14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: a randomised trial

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Summary

Background **Evidence from Europe, Asia, and North America suggests that standard three-drug regimens of a proton-pump inhibitor plus amoxicillin and clarithromycin are significantly less effective for eradication of *Helicobacter pylori* infection than are 5-day concomitant and 10-day sequential four-drug regimens that include a nitroimidazole. These four-drug regimens also entail fewer antibiotic doses than do three-drug regimens and thus could be suitable for eradication programmes in low-resource settings. Few studies in Latin America have been done, where the burden of *H pylori*-associated diseases is high. We therefore did a randomised trial in Latin America comparing the effectiveness of four-drug regimens given concomitantly or sequentially with that of a standard 14-day regimen of triple therapy.**

Methods **Between September, 2009, and June, 2010, we did a randomised trial of empiric 14-day triple, 5-day concomitant, and 10-day sequential therapies for *H pylori* in seven Latin American sites: Chile, Colombia, Costa Rica, Honduras, Nicaragua, and Mexico (two sites). Participants aged 21–65 years who tested positive for *H pylori* by a urea breath test were randomly assigned by a central computer using a dynamic balancing procedure to: 14 days of lansoprazole, amoxicillin, and clarithromycin (standard therapy); 5 days of lansoprazole, amoxicillin, clarithromycin, and metronidazole (concomitant therapy); or 5 days of lansoprazole and amoxicillin followed by 5 days of lansoprazole, clarithromycin, and metronidazole (sequential therapy). Eradication was assessed by urea breath test 6–8 weeks after randomisation. The trial was not masked. Our primary outcome was probablity of *H pylori* eradication. Our analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, registration number NCT01061437.**

Findings **1463 participants aged 21–65 years were randomly allocated a treatment: 488 were treated with 14-day standard therapy, 489 with 5-day concomitant therapy, and 486 with 10-day sequential therapy. The probability of eradication with standard therapy was 82·2% (401 of 488), which was 8·6% higher (95% adjusted CI 2·6–14·5) than with concomitant therapy (73·6% [360 of 489]) and 5·6% higher (–0·04% to 11·6) than with sequential therapy (76·5% [372 of 486]). Neither four-drug regimen was significantly better than standard triple therapy in any of the seven sites.**

Interpretation **Standard 14-day triple-drug therapy is preferable to 5-day concomitant or 10-day sequential four-drug regimens as empiric therapy for *H pylori* infection in diverse Latin American populations.**

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Introduction

Helicobacter pylori infects most of the world's adult population and is the principal cause of gastric cancer, accounting for an estimated 60% of all cases.[1–3] Gastric cancer is second only to lung cancer as a cause of cancer death worldwide, and almost all of the nearly 1 million cases and 0·75 million deaths each year occur in east Asia and Latin America.[4] Although gastric cancer death rates have fallen in recent decades, the number of deaths has actually increased as a consequence of ageing populations, and gastric cancer is projected to rank among the ten leading global causes of death by 2030.[5,6] *H pylori* is also the main cause of peptic ulcer disease, which accounts for the loss of about 4·6 million disability-adjusted life-years every year worldwide, with most of the burden borne by populations in low-income and middle-income countries.[7] Population-wide eradication programmes seem to offer the most direct approach to reducing the enormous human and economic consequences of *H pylori* infection; however, none has been implemented to date.[8]

Large programmes for *H pylori* eradication require a practical and inexpensive antibiotic regimen that is effective in the specific locale where it will be used. Standard antibiotic regimens for *H pylori* usually entail a proton-pump inhibitor, amoxicillin, and clarithromycin, taken together over 7–14 days.[9–11] However, the effectiveness of these triple-therapy regimens seems to have diminished over time, largely as a result of emerging resistance of the organism to clarithromycin.[12,13] Recent meta-analyses have shown that regimens that add a nitroimidazole (metronidazole or tinidazole) to triple

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See Comment page 462

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For more on the **Rome III diagnostic questionnaire** see http://www.theromefoundation.org

therapy and are given either sequentially for 10 days or concomitantly for 5 days are significantly more successful at eradication of *H pylori* infection than are triple-therapy regimens.[14–16] These regimens also require fewer doses of antibiotics and thus might be more affordable in low-resource settings. Almost all the evidence supporting these four-drug regimens comes from Europe and Asia; few data are available from Latin America, a region with some of the world's highest rates of gastric cancer mortality.[17] We therefore undertook a randomised trial in Latin America comparing the effectiveness of four-drug regimens given concomitantly or sequentially with that of a standard 14-day regimen of triple therapy. The trial also provided insights into the feasibility of community-based programmes of *H pylori* eradication.

