Digestive Diseases and Sciences (2019) 64:2691–2692
https://doi.org/10.1007/s10620-019-05747-8

EDITORIAL

Emerging Regimens for *H. pylori* Infection Should Enhance Efficacy and Circumvent Resistance

Colin W. Howden[1]

Published online: 25 July 2019

Treatment of *H. pylori* infection is complicated and often unsuccessful. Until recently, there had been few important advances in the ability to treat *H. pylori* infection. The pharmaceutical industry had not been focusing on this issue—although that may finally be changing. Most physicians in the USA do not have access to reliable antimicrobial sensitivity testing for *H. pylori*. Therefore, treatment is generally empiric—but should be based on some understanding of an individual patient's previous antibiotic exposure and whether or not the patient is penicillin-allergic. Nevertheless, information about the former may be unavailable—and estimates of the latter are often grossly inflated; most patients claiming a history of penicillin "allergy" are not truly allergic [1]. Therefore, physicians may have to make treatment choices based on potentially unreliable information. Some patients who may have unknowingly received a macrolide antibiotic in the past may be treated with a clarithromycin-containing regimen for *H. pylori* infection; such treatment is likely to fail since *H. pylori* may have become clarithromycin-resistant. Some patients who incorrectly perceive they are "allergic" to penicillin may be inappropriately and unnecessarily deprived of amoxicillin as part of their treatment regimen.

The 2017 practice guideline from the American College of Gastroenterology (ACG) [2] recommended that treatment decisions should reflect any history of exposure to clarithromycin and other macrolides, and the presence or absence of true penicillin allergy. Yet, regardless of these considerations, all roads seemed to be leading toward bismuth-based quadruple therapy consisting of a PPI, bismuth subsalicylate, tetracycline, and metronidazole (see Figure 1 from Ref. [2]). In this issue of *Digestive Diseases and Sciences*, Alsamman et al. from Brown University in Rhode Island have reviewed the records of 1710 patients treated for *H. pylori* infection between 2015 and 2017; full information was obtainable for 1101 [3]. Although this study was not a randomized controlled trial, its results represent the most current information on how treatments for *H. pylori* infection may be performing in a "real-world" setting—albeit in a single state in the USA. They found that 87% of 585 patients receiving bismuth-based quadruple therapy for 14 days achieved successful eradication of *H. pylori* infection, the highest eradication rate among the many regimens that their patients had received. Other important findings for bismuth-based quadruple therapy were that 14-day treatment was superior to 10-day treatment and that it was more effective than treatment with a proton pump inhibitor (PPI), clarithromycin, and amoxicillin.

Should bismuth-based quadruple therapy be the first-line treatment of choice in 2019? Can concerns about antimicrobial sensitivity testing and possible penicillin allergy be circumvented and should clinicians simply take a "shot in the dark" with this approach? There is certainly much to commend such a strategy. The effectiveness of the regimen is unrelated to the possibility of clarithromycin resistance, and concern about possible allergy to penicillin does not apply. Furthermore, bismuth is cheap and easy to obtain over-the-counter and is well tolerated. Nonetheless, the regimen is complicated for some patients to follow, and tetracycline may be expensive to acquire and its availability is not always guaranteed. Intermittent difficulties with obtaining tetracycline have led some to replace it with doxycycline, which Alsamman et al. found to be a poor substitute. Although only 64 of their patients were treated with doxycycline rather than tetracycline, eradication rates were clearly inferior. The 14-day regimen of standard bismuth-based quadruple therapy including tetracycline was the only one that achieved success in close to 90% of patients [3].

Based on the above considerations, bismuth-based quadruple therapy is probably the best empiric choice. Furthermore, a study from China found that empiric use

✉ Colin W. Howden
chowden@uthsc.edu

[1] Division of Gastroenterology, University of Tennessee College of Medicine, 956 Court Avenue, Suite H210, Memphis, TN 38163, USA

of a bismuth-based quadruple regimen was as effective as targeted therapy based on antimicrobial sensitivity testing [4]. Still, can it be further improved given its relative complexity and possible problems with tetracycline cost and availability? Physicians should be aware of some developing approaches to treating this chronic infection that may be simpler for patients to take and yet maintain effectiveness in practice.

