Challenging the dogma: a randomized trial of standard vs. half-dose concomitant nonbismuth quadruple therapy for *Helicobacter pylori* infection

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Abstract

Background: Current treatment of *Helicobacter pylori* consists of three or four drugs for 7–14 days with important associated cost and adverse events.

Aims: This study compared efficacy and safety of standard dose vs. half-dose concomitant nonbismuth quadruple therapy (NBQT) for 7 days. The standard dose consisted of twice daily rabeprazole 20 mg, amoxicillin 1 g, metronidazole 500 mg, and clarithromycin 500 mg.

Methods: This was a prospective randomized trial. ^{14}C -urea breath test was performed ≥ 4 weeks after treatment and ≥ 2 weeks off acid suppressive therapy. Compliance and adverse events were monitored during treatment.

Results: A total of 200 consecutive treatment-naïve patients were enrolled. Baseline characteristics were similar between groups, with 15.5% of subjects reporting prior macrolide use. Eradication occurred in 78% (95% CI 68.6–85.7%) in both groups on intention-to-treat analysis. Per-protocol rates were 82.1 vs. 83.9% for standard-dose patients vs. half-dose patients, respectively ($p = \text{NS}$). Adverse events (only mild) were reported in 57 vs. 41% of standard-dose patients vs. half-dose patients ($p = 0.024$), with metallic taste and nausea notably less frequent in the latter (36 vs. 12% and 18 vs. 7%, respectively; $p < 0.05$ for both). Overall, eradication failed in 38.7% of prior macrolide users vs. 18.9% without such exposure ($p = 0.019$). On multivariate logistic regression, prior macrolide exposure was the only factor associated with failed eradication (OR 2.60, 95% CI 1.06–6.39; $p = 0.038$). Treatment was cheaper with the half-dose regimen.

Interpretation: A 50% reduction in antibiotic dosage does not diminish efficacy of concomitant nonbismuth quadruple therapy but leads to significant reduction in cost and adverse events. Seven-day concomitant NBQT is suboptimal for *H. pylori* independent of prior macrolide exposure.

Keywords

Adverse events, dyspepsia, eradication, gastritis, pylori

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Introduction

Helicobacter pylori is a common infection worldwide, particularly in developing countries.¹ *H. pylori* infection is associated with chronic gastritis, peptic ulcer disease, and gastric adenocarcinoma and non-Hodgkin's mucosa-associated lymphoid tissue lymphoma of the stomach.^{2,3} Eradication of this organism has been shown to improve gastric inflammation,

accelerate ulcer healing, eliminate ulcer diathesis, and even reverse early mucosa-associated lymphoid tissue

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lymphoma.^{4–6} Several treatment regimens for the eradication of *H. pylori* have been adopted in different regions of the world with varying results, but the search continues for a safe, tolerable, cheap, and highly effective regimen. To be considered effective, a treatment regimen should achieve at least an 80% eradication rate,⁷ with some experts suggesting that the target eradication rate should be closer to 90–95%.⁸ The most commonly used regimen worldwide is the so-called triple regimen consisting of a proton pump inhibitor (PPI) and clarithromycin in combination with amoxicillin or, in the case of penicillin allergy, metronidazole.^{6,7} Despite recent evidence that the efficacy of this ‘heritage’ clarithromycin-based triple therapy is waning – to unacceptably low levels in some populations – it remains the most commonly used first-line therapy for eradication of *H. pylori*.⁸

The addition of metronidazole to legacy triple therapy, whether part of the sequential or concomitant regimen, as so-called nonbismuth quadruple therapy (NBQT), has been shown to improve eradication rates of *H. pylori*, including clarithromycin-resistant strains.^{9,10} A meta-analysis by Essa et al.¹¹ comparing all three aforementioned regimens concluded that sequential and concomitant quadruple therapy are equally effective and superior to standard triple therapy (STT). The concomitant regimen was found to be less complex than the sequential regimen and was therefore recommended in regions where STT was rendered ineffective. A recent study from Spain and Italy,¹² regions of relatively high clarithromycin resistance (19–20%), suggested that more than 90% of *H. pylori* infections can be eradicated with a 14-d course of concomitant or hybrid (PPI and amoxicillin for 14 days with addition of clarithromycin and nitroimidazole for the final 7 days) NBQT including high-dose PPI (omeprazole 40 mg b.i.d.).

