Neither 10- nor 14-Day Sequential Treatment is better than Standard Triple Therapy for Helicobacter Pylori Eradication

Emanuel Warrington, MD*; Orlando López-Román, MD*; Rafael Tirado-Montijo, MD*; Rafael Urbina, MD*; Marcia Cruz-Correa, MD, PhD†; Doris H. Toro, MD, FACP, FACG, AGAF*

Objective: *Helicobacter pylori* is a bacterial pathogen associated with chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa–associated lymphoid tissue lymphoma. Current treatment guidelines support a 7- to 14-day, triple-drug protocol consisting of a proton-pump inhibitor (PPI), clarithromycin, and either amoxicillin or an imidazole. The initial eradication rates for this regimen were 80 to 90%. Nevertheless its effectiveness has declined as the antibiotic resistance to clarithromycin and metronidazole has emerged. In Puerto Rico the reported resistance of *H. pylori* to clarithromycin is 16% and to metronidazole, 3.7%. Sequential therapy for *H. pylori* eradication, 5 days of treatment with a PPI and amoxicillin followed by 5 days of treatment with the PPI and 2 other antibiotics (clarithromycin and an imidazole), was introduced as an effective alternate regimen. This is a prospective clinical trial intended to compare the efficacy of first-line, standard 10-day triple-drug therapy with those of both 10- and 14-day sequential therapy in eradicating *H. pylori* at the San Juan Veterans Affairs Hospital in a population that is naïve to previous treatment.

Methods: This was a prospective, open-label, randomized clinical trial.

Results: Based on the intention-to-treat analysis, the eradication rate was 83.7% (72 of 86 patients) in the standard triple-therapy group, 80.0% (68/85) in the 10-day sequential-therapy group, and 79.1% (68/86) in the 14-day sequential-therapy group. There were no significant statistical differences between the eradication rates among therapies.

Conclusion: Sequential-therapy treatment regimens are not better than standard triple therapy for the eradication of *H. pylori* infection, regardless of the treatment duration. [*P R Health Sci J 2016;35:203-208*]

Key words: Helicobacter pylori, Veterans, Breath test, Proton pump inhibitors, Amoxicillin

Helicobacter pylori is a bacterial pathogen that causes chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa–associated lymphoid tissue lymphoma. Currently, the international guidelines for treatment support a 7- to 14-day, triple-drug regimen consisting of a proton-pump inhibitor (PPI), clarithromycin, and either amoxicillin or an imidazole (1,2). The initial cure rates using the 3-drug regimen were 80 to 90%, but these rates were evaluated over 15 years ago, when resistance to clarithromycin was lower than it is today (3). It is known that the resistance to clarithromycin and to metronidazole have significantly increased in recent years (4). The eradication rates of *H. pylori* with PPI-based triple therapy have declined parallel to antibiotic resistance and have been reported to be approximately 75% in the United States and lower than 50% in some areas of Europe (5,6). First-line therapies for bacterial infections should ideally have cure rates of 90% or greater (7); these lower rates demonstrate the need for a regimen with greater efficacy for the eradication of *H. pylori*.

Sequential therapy for *H. pylori* was introduced in Italy in 2000 as an effective new treatment (8). This sequential administration strategy consists of 5 days of treatment with a PPI and amoxicillin, followed by 5 days of treatment with the PPI and 2 other antibiotics (clarithromycin and an imidazole). One study hypothesizes that this approach weakens bacterial

*VA Caribbean Healthcare System, San Juan, Puerto Rico; †University of Puerto Rico Comprehensive Cancer Center, San Juan, Puerto Rico

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Address correspondence to: Doris H. Toro, MD, FACP, FACG, AGAF, VA Caribbean Healthcare System, 10 Casia Street, San Juan, PR 00921. Email: Doris.Toro@va.gov

cell walls with the amoxicillin in the initial phase, thus preventing the development of drug efflux channels that inhibit clarithromycin from binding to ribosomes. Hence, the efficacy of the clarithromycin and the imidazole are improved in the second phase (9).

Initial head-to-head studies showed that sequential therapy was superior to standard triple therapy. A meta-analysis in 2008 of 10 randomized control trials involving 2747 patients demonstrated that the pooled eradication rates were 93.4% (CI: 91.3%–95.5%) for sequential therapy and 76.9% (CI: 71.0%–82.6%) for standard triple therapy, with a relative risk reduction of 71% (CI: 64%–77%) (10). To our knowledge there is only 1 ongoing clinical trial in the United States investigating the effectiveness of 10-day sequential therapy in the eradication of *H. pylori* infection; however, the benefits (or relative lack thereof) of 14-day sequential therapy have not been studied (11).