One possibility is dual therapy with a PPI and amoxicillin. Treatment with high-dose PPI and at least 3 gm/d of amoxicillin for 14 days produced eradication rates of 70–89% in patients with at least one prior failed attempt at eradication [2]. Advantages of this approach are obvious: First, it would simplify treatment; second, since it obviates the need for clarithromycin, concerns about possible resistance become invalid; and third, resistance of *H. pylori* to amoxicillin remains extremely uncommon [2, 5]. The 2017 ACG practice guideline made a conditional recommendation for this regimen as a salvage treatment based on evidence considered to be of low quality [2]. Nevertheless, given concerns about increasing resistance to clarithromycin, this may become more frequently used first-line treatment—especially for patients with a history of macrolide use for an unrelated condition.

A second possibility is replacing the PPI with a potassium-competitive acid blocker (P-CAB) in either a dual regimen with amoxicillin, or a triple combination with amoxicillin and clarithromycin. Vonoprazan is the P-CAB that has been most extensively studied to date. In a systematic review and meta-analysis, Jung et al. [6] included 10 trials that had compared vonoprazan-based triple therapy with PPI-based triple therapy. Pooled eradication rates were 87.9% and 72.8%, respectively. Rates of adverse events and treatment discontinuation were similar between the regimens. Dual therapy with vonoprazan and amoxicillin also appears promising. Furuta et al. [7] reported a 93.8% eradication rate with vonoprazan 20 mg *bid* and amoxicillin 500 mg *tid*, compared with 94.3% with vonoprazan 20 mg *bid*, clarithromycin 200 mg *bid*, and amoxicillin 750 mg *bid*, with both regimens given for 7 days. Further trials of vonoprazan-based dual and triple regimens for *H. pylori* infection are planned for North America and Europe.

The third development is of a combination product (RHB-105; RedHill Biopharma, Raleigh, NC) containing omeprazole, rifabutin, and amoxicillin. In the "ERADICATE Hp2" trial [8], RHB-105 given for 14 days successfully eradicated *H. pylori* infection in 84% of patients compared with 58% of subjects receiving the same doses of omeprazole and amoxicillin. If this product is approved by the Food and Drug Administration (FDA), the recommended dose would be four capsules taken three times daily for 14 days—with total daily doses of omeprazole 120 mg, rifabutin 150 mg, and amoxicillin 3 gm. This should simplify treatment since patients would take 12 capsules of a single combination product rather than three or four different medicines in different doses. Furthermore, rifabutin resistance is very uncommon. In the trials leading to FDA submission, no acquired resistance to rifabutin was encountered. The possible myelotoxicity of rifabutin should not be an issue given that the total dose would be 150 mg daily for 14 days.

It is unlikely that determination of the sensitivity and resistance profile of *H. pylori* before initiating treatment will become widely available any time soon. Therefore, bismuth-based quadruple therapy constitutes a fairly safe bet given its proven safety and efficacy. However, the emergence of simpler 14-day regimens as outlined above may change routine practice. Anything that simplifies the current somewhat cumbersome approach to treating this infection should be welcomed—assuming that effectiveness and safety are confirmed in randomized controlled trials and appropriate post-marketing surveillance.

References

1. Macy E. Penicillin allergy: optimizing diagnostic protocols, public health implications, and future research needs. *Curr Med Opin Allergy Clin Immunol*. 2015;15:308–313.
2. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2017;112:212–239.
3. Alsamman MA, Vecchio EC, Shawa K, Acosta-Gonzales G, Resnick MB, Moss SF. Retrospective analysis confirms tetracycline quadruple as best *Helicobacter pylori* regimen in the United States. *Dig Dis Sci*. (Epub ahead of print). https://doi.org/10.1007/s10620-019-05694-4.
4. Chen Q, Long X, Ji Y, et al. Randomised controlled trial: susceptibility-guided therapy versus empiric quadruple therapy for first-line *Helicobacter pylori* treatment. *Aliment Pharmacol Ther*. 2019;49:1385–1394.
5. Shiota S, Reddy R, Alsarraj A, El-Serag HB, Graham DY. Antibiotic resistance of *Helicobacter pylori* among male United States veterans. *Clin Gastroenterol Hepatol*. 2015;13:1616–1624.
6. Jung YS, Kim EH, Park CK. Systematic review with meta-analysis: the efficacy of vonoprazan-based triple therapy on *Helicobacter pylori* eradication. *Aliment Pharmacol Ther*. 2017;46:106–114.
7. Furuta T, Yamade M, Uotani T, et al. Vonoprazan-based dual therapy with amoxicillin is as effective as the triple therapy for the eradication of *H. pylori*. *Gastroenterology*. 2018;154:S-927.
8. https://www.redhillbio.com/RedHill/Templates/showpage.asp?DBID=1&LNGID=1&TMID=178&FID=1384&PID=0&IID=10196. Accessed 1 Jun 2019.