Methods

Study design and patients

The trial (SWOG S0701) was a randomised trial of empiric 14-day triple, 5-day concomitant, and 10-day sequential therapies for *H pylori* infection in seven Latin American sites: Chile (Santiago), Colombia (Túquerres), Costa Rica (Guanacaste), Honduras (Santa Rosa de Copán), Mexico (Ciudad Obregón and Tapachula), and Nicaragua (León). Between September, 2009, and June, 2010, study research staff recruited potential participants from the general population of adult men and women aged 21–65 years and explained the purpose and eligibility requirements of the study to them. Staff in Colombia, Costa Rica, and Nicaragua selected individuals from a census of households, in Chile they selected potential participants from a list of individuals served by a large public primary care clinic, and in Honduras and Mexico (two sites) they recruited participants by walking house-to-house within the local community or through announcements at primary care clinics.

Study participants in Tapachula (Mexico), Nicaragua, and Chile were predominantly urban, and those in the other sites were from small, rural communities. Potential participants were deemed ineligible if they had been treated in the past for *H pylori* infection, had serious illnesses that might end their lives before completing the study, or had other disorders that required or precluded treatment with antibiotics or proton-pump inhibitors. They also had to agree to abstain from alcohol use for at least 2 weeks. Those who expressed an interest in participating and gave signed, informed consent then completed an interview regarding socioeconomic characteristics and health history and a detailed gastrointestinal-symptom-history assessment with the validated Spanish language version of the Rome III diagnostic questionnaire for the adult functional gastrointestinal disorders.[18,19] The institutional review boards for each clinical centre and for the SWOG Statistical Center, Seattle, WA, USA approved the study protocol.

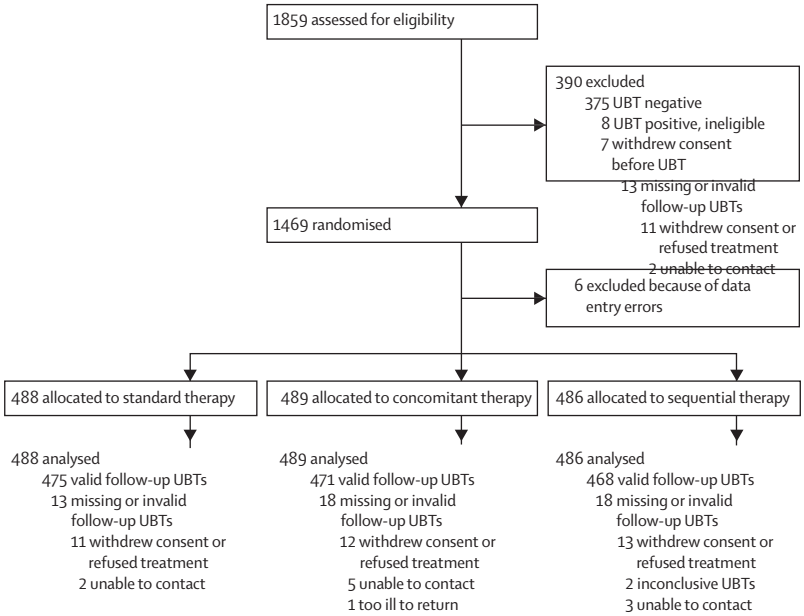

Figure: **Trial profile**
UBT=urea breath test.

Procedures

Participants provided a urea breath test for *H pylori* infection by exhaling into foil balloons before, and 30 min after, consuming a 75 mg dose of ^{13}C-labelled urea with water. Staff at each centre analysed the breath samples using an infrared mass spectrometry device (IRIS, Wagner Analysen Technik, Bremen, Germany) that produced a computer-generated result of positive (change relative to baseline ≥4·0%) or negative (change relative to baseline <2·5%); intermediate values were classified as inconclusive. If a participant reported use of an antibiotic or proton-pump inhibitor within the past 15 days, or if the result from the urea breath test was inconclusive, the test was rescheduled for a later date.