We have recently shown that a 10-day half-dose triple regimen – where the dose of all three components of the STT is reduced by 50% – can achieve similar eradication rate as its standard-dose counterpart but with significant reduction in adverse events and cost. The overall eradication rate was, however, suboptimal (77.6% with standard-dose therapy and 77.2% with half-dose triple therapy on ITT), signalling a 13.8% decline in eradication rate of the exact standard-dose regimen over a 6-year period within the same geographic area and institution.^{13,14} Based on the reported superiority of NBQT and the promising concept of reduced-dose combination therapy, this study was designed to investigate the efficacy and safety of 7-day standard-dose vs. half-dose concomitant NBQT regimen for the eradication of *H. pylori* infection.

Materials and methods

Study design

From December 2011 to August 2012, 200 consecutive adult patients with *H. pylori* infection, documented by either urea breath test (UBT) or rapid urease assay, were enrolled in the study. Patients were excluded if they were allergic to any of the drugs used, had taken antibiotics recently (within 2 weeks of enrolment), had severe ulcers or bleeding, gastric perforation or obstruction, previous gastrectomy, or gastric cancer, were pregnant or lactating, had received prior eradication therapy for *H. pylori*, or had severe concomitant disease or a condition making the treatment unlikely to be effective (e.g. alcoholism or drug addiction). The study was approved by the Institutional Review Board at the American University of Beirut and registered at clinicaltrials.gov (ID: NCT01219764).

After informed consent, patients were randomized using a computer-generated random-numbers table into one of two treatment groups. Patients in the standard-dose group were assigned to receive rabeprazole 20 mg b.i.d. (before meals), amoxicillin 1 g b.i.d. (with or after meals), clarithromycin 500 mg b.i.d. (with or after meals), and metronidazole 500 mg b.i.d. (with or after meals) for 7 days. Patients in half-dose arm received all four drugs but at 50% posology. A brief questionnaire was filled out for each patient regarding demographics including age, sex, height, weight, smoking status, previous use of clarithromycin or azithromycin, and current use of PPIs. All study participants were contacted by telephone on days 3 and 7 of the treatment period to evaluate compliance and inquire about possible adverse events. Patients were specifically asked if they experienced nausea, diarrhoea, abdominal pain, or metallic taste during the course of treatment. ¹⁴C-UBT were performed a minimum of 4 weeks after therapy or use of any antibiotic and a minimum of 2 weeks off any acid-suppressive therapy.

Statistical analysis

The primary end point of the study was the rate of *H. pylori* eradication. The sample size calculation for a noninferiority trial, assuming an eradication rate in the standard and half-dose groups of 90% and a noninferiority limit of 10–11% with 80% power, was 93 to 112 patients per arm. Secondary end points included adverse events and overall cost, factoring in the cost of failed therapy (i.e. use of a second-line eradication regimen and repeat UBT testing). All data entry and statistical analysis were carried out using SPSS version 16.0 for Windows (SPSS, Chicago, IL, USA). Chi-squared and Fisher

exact tests were used to compare the major outcomes between these groups. A p -value <0.05 was considered statistically significant.

Eradication rates were evaluated by both intention-to-treat (ITT) and per protocol (PP) analyses. The ITT analysis included all study participants who took at least one dose of the study medications. Patients who were subsequently lost to follow up after starting treatment or whose infection status was unknown after treatment were considered treatment failures for the purpose of the ITT analysis. The PP analysis included only patients who completed a full course of therapy according to study instructions and returned for a post-treatment UBT. Differences in adverse events were compared between groups using Chi-squared and Fisher exact tests. Univariate testing using Chi-squared and Fisher exact tests was also used to determine whether any of the patient's characteristics obtained from the patient questionnaire were significant factors affecting the response to treatment in both groups.

