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RAPID COMMUNICATION

Optimal length of triple therapy for *H pylori* eradication in a population with high prevalence of infection in Chile

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Abstract

AIM: To compare the efficacy of 7-d versus 14-d triple therapy for the treatment of *H pylori* infection in Chile, with a prevalence of 73% in general population.

METHODS: *H pylori*-infected patients diagnosed by rapid urease test, with non-ulcer dyspepsia or peptic ulcer disease were randomized to receive omeprazole 20 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid for 7 (OAC7) or 14 (OAC14) d. Primary outcome was eradication rate 6 wk after the treatment. Subgroup analysis was carried out considering the eradication rate among patients with or without peptic ulcer disease and eradication rate among smokers or non-smokers.

RESULTS: One hundred and thirty-one patients were randomized to OAC7 (n = 69) or OAC14 (n = 62). The overall eradication rate (intention-to-treat) was 78.3% in OAC7 and 85.5% in OAC14 groups, without a significant difference (P =0.37). No significant difference in the eradication rate was found among the patients with peptic ulcer disease (n = 31) between the OAC7 group (85.7%) and OAC14 group (87.5%). However, smokers had an obviously lower eradication rate compared to non-smokers, particularly in the OAC7 group (57.1% in smokers *vs* 83.6% in non-smokers; P = 0.06). Adverse effects rate were similar between both groups.

CONCLUSION: Short-term efficacy of triple therapy with OAC for 7 d is comparable to 14 d in this high-prevalence population. Longer follow-up, and studies focused to some subgroups of patients (smokers and non-ulcer patients) are necessary to support widespread use of 7-d instead of 10-14-d triple therapy in a developing country like Chile.

Key words: *Helicobacter pylori*; Antibiotic treatment; Omeprazole; Amoxicillin; Clarithromycin; Quasi-randomized controlled trial

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INTRODUCTION

H pylori causes chronic gastritis and is associated with a higher incidence of peptic ulcer, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma[1].

Peptic ulcer disease and localized, low-grade MALT lymphoma are undisputed indications for treatment[2]. In other conditions, such as gastric cancer among first-degree relatives, patients with atrophic gastritis and dyspeptic patients with proven infection, there is a general consensus that *H pylori* eradication is also indicated. Even asymptomatic subjects with *H pylori* infection for any reason should be informed about risk of infection-related complications, and cost-benefit of treatment discussed in a case-by-case analysis[3,4].

Although several different treatment regimens have been proposed for *H pylori* eradication, triple therapy with a proton pump inhibitor (PPI), clarithromycin and amoxicillin is the most accepted therapy worldwide[5,6]. The eradication rate obtained with this combination is rather variable, ranging from less than 50%[7] to more than 95%[8]. There are important regional or geographical differences in success rates that have not been completely understood[6]; length of treatment, antibiotic dosage, bacterial resistance and other factors could be related to this variability.

In Europe, short (7 d) and low-dose antibiotic

treatment (clarithromycin 250 mg bid plus amoxicillin 500 mg bid) is usually recommended[5,9,10] while in the United States, 10 to 14 d of treatment is still preferred[11,12]. In 1997, the Asia Pacific Consensus Conference on the management of *H pylori* recommended a number of 7-d regimens[13]. The Latin American Consensus recommended 7 to 14-d treatment, with 10-d as the preferred regimen[14]. However, some recent studies from Asia have reported the eradication rates as low as 40.8%, even using triple therapy with PPI and antibiotics for 14 d[7].

Many recent studies have compared PPI-based triple therapies in short (7 d or less) and extended (10-14 d) schedules, and few have found significant differences in eradication rates although a trend towards better results with longer therapies is observed. However, as the number of patients is reduced, a B-type error may be present[8,15-17]. A recent meta-analysis on this topic showed that prolonging PPI-based triple therapy beyond 7 d improved treatment cure rates, and significant differences were found when 14-d therapies were compared to 7-d schedules[18]. Calvet *et al*[18] highlighted the importance of studies evaluating the cost-effectiveness of different lengths of therapy and suggested that geographical differences must be taken into account. To our knowledge, none of the included reports came from developing or high-prevalence countries. Because developing countries represent most of the infected population in the world, experiences coming from these areas are very important.

