EDITORIAL

Available from: http://www.jgld.ro/wp/archive/y2017/n2/a5/
DOI: http://dx.doi.org/ 10.15403/jgld.2014.1121.262.hpy

It is Time to Rethink *H. pylori* Therapy

Bich N. Dang, David Y. Graham

Michael E. DeBakey VA Medical Center,
Houston, Texas, U.S.A.

Address for correspondence:
David Y. Graham, MD
Professor of Medicine,
Molecular Virology and Microbiology
Baylor College of Medicine
Michael E. DeBakey VAMC
2002 Holcombe Blvd.
Rm 3A-318B (111D)
Houston, TX 77030, U.S.A.
dgraham@bcm.edu

Received: 25.05.2017
Accepted: 25.05.2017

A recent report by Di Ciaula et al. from two referral centers in Southern Italy provides data on contemporary eradication rates in more than 2000 patients evaluated for *H. pylori* therapy; 60% were treatment naïve [1]. Various empiric therapies were utilized; susceptibility testing was not done. The prevalence of clarithromycin resistance in the population was estimated as approximately 30%. Although many regimens were used, acceptable or excellent cure rates were achieved only with 10 day sequential therapy (89.9%) and 10 day bismuth quadruple therapy (100%). Standard 7 day clarithromycin triple therapy cured 71% and levofloxacin triple therapy cured only 57%. The authors concluded that current practices put patients at risk for poor outcomes and point to the need for using therapy based on local susceptibility patterns [1].

Following the introduction of penicillin in the late 1940s, patients with pneumonia routinely received effective therapy with 600,000 units of penicillin b.i.d. The development of penicillin resistant strains in the 1970s provided a rude awakening and resulted in changes in practice. It also spurred the creation of local, regional, and global antimicrobial surveillance programs to track resistance patterns and inform guidelines for empirical antimicrobial therapy. This resulted in greater treatment uniformity and better outcomes.

In the same vein, the rise in antimicrobial resistant *H. pylori* has forced gastroenterologists to realize that *H. pylori* should be investigated and treated as other infectious diseases [2]. Infectious disease clinicians use culture and susceptibility data to select therapies to which the organism is known to be susceptible. Antibiotics are used empirically when the choice can be based on local and region-specific susceptibility data. This approach ensures high cure rates and optimizes antibiotic use. Susceptibility data are needed for *H. pylori* and it behooves the GI community to lobby, demand local, national, and even global surveillance systems to track resistance patterns and inform strategies for dealing with emerging resistance [3].

By 2000, it was clear that in Italy clarithromycin resistance had compromised standard triple therapy and cure rates of 75% or less were common [4, 5]. Despite low cure rates, national and international guidelines continued to recommend clarithromycin containing triple therapy until recently. In Italy, the failure of clarithromycin triple therapy resulted in the introduction of sequential therapy, a new clarithromycin containing regimen that added a fourth antibiotic, metronidazole [6]. Development of sequential therapy focused on comparisons of the new regimen to then known ineffective clarithromycin triple therapies rather than attempting to fully understand the strengths and limitations of sequential therapy. Sequential therapy ultimately proved ineffective as it was undermined by metronidazole and dual metronidazole-clarithromycin resistance in many regions and was eventually abandoned as obsolete.

Comparative trials in infectious diseases are typically done using highly effective regimens and are structured as non-inferiority studies which can also show which of the two regimens is inferior [7]. Infectious disease doctors are unimpressed and uninfluenced by comparisons demonstrating that a therapy that provides excellent results with susceptible infections, proves to be inferior in populations where resistance to the drug is common. Few gastroenterologists would accept a superiority claim for a skin infection if the study had compared two antibiotics in a population with high-level resistance to one of them and yet the *H. pylori* literature has many examples of claims of superiority for one therapy over another when one or both produced unacceptable poor results because of their use in populations where resistance was common [2]. Valid comparative studies require that both regimens are active against *H. pylori* and achieve good to excellent cure rates. In

contrast to the typical gastroenterology disease, there is no placebo response with *H. pylori* therapy making treatment evaluation markedly easier.

The authors of the Italian study suggest that in Southern Europe it may be time to change practices and possible even abandon empiric therapy [1]. There are many *H. pylori* treatment regimens that will reliably cure > 90%, usually > 95%, of susceptible infections. When susceptibility data are available, therapies should be tailored accordingly. In such cases, triple therapy (i.e., a proton pump inhibitor, PPI, and amoxicillin + clarithromycin or amoxicillin + metronidazole) remains highly effective and should be not discarded. Because the ability to obtain regional or local susceptibility data will not happen quickly, empiric therapy is still needed. The data available to the clinician regarding local cure rates and prior antibiotic use provide clues to what are good vs. poor choices. Overall, the data from Southern Italy are consistent with a low prevalence of metronidazole resistance which is reflected in 10 day sequential therapy being reasonably effective and 10 day bismuth quadruple therapy being highly effective [1]. In the presence of a low prevalence of metronidazole resistance, one should consider 14-day metronidazole triple therapy, as it is highly likely to be both successful and better tolerated than bismuth quadruple therapy.