Results

A total of 200 patients infected with *H. pylori* were randomized to either standard-dose ($n=100$) or half-dose arm ($n=100$). The clinical and demographic characteristics of the study subjects are summarized in Table 1. There was no significant difference in age, sex, body mass index, smoking status, previous use of macrolides, or current use of PPIs between the two groups. Of the study patients, 181 had oesophagogastroduodenoscopy and 43 (23.8%) had documented peptic ulcer disease: 21/92 (22.8%) in the standard-dose arm vs. 22/89 (24.7%) in the half-dose arm, respectively ($p=0.54$). Overall, 10 patients (three in the standard-dose group and seven in the half-dose group) did not complete the study and/or return for UBT after treatment; two patients from the standard-dose group stopped treatment on day 3 and then resumed 2 days later because of severe nausea (Figure 1). On ITT analysis, the eradication rate for

both groups was 78 out of 100 (78.0%, 95% CI 68.6–85.7%) and on PP analysis, the eradication rate was 78/95 (82.1%, 95% CI 72.9–89.2%) in the standard-dose group vs. 78/93 (83.9%, 95% CI 74.8–90.7%; $p=0.71$) in the half-dose group (Figure 2). There was no difference in *H. pylori* eradication rates between those with or without endoscopically proven peptic ulcer disease.

All patients were evaluated for compliance and adverse events on days 3 and 7 of treatment. Compliance, self-reported during phone interview on day 7 of treatment, was 98 and 100% in both groups (Figure 1). In total, 57.0% of patients in the standard-dose group vs. 41.0% in the half-dose group reported at least one adverse event during therapy ($p=0.024$). Metallic taste was the most commonly reported adverse effect in both groups (36% in the standard-dose group vs. 12% in the half-dose group on day 7 of treatment, respectively; $p<0.001$). Nausea was the second most common side effect (18% in standard-dose group vs. 7% in half-dose group on day 7 of treatment; $p=0.019$) (Table 2).

Treatment failure was noted in 12/31 patients (38.7%) who reported prior macrolide use compared to 32/169 (18.9%) patients who did not (ITT; $p=0.019$) (Figure 3). On multivariate analysis, age, sex, body mass index, smoking status, peptic ulcer disease, and use of PPIs before treatment did not have any significant impact on the observed eradication rates. Previous macrolide use was the only variable significantly associated with an increased risk of ineffective eradication (OR 2.60, 95% CI 1.06–6.39; $p=0.038$). Given absolute parity in the eradication rate in both groups, the cost of treatment (based on local retail price) was significantly less in patients receiving the half-dose regimen (ITT analysis; $p<0.05$).

Discussion

The ideal *H. pylori* treatment regimen should be effective, simple, affordable, and tolerable with minimal side effects. The recent Maastricht III consensus guidelines

Table 1. Patient characteristics

	Standard-dose ($n=100$)	Half-dose ($n=100$)	p -value
Age	47.3 $\pm$ 17.2	44.7 $\pm$ 15.5	0.264
Body mass index	26.8 $\pm$ 5.5	25.6 $\pm$ 4.3	0.086
Male gender	48	57	0.203
Smoking	48	51	0.671
Prior macrolide use	16	15	0.845
Current PPI use	42	34	0.221

Values are mean $\pm$ SD or n .
PPI, proton pump inhibitor.

recommend the use of either triple or bismuth-based quadruple therapy as first-line therapy but caution that clarithromycin-based regimens should be abandoned when local resistance to this macrolide antibiotic exceeds 15–20%. Worldwide resistance data confirm a time-dependent increase in clarithromycin resistance and a parallel decline in the eradication rates

of STT.^{15–19} Several randomized controlled trials have demonstrated that NBQT, involving the addition of metronidazole or tinidazole to STT, is equally well tolerated but more effective than STT, including for clarithromycin-resistant strains.^{9,10} In 2009, a meta-analysis of 15 studies involving 1723 patients calculated a mean ITT cure of 90% for NBQT.