Study staff contacted participants at least once during treatment to encourage adherence and to remind them to return any unused doses at their follow-up visit, which was scheduled to occur 6–8 weeks after randomisation. During follow-up visits, participants completed another interview assessing adherence to therapy, their reasons for missing any doses of the regimens, and the occurrence of any new or worsened medical disorders that led them to seek medical attention. Study staff counted the number of drug doses returned and administered the follow-up urea breath test.

Randomisation and masking

Participants who had a positive urea breath test and met all other eligibility criteria were randomly assigned, in equal proportions, to one of three treatment groups: standard triple therapy of lansoprazole 30 mg, amoxicillin 1000 mg, and clarithromycin 500 mg taken twice a day for

14 days; concomitant therapy of lansoprazole 30 mg, amoxicillin 1000 mg, clarithromycin 500 mg, and metronidazole 500 mg taken twice a day for 5 days; or sequential therapy of lansoprazole 30 mg and amoxicillin 1000 mg taken twice a day for 5 days followed by lansoprazole 30 mg, clarithromycin 500 mg, and metronidazole 500 mg taken twice a day for 5 days. Each clinical centre purchased its own supply of the drugs, as generic (off-patent) preparations, from suppliers in country, except the centres in Honduras and Nicaragua, which both used the same supplier in Honduras. The drug suppliers provided quality-control data for the content and dissolution of each drug. Randomisation was implemented centrally through a dynamic balancing procedure at the SWOG Statistical Center to ensure balance within centre by age and sex across the three regimens. Staff at the clinical centres entered data for potentially-eligible, consented individuals into the SWOG Statistical Center computer using a web-based data entry system. If the participants met all eligibility requirements, the computer assigned them to a treatment group and immediately transmitted the treatment assignment to the clinical centre. All participants were randomly assigned in a 1:1:1 ratio within 2 weeks after a positive urea-breath-test result. The trial was not masked.

Statistical analysis

We designed the study to address two primary hypotheses. The first hypothesis was that 5-day concomitant therapy was not inferior to 14-day standard therapy, whereby inferiority was defined as a difference in eradication probability of 5% or greater in favour of standard therapy. We reasoned that the shorter duration and lower cost associated with concomitant therapy would make it preferable to standard therapy if it were not appreciably less effective in eradication of *H pylori* infection. Our second hypothesis was that 10-day sequential therapy would be more effective than 14-day standard therapy, because a four-drug sequential regimen would be preferred over standard three-drug therapy only if it were clearly superior in eradication of *H pylori* infection. Assuming an eradication rate of 80% for standard therapy, 10% missing follow-up urea-breath-test results, and 210 randomised participants per centre (1470 total), each treatment group comparison would have 82% power to detect a difference of 8% or greater, based on a two-sided, 0·025-level test. Although a meta-analysis by Essa and colleagues[16] suggested that concomitant therapy was about 10% better than sequential therapy, if the therapies were actually equivalent the trial would have 46% power to reject the inferiority of concomitant therapy, based on a one-sided, 0·025-level test.

Our primary statistical analyses adhered to the intention-to-treat principle and included all randomised eligible participants, with those without a definitive follow-up urea breath test judged to be treatment failures (urea-breath-test positive). To compare concomitant versus standard therapy, we used a two-sample Z test of the null hypothesis, in which the difference in the estimated probabilities of eradication was 5% or greater