The scarce available information suggests that results obtained in developing countries usually are worse than those obtained in developed countries with the same therapy[19,20], but to our knowledge, there are no published systematic reviews on this particular topic.

Chile has a 73% (95% CI: 70%-76%) prevalence of *H pylori* infection in adult population and 79.5% in areas with high risk of gastric cancer[21]. This study was carried out in an urban area of Santiago with a high risk of gastric cancer and a frequency of *H pylori* infection among symptomatic patients of 78.7%[22]. *In vitro* antibiotic resistance was studied in 91 *H pylori* strains in Chile. All strains were susceptible to amoxicillin and only two strains (2.2%) were resistant to clarithromycin. Forty-two percent of strains were resistant to metronidazole and 13% were resistant to bismuth subcitrate[23]. Therefore, amoxicillin and clarithromycin plus proton pump inhibitors are recommended to eradicate *H pylori* in Chile. A randomized-controlled trial evaluated the efficacy of a short-term triple therapy among Chilean patients with peptic ulcer disease, with 3 d of azithromycin (500 mg OD) and 7 d of amoxicillin (750 mg tid) and a high (40 mg bid) or low (20 mg bid) dose of omeprazole; and the eradication rates were 57% and 61%, respectively[24], suggesting that short-term triple therapy with azithromycin has poor efficacy. However, there are no studies comparing short-term and extended triple therapy schedules with clarithromycin in a Chilean population.

This study aimed to compare the efficacy of 7-d versus 14-d course of omeprazole, amoxicillin and clarithromycin to eradicate *H pylori* infection in symptomatic patients from an urban area with high prevalence of *H pylori* infection.

MATERIALS AND METHODS

Protocol

The study was a quasi-randomized, open, comparative trial with two parallel treatment arms, performed in an outpatient care setting. Hispanic patients from an urban area of Santiago, with high prevalence of *H pylori* infection[21,22] and high risk of gastric cancer among patients with dyspepsia or abdominal pain[25], who were referred by gastroenterologists or general practitioners to an outpatient clinic with the indication of an upper gastro-intestinal (UGI) endoscopy to be performed in the endoscopy unit of the outpatient clinic of the Catholic University of Chile, were invited to participate in this study if *H pylori* infection was found. *H pylori* infection was assessed by a positive rapid urease test (RUT) (ProntoDry™, Medical Instruments Corporation, Brignais, France) on two or more antral biopsies[26,27]. Patients older than 18 years with positive RUT on antral biopsy were considered elegible. They were interviewed to check for inclusion criteria. After taking informed consent, the patients were randomized to receive either 7 or 14 d of omeprazole 20 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid. Exclusion criteria were: (1) Previous attempt of *H pylori* eradication; (2) concomitant or recent (within 3 mo) use of PPI, antibiotics or non-steroidal anti-inflammatory drugs; (3) total or partial gastrectomy; (4) gastric cancer suspected or demonstrated; and (5) known allergies to any of the drugs included in this study. Previous antibiotic exposure, defined as antibiotic usage more than 3 and less than 24 mo before exclusion, was registered at the first interview.

At least 6 wk after the end of therapy, all patients underwent a second UGI endoscopy, and RUT on antral biopsies was performed again in order to document *H pylori* eradication. Those patients not eradicated at this time received a second-line treatment beyond the study protocol. Primary outcome was *H pylori* eradication. Secondary outcome was the occurrence of adverse effects. Subgroup analyses were also performed.