H. pylori infection is common in Puerto Rico and has a reported resistance to clarithromycin of 16% and to metronidazole of 3.7% (12). Furthermore, at least one study has shown that more than 60% of the *H. pylori* patients are infected with multiple strains of the bacterium (12). Currently at our institution, a 10-day, standard triple drug is given as the first-line treatment for *H. pylori* infection. We therefore decided to perform a prospective clinical trial to compare the efficacy of the first-line, standard 10-day triple-drug therapy with those of 10- and 14-day sequential therapies in eradicating *H. pylori* in the veteran population that is naïve to previous treatment.

Patients and Methods

A prospective, open-label, randomized clinical trial was performed at the Gastroenterology Department of the Veterans Administration Caribbean Healthcare System (VACHS) in San Juan, Puerto Rico. The study was approved by the VACHS Institutional Review Board prior to its beginning (MIRB# 00574).

Eligibility criteria

All consecutive patients with decision-making capacity who underwent an upper endoscopy (EGD) for any indication were considered for enrollment in the study. During the EGD, *H. pylori* infection was determined using a rapid urease test (RUT) and gastric biopsies of the antrum and body for histologic evaluation. Only patients who were naïve to previous treatment for *H. pylori*, were 21 years old or older, and had both an RUT and histology positive for *H. pylori* were included in this study. Patients with a history of antibiotic use during the 4 weeks prior to the study, with a history of prior gastric surgery, liver cirrhosis, or kidney failure, with an allergy to any antibiotic that might be given as therapy, who were pregnant or lactating, or with a history of concomitant Coumadin use were excluded from the study. Written informed consent was obtained from all eligible, consenting participants.

Outcomes

The primary goal of this study was to compare the eradication rates of 10-day sequential therapy (10-ST) and 14-day sequential therapy (14-ST) with that achieved with standard triple-antibiotic therapy (STT). Eradication status was determined after the performance of a 13C urea breath test (UBT) at least 6 weeks after the end of therapy. All patients were asked to stop treatment with the proton-pump inhibitor and histamine-2 blocker for at least 2 weeks before the UBT. Eradication was considered to have been achieved on the basis of a negative UBT, an unbiased measure of effectiveness. If a given patient's UBT was positive for urease-splitting bacteria or if that patient presented with 2 consecutive UBTs reported as being indeterminate, then the treatment for that particular subject was considered to have failed.

The secondary aims were to evaluate for treatment-associated side effects (when present) and to correlate treatment adherence of each of the study groups with their respective eradication rate. To assess side effects, we asked both open-ended and specific questions based on the anticipated side effects. Adherence was defined as the consumption (by each patient) of more than 90% of the prescribed drugs and was determined by pill count during a follow-up visit.

Randomization

Patients were consecutively randomized to each of the treatment regimens in a 1:1:1 ratio. The treatment groups were as follows: A) amoxicillin, 1gm twice a day for 10 days, clarithromycin, 500mg twice a day for 10 days, and omeprazole, 20mg twice a day for 10 days (STT group: 88 patients); B) amoxicillin, 1gm twice a day, and omeprazole, 20mg twice a day, both for first 5 days of therapy, followed by clarithromycin, 500mg twice a day, metronidazole 500mg twice a day, and omeprazole 20mg twice a day, all for the subsequent 5 days (10-ST group: 88 patients); C) amoxicillin, 1gm twice a day, and omeprazole, 20mg twice a day, both for the first 7 days of therapy, followed by clarithromycin, 500mg twice a day, metronidazole, 500mg twice a day, and omeprazole, 20mg twice a day, all for the subsequent 7 days (14-ST group: 88 patients).

Statistical analysis

Overall eradication rates and their 95% confidence intervals were obtained by intention-to-treat (ITT) and per-protocol analyses (PP). Sample size was calculated to detect a 15% difference in eradication, with a power of 0.80 and a significance level of 0.5. The intention-to-treat and per-protocol analyses were limited to those who took more than 90% of their medications and completed a follow up. Hypothesis testing was evaluated using Pearson's chi-squared testing or one-way ANOVA, as appropriate. The differences between baseline characteristics among study participants and side-effect profiles were calculated using one-way ANOVA and a chi-squared test/ Fisher's exact test.