	14-day standard therapy (N=488)	5-day concomitant therapy (N=489)	10-day sequential therapy (N=486)	Total (N=1463)
Centre				
Santiago (Chile)	69 (14%)	70 (14%)	70 (14%)	209 (14%)
Túquerres (Colombia)	71 (15%)	72 (15%)	69 (14%)	212 (15%)
Guanacaste (Costa Rica)	70 (14%)	70 (14%)	70 (14%)	210 (14%)
Copán (Honduras)	70 (14%)	72 (15%)	71 (15%)	213 (15%)
Tapachula (México)	71 (15%)	69 (14%)	70 (14%)	210 (14%)
Obregón (México)	70 (14%)	69 (14%)	71 (15%)	210 (14%)
León (Nicaragua)	67 (14%)	67 (14%)	65 (13%)	199 (14%)
Sex				
Women	287 (59%)	288 (60%)	286 (59%)	861 (59%)
Men	201 (41%)	201 (41%)	200 (41%)	602 (41%)
Age (years)				
20–29	66 (14%)	66 (14%)	91 (19%)	223 (15%)
30–39	137 (28%)	139 (28%)	117 (24%)	393 (27%)
40–49	142 (29%)	117 (24%)	127 (26%)	386 (26%)
≥50	143 (29%)	167 (34%)	151 (31%)	461 (32%)
Years of education				
≤4	88 (18%)	77 (16%)	80 (17%)	245 (17%)
5–8	135 (28%)	166 (34%)	143 (29%)	444 (30%)
9–12	146 (30%)	135 (28%)	136 (28%)	417 (29%)
≥13	71 (15%)	71 (15%)	70 (14%)	212 (14%)
Not reported	48 (10%)	40 (8%)	57 (12%)	145 (10%)
Chronic dyspeptic symptoms				
Present	125 (26%)	121 (25%)	127 (26%)	373 (26%)
Absent	363 (74%)	368 (75%)	359 (74%)	1090 (75%)

Data are n (%).

***Table 1*: Participant characteristics by treatment group**

	Standard therapy (N=475)	Concomitant therapy (N=471)	Sequential therapy (N=470)	Total (N=1416*)
Amount of drugs taken†				
All (100%)	427 (90%)	442 (94%)	437 (93%)	1306 (92%)
Nearly all (>80%)	7 (2%)	0 (0)	2 (<1%)	9 (<1%)
Most (50–80%)	24 (5%)	14 (3%)	21 (4%)	59 (4%)
Less than half (<50%)	10 (2%)	8 (2%)	5 (11%)	23 (2%)
Undetermined (but not all)	7 (2%)	5 (1%)	5 (1%)	17 (1%)
None	0 (0)	2 (<1%)	0 (0)	2 (<1%)
Reasons for not taking all drugs‡				
Concern about having or developing side-effects	41 (9%)	28 (6%)	33 (7%)	102 (7%)
Unrelated illness or injury	3 (1%)	1 (<1%)	5 (1%)	9 (<1%)
Forgot or inconvenient	36 (8%)	25 (5%)	37 (8%)	98 (7%)
Reason not given	0 (0)	3 (<1%)	2 (<1%)	5 (<1%)

Data are n (%). *Includes 1414 participants with a valid follow-up urea breath test and two (from the sequential therapy group) whose urea breath test results were inconclusive. †Based on count of returned drugs and self-report among participants who returned for a follow-up urea breath test. ‡Multiple responses allowed.

***Table 2*: Adherence to treatment of patients that returned for 6-week follow-up, by treatment group**

in favour of the standard regimen, based on a one-sided test of non-inferiority. Comparison of sequential versus standard therapies was based on a two-sample *Z* test for no difference between eradication probabilities. Sensitivity to missing data assumptions was examined by excluding data from participants without a conclusive follow-up urea breath test. To establish how poor adherence could have affected our conclusions, we further restricted the analyses to participants with a definitive urea breath test who had taken at least 80% of their assigned study drugs.

Secondary analyses assessed variability in treatment outcome by sex, age, presence of chronic dyspeptic symptoms, and clinical centre. Tests of interaction were calculated as deviance tests comparing logistic regression models with the treatment group indicators, the designated covariate, and their interaction terms, with those without the interaction terms.

All analyses were done with SAS version 9.2 and R version 2.12.2 statistical software. Bonferroni-adjusted 95% CIs were used to account for the two primary comparisons, and p values less than 0·025 were classed as statistically significant. No corrections for multiplicity were applied to secondary analyses, because they were considered to be exploratory. All p values were two-sided except the test of non-inferiority.

This trial is registered with ClinicalTrials.gov, registration number NCT01061437.