The endoscopic findings were categorized as: (1) Peptic ulcer disease, when a discrete mucosal defect, at least 5 mm wide or with perceptible depth was observed in the gastric or duodenal mucosa; (2) erosive non-ulcer disease, when multiple (more than three) small (less than 5 mm) superficial mucosal defects, with a flat edge and no depressed base were observed in the gastric or duodenal mucosa, or esophageal mucosal breaks were seen, according to Los Angeles classification[26]; (3) normal endoscopy, when no evident lesions were observed. Non-erosive, non-specific changes on the esophageal, gastric or duodenal mucosa were classified as normal.

Recruitment of patients was performed from January 2003 to July 2004. The study was performed in accordance with the principles of good clinical research practice and the Declaration of Helsinki.

Assignment

Randomization was open, by means of the last digit of the identification number: odd numbers were assigned to the OAC7 group and even numbers to the OAC14 group.

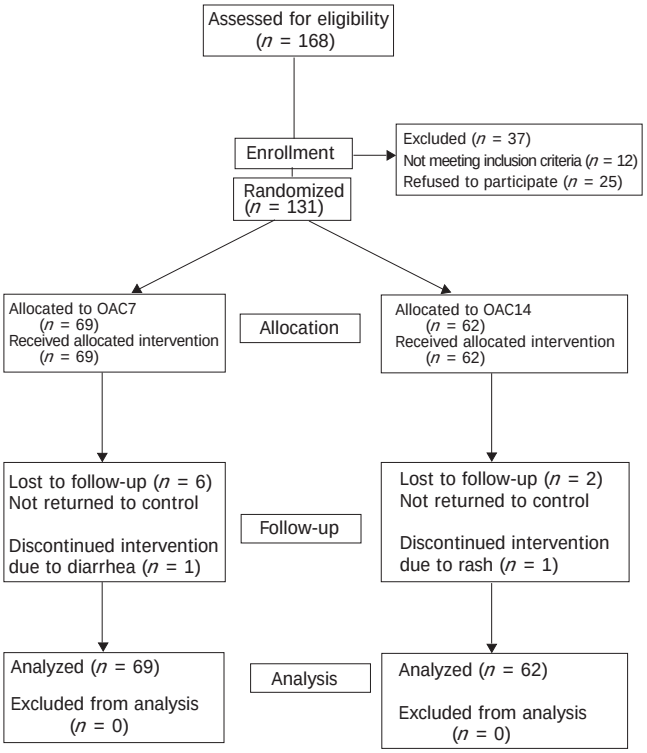

Figure 1 Study design and flow chart.

Compliance was assessed by the pill count method during a second interview after treatment. Adverse effects were registered and graded throughout and after treatment by the investigators as follows: none; mild (aware of symptoms, but easily tolerated); moderate (discomfort sufficient to cause interference with normal activities); and severe (incapacitating, with inability to perform normal activities).

Clinical characteristics of the groups

Patient flow chart, considering eligibility, randomization process and allocation of patients to OAC7 or OAC14 and follow-up of patients from both groups is described in detail in Figure 1.

Statistical analysis

Statistical effect size estimation was done. A sample size of 112 patients was estimated considering an effect size of 15% and a confidence interval ranging from 9% to 23% (with 80% power and 95% of confidence). The demographic and clinical characteristics of the patients were compared with Student's *t*-test for independent samples or Fisher's exact test for discrete variables (sex, adverse effects and presence or absence of eradication). Eradication was analyzed both on an intention-to-treat and on a per-protocol basis. Results were expressed as mean ± standard deviation (SD). $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS version 10.0 (Standard version, SPSS Inc.).

RESULTS

One hundred and sixty-eight patients were considered eligible and 37 of them were excluded from the study for the following reasons. Twenty-five were excluded because they refused to consent, 4 with suspected or proven gastric cancer, 6 because of previous adverse reactions to amoxicillin or penicillin and 2 patients because of recent use of antibiotics. Finally, 131 patients were included.