All the authors had access to the study data and reviewed and approved the final manuscript. The authors did not receive any writing assistance.

Results

Study flow and Overall compliance

Our study population consisted mainly of men; the mean age of the sample was 64 years. The most common indications for endoscopy were evaluation for anemia or occult gastrointestinal bleeding and upper gastrointestinal symptoms such as dyspepsia or heartburn. The demographics of the included participants, including baseline characteristics as well as indications for which upper endoscopy was performed, are included in Table 1. Figure 1 summarizes the trial flow.

Table 1. Baseline characteristics*

Variable	Therapy randomly assigned		
	STT (n = 88)	10-ST (n = 88)	14-ST (n = 88)
Mean age, yr ± SD	64.4± 11.1	64.0 ± 11.7	63.1 ± 10.4
Patients, %			
Men	92.1	98.9	95.5
Women	8.0	1.1	4.6
EGD Indication, %			
Dyspepsia	17.2	18.2	19.3
GERD	8.1	10.2	18.2
FOBT	25.3	21.6	23.9
Anemia	19.5	23.9	14.8
Dysphagia	9.2	9.1	6.8
Abnormal imaging	8.1	8.0	9.1
Others†	12.6	9.1	8.0

*No differences were found between therapy groups (P>0.05). Oneway Anova and Chi-square test/Fisher exact test were used, as appropriate. †Includes diarrhea, gastrointestinal bleed, Barrett's, weight loss and nausea/vomiting.

Two hundred sixty-four patients (252 men and 12 women, aged 29-87 years) with confirmed (by histology and RUT) *H. pylori* infection were enrolled in the study, with 88 patients being assigned to each of the treatment groups. Overall, 257 out of 264 (97.3%) completed the treatment phase of the study as well as undergoing a follow-up UBT to evaluate for *H. pylori* eradication. Two drop-outs occurred in the STT group, 3 in the 10-ST group, and 2 in the 14-ST group, mostly due to non-compliance with study procedures. These individuals were not included in the ITT analysis.

Adherence to antibiotic therapy was similar in all treatment groups. Patients receiving STT and 10-ST had identical adherence rates (94.3%), while patients receiving 14-ST had an 88.6% adherence rate. This difference between treatment groups was not statistically significant (p = 0.259) (Table 2).

Table 2. Adherence to antibiotic therapy and reported side effects among patients who adhered to therapy (per protocol sample)

	Therapy, n (%)			P-value*
	STT(N=88)	10 –ST(N=88)	14-ST(N=88)	
Adherence ≥ 90%	83 (94.3)	83 (94.3)	78 (88.6)	0.259
Side effects				0.287
None	53 (63.9)	52 (64.2)	47 (60.3)	
Abdominal discomfort	10 (12.1)	10 (12.4)	4 (5.1)	
Metallic taste	11 (13.3)	8 (9.9)	10 (12.8)	
Nausea/ Vomiting	0 (0.0)	2 (2.5)	1 (1.3)	
Diarrhea	8 (9.6)	5 (6.2)	9 (11.5)	
Others‡	1 (1.2)	4 (4.9)	7 (9.0)	

*Chi-squared test was used to examine differences in adherence between therapy groups whereas Fisher's exact test was used for side effects. ‡Includes dizziness, headache, rash, myalgia, major depression, weakness, constipation, leg edema, and chest pain.