Figure 1. Study consort flow diagram.

Figure 2. Rates of eradication according to group assignment. ITT, intention-to-treat; PP, per-protocol.

The concomitant version of NBQT was found to be as effective as sequential therapy, yet simpler^{11,20} and was recommended by some as first line therapy for *H. pylori* in regions where STT has been rendered relatively ineffective.¹¹ More recently, multiple trials of concomitant NBQT have confirmed an ITT eradication rate of 75–96.4% (per-protocol rates consistently superior to 80%) with a possible advantage for longer treatment duration (Table 3).^{15,16,21–32}

The results of this randomized trial appear to confirm our earlier observation¹³ that reduced-dose regimens (down to 50% posology) performs similarly to standard-dose regimens with the added benefit of reduced cost and adverse events. To date, three

randomized controlled trials, involving a total of 475 patients, have examined the value of 50% reduction in the dose of all administered antibiotics for *H. pylori* (two STT and the current concomitant NBQT) and have all confirmed similar eradication rates to the standard-dose comparator (Table 4), with a reduction in adverse events and cost.^{13,33} This concept is attractive and challenges the prevailing dogma in the treatment of *H. pylori*. One theoretical concern, however, is that these low-dose regimens may produce prolonged sub-minimum inhibitory concentration effects which may, in turn, contribute to development of resistant strains. However, the posology of antibiotics commonly used in *H. pylori* treatment regimens has been

Table 2. Side effects reported during treatment

	Standard dose (n = 100)	Half-dose (n = 100)	p-value
Day 3			
Nausea	23	16	0.212
Diarrhoea	12	13	0.831
Metallic taste	45	19	<0.001
Abdominal pain	12	10	0.651
Day 7			
Nausea	18	7	0.019
Diarrhoea	12	10	0.651
Metallic taste	36	12	<0.001
Abdominal pain	10	7	0.447

Figure 3. Failure of eradication according to macrolide exposure history.

largely empirical and has relied traditionally on standard single-agent antibiotic dosing standards such as those used, for example, for respiratory tract infections in adults. In fact, there is very limited information on antibiotic penetration and tissue levels in the gastric mucus layer and crypts where *H. pylori* lives. McNulty et al.³⁴ measured gastric mucosal concentrations of amoxicillin in patients at upper gastrointestinal endoscopy 38–480 min after a 500 mg oral dose of amoxicillin and found that high concentrations were

achieved (range 15–322 mg/kg); the lowest gastric mucosal concentration after 2 hours was 100 times the MIC₉₀ of 0.12 mg/l.³⁴ Nakamura et al.³⁵ measured plasma, gastric mucosa, and gastric juice concentrations following either low- or high-dose amoxicillin (750 or 1000 mg b.i.d.) and clarithromycin (400 or 500 mg b.i.d.) given in combination with omeprazole 20 mg b.i.d. to 12 male volunteers in an open crossover study. Amoxicillin and clarithromycin concentrations were highest in gastric juice followed by gastric

Table 3. Trials published since 2010 investigating concomitant NBQT

Authors	Year	No. of patients	Eradication ITT (%)	Eradication PP (%)	Course (days)	Region
Wu et al. ²¹	2010	117	93	93	10	Taiwan
Toros et al. ²²	2011	84	75	75	14	Turkey
Greenberg et al. ²³	2011	489	73.6	76.4	5	Latin America
Molina-Infante et al. ¹⁶	2012	209	87	89	10	Spain
Yanai et al. ²⁴	2012	59	94.9	98.3	7	Japan
Kongchayanun et al. ²⁵	2012	55	89.1	89.1	5	Thailand
Kongchayanun et al. ²⁵	2012	55	96.4	96.4	10	Thailand
Huang et al. ²⁶	2012	84	88.1	94.6	10	China
Kao et al. ²⁷	2012	319	93.7	96.4	7	Taiwan
Georgopoulos et al. ¹⁵	2013	127	90.5	93.3	10	Greece
Kim et al. ²⁸	2013	135	80.7	91.4	5	Korea
Lim et al. ²⁹	2013	78	80.8	81.3	14	Korea
McNicholl et al. ³⁰	2013	168	87	91	10	Spain
Molina-Infante et al. ³¹	2013	172	91.7	96.1	14	Spain and Italy
Zullo et al. ³²	2013	90	85.5	91.6	5	Italy
Current study	2013	200	78	82.9	7	Lebanon