Table 1 Baseline characteristics of patients *n* (%)

	OAC7 (*n* = 69)	OAC14 (*n* = 62)
Age (yr)	47.5 ± 16	45 ± 15
Male	27 (39.1)	18 (29)
Smokers	14 (20.3)	21 (33.9)
Previous antibiotic exposure		
Betalactamics	56 (81.2)	51 (82.3)
Clarithromycin	13 (18.8)	18 (29)
Metronidazol	13 (18.8)	12 (19.4)
Tetracyclines	32 (46.4)	26 (41.9)
Endoscopic diagnosis		
Ulcer disease	14 (20.3)	24 (38.7)
Non-ulcer disease	44 (63.8)	30 (48.4)
Normal	11 (15.9)	8 (12.9)

Table 2 Eradication rate after treatment and subgroup analyses *n* (%)

Eradication rate according to:	OAC7 (*n* = 69)	OAC14 (*n* = 62)	*P*
Length of treatment	54 (78.3)	53 (85.5)	0.37
Smoking status			
Smoker	8 (57.1)	17 (81)	0.15
Non smoker	46 (83.6)	36 (87.8)	0.88
Endoscopic diagnosis			
Ulcer disease	12 (85.7)	21 (87.5)	1.0
Non-ulcer disease	35 (79.5)	25 (83.3)	0.77
Normal	7 (63.6)	7 (87.5)	0.34
Previous antibiotic exposure			
Betalactamics	46 (82.1)	43 (84.3)	0.8
Clarithromycin	10 (76.9)	16 (88.9)	0.63
Metronidazol	9 (69.2)	10 (83.3)	0.64
Tetracycline	25 (78.1)	20 (76.9)	1.0

Sixty-nine patients were randomized to the OAC7 group and 62 patients to the OAC14 group. Demographic characteristics at baseline were similar between both groups (Table 1), including previous antibiotic exposure and endoscopic diagnosis.

On a per-protocol analysis, eradication of *H pylori* infection was achieved in 54 of 63 patients (85.7%) in OAC7 group and 53 of 60 patients (88.3%) in OAC14 group. On an intention-to-treat analysis, eradication was achieved in 54 of 69 patients (78.3%) in OAC7 group and 53 of 62 patients (85.5%) in OAC14 group. The differences did not reach statistical significance ($P = 0.37$) (Table 2). Most treatment failures ($n = 16$) received a second-line treatment beyond the study protocol.

Sub-group analysis

Eradication rate for subgroups of patients is presented in Table 2. Smokers showed a lower eradication rate compared to non-smokers. Interestingly, the difference was more evident in the OAC7 group, with 57.1% and 83.6% eradication rate in smokers and non-smokers, respectively

($P = 0.06$), almost reaching a statistical significance. Although the non-ulcer patients had a lower eradication rate compared to the ulcer patients, the difference did not reached statistical significance.

In addition, eradication rates between groups were not significantly affected by previous antibiotic exposure. The patients previously exposed to penicillin had eradication rates of 82.1% and 84.3% in OAC7 and OAC14 groups, respectively ($P = 0.8$), while the patients previously exposed to clarithromycin had eradication rates of 76.9% and 88.9% in OAC7 and OAC14 groups, respectively ($P = 0.63$).

Adverse effects and compliance

Abdominal pain, nausea and diarrhea were the most common adverse effects in both groups (Table 3). Most were mild. Only 2 patients discontinued treatment because of adverse effects (diarrhea and rash), after taking 71% and 90% of scheduled medication, respectively. Frequency of adverse effects was similar in both groups (29% in OAC7 versus 37% in OAC14 groups).

Eight patiens did not return to be evaluated for the eradication of *H pylori*, 6 from the OAC7 group and 2 from the OAC14 group. As shown in Figure 1, complete follow-up was achieved in 123 patients (93.9%).