	N	*Helicobacter pylori* eradication	Difference from standard group (adjusted 95% CI for difference)
Intention to treat (N= 1463)			
14-day standard therapy	488	401 (82·2% [78·5 to 85·5])	..
5-day concomitant therapy	489	360 (73·6% [69·5 to 77·5])	8·6% (2·6 to 14·5)
10-day sequential therapy	486	372 (76·5% [72·5 to 80·2])	5·6% (–0·4 to 11·6)
Definitive 6-week UBT (N=1414)			
14-day standard therapy	475	401 (84·4% [80·8 to 87·6])	..
5-day concomitant therapy	471	360 (76·4% [72·3 to 80·2])	8·0% (2·2 to 13·7)
10-day sequential therapy	468	372 (79·4% [75·5 to 83·1])	4·9% (–0·9 to 10·8)
Adherent to therapy (N=1314)			
14-day standard therapy	434	378 (87·1% [83·6 to 90·1])	..
5-day concomitant therapy	442	348 (78·7% [74·6 to 82·5])	8·4% (2·7 to 14·0)
10-day sequential therapy	438	355 (81·1% [77·1 to 84·6])	6·0% (0·3 to 11·8)

Data are number (% [95% CI]) unless otherwise indicated. UBT=urea breath test.

***Table 3:* *Helicobacter pylori* eradication by treatment group for three definitions of analysis population**

	N	*Helicobacter pylori* eradication	Difference from standard group (adjusted 95% CI)	p value for interaction*
Sex	..	..	..	0·91
Women	861	..	..	..
14-day standard	287	234 (81·5%)	..	..
5-day concomitant	288	207 (71·9%)	9·7% (1·8 to 17·5)	..
10-day sequential	286	214 (74·8%)	6·7% (–1·4 to 14·8)	..
Men	602	..	..	
14-day standard	201	167 (83·1%)	..	..
5-day concomitant	201	153 (76·1%)	7·0% (–2·0 to 15·9)	..
10-day sequential	200	158 (79·0%)	4·1% (–5·2 to 13·3)	..
Age	..	..	..	0·21
21–40 years	663	..	..	..
14-day standard	222	182 (82·0%)	..	..
5-day concomitant	220	164 (74·5%)	7·4% (–1·3 to 16·2)	..
10-day sequential	221	160 (72·4%)	9·6% (0·3 to 18·9)	..
41–65 years	800	..	..	..
14-day standard	266	219 (82·3%)	..	..
5-day concomitant	269	196 (72·9%)	9·5% (1·4 to 17·5)	..
10-day sequential	265	212 (80·0%)	2·3% (–5·6 to 10·3)	..
Chronic dyspeptic symptoms	..	..	..	0·38
Absent	1090	..	..	..
14-day standard	363	297 (81·8%)	..	..
5-day concomitant	368	277 (75·3%)	6·5% (–0·2 to 13·3)	..
10-day sequential	359	281 (78·3%)	3·5% (–3·4 to 10·5)	..
Present	373	..	..	..
14-day standard	125	104 (83·2%)	..	..
5-day concomitant	121	83 (68·6%)	14·6% (2·5 to 26·7)	..
10-day sequential	127	91 (71·7%)	11·5% (–0·9 to 24·0)	..

(Continues on next page)

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the study and participated in the decision to submit for publication.

Results

1859 potentially-eligible adults agreed to participate in the study and completed the screening interview and intake questionnaire, but seven withdrew before the urea breath test (figure). The test was positive for 1471 (79%) of 1852 tested participants. Eight patients with a positive test were not randomly assigned because they opted not to be treated, could not be randomly assigned within 2 weeks of their urea breath test, or had a disqualifying factor (eg, pregnancy). Six participants with a negative urea breath test, who were randomly assigned incorrectly because of data entry errors, were withdrawn from the study before receiving treatment, and their data were not included in any of the following analyses. Of the eligible participants who were randomised, 861 (59%) of 1463 were women, 847 (58%) of 1463 were age 40 years or older, and 373 (25%) of 1463 had chronic dyspeptic symptoms as classified by the Rome III criteria. Participant characteristics were balanced between the three treatment groups (table 1). 47 participants did not return for their follow-up urea breath test, and two participants had follow-up tests that were inconclusive after two repeat tests. Thus, we obtained definitive follow-up urea-breath-test results for 1414 (97%) of 1463 of the randomised eligible participants (figure).

Table 2 shows adherence to treatment of patients that returned for 6-week follow-up. 1313 (92%) of

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