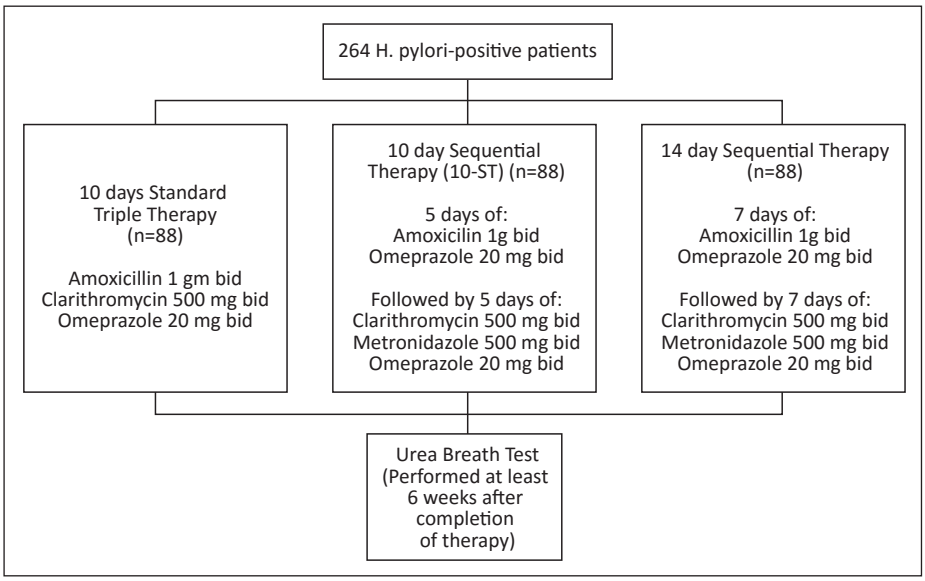

Figure 1. Study flow and randomization strategy

H. pylori eradication

The eradication rate was 83.7% (72 of 86 patients) in the STT group, 80.0% (68/85) in the 10-ST group, and 79.1% (68/86) in the 14-ST group, according to the ITT analysis. Following a per-protocol analysis, the eradication of *H. pylori* infection was determined to have been achieved in 84.3% (70/83) of the members of the STT group, 81.5% (66/81) of members of the 10-ST group, and 79.5% (62/78) of members of the 14-ST group (Figure 2).

In this study, the eradication rate of STT was marginally superior to those of both 10-ST and 14-ST, although no significant differences were observed. There

were no differences either when comparing the eradication rate of 10-ST with that of 14-ST (Pearson's chi-square = 0.6746; P = 0.714) or when comparing that of STT to that of either 10-ST or 14-ST.

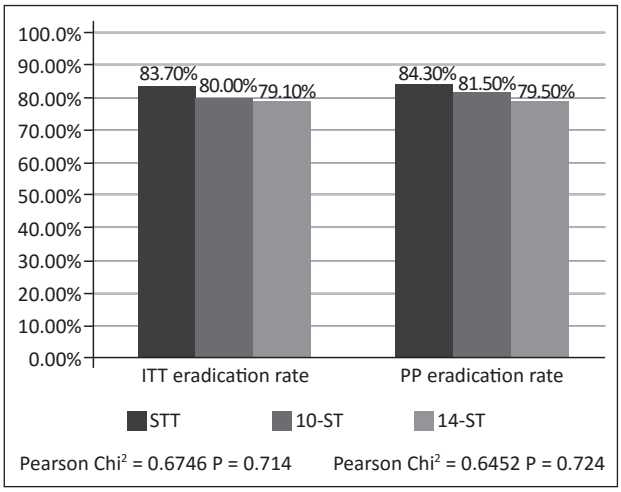

Figure 2. Helicobacter pylori eradication rates (ITT and PP)

Side-Effects profile

Data on the reported side effects are found in Table 2. The majority of patients did not report any major side effects associated with antibiotic therapy. The most commonly reported side effects were abdominal discomfort and a metallic taste; however no differences were found between the different treatment groups when we compared the frequency of the side effects.

Discussion

The effective eradication of *H. pylori* continues to be a challenge for many clinicians. Multiple strategies have been proposed to increase the cure rate of this infection, but none has achieved optimal results. Since the early part of the 2000s, sequential therapy has been proposed as an alternative (to the first-line STT) for treatment (8). The initial data obtained, mostly from studies performed in Europe, were very promising; however, further validation of this treatment strategy is wanting. Since the pattern of antibiotic resistance varies throughout the world, the effectiveness of sequential therapy in the United States is still a matter for research.

The present study suggests that sequential regimens are not better than standard triple therapy (STT), regardless of the treatment duration. A recently published meta-analysis demonstrated that sequential therapy was superior to a 7-day standard triple-therapy regimen, but when compared with a longer duration of STT (10 or 14 days), the difference disappeared (13). Other studies lengthening the duration of sequential therapy have been performed to determine whether longer therapy will help improve the eradication rates of *H. pylori* infection (14,15). The largest of these studies showed an eradication rate of 90.7% in the 14-day sequential-therapy group, 87.0% in the 10-day sequential-therapy group, and 82.3% in the 14-day standard triple-therapy group. Treatment efficacy was better in the 14-day sequential-therapy group than it was in the 14-day standard triple-therapy group (p = 0.003) (15). These findings suggest that longer therapy with a sequential regimen would provide better eradication rates; however, this study was conducted in areas with clarithromycin and metronidazole resistance of about 10% and 24%, respectively (15). In Puerto Rico, the reported resistance to clarithromycin is 16%, while the resistance to metronidazole is reported to be as low as 3.7%; these differences in resistance patterns among the studied populations may account for our study results (12). Our data does not support the notion that increasing the length of a sequential regimen to 14 days will improve the eradication rates of *H. pylori* infection. Moreover, this study also demonstrates that there was a minimal reduction in eradication rates in both the ITT and the PP analyses. Compliance rates were lower for the 14-ST group than they were for either the 10-ST group or the SST group, suggesting that shorter regimens with better eradication rates might be preferable to longer and more complex treatment alternatives. Differences in the susceptibility patterns of different populations might be a possible explanation for our study findings.