Table 3 Adverse events during treatment *n* (%)

	OAC7 (*n* = 69)	OAC14 (*n* = 62)	Total (*n* = 131)
Abdominal pain	10 (14.5)	8 (12.9)	18 (13.7)
Nausea	7 (10.1)	11 (17.7)	18 (13.7)
Diarrhea	9 (13.0)	5 (8)	14 (10.7)
Taste disturbance	2 (2.9)	7 (11.3)	9 (6.9)
Headache	2 (2.9)	5 (8.1)	7 (5.3)
Vomiting	1 (1.58)	2 (3.2)	3 (2.3)
Loss of appetite	2 (2.9)	1 (1.6)	3 (2.3)
Rash	0	2 (3.2)	2 (1.5)
Discolored faeces	1 (1.4)	1 (1.6)	2 (1.5)
Tongue discoloration	1 (1.4)	0	1 (0.76)
Total	20 (29)	23 (37)	43 (33)

DISCUSSION

The ideal regimen for *H pylori* eradication is far from settled, and the search is ongoing[27,28]. The current standard triple therapy with two antibiotics and a PPI is being challenged by quadruple therapy (bismuth, PPI and two antibiotics) and lately by the so-called "sequential therapy" (PPI plus three antibiotics)[29,30]. The length of treatment is an important factor because it influences cost of treatment, and it may be related to eradication rates, adverse effects and compliance. The search for effective, but shorter therapies is totally justified. However, information about this topic has come almost exclusively from developed countries with low-prevalence of infection, and there are evidences to suggest that regional or geographical differences in the efficacy of therapy against *H pylori* could be related to socio-economic status[31].

The published trend toward similar results of two-week versus one-week triple therapy for *H pylori* eradication may not hold true for developing, high-prevalence countries. Where there is higher antibiotic resistance and bacterial load, this might compromise the outcome of shorter treatments. A recent report, coming from Alaska, showed an eradication rate of 34%, even using 14-d triple therapy[32]. Validated local information is very important to define standard therapy for *H pylori* infection in different geographical areas.

This is the first quasi-randomized controlled trial comparing 7-d versus 14-d triple therapy for *H pylori* eradication in this high-prevalence Hispanic population. This study seems to reproduce the results obtained in similar studies from developed countries, showing a slight (7.2%) but non-statistically significant improvement in eradication rate when PPI-based triple therapy is extended from 7 to 14 d. This is below the 15% conventionally defined as clinically significant (see Methods) and suggests that, at least in this population, one or two-week triple therapies are comparable in terms of eradication rate, with clear cost-advantages for the one-week regimen.

The subgroup analyses, although underpowered to detect significant differences, also confirmed previous reports, showing that smokers[33,34] seem to be more resistant to eradication therapy for *H pylori*. With respect to non-ulcer patients, some but not all reports identify this condition as a significant risk factor for treatment failure[35,36]. A recent single study[37] and also a systematic review found a trend to a worse response to treatment only when using 7-d regimen[38]. If confirmed by adequately designed studies, smokers and non-ulcer patients might constitute a subgroup of patients that should be treated for 10 or 14 d instead of 7 d[37].

These patients had not a long-term follow-up after treatment. Besides eradication rate, reinfection or recrudescence of infection are other critical factors to determine final effectiveness of therapy. As expected, there is a marked paucity of information coming from developing, high-prevalence countries. A recent report from Vietnam showed a 23.5% reinfection rate one year after treatment, with most strains being identical to the pre-treatment isolates[39]. Another report from Iran showed a 20.4% reinfection rate 3 years after treatment[40]. It has been reported that patients with duodenal ulcer from the same population have a 13% reinfection rate after 3 years of a 14-d triple therapy, with most cases occurring during the first year[41], very similar to the 10% reinfection rate found in Bangladesh, 3 to 18 mo after treatment[42]. Available information suggests that recrudescence accounts for the majority of early recurrences after treatment[43]. It has been convincingly demonstrated that early reinfection rate is inversely related to the initial eradication rate obtained with therapy[44], and it is possible that the small difference (7.2%) in short-term eradication rate between 7 and 14-d regimens may later determine a higher than expected "reinfection" rate in the OAC7 group. We are not aware of any published study comparing long-term reinfection rate after 7 and 14-d regimens. Longer follow-up of this cohort of patients may help to answer this question.

