Eradiication of Helicobacter Pylori: In Search of a Better Therapy

Marco Manfredi1**, and Gian Luigi de’Angelis2
1Department of Medicine, Sant’Anna Hospital, Reggio Emilia, Italy
2Pediatrics Department, University of Parma, Parma, Italy

From the moment Helicobacter pylori was discovered in 1982, gastroenterologists realized that it is not a common bacterial infection. And in fact, various changes have had to be made to therapeutic approaches in an attempt to eradicate it [1].

Unlike more common infections, for which we usually have a wide range of treatment options, H. pylori is sensitive to only a few medications, and their widespread use (and, sometimes, abuse) in fighting infections, particularly in the respiratory tract, has led to a reduction in their effectiveness against this bacterium [1]. The situation is exacerbated by the fact that H. pylori itself generates pharmacological resistance that differs with geographic area and also compromises successive second and third-line therapies. [2-4]. What’s more, H. pylori have a number of properties that are highly peculiar and perhaps unique. First of all, it lives in the stomach, an unusual environment (before H. pylori was discovered, it was thought that the stomach was a sterile environment which could not host pathogens). Also, since H. Pylori is found inside the gastric epithelial cells, it is harder to reach with concentrations of medication that are high enough to effect elimination [5].

In the late 1980s and early 1990s, a triple therapy was widely used that combined ranitidine with antibiotics with or without bismuth [6,7]. Subsequently, the usefulness of PPIs was recognized not only to reduce gastric acidity to a greater degree than ranitidine, thus creating an environment that is less favourable to H. pylori growth, but also to damage H. pylori itself [8], which has proton pumps that are similar to those found in humans [9]. After it was established that an antibiotic alone was insufficient for obtaining an adequate eradication rate, a standard triple therapy (PPI + two antibiotics) began to be administered [10-12]. This has been the most widely used treatment for at least two decades. Over the years, studies have been carried out with different combinations of antibiotics (PPI with amoxicillin + clarithromycin or amoxicillin + metronidazole or clarithromycin + metronidazole) [1]. The standard triple therapy no longer has acceptable eradication rates (74-78%), since the rate of optimum effectiveness for an antibiotic is considered to be at least 80%; however, the triple therapy is still the recommended first-line treatment in major international guide lines (European, American, Asiatic) [1, 13-15].

The eradication rates do not vary significantly with duration of therapy (7, 10 or 14 days), but it must also be remembered that the longer the therapy is continued, the greater the side effects [1,16]. In all probability, the effectiveness of the triple therapy was due not only to the infrequent resistance of H. pylori to amoxicillin (which is the reason why this antibiotic is used in almost all eradicating treatments around the world), but also because this therapy began to be used many years ago, when resistance to clarithromycin and metronidazole was much lower than it is today [2,4]. Over the past few decades, the excessive use of antibiotics - especially to treat infections of the respiratory tract - has evidently reduced the effectiveness of the triple therapy.

Many studies have evaluated other therapeutic regimens using various durations of therapy, combinations of medications and numbers of antibiotics (dual-therapy, sequential, quadruple with or without bismuth, ...) [17-22]. Perhaps the most innovative therapy is still the sequential regimen [23,24]. A number of recent studies and meta-analyses have confirmed that this treatment is very effective, even in cases that are resistant to clarithromycin and imidazoles. As is true for virtually all eradicating therapies, the key antibiotic is amoxicillin administered during the first 5 days of therapy, which is able to weaken the H. pylori bacteria wall and prevent the formation of so-called clarithromycin efflux channels - perhaps the major cause of the ineffectiveness of this antibiotic [25-27].

The greatest detractors of sequential therapy maintain that the sequentiality of the drugs itself (the fundamental therapeutic action) makes it difficult to take the antibiotics with precision, which ultimately has a negative effect on effectiveness. However, it has been shown that in clinical practice, patients who are non-compliant with regard to taking drugs are no different from those who take the triple therapy [28].

Given the ever increasing resistance to clarithromycin, studies on changing the sequence have recently been completed; that is, quinolones and rifabutin are used instead of clarithromycin. However, the results have been mixed [29,30].

Subsequently, several authors began to evaluate the therapeutic effectiveness of using as first-line treatment the antibiotics that are normally allocated to the second or third therapeutic choice. The authors banked on the fact that if these antibiotics are effective in patients who have already been subjected to multiple eradicating therapies, then, a fortiori, they will be effective when used as first-line therapy (triple therapy with quinolones, with rifabutin…) [31-33]. Unfortunately, although a good initial result was obtained with drugs normally used as second and third-line therapy, they did not meet expectations of clearly increasing the percentage of eradication and did not solve the problem of antibiotic resistance; for example, quinolones generate resistance very quickly, but the best results are obtained by extending therapy for 14 days. Also, these drugs are expensive. As a result, they are now considered to be better as second-line choices. Rifampicin is saddled with rather serious side effects (such as melotoxicity) [31-35].