It is worth mentioning that all 3 different antibiotic regimens used during this study had suboptimal success rates and that none achieved an eradication rate of greater than 90%. This finding reinforces the need to evaluate patients for treatment response while we continue to search for other treatment alternatives in this population.

The prevalence of antibiotic resistance to clarithromycin is variable, and has been reported to range from 2 to 12% in North America (16). In many countries, metronidazole resistance has been reported to be greater than 40%, and often more than 80% (17). The effectiveness of a given antibiotic regimen is related to the prevalence of resistant bacterial strains in a given region. When selecting which treatment strategy to use for the treatment of *H. pylori* infection, multiple factors should be considered. Those factors include the prevalence of resistant strains and the history of prior antibiotic use (17). Additional studies dealing with *H. pylori* antibiotic susceptibility should be performed to determine which therapies could be of benefit to the members of this population. If the antibiotic resistance pattern in a particular region suggests the presence of a low incidence of clarithromycin resistance, then standard triple therapy might still be a viable option for treatment.

To our knowledge, this is the first work in the United States reporting that sequential therapy is not superior to current treatment strategies in the eradication of *H. pylori*, as has been suggested by Europeans studies. Furthermore, the complexity of the sequential regimen may impact compliance, especially if treatment is prolonged for 14 days. Our findings question the validity of the theory that using this sequential, rather than the concurrent, approach weakens the *H. pylori* cell wall, making it more susceptible to clarithromycin. We hypothesize that is the

H. pylori strain susceptibility to clarithromycin, rather than the specific strategy of drug administration, that determines whether sequential therapy is successful or not. In our population, in which clarithromycin resistance approaches 20%, we obtained eradication rates slightly over 80%, regardless of whether a given patient was undergoing sequential or concurrent therapy. These findings support the hypothesis set forth above.

This study has some limitations. The most important is the sample size. Although the purpose of our study was not to evaluate *H. pylori* incidence and prevalence in our population, the sample size was affected by the lower-than-estimated *H. pylori* prevalence, resulting in a slow recruitment process. The lower-than-estimated *H. pylori* prevalence is probably related to the widespread screening of patients with upper gastrointestinal symptoms of *H. pylori* infection and the early treatment of those that test positive. The study was originally powered to detect at least a 15% difference between treatment groups. Smaller differences (<15%) in treatment efficacy cannot be detected with the current study's sample size. However, recommending an intricate therapy, with lower adherence rates and minimal improvements in efficacy, would not be of relevance to clinical practice. The study design might be considered a limitation as well, as this was a randomized, open-label clinical trial. However using UBT as the outcome measure to assess treatment response reduced the inherent bias of the design. Another limitation is the fact that the previous studies documenting the efficacy of sequential therapy for *H. pylori* treatment were done in Europe. The genetic profile of Europeans is probably very different from the genetic profile of our study population. The question remains whether this genetic difference could explain the fact that, in this study, neither 10-day nor 14-day sequential therapy was clearly superior to the standard triple therapy. These results contradict the previously documented findings of the European studies. Furthermore the differences in the antibiotic sensitivity profiles of the European *H. pylori* strains from those of the *H. pylori* strains in Puerto Rico could also account for these differences in results.

In conclusion, this study shows that neither 10-day nor 14-day sequential therapy is clearly superior to the standard triple therapy currently recommended in the international guidelines. The eradication rates of *H. pylori* infection are yet suboptimal, and further studies either in search of newer therapeutic regimens or that would determine whether certain populations would benefit from different therapeutic approaches are needed. Until better treatment regimens become available, it is imperative that we either assess bacterial susceptibility patterns prior to the initiation of treatment or confirm successful eradication after empiric treatment. The era of empiric treatment for *H. pylori* infection is coming to an end; but until a more effective regimen is developed, the current guidelines may need to be updated.