In summary, this quasi-randomized comparative trial showed that 7-d and 14-d PPI-based triple therapies

are comparable in eradicating *H pylori* in a population with a high prevalence of infection, at least in the short-term follow-up. It is possible that smokers and non-ulcer patients might be candidates for a longer period of treatment. Because of the potentially higher reinfection risk in these sub-groups of the population and the demonstrated inverse relationship between initial eradication rate and recrudescence of infection, it is reasonable to prolong the follow-up of this cohort of patients for at least one year, before to recommend a 7-d triple therapy as the standard treatment for *H pylori* infection in this population.

REFERENCES

1 **Suerbaum S**, Michetti P. Helicobacter pylori infection. *N Engl J Med* 2002; **347**: 1175-1186
2 **Bazzoli F**, Bianchi Porro G, Bianchi MG, Molteni M, Pazzato P, Zagari RM. Treatment of Helicobacter pylori infection. Indications and regimens: an update. *Dig Liver Dis* 2002; **34**: 70-83
3 **Forman D**, Graham DY. Review article: impact of Helicobacter pylori on society-role for a strategy of 'search and eradicate'. *Aliment Pharmacol* Ther 2004; **19** Suppl 1: 17-21
4 **Miehlke S**, Bayerdorffer E, Graham DY. Treatment of Helicobacter pylori infection. *Semin Gastrointest Dis* 2001; **12**: 167-179
5 **Malfertheiner P**, Megraud F, O'Morain C, Hungin AP, Jones R, Axon A, Graham DY, Tytgat G. Current concepts in the management of Helicobacter pylori infection--the Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther* 2002; **16**: 167-180
6 **Nash C**, Fischbach L, Veldhuyzen van Zanten S. What are the global response rates to Helicobacter pylori eradication therapy? *Can J Gastroenterol* 2003; **17** Suppl B: 25B-29B
7 **Altintas E**, Sezgin O, Ulu O, Aydin O, Camdeviren H. Maastricht II treatment scheme and efficacy of different proton pump inhibitors in eradicating Helicobacter pylori. *World J Gastroenterol* 2004; **10**: 1656-1658
8 **Della Monica P**, Lavagna A, Masoero G, Lombardo L, Crocella L, Pera A. Effectiveness of Helicobacter pylori eradication treatments in a primary care setting in Italy. *Aliment Pharmacol Ther* 2002; **16**: 1269-1275
9 **Bazzoli F**, Zagari M, Pozzato P, Varoli O, Fossi S, Ricciardiello L, Alampi G, Nicolini G, Sottili S, Simoni P, Roda A, Roda E. Evaluation of short-term low-dose triple therapy for the eradication of Helicobacter pylori by factorial design in a randomized, double-blind, controlled study. *Aliment Pharmacol Ther* 1998; **12**: 439-445
10 **Current European concepts in the management of Helicobacter pylori infection**. The Maastricht Consensus Report. European Helicobacter Pylori Study Group. *Gut* 1997; **41**: 8-13
11 **Howden CW**, Hunt RH. Guidelines for the management of Helicobacter pylori infection. Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. *Am J Gastroenterol* 1998; **93**: 2330-2338
12 **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
13 **Lam SK**, Talley NJ. Report of the 1997 Asia Pacific Consensus Conference on the management of Helicobacter pylori infection. *J Gastroenterol Hepatol* 1998; **13**: 1-12
14 **Coelho LG**, Leon-Barua R, Quigley EM. Latin-American Consensus Conference on Helicobacter pylori infection. Latin-American National Gastroenterological Societies affiliated with the Inter-American Association of Gastroenterology (AIGE). *Am J Gastroenterol* 2000; **95**: 2688-2691