Table 4. Randomized controlled trials examining standard-dose vs. half-dose antibiotic therapy for *H. pylori* infection

Authors	Year	No. of patients	Standard dose	Half-dose	Eradication rate (%: ITT/PP)
Keshavarz et al. ³³	2007	160	Omeprazole 20 mg b.i.d. Amoxicillin 1000 mg b.i.d. Clarithromycin 500 mg b.i.d. 14 days	Omeprazole 20 mg b.i.d. Amoxicillin 500 mg b.i.d. Clarithromycin 250 mg b.i.d. 14 days	Standard: 83.8/89 Half: 85/88
Mansour et al. ¹³	2011	115	Rabeprazole 20 mg b.i.d. Amoxicillin 1000 mg b.i.d. Clarithromycin 500 mg b.i.d. 10 days	Rabeprazole 10 mg b.i.d. Amoxicillin 500 mg b.i.d. Clarithromycin 250 mg b.i.d. 10 days	Standard: 77.6/78.9 Half: 77.2/81.5
Current study	2013	200	Rabeprazole 20 mg b.i.d. Amoxicillin 1000 mg b.i.d. Clarithromycin 500 mg b.i.d. Metronidazole 500 mg b.i.d. 7 days	Rabeprazole 10 mg b.i.d. Amoxicillin 500 mg b.i.d. Clarithromycin 250 mg b.i.d. Metronidazole 250 mg b.i.d. 7 days	Standard 78/82.1 Half 78/83.9

mucosa, and were both superior to plasma levels. After 6 hours, antibiotics were no longer detectable in mucosa samples. However, plasma and gastric juice concentrations remained above the minimum inhibitory concentration for amoxicillin- and clarithromycin-susceptible bacteria, including in recipients of the low-dose therapy.³⁵

An important result of this study is the significant reduction in cost and adverse events with the half-dose concomitant NBQT. Although adverse events are often mild with first-line *H. pylori* regimens, they remain frequent and are an important cause for noncompliance and suboptimal adherence with detrimental clinical outcomes. In *H. pylori* clinical trials, approximately 5–10% of enrolled subjects drop out or are excluded from per-protocol analysis because of adverse events, poor compliance, or adherence³⁶ and this number increases with longer duration of treatment.³⁷ In the recent trial by Moline-Infante et al.,¹² patients receiving the hybrid version of the 14-day NBQT (diminished pill burden by reduced exposure to clarithromycin and metronidazole to the last 7 days) had less adverse events (47 vs. 56%; $p=0.06$) and greater compliance (98.8 vs. 95.2%; $p=0.05$) than the concomitant NBQT version. Despite the long duration of therapy in that study, a heavy pill burden (112 tablets) and frequent, albeit mild, adverse effects, a remarkable 93.5% of 343 patients were ‘fully compliant’ with the prescribed concomitant NBQT and only 6% withdrew because of adverse events.¹² The real-world scenario is, however, different and is likely to be worse.

Drug therapies often possess different performance characteristics in controlled clinical trials compared to the real world (effectiveness vs. efficacy). Outcomes in clinical trials are often favoured because of the homogeneous nature of the study population, close patient follow up, the presence of well-defined protocols, adherence controls (e.g. pill counts, phone calls), financial incentive (free drug supplies, tests, and follow up), and patient motivation. Patient adherence is thus a critical variable that influences the ultimate effectiveness of treatment and adverse events are an important determinant to such adherence.

In our study, both standard-dose and half-dose concomitant NBQT for 7 days resulted in suboptimal eradication rates (<80%). Despite limited direct comparative data, a longer duration of NBQT is likely to result in improved eradication (Table 3). Prolonging the duration of therapy may add what amounts to 0.5–1%-per-day benefit in eradication rates but is expected to result in significant increase in adverse events and cost, as well as diminished compliance and adherence.