Resumen

Objetivo: Helicobacter Pylori es una bacteria asociada a gastritis crónica, úlceras pépticas, cáncer y linfoma de estómago. La terapia estándar consiste en tres medicamentos; un inhibidor de la bomba de protones (IBP) con claritromicina y amoxicilina o imidazol por 7-14 dias.1,2 La efectividad es de un 80-90%.3 Sin embargo mientras la resistencia del H. pylori a claritromicina y metronidazol ha aumentado, la taza de erradicación del régimen estándar ha disminuido. En Puerto Rico se reporta una resistencia del H. pylori a claritromicina de un 16% y de 3.7% a metronidazol. La terapia secuencial, 5 días de un IBP y amoxicilina seguido por 5 días de un IBP y otros dos antibióticos (claritromicina y imidazol), se ha presentado como una alternativa al régimen estándar. Este estudio prospectivo comparó la eficacia de la terapia estándar de 10 días versus 10 o 14 días de terapia secuencial en la erradicación de H. pylori en el Hospital de Veteranos de San Juan en pacientes que nunca habían sido tratados. Métodos: Este fue un estudio abierto, prospectivo y randomizado. Resultados: Basado en el análisis de intención de tratar, la taza de erradicación fue de un 83.7% (72 de 86 pacientes) para el grupo en la terapia estándar y de 80.0% (68/85) para el grupo en terapia secuencial de 10 días y de 79.1% (68/86) para el grupo en la terapia secuencial de 14 días. No hubo diferencias estadisticas significativas en las tasas de erradicacion entre los grupos estudiados. Conclusión: La terapia secuencial no es mejor que la terapia estándar para la erradicación del H. pylori irrespectivamente de la duración de la misma.

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References

1. 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;102:1808–1825.
2. Malfertheiner P, Megraud F, O'Morain C, et al. Current concepts in the management of Helicobacter pylori infection: The Maastrict III Consensus Report. Gut 2007;56:772–781.
3. Harford W, Lanza F, Arora A, et al. Double-blind, multicenter evaluation of lansoprazole and amoxicillin dual therapy for the cure of Helicobacter pylori infection. Helicobacter 1996;1:243–250.
4. Megraud F, Coenen S, Versporten A et al.; Study Group participants. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut 2013;62:34–42.
5. Laine L, Fennerty MB, Osato M, 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 2000:95:3393–3398.

6. 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;13:857–864.
7. Hopkins RJ. In search of the holy grail of Helicobacter pylori remedies. Helicobacter 2001;6:81–83.
8. Zullo A, Rinaldi V, Winn S, et al. A new highly effective short-term therapy schedule for Helicobacter pylori eradication. Aliment Pharmacol Ther 2000;14:715–718.
9. De Francesco V, Margiotta M, Zullo A, et al. Clarithromycin-resistant genotypes and eradication of Helicobacter pylori. Ann Intern Med 2006;144:94–100.
10. Jafri NS, Hornung CA, Howden CW. Meta-analysis: Sequential therapy appears superior to standard therapy for Helicobacter pylori infection in patients naive to treatment. Ann Intern Med 2008; 148:923–931.
11. Conventional therapy vs sequential therapy in treatment of Helicobacter pylori infection. Available at: http://clinicaltrials.gov/ct2/show/NCT01723059
12. Lebron R. Susceptibility patterns and genotypic characterization of Helicobacter pylori clinical isolates from Puerto Rico. Department of Microbiology University of Puerto Rico. PHJ 2009.
13. Gatta L, Vakil N, Vaira D, Scarpignato C. Global eradication rates for Helicobacter pylori infection: systematic review and meta-analysis of sequential therapy. BMJ 2013;347:f4587.
14. Harmandar FA, Ustundag Y, Buyukuysal C, Ilikhan S, Gun BD. The efficacy of clarithromycin based sequential therapy in eradication of Helicobacter pylori in Turkey. Gut 2012;61(suppl3):A443.
15. Liou JM, Chen CC, Chen MJ, et al. Sequential versus triple therapy for the first-line treatment of Helicobacter pylori: a multicentre, open-label, randomised trial. Lancet 2013;381:205–213.
16. Kato M, Yamaoka Y, Kim JJ, et al. Regional differences in metronidazole resistance and increasing clarithromycin resistance among Helicobacter pylori isolates from Japan. Antimicrob Agents Chemother 2000;44: 2214–2216.
17. Graham DY, Lee YC, Wu MS. Rational Helicobacter pylori therapy: evidence-based medicine rather than medicine-based evidence. Clin Gastroenterol Hepatol 2014;12:177–186.