15 **Laine L**, Estrada R, Trujillo M, Fukanaga K, Neil G. Randomized comparison of differing periods of twice-a-day triple therapy for the eradication of Helicobacter pylori. *Aliment Pharmacol Ther* 1996; **10**: 1029-1033
16 **Fennerty MB**, Kovacs TO, Krause R, Haber M, Weissfeld A, Siepman N, Rose P. A comparison of 10 and 14 days of lansoprazole triple therapy for eradication of Helicobacter pylori. *Arch Intern Med* 1998; **158**: 1651-1656
17 **Louw JA**, Van Rensburg CJ, Moola S, Kotze D, Marks IN. Helicobacter pylori eradication and ulcer healing with daily lansoprazole, plus 1 or 2 weeks co-therapy with amoxycillin and clarithromycin. *Aliment Pharmacol Ther* 1998; **12**: 881-885
18 **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
19 **Rollan A**. Eradication of Helicobacter pylori in developing countries. *Rev Med Chil* 1997; **125**: 939-949
20 **Buiatti E**, Munoz N, Vivas J, Cano E, Peraza S, Carillo E, Castro D, Sanchez V, Andrade O, Benz M. Difficulty in eradicating Helicobacter pylori in a population at high risk for stomach cancer in Venezuela. *Cancer Causes Control* 1994; **5**: 249-254
21 **Rollan A**, Ferreccio C, Harris P, Serrano C, Jara A, Venegas A. Riesgo de mortalidad por cáncer gástrico e infección por Helicobacter pylori: Resultados de un estudio poblacional (abstract). *Gastroenterol Latinoam* 2005; **16**: 390
22 **Ortega J**, Calvo A, Gabrielli L, Pruyas M, Villarroel L, Soza A, Riquelme A, Abbott E, Pattillo A, Rollan A. Frecuencia de infección benigna por Helicobacter pylori en pacientes con patología gastrointestinal benigna (abstract). *Gastroenterol Latinoam* 2005; **16**: 336
23 **Gonzalez C**, Garcia A, Daroch F, Kawaguchi F, Solar H, Rivera N, Vega E. In vitro antimicrobial susceptibility of Helicobacter pylori strains: isolation of strains resistant to clarithromycin. *Rev Med Chil* 2001; **129**: 643-646
24 **Flores S**, Opazo H, Valderrama D, Aguilera R, Marchese A, Valderrama S. Triple therapy of short-term with azithromycin, amoxycillin and omeprazole for the eradication of Helicobacter pylori. *Rev Med Chil* 2000; **128**: 509-512
25 **Calvo A**, Pruyas M, Nilsen E, Verdugo P. Populational research of gastric cancer in digestive symptomatic patients, from 1996 to 2000. *Rev Med Chil* 2001; **129**: 749-755
26 **Lundell LR**, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, Tytgat GN, Wallin L. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; **45**: 172-180
27 **Scarpignato C**. Towards the ideal regimen for Helicobacter pylori eradication: the search continues. *Dig Liver Dis* 2004; **36**: 243-247
28 **Bazzoli F**, Pozzato P, Rokkas T. Helicobacter pylori: the challenge in therapy. *Helicobacter* 2002; **7** Suppl 1: 43-49
29 **Bytzer P**, O'Morain C. Treatment of Helicobacter pylori. *Helicobacter* 2005; **10** Suppl 1: 40-46
30 **Francavilla R**, Lionetti E, Castellaneta SP, Magista AM, Boscarelli G, Piscitelli D, Amoruso A, Di Leo A, Miniello VL, Francavilla A, Cavallo L, Ierardi E. Improved efficacy of 10-Day sequential treatment for Helicobacter pylori eradication in children: a randomized trial. *Gastroenterology* 2005; **129**: 1414-1419
31 **Perri F**, Qasim A, Marras L, O'Morain C. Treatment of Helicobacter pylori infection. *Helicobacter* 2003; **8** Suppl 1: 53-60
32 **Gessner BD**, Bruce MG, Parkinson AJ, Gold BD, Muth PT, Dunaway E, Baggett HC. 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**: 1261-1268
33 **De Francesco V**, Zullo A, Hassan C, Della Valle N, Pietrini L, Minenna MF, Winn S, Monno R, Stoppino V, Morini S, Panella C, Ierardi E. 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**: 322-326