A therapeutic plan has recently been developed that involves quadruple therapy with omeprazole plus a single capsule containing three antibiotics (bismuth subcitrate, metronidazole and tetracycline) for ten days, which resulted in a good eradication rate (92-93%) [36] that improved to excellent (97.1%) when therapy was prolonged for two weeks [37]. This format offers the advantages of taking three antibiotics

**Corresponding author: Marco Manfredi, Department of Medicine, AUSL of Reggio Emilia, Sant’Anna Hospital, Castelnovo ne’Monti, Reggio Emilia, Italy, E-mail: marco.manfredi8@gmail.com

Received December 18, 2012; Accepted December 19, 2012; Published December 22, 2012


Copyright © 2013 Manfredi M, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
in a single capsule and overcoming resistance to metronidazole. The side effects seem to be similar to those of the standard triple therapy.

Even though bismuth is not widely available, quadruple therapy containing it is regaining significant popularity after being abandoned for some time due to the appearance of resistance.

This therapy is effective if prolonged for 14 days, but is perhaps the therapeutic scheme with the greatest risk of side effects [1,38].

Over the past few years, the addition of adjuvants - i.e. natural substances known for their infection-fighting properties as well as for their general benefits to human health has begun to be evaluated, especially in an attempt to reduce the side effects associated with multiple antibiotic therapies. In various meta-analyses, the use of adjuvant has been shown to be effective not only for improving compliance, but also for raising eradication rates. The best adjuvant appears to be lactobacilli and bifidobacteria. Besides reducing the side effects of triple therapy, their bacteriocins weaken *H. pylori* by lowering the intragastric microbe level, which enhances the action of the antibiotics [39,40]. One of our studies has shown that the use of adjuvants (lactoferrin and probiotics) together with sequential therapy does not increase its already high eradication rate, but clearly alleviates its side effects, thus providing patients with better quality of life (we did not obtain additional improvements in compliance when lactoferrin was added to probiotics) [41].

Other studies have also investigated the effect of natural substances (such as olive oil and chewing gum) on *H. pylori* microbial load and confirmed that, in any case, various materials in nature may have infection-fighting properties but are perhaps difficult to standardize in clinical practice [42,43].

According to one of the greatest international experts on *H. pylori*, the therapy of choice should be the one that offers the highest eradication rate and thus produces the smallest proportion of patients requiring repetition of treatment [44]. Treatment failure not only increases the percentage of second-line therapies, but also raises the expense of treatment and the percentage of patients who are lost at follow up. Thus, according to Graham, if a choice must be made between two therapies, it is illogical and unethical to advise using the one with the lower eradication rate as the initial therapy [45]. The purpose of anti-*H. Pylori* therapy should be to treat all patients with therapies that offer at least a 90% eradication rate (and preferably 95% or higher). The best locally available therapy should be used both as the first-line and the second-line treatment. After a therapy (such as sequential or concomitant) containing clarithromycin has failed, the best current therapy is the quadruple treatment with bismuth (where available) or the fluoroquinolone-containing triple therapy, which is optimally administered for at least 14 days. Levofloxacin should be avoided in areas with known resistance to this antibiotic [33,45].

However, all things considered, the variable that best facilitates eradication is still antibiotic sensitivity [46], so perhaps the most advantageous therapeutic approach is the so-called tailored therapy based on a culture examination of biopsied gastric tissue (all infectious diseases should be subjected to treatment based on culture examination and antibiotic sensitivity). Alternatively, therapy based on local antibiotic resistance is still an option [47].

Some ten years ago, our group showed that treating a group of children with the tailored therapy led to very high eradication rates [48]. Other studies have confirmed the high eradication rate using treatments based on antibiotic sensitivity [49-51].

We agree with the recommendations of Graham, who advises making local adaptations to suit the different generic sensitivities to antibiotics, which in any case vary not only from country to country, but also between different areas in the same country. With tailored therapy, the latter principle is followed in any case, and personalized therapeutic schemes can also be offered. Smaller doses of antibiotics could be tried that are adequate to ensure the various MICs, in an attempt to reduce resistance and side effects. The disadvantage to this approach is the relative difficulty of obtaining a culture of *H. pylori* (a percentage of patients must be treated empirically in any case) and the limited availability of this method. The high cost of a culture examination could be offset by the higher eradication rate and consequent reduced need to repeat multiple therapeutic cycles.

Finally, since all antibiotic therapies generate unpleasant (but usually not serious) side effects, we believe that the combination with probiotics helps the patient withstand therapy which, even if it is personalized according to the antibiogram, may easily result in unpleasant ailments (especially of the gastrointestinal tract), because it consists of multiple drugs.

References


50. Hsu PI, Wu DC, Wu JY, Graham DY (2011) Modified sequential Helicobacter pylori therapy: proton pump inhibitor and amoxicillin for 14 days with clarithromycin and metronidazole added as a quadruple (hybrid) therapy for the final 7 days. Helicobacter 16: 139-145.