication rates. *Aliment Pharmacol Ther*. 1999;13:1047-55. [PMID: 10468680]

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