Our general recommendation is that while susceptibility-guided therapy is always best, when it is not possible, one should have at least two different empiric regimens to allow choices especially when patients cannot (allergic) or will not take one of the regimens. In many areas the current best choices are concomitant therapy and bismuth quadruple therapy [8]. Concomitant therapy is a 4-drug regimen (PPI, amoxicillin, metronidazole, clarithromycin) that effectively gives clarithromycin and metronidazole triple therapies simultaneously. The concept is that it remains useful when neither clarithromycin and metronidazole resistance is common and is only undermined by dual clarithromycin-metronidazole resistance. Concomitant therapy always provides one unneeded antibiotic (either clarithromycin or metronidazole) but this cannot be avoided when using empiric therapy [8]. When this 4-drug combination is desired, concomitant therapy will always be equal to, or superior to, sequential therapy and is preferred. The alternative is bismuth quadruple therapy using either generic components or a prepackaged drug such as Pylera™. As noted above, if metronidazole resistance is low, 14 metronidazole triple therapy is likely a better choice. If metronidazole resistance is likely (e.g., having taken metronidazole previously), the best results are obtained with 14 day bismuth quadruple therapy using 1,500 or 1,600 mg of metronidazole. In the absence of resistance, 7 days should suffice. Pylera™ is available in bottles and prepackaged for 10 day therapy which is acceptable in Southern Italy, but in areas where metronidazole resistance is more common or unknown, 14 day therapy is a better choice [9, 10]. For all patients, double dose PPI should be used that contains 40 mg of omeprazole or an equivalent [8]. Pantoprazole should be avoided as 40 mg of pantoprazole is equivalent to only 9 mg of omeprazole [8, 11].

What specifically has been learned from this detailed and real life experience in Southern Italy? First, gastroenterologists need to start thinking about *H. pylori* as if they were infectious disease specialists. One begins with a detailed antibiotic use history since prior use strongly suggests that resistance will be present. One also needs to review what therapy to use based on what is proven to work well locally. We also should consider the patient's allergies and dislikes when choosing a regimen that the patient is likely to take successfully. If local susceptibility patterns are known, one should use that information to select an empiric therapy. One should consider obtaining gastric cultures for susceptibility testing especially in patients who have received antibiotics that would be used again or who have previously failed *H. pylori* eradication therapy. The results could be then used to tailor therapy. It is important to also educate our patients on what to expect in terms of potential side effects and encourage them to take all the medications as prescribed. We agree with the authors of the recent analysis of treatment data in Southern Italy: it is time to change our approach to *H. pylori* eradication therapy [1].

Conflicts of interest: Dr. Dang has no conflicts to declare. Dr. Graham is a consultant for RedHill Biopharma regarding novel *H. pylori* therapies and has received research support for culture of *Helicobacter pylori* and is the PI of an international study of the use of antimycobacterial therapy for Crohn's disease. He is also a consultant for BioGaia in relation to probiotic therapy for *H. pylori* infection and for Takeda in relation to *H. pylori* therapies.

Authors' contributions: The authors contributed equally to the preparation of the manuscript.

Acknowledgements: Dr. Dang is supported in part by the facilities and resources of the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service. Dr. Dang is an investigator at the Center for Innovations in Quality, Effectiveness and Safety (#CIN 13-413), Michael E. DeBakey VA Medical Medical Center, Houston Texas. Dr. Dang is a current recipient of the K23 Mentored Patient-Oriented Research Career Development Award K23 MH100965 from the National Institutes of Health. Dr. Graham is supported in part by the Office of Research and Development Medical Research Service Department of Veterans Affairs, Public Health Service grant DK56338 which funds the Texas Medical Center Digestive Diseases Center.

REFERENCES

1. Di Ciaula A, Scaccianoce G, Venerito M, et al. Eradication rates in Italian subjects heterogeneously managed for Helicobacter pylori infection. Time to abandon empiric treatments in Southern Europe. J Gastrointestin Liver Dis 2017;26. 129-137. doi:10.15403/jgld.2014.1121.262.itl
2. Graham DY, Dore MP. Helicobacter pylori therapy: a paradigm shift. Expert Rev Anti Infect Ther 2016;14:577-585. doi:10.1080/14787210.2016.1178065
3. Dang BN, Graham DY. Helicobacter pylori infection and antibiotic resistance: a WHO high priority? Nat Rev Gastroenterol Hepatol 2017 May 3. doi:10.1038/nrgastro.2017.57
4. Yamaoka Y, Graham DY, Lu H. Should triple therapy for Helicobacter pylori infection be abandoned as no longer effective? US Gastroenterology 2008;4:65-67.

5. 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. doi:10.1046/j.1365-2036.2002.01244.x
6. Zullo A, Gatta L, de Francesco V, et al. High rate of Helicobacter pylori eradication with sequential therapy in elderly patients with peptic ulcer: a prospective controlled study. Aliment PharmacolTher 2005;21:1419-1424. doi:10.1111/j.1365-2036.2005.02519.x
7. Geisler WM, Uniyal A, Lee JY, et al. Azithromycin versus doxycycline for urogenital Chlamydia trachomatis infection. N Engl J Med 2015;373:2512-2521. doi:10.1056/NEJMoa1502599
8. Shiotani A, Lu H, Dore MP, Graham DY. Treating Helicobacter pylori effectively while minimizing misuse of antibiotics. Cleve Clin J Med 2017;84:310-318. doi:10.3949/ccjm.84a.14110
9. Dore MP, Lu H, Graham DY. Role of bismuth in improving Helicobacter pylori eradication with triple therapy. Gut 2016;65:870-878. doi:10.1136/gutjnl-2015-311019
10. Graham DY, Lee SY. How to effectively use bismuth quadruple therapy: The good, the bad, and the ugly. Gastroenterol Clin North Am 2015;44:537-563. doi:10.1016/j.gtc.2015.05.003
11. Kirchheiner J, Glatt S, Fuhr U, et al. Relative potency of proton-pump inhibitors-comparison of effects on intragastricpH. Eur J Clin Pharmacol 2009;65:19-31. doi:10.1007/s00228-008-0576-5