34 **Matsuo K**, Hamajima N, Ikehara Y, Suzuki T, Nakamura T, Matsuura A, Tajima K, Tominaga S. Smoking and polymorphisms of fucosyltransferase gene Le affect success of H. pylori eradication with lansoprazole, amoxicillin, and clarithromycin. *Epidemiol Infect* 2003; **130**: 227-233

35 **Broutet N**, Tchamgoue S, Pereira E, Lamouliatte H, Salamon R, Megraud 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

36 **Wong WM**, Xiao SD, Hu PJ, Wang WH, Gu Q, Huang JQ, Xia HH, Wu SM, Li CJ, Chen MH, Cui Y, Lai KC, Hu WH, Chan CK, Lam SK, Wong BC. Standard treatment for Helicobacter pylori infection is suboptimal in non-ulcer dyspepsia compared with duodenal ulcer in Chinese. *Aliment Pharmacol Ther* 2005; **21**: 73-81

37 **Calvet X**, Ducons J, Bujanda L, Bory F, Montserrat A, Gisbert JP. Seven versus ten days of rabeprazole triple therapy for Helicobacter pylori eradication: a multicenter randomized trial. *Am J Gastroenterol* 2005; **100**: 1696-1701

38 **Huang JQ**, Zheng GF, Hunt RH, Wong WM, Lam SK, Karlberg J, Wong BC. Do patients with non-ulcer dyspepsia respond differently to Helicobacter pylori eradication treatments from those with peptic ulcer disease? A systematic review. *World J Gastroenterol* 2005; **11**: 2726-2732

39 **Wheeldon TU**, Hoang TT, Phung DC, Bjorkman A, Granstrom M, Sorberg M. Long-term follow-up of Helicobacter pylori eradication therapy in Vietnam: reinfection and clinical outcome. *Aliment Pharmacol Ther* 2005; **21**: 1047-1053

40 **Zendehdel N**, Nasseri-Moghaddam S, Malekzadeh R, Massarrat S, Sotoudeh M, Siavoshi F. Helicobacter pylori reinfection rate 3 years after successful eradication. *J Gastroenterol Hepatol* 2005; **20**: 401-404

41 **Rollan A**, Giancaspero R, Fuster F, Acevedo C, Figueroa C, Hola K, Schulz M, Duarte I. The long-term reinfection rate and the course of duodenal ulcer disease after eradication of Helicobacter pylori in a developing country. *Am J Gastroenterol* 2000; **95**: 50-56

42 **Hildebrand P**, Bardhan P, Rossi L, Parvin S, Rahman A, Arefin MS, Hasan M, Ahmad MM, Glatz-Krieger K, Terracciano L, Bauerfeind P, Beglinger C, Gyr N, Khan AK. Recrudescence and reinfection with Helicobacter pylori after eradication therapy in Bangladeshi adults. *Gastroenterology* 2001; **121**: 792-798

43 **Peitz U**, Hackelsberger A, Malfertheiner P. A practical approach to patients with refractory Helicobacter pylori infection, or who are re-infected after standard therapy. *Drugs* 1999; **57**: 905-920

44 **Gisbert JP**. The recurrence of Helicobacter pylori infection: incidence and variables influencing it. A critical review. *Am J Gastroenterol* 2005; **100**: 2083-2099

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