Whether the added benefit with respect to eradication rates is consistent in the case of clarithromycin-resistant strains is largely untested. In the absence of shorter, simpler, and safer alternatives, the use of 14-day NBQT may be an acceptable option in the era of increased resistance to clarithromycin. However, in our study, 38.7% of patients with a history of prior macrolide use failed to eradicate *H. pylori* compared to 18.9% of those with no such history. A history of prior macrolide use leads to more complex resistant

Figure 4. Clarithromycin sales in Lebanon 2008–2013 (data with permission from IMS Health Lebanon).

strains and the rates of resistance are directly proportional to the courses of macrolides used.^{38,39} A recent multicentre European survey study showed a steady increase in clarithromycin resistance, with almost doubling over a 10-year period from 9.8 to 17.5%.^{40,41} Studies have suggested that this global increase in clarithromycin resistance appears to correlate with increase prescription usage of clarithromycin, roxithromycin, and azithromycin.^{41,42} Although we did not perform *in vitro* susceptibility testing, the high rate of treatment failure noted in prior macrolide users in our study appears to support this conclusion. Data from IMS Health show a steady increase in the usage of clarithromycin in Lebanon, with approximately 75% growth over a period of 5 years (Figure 4).

In the recent multicentre Spanish–Italian study, 14-day of concomitant NBQT was successful at eradicating all clarithromycin-resistant strains of *H. pylori*. However, this was applicable to only eight patients (of 68 undergoing *in vitro* culture and susceptibility). Based on the above and in the absence of stronger evidence to the contrary, we believe that all clarithromycin-based regimens should be avoided in patients with known or documented history of prior macrolide use. Such an important variable should be sought in every patient considered for *H. pylori* treatment.

There are a few limitations to our study. Culture and *in vitro* susceptibility testing were not performed and hence the exact role of antibiotic resistance (namely to clarithromycin and metronidazole) in eradication failure cannot be evaluated. Moreover, information on prior macrolide use was collected from patients using a questionnaire and may therefore be subject to recall bias. Although this is one of the largest controlled trials on concomitant NBQT (Table 3), it was powered at 80% with a delta of 10% for noninferiority assuming an eradication rate of 90% in both study arms. Eradication rates in this study were, however, suboptimal in both arms. This notwithstanding, given absolute parity on ITT analysis, it is somewhat unlikely that we missed a true or clinically significant difference between both regimens. Lastly, the potential effect of *CYP2C19* genetic polymorphism on PPI metabolism and, consequently, the stability of the acid-labile antibiotics amoxicillin and clarithromycin was not investigated. This may conceivably be of added importance when one uses reduced-dose PPIs in *CYP2C19* ultra-metabolizers, a common phenotype in Western populations. It is important to note, however, that rabeprazole undergoes primarily a nonenzymic hepatic metabolism and that multiple studies have confirmed equivalent eradication rates between standard-dose and reduced-dose rabeprazole in clarithromycin-based triple therapy and independent of *CYP2C19* genetic polymorphism.⁴³ The equivalent eradication rates in our study in a

population with matching *CYP2C19* profile to people of European origin⁴⁴ appears to fall in line with this observation.

In conclusion, a 7-day half-dose concomitant NBQT is equally effective but better tolerated and cheaper than its standard-dose equivalent in the treatment of *H. pylori*. The concept of reduced-dose antimicrobials in multidrug *H. pylori* regimens seems partially validated and deserves further evaluation in large randomized controlled trials. Such a strategy can lead to significant cost savings, reduced adverse events, and enhanced compliance, adherence and treatment uptake and may constitute a paradigm shift in the treatment of *H. pylori*. Although likely, it remains unproven whether the half-dose strategy remains effective with extended concomitant NBQT for 10 or 14 days and leads to acceptable eradication rates.

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Conflict of interest

The authors declare that there is no conflict of interest.

